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Clinical management of CKD patients in Italy: results from the IRIDE study

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ABSTRACT

Background: Lack of adequate management of chronic kidney disease (CKD) often results in delayed diagnosis and inadequate treatment. This study assessed the clinical management and outcome of stage 1–5 CKD patients.

Methods: Patients were prospectively followed for 3 years in 25 nephrology centers across Italy. Clinical characteristics were measured at baseline and every 6 months. Outcome measures included CKD staging, presence of comorbidities, treatment, mineral bone disorder (MBD) parameters, and patient outcomes.

Results: Of 884 enrolled patients (59.7% males, aged 66.2±14.6 years) 587 (66.4%) completed the study. The majority of patients were referred by a general practitioner (44.7%) and had stage 3 or 4 CKD (40.9% and 23.8%, respectively). 91.3% of patients had at least 1 concomitant disease, most frequently hypertension (80.1%) and dyslipidemia (42.5%). 94.6% of patients were receiving cardiovascular medication and 52.6% were receiving lipid-lowering medication. Approximately 40% of patients had proteinuria and intact parathyroid hormone levels outside the normal range. As expected, stages 4 and 5 CKD patients had a higher prevalence of proteinuria (68% and 74%), MBD (59 and 88%), and anaemia (28% and 73%), as well as a higher risk of hospitalization (34.3% and 51.9%) and need for dialysis (69.5% and 70%). Overall probability of survival over 36 months was 90.6%.

Conclusions: This is the first Italian prospective study performed with a large cohort of CKD patients over a 3-year period. Considering the multifactorial burden of diseases associated with CKD patients, the need for greater attention to CKD and related disorders is paramount.

INTRODUCTION

Chronic kidney disease (CKD) represents one of the most serious public health concerns worldwide. The incidence and prevalence of renal diseases associated with unsatisfactory outcomes, and therefore with elevated healthcare expenditures, appear to be increasing in the United States. According to estimates from a large cross-sectional study recently performed in 12 countries, the prevalence of CKD is 14.3% (95% CI, 14.0–14.5) in the general population and 36.1% (95% CI, 34.7–37.6) in high-risk populations [1]. More than 400,000 Americans suffer from end-stage renal disease (ESRD) and 300,000 patients are in need of dialysis [2]. Although it has been calculated that 8 million adults in the United States suffer from stage 3 (or worse) CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2), little information is available concerning mortality rates and cardiovascular events in patients with low eGFR levels that are not on dialysis [3].

In the United States, cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients; in particular, the rate of CVD in patients on dialysis is 15 times that of the general population and CVD is the main cause of death in patients with ESRD [4]. Up to 45% of patients with CKD in the pre-dialysis phase may risk death before ever starting dialysis treatment. Similarly, patients suffering from early phase CKD present with a greater prevalence of CVD risk factors compared with those with normal renal function, thus explaining the higher rates of CVD in this population [5-13]. Epidemiologic data in Italy emphasize the growing number of uremic patients undergoing dialysis. Estimates from the Italian dialysis and transplant registry reported approximately 45,000 to 49,000 patients on dialysis from 2011–2013 [14]. In contrast, data related to the real-life clinical management and outcomes of stage 1 through 5 CKD patients not on dialysis is extremely limited, with few studies conducted in Italy [15,16]. The aim of IRIDE (**I**talian obse**R**vat**I**onal study on management of CK**D** pati**E**nts and related costs), a multicenter, prospective, observational study, was to describe the course of the disease and the clinical management of Italian patients with CKD over a 3-year period.

MATERIALS AND METHODS

Patients

IRIDE was a prospective observational study involving 25 centers across Italy. Criteria for the selection of centers included that they have a nephrology outpatient clinic with a high number of patients visited per week (>20). Data were collected from each center every 6 months for a total of 36 months (7 visits). Patients included in the study were adults (>18 years old) with CKD

without the need for dialysis and were followed at the nephrology outpatient clinic during the survey period. All patients were required to provide a signed consent form before participation in the study. Exclusion criteria included a) subjects presenting with comorbidities with a life expectancy of <1 year (e.g., advanced phase malignancies, advanced liver disease); b) subjects enrolled in a clinical trial (interventional study) on erythropoietin-stimulating agents (ESAs), vitamin D, or phosphate binders at the start of the study; c) renal transplant recipients; and d) subjects who had already taken part in the study.

Study objectives and parameters measured

A baseline visit was conducted to obtain demographic and clinical patient data, including the following information: 1) referral history, 2) presence and type of previous hospitalizations, 3) presence and type of other pathologic diseases, 4) current medication, and 5) biochemical and renal parameters. Additional information was collected by the nephrologist at each clinical visit every semester to determine the general condition, the staging and progression of CKD, concomitant diseases and associated hospitalizations, the therapeutic scenario, and patient outcome. The management of CKD mineral bone disorders (MBDs) was also assessed [11]. Renal function was evaluated through the eGFR by the abbreviated MDRD(Modification of Diet in Renal Disease) equations for non-standardized creatinine. CKD was classified according to Kidney Disease Improving Global Outcomes guidelines [17].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median values. Statistical analysis was performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA). Nonparametric continuous variables were compared using the Mann-Whitney U-test. The Kaplan–Meier (KM) method was used to estimate the time to onset of outcomes and change of disease stage. Due to a lack of data on the incidence of other outcome variables reported from previous studies, sample size was calculated on the basis of “secondary hyperparathyroidism”: assuming that secondary hyperparathyroidism can be expected to occur in approximately 40% of patients with stage 4 CKD over a 3-year follow-up period. Since patients with stage 4 CKD account for approximately 17% of the sample population, we estimated that 1,000 subjects would allow for an estimate of a 95% confidence interval for the frequency of the outcomes foreseen by the study in the most restrictive condition (50%) with ±1.6% precision. Where comparisons were made, p values are two-tailed and n values refer to the number of patients examined. $p \leq 0.05$ was considered statistically significant.

RESULTS

Baseline clinical characteristics

The IRIDE study was conducted from December 2010 to September 2014. Of the original study population (n=884), 587 patients (66.4%) completed the 3-year observation period, according to study protocol. A total of 868 patients were evaluable after the first visit as described in the study protocol. The most common reasons for not completing the study included death (n=71; 8.1%), dialysis (n=101; 11.4%), or lost to follow up (n=113; 12.8%). Other reasons included patients who withdrew consent (n=7; 0.8%), did not fulfil inclusion/exclusion criteria (n=3; 0.34%), or other (n=2; 0.23%). Patient baseline clinical characteristics by staging of CKD are presented in **Table 1**. The mean age of patients at baseline was 66.2±14.6, 59.7% (n=518) were men, and 0.7% were of African descent. The majority of patients were referred to the nephrology department by a general practitioner (44.7%) and had mean disease duration of 7 years (ranging from 5 years in patients with stage 2 CKD to 9.3 years in patients with stage 5 CKD). Most patients (91.3%) had at least one other comorbid condition. At the first visit, 80.1% of patients were diagnosed with hypertension, 42.5% with dyslipidemia, 32.9% with CVD (excluding hypertension, dyslipidemia, or diabetes), and 12.6% of patients were 25OH vitamin D deficient. Both male and female patients presented with comorbid conditions to a similar extent. Most of the patients in the study (94.6%) were receiving cardiovascular medication and 52.6% were receiving lipid-lowering medication. Other medications included ESA (16.6%), iron-based therapy (7.9%) and vitamin D supplementation (12.5%)

Staging of chronic kidney disease

The staging information of CKD for patients that attended the 7 clinical visits is presented in **Table 1** and **Supplemental Figure 1**. Stages of CKD were represented as follows: stage 1 (7.9%); stage 2 (18.2%); stage 3a (19.2%); stage 3b (21.7%); stage 4 (23.8%); and stage 5 (9.1%). Despite the fact that some patients increased or decreased CKD staging at each visit, the proportion of patients at each stage did not change during the study period (**Supplemental Figure 1**). Furthermore, the stage of CKD did not change in the majority of patients among study visits (approximately 70%). The probability of experiencing a stage worsening was 38% for both initial stage 1 and stage 2, 59% in stage 3, 40% in stage 4, and 77% in stage 5 (**Figure 1**). Stratifying patients by gender revealed an increase in the proportion of female patients with increasing staging (33.3% of female patients had stage 1 CKD vs. 53.2% of female patients who had stage 5 CKD) and a corresponding reduction in the proportion of male patients with increasing staging (**Supplemental Figure 2**).

Cardiovascular disease, hospitalizations, and mortality over the follow-up period

The proportion of male and female patients with cardiovascular pathologies diagnosed at the first visit are summarised in **Figure 2a**. The proportion of patients with hypertension (80.1%), dyslipidemia (42.5%), and diabetes (28.8%) did not change over the follow up period. Interestingly, the proportion of patients with new cardiac complications increased over the 36-month period to a greater extent in male patients compared with female patients (**Figure 2b**).

Patients with stages 3 and 4 CKD had a higher risk of CVD occurrence over a 36-month period. Patients with stages 4 and 5 CKD had the highest rate of hospitalizations (34.3% [n=71] and 51.9% [n=41], respectively) and the rate of hospitalizations decreased over the follow-up period from 53 patients (6.1%) at visit 1 to 16 patients (1.8%) at the final visit (36 months; **Table 2**). Seventy patients (8.1%) died during the study period and patients with stage 4 CKD had the highest rate of mortality over the 36-months period (14.5%; **Table 2**). The overall probability of survival was 90.6%.

Proteinuria and probability of starting dialysis over the follow-up period

In the majority of patients (52.2%), proteinuria was measured by 24-hour urine collection, and in 0.8% of cases, the albumin:creatinine ratio was employed; for 24.7% of patients, only urine dipstick or albuminuria (10.1%) were available. At the first visit, 45.9% of patients had proteinuria, decreasing over subsequent visits to 37.8% at the final visit (36 months). The probability of increasing proteinuria over the 36-month follow-up period was 78% for stage 1, 68% for stage 2, 65% for stage 3, 68% for stage 4, and 74% for stage 5. The probability of starting dialysis was higher for male patients (approximately 12%) than female patients, but failed to reach statistical significance (Log rank test, p=0.085; **Figure 2c**).

Mineral bone density parameters and therapeutic management over the follow-up period

Mean levels of MBD parameters remained largely unchanged over the 7 visits, apart from a slight increase in phosphorus (P) levels (from 3.55 mg/dL at

baseline to 3.68 mg/dL at 36 months; p=0.035, **Table 2**). Levels of MBD parameters by CKD stage over the 3-year follow-up are shown in **Supplemental Figure 3**. While levels of intact parathyroid hormone (iPTH) and P were correlated with increased staging of CKD (**Supplemental Figure 3A** and **Figure 3B**), this trend was not observed for calcium (Ca) levels (**Supplemental Figure 3C**). The proportion of patients below, within, or above normal laboratory ranges for MBD parameters did not significantly change over the 7 visits (**Table 2**). The maximum proportion of patientswith iPTH levels (25.3%) within the normal laboratory range was observed at visit 2; the maximum proportion of patients with P and Ca above normal laboratory ranges (17.7% and 13.9% of patients, respectively) was observed at visit 3 (**Table 2**). A total of 13% of patients were 25OH vitamin D deficient (visit 1 and visit 4), ranging from 10% to 13% across the 7 visits. 27% of patients were treated with calcitriol and 8% were treated with paricalcitol, over the course of the study, mostly in patients with stages 3, 4 and 5 CKD.

Patients with stages 4 and 5 CKD had a higher risk for the occurrence of MBD over the 36-month period, defined as ≥1 of the 3 parameters (iPTH, P, or Ca) outside normal ranges for laboratory values.

Anemia and therapeutic management over the follow-up period

The probability of becoming anemic by CKD staging was 0% for stage 1, 3% for stage 2, 7% for stage 3, 28% for stage 4, and 73% for patients with stage 5 CKD. A maximum of 5.3% of patients required ESA treatment (visit 1 to visit 2). Patients with stages 4 and 5 CKD had a higher risk of anemia over the 36-month period. Approximately 3% of patients were treated with erythropoietin and approximately 12% of patients were treated with darbepoetin alpha

(mostly patients with stages 4 and 5 CKD). Approximately 13% of patients were treated with iron over the course of the study, mainly those with stages 4 and 5 CKD.

Therapeutic management of cardiovascular diseases over the follow-up period

The proportion of patients treated with angiotensin-converting enzyme inhibitors and/or angiotensin II antagonists was 70%; these numbers did not change over the study period. Thirty-nine percent of patients were treated with furosemide (mainly patients with stages 3–5 CKD). The proportion of patients treated with insulin (13%) remained stable over the study period. Thirty-four percent and 38% of patients were treated with beta-blockers or Ca antagonists, respectively. Approximately half of the patients in the study were treated with statins.

DISCUSSION

This prospective multicenter study, conducted across 25 sites, provides an important epidemiologic picture and insight of CKD and its management in 868patients in a real-world setting in Italy. Unfortunately, awareness of CKD is relatively low in Italy [18]. Consequently, the number of patients with CKD (stages 1–4) is often underestimated. The IRIDE study was specifically designed to describe the CKD population in terms of therapeutic management and outcome. This study provides information on current clinical practice and evidence of patients seeking advice from the nephrologist and their clinical status. It also yields important data on the short- to long-term development of CKD in the “real world,” combined with underlying comorbid conditions and treatment administered relative to current CKD guidelines.

The high rate of hospitalization, particularly during the advanced stages of CKD, confirms the clinical complexity and higher comorbidity of patients with CKD [2,19]. Not surprisingly, in the IRIDE study population, the rate of hospitalization reflects the increasing severity of CKD. These findings highlight the need for a multifaceted approach to this disease.

This study is of particular value, as it provides longitudinal data for a period of 36 months in patients with CKD. To date, few studies reporting data on the Italian population with CKD are available. Notably, patient compliance was high, with only a 35% drop-out rate over 3 years.

In addition, the number of patients with comorbid diseases increased slightly over the follow-up period. Seventy patients died over the 3-year follow-up period; patients with stage 4 CKD had a higher risk for death over the 36-month period (14.5%), which was expected in this high-risk population.

However, the overall probability of not experiencing a new cardiovascular complication over 3 years was 80%, suggesting good management of these patients. A recent prospective epidemiologic study performed in Italy evaluated 30,326 patients over a 7-year period and recorded 6,592 deaths (21.7%); the mortality rate observed in the IRIDE study was 8.2% [15]. Admittedly, patients in the IRIDE study were younger (mean age, 66.2 vs. 71 years old) and there was a lower proportion of patients with stages 3 and 4 CKD (64.7 vs. 85.7%). The effect of gender on CKD progression remains a topic of debate; the majority of evidence points towards better outcomes in female patients [20,21]. This has been further confirmed in a recent meta-analysis, where male sex and substantial proteinuria were found to be significant perpetuating factors for the progression from late-stage CKD to ESRD [22]. Findings from the IRIDE study confirm this difference, in which a higher proportion of male patients had stages 4 and 5 CKD. Male patients also had a higher probability of beginning dialysis treatment compared with female patients. In addition, the probability of patients developing proteinuria over the 3-year follow-up was 70%. Further studies evaluating the mechanisms leading to CKD progression, including differences related to gender , are needed [23].

In the present study, only a limited use of Ca carbonate, vitamin D supplements, and iron-based therapy was reported for the management of patients with CKD and MBDs. The sparing use of these medications can be partly explained by the fact that these patients had normal values of metabolites, such as P and Ca, at baseline. Furthermore, parathyroid hormone and alkaline phosphatase dosages often were not performed in this population. In this regard, the relatively small number of patients receiving treatment for

MBDs in this CKD population, with respect to other medications (antihypertensive drugs and diuretics,) may account for the absence (or masking) of any temporal effect of this treatment on biochemical and electrolyte parameters and the lack of principal data makes it difficult to draw exhaustive conclusions.

The probability of developing anaemia, defined as the need for erythropoietin treatment, was as high as 73% in patients with stage 5 CKD. Regarding the treatment of anaemia in patients with CKD not on dialysis, it is possible that nephrologists may be more inclined to prescribe a fixed low dose of erythropoietin in light of concerns arising from the potential negative effects of exceeding the narrow recommended target range [9]. Caution is particularly needed when treating anaemia with ESA therapy in patients with type 2 diabetes (28.8% in the present study) not undergoing dialysis.

Study limitations

There are several potential limitations that need to be addressed, such as the staging of CKD, which was based on eGFR as measured by the abbreviated MDRD method. This method, in fact, underestimates glomerular filtration rate at higher values of renal function [24,25]. However, this intrinsic error is more consistent in the measurement of glomerular filtration rate in healthy individuals, where the prevalence of undiagnosed CKD can be underestimated [26]. It is important to highlight that this was a multicenter study, with a relatively large number of patients (n=868), and therefore can be extended to represent real-life changes over a 3-year period for the entire Italian peninsula. Consistent with limitations of an observational design, our study provides

important clinical insights into the management of CKD, but does not provide direct information on the effect of treatment on patient outcome.

Conclusion

In summary, the management of CKD in nephrology practice is essential for reducing disease progression and for providing improved control of secondary diseases. Findings from the IRIDE study indicate that greater attention is required for the control of renal function, proteinuria, and MBD. In fact, the probability of developing proteinuria over the 36-month follow-up period was around 70%, irrespective of the initial stage. The importance of raising awareness of the management of CKD in both the general practitioner and specialist alike cannot be underestimated, particularly as more therapeutic options are becoming available for these patients.

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FIGURE LEGENDS

Figure 1. Probability of increasing staging. Kaplan–Meier survival estimate of probability of stage worsening stratified by different CKD stages over the 36-month study period. CKD, chronic kidney disease.

Figure 2. Cardiovascular pathologies in male and female patients. A) Range of cardiovascular diseases stratified for male and female patients. B) The proportion of male and female patients with cardiac complications or arrhythmia (C) Kaplan–Meier survival estimates of probability of increasing proteinuria in male vs. female patients over the 36-month follow-up period. Data are expressed as percentages. CKD, chronic kidney disease.

Supplemental Figure 1. Staging and variation in CKD for patients over the 7 visits. Data are expressed as percentage. CKD, chronic kidney disease.

Supplemental Figure 2 CKD staging in male and female patients Proportion of male and female patients with increasing staging over the 7 visits. Data are presented as percentages**.**

Supplemental Figure 3. Levels of MBD parameters by CKD staging for the 7 visits. A) Levels of iPTH by CKD stage for the 7 visits. B) Levels of phosphorus by CKD stage for the 7 visits. C) Levels of calcium by CKD stage for the 7 visits. Data are expressed as mean values. CKD, chronic kidney disease; iPTH, intact parathyroid hormone; MBD, mineral bone disorder