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ORIGINAL ARTICLE

The PIRP project (Prevenzione Insufficienza Renale Progressiva): how to integrate hospital and community maintenance treatment for chronic kidney disease

Antonio Santoro[1] · Dino Gibertoni[2] · Paola Rucci[2] · Elena Mancini[1] · Decenzio Bonucchi[3] · Andrea Buscaroli[4] · Anselmo Campagna[5] · Gianni Cappelli[6] · Salvatore David[7] · Maria Cristina Gregorini[8] · Gaetano La Manna[9] · Giovanni Mosconi[10,11] · Angelo Rigotti[12] · Roberto Scarpioni[13] · Alda Storari[14] · Marcora Mandreoli[15]

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Abstract

Chronic kidney disease (CKD) represents a global health burden with great economic impact on healthcare and therefore it requires appropriate interventions by Health Care Systems. The PIRP (Prevenzione Insufficienza Renale Progressiva) project is endorsed and funded by the Emilia-Romagna Regional Health Board and involves all the Nephrology Units of the Emilia-Romagna Region (Italy). The project has a predominantly clinical purpose and is expected to bring about a continuous quality improvement in the treatment of patients with CKD. Its aims are to intercept patients in an early phase of CKD, to delay their illness progression and to prevent cardiovascular complications. An integrated care pathway involving nephrologists, general practitioners (GPs) and other specialists has been created to identify patients to whom ambulatory care targeted on effective, efficient pharmaceutical and dietary treatment as well as on lifestyle modifications is subsequently provided. With the cooperation of GPs, in its 13 years of activity the project identified and followed up more than 25,000 CKD patients, who attended the Nephrology units with more than 100,000 visits. The effects of a closer and joint monitoring of CKD patients by GPs and nephrologists can be quantified by the reduction of the mean annual GFR decline (average annual CKD-EPI change: − 0.34 ml/min), and by the decrease in the overall incidence of patients who annually started dialysis in the Emilia-Romagna Region, that dropped from 218.6 (× million) in 2006 to 197.5 (× million) in 2016, corresponding to about 100 cases.

Keywords Chronic kidney disease · Registries · General Practitioners · eGFR · CKD management · Public health intervention

✉ Antonio Santoro
antonio.santoro@unibo.it

1 Nephrology, Dialysis and Hypertension Unit, Policlinico S. Orsola-Malpighi, Bologna, Italy

2 Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

3 SSD Nephrology and Dialysis, Ospedale Ramazzini, Carpi, Italy

4 Nephrology and Dialysis Unit, Ospedale S. Maria delle Croci, Ravenna, Italy

5 Health Policies Department, Emilia-Romagna Region, Bologna, Italy

6 Nephrology and Dialysis Unit, University Hospital of Modena, Modena, Italy

7 Nephrology and Dialysis Unit, Ospedale Maggiore, Parma, Italy

8 Nephrology and Dialysis Unit, Arcispedale S. Maria Nuova, Reggio Emilia, Italy

9 Nephrology, Dialysis and Transplantation Unit, Policlinico S. Orsola-Malpighi, Bologna, Italy

10 Nephrology and Dialysis Unit, Ospedale Morgagni-Pierantoni, Forlì, Italy

11 Nephrology and Dialysis Unit, Ospedale M. Bufalini, Cesena, Italy

12 Nephrology and Dialysis, Ospedale degli Infermi, Rimini, Italy

13 Nephrology and Dialysis Unit, Ospedale "Guglielmo da Saliceto", Piacenza, Italy

14 Nephrology and Dialysis Unit, Arcispedale S. Anna, Ferrara, Italy

15 Nephrology and Dialysis Unit, Ospedale S. Maria della Scaletta, Imola, Italy

Introduction

Chronic kidney disease (CKD) represents a global health burden with great economic impact on healthcare systems. CKD, defined by indicators of kidney damage—imaging, proteinuria (commonly using albumin-to-creatinine ratio, ACR)—and decreased renal function has a global prevalence estimated between 11 and 13% with the majority of patients in CKD-EPI stage 3 [1]. In Italy, CKD prevalence estimated by a National Health Examination Survey was lower (7.05%, 95% CI 6.48–7.65), with early stages representing 59% of cases [2], while a previous study conducted in North-Eastern Italy found a similar prevalence [3].

Still, the number of patients with CKD is expected to grow, as a consequence of ageing of the general population and of the increase of age-related pathologies, such as hypertension and type 2 diabetes, which today represent the main causes of CKD [4].

CKD is associated with increased morbidity and mortality compared with the general population, especially in the advanced stages [5]. However, even patients in stage 2 and 3 have an increased risk of hospitalization and of fatal and non-fatal cardiovascular (CV) events [6]. Dialysis treatment and kidney transplantation are the endpoints for many patients with CKD and both have high social costs (the chronic dialysis patient is forced to interrupt his/her activity every other day for 4–5 h) and require a large allocation of resources [7].

The identification of CKD at an initial stage is then essential in order to undertake as soon as possible a multifaceted conservative therapy, whose efficacy in slowing down the progression of renal dysfunction and of cardiovascular damage has been widely recognised [8–10]. However, early identification of patients with CKD is not easy, because patients, at least in the initial stages, often remains asymptomatic for a long time or have non-specific symptoms such as lethargy, itch, loss of appetite. Therefore, patients with CKD may be referred to the specialist nephrologist only in a later stage of the disease when clinical signs show up. Another factor favouring late-referral is the lower awareness of CKD by general practitioners (GPs) and other specialists, as compared with other chronic diseases such as cardiac diseases, essential hypertension, diabetes, dyslipidemia, COPD. Unfortunately, late nephrological referral is associated with increased risk of mortality and hospitalisation in both the pre-dialysis phase and during the dialysis treatment [11, 12]. The KDIGO guidelines [13] advise referring the patient with CKD diagnosis as soon as possible to nephrological consultancy and not to delay treatment any further, when the glomerular filtrate rate value has been reduced to less than 30 ml/min.

Achieving early identification of patients with CKD in order to implement effectively all the actions necessary to prevent renal function decline and the associated CV complications were the reasons that led the nephrologists of the Emilia-Romagna region (North-Eastern Italy), to develop in 2004 the PIRP (Prevenzione Insufficienza Renale Progressiva) project. In this paper we describe the PIRP project, and summarize the results achieved in its first 13 years of activity.

Methods

The PIRP project is endorsed and funded by the Emilia-Romagna Regional Health Board (deliberation n.696 issued on May 14, 2018; GPG/2018/747) and involves all the 12 Nephrology Units in the region. Emilia-Romagna is a region in North-Eastern Italy, with a population of almost 4.5 million inhabitants as of 1.01.2017, of which 23.7% are aged 65 years or more [14]. The PIRP project has a predominantly clinical purpose and is expected to bring about a continuous quality improvement in the treatment of patients with CKD. Its aims are (1) to delay the recourse to dialysis therapy, (2) to reduce morbidity and mortality by intercepting CKD patients in an early phase of the disease, slowing down the CKD progression and preventing CV complications. The project is designed to achieve its aims by means of an effective, efficient ambulatory care for CKD patients, obtained by promoting integrated care pathways which involve nephrologists, GPs and other specialists (cardiologists, diabetologists, internal medicine doctors, etc.).

The PIRP project started in 2004 with a training—information phase, followed by the implementation phase. *The training—information phase* was specifically addressed to the GPs and consisted in teaching seminars carried out throughout the region to disseminate knowledge about CKD, to improve early identification of the population at risk, to promote effective prevention strategies (lifestyle modification, correction of modifiable risk factors) and treatments, and to avoid inappropriate drug utilization (Table 1). Refresher courses for GPs have been made in more recent years. At the same time, all the clinical analysis laboratories of the region adopted the standard equations for estimating the glomerular filtration rate (eGFR), using at first the MDRD equation and currently the CKD-EPI equation. The eGFR value was introduced in the standard lab reports, to help GPs to identify patients with decreased renal function at each stage of the disease that are eligible to be enrolled in the PIRP project. Moreover, to enhance their compliance to the nephrological diet, CKD patients benefitted of a price reduction on low protein foods supported by the local Health Authorities of Emilia-Romagna region.

Table 1 Monitoring and co-management of CKD patients in the PIRP project

	CKD stage (eGFR ml/min)				
	1 (> 90)	2 (60–90)	3 (30–59.9)	4 (15–29.9)	5 (< 15)
Frequency of clinical review	Every 12–18 months (exceptions: pts with heavy proteinuria, glomerulonephritis or autoimmune disease)		6 months	2–3 months	1–2 months, according to individual trajectory of GFR decline
Clinical assessment	BP, weight, ABPM if necessary, control of fluid overload				
Lab assessment	Laboratory studies needed to diagnose and stage CKD		6 months: renal function, urine examination, serum electrolytes, blood sugar, lipids, blood count, iron balance, Ca-phosphorus balance, PTH (6–12 months)	Examination schedule shared with nephrologists, based on the rate of progression of CKD and any other complications and co-morbidities	
Management	CKD risk identification; diagnosis of primary nephropathy; cardiac and kidney risk factors modification Treat BP to target < 130/80 mmHg or < 125/75 mmHg. If significantly proteinuria is present achieve the best glycemic control Caution: drug-induced nephrotoxicity		As for stages 1–2+ treat complications, drugs dosing/safety review; achieve LDL col target, diet modification in protein, sodium, etc.	As for stage 3+ diet protein and phosphate restriction if necessary, evaluation of nutritional assessment	As for stage 4+ dialysis education; dialysis access surgery or transplant preparation? Maximization of conservative treatment based on a specific request from the patient
Lifestyle modifications and clinical action plan	Education and promotion of a correct lifestyle (physical activity, control weight, smoke cessation). Reduce or avoid inappropriate drug utilization		Reduce/avoid nephrotoxic drugs, prevention of contrast induced nephropathy; adjustment of the dose of drugs with renal excretion	Limit potentially nephrotoxic drugs and radiological investigations with contrast media; reassess the posology of renal excretion drugs, protect the peripheral venous bed	
Integrated co-management GP/Nephrologist	GP ■■■ Nephrologist ■	GP ■■□ Nephrologist ■□	GP ■□ Nephrologist ■■□	GP ■ Nephrologist ■■■	GP □ Nephrologist ■■■□

The total burden of patient management is indicated by four full squares (■■■■), and a hollow square (□) corresponds approximately to the half of a full square

The implementation phase consisted in opening specialized outpatient facilities dedicated to the treatment and management of progressive renal insufficiency at the Nephrology Units. Patients' access to the "PIRP Facilities" is managed by GPs and operated by a centralised booking office. The tasks of the PIRP facilities are: (1) patient profiling and assessment of the renal insufficiency stage; (2) co-morbidity assessment, planning of lab tests and specialty visits when needed; (3) estimation of the disease progression rate and (4) definition of the appropriate personalized therapy and diet. A nutrition therapy is suggested to all patients with eGFR < 60 ml/min and depending on particular clinical needs [15].

A protocol defined in agreement with the GPs specifies the conditions under which the patient should be followed up by the PIRP specialists (Table 1). Thus, at every PIRP visit, depending upon the stage of renal insufficiency, the progression rate and the presence of co-morbid diseases, the patient is treated by the nephrologists' team or is referred back to the GP (patients with CKD at early stages and without co-morbidities). However, the patient's co-management between the GP and the nephrologist is maintained through the use of a dedicated website and an e-mail account that permanently connect the GP to the nephrological team.

The PIRP database

When patients enter the project, their data are stored in a web-based database (SofTime90, Bologna), which is part of the Emilia-Romagna regional Transplantation Information system and is hosted on a server located at the S. Orsola-Malpighi Hospital in Bologna. A scheme summarizing the various sources feeding the PIRP database is provided in Fig. 1. The database is accessible by the nephrology units users for data entry and consultation and includes patient's socio-demographic characteristics, anamnestic data and, for each follow-up visit, data regarding blood and urine examinations, comorbidities, risk factors, pharmacological and dietary treatment.

Patient outcomes are retrieved from administrative databases of the Emilia-Romagna region. Specifically: mortality is retrieved biannually from the regional Emilia-Romagna registry of mortality; RRT inception is retrieved annually from the Regional Dialysis Registry; hospitalizations are retrieved three times a year from the Regional Hospital Discharges Registry. The quality of data in the PIRP database is checked on a regular basis and inconsistencies or missing data are notified by the Registry data manager to the nephrologist who entered the data. Bimonthly and annual reports on the amount and quality of data collected, as well as on the patient characteristics of the PIRP population, are provided to the PIRP nephrologists and to the regional healthcare agency. The database is also used as a source of data for clinical and epidemiological studies on CKD patients [5, 16–18].

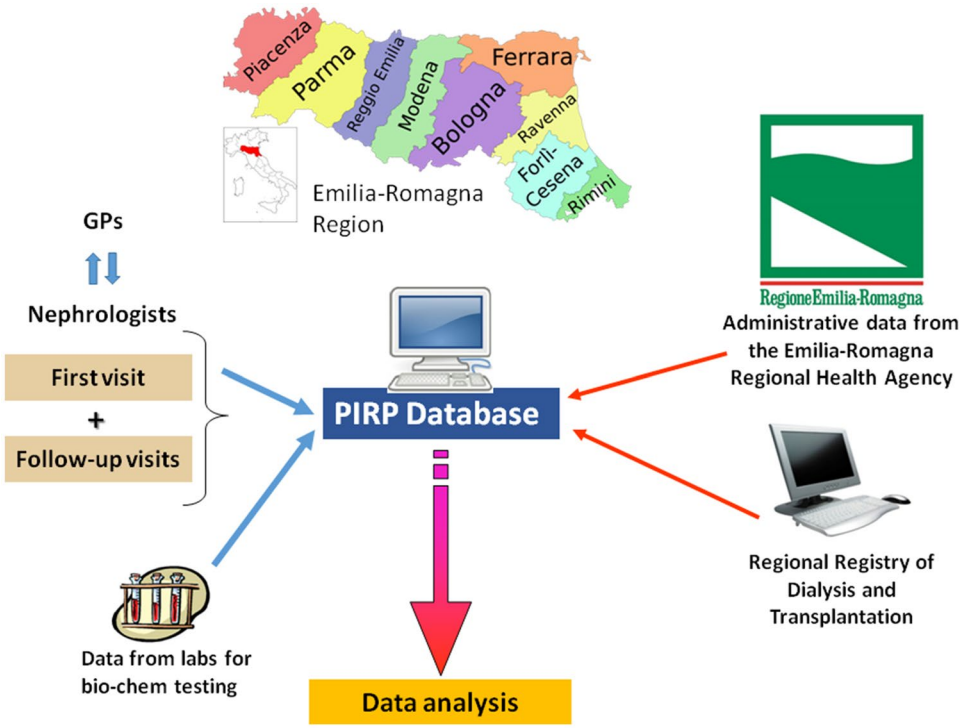

Fig. 1 Data framework of the PIRP database

Statistical analysis

PIRP patients' characteristics at baseline and at their last visit were reported overall and by CKD-EPI stage at baseline, merging stages 1 and 2 because of their low frequency. As for treatment, we compared the incidence of the most important drug classes for CKD before and after patients' entry in the PIRP project. Percentages of hospitalized patients by CKD-EPI stage were calculated for total, surgical, non-surgical and cardio-vascular-related admissions. Data were censored at death, RRT, loss to follow-up or on December, 31st. 2017.

Several longitudinal analyses were performed to describe how the recruited patients' characteristics changed on time and how their renal function evolved during follow-up. Specifically, we compared the distribution functions of eGFR at baseline in four different time frames; we estimated the linear slopes of eGFR in patients with the same CKD stage at baseline and investigated whether the mean change in eGFR was related to the length of follow-up and the year of enrolment in the PIRP project using a multiple linear regression model. Nine demographical and clinical covariates were included as potential confounders: age, gender, systolic pressure, phosphates, eGFR stage at baseline, underlying nephropathy and the indicators of proteinuria, diabetes and cardio-vascular comorbidities. Multiple imputation was used to estimate missing data of the proteinuria and phosphates (28.6% and 35.3% missing respectively) variables. The annual incidence rate of RRT was calculated as the ratio between the number of patients starting dialysis in the Emilia-Romagna region in a calendar year and the adult resident regional population at January 1st of each year, multiplied by 1 million, while the incidence rate of RRT among PIRP patients was calculated using the number of PIRP as of January 1st of each year as the denominator. The number of residents in Emilia-Romagna was obtained from the regional Bureau of Statistics [14].

Stata v.15.1 was used to perform all analyses and to produce all figures.

Results

From the start of the project the number of patients followed up and recorded in the PIRP database increased linearly from 365 to 25,257, while nephrological visits increased exponentially from 539 up to 101,340 as of December 31, 2017.

Baseline data

At the study entry, most patients were in Stage 3b (36.1%) or Stage 4 (35.5%), were male (65.1%) and their mean age was 72.5 years, with younger patients in CKD stages 1–3b (Table 2). The most common nephropathy was hypertension-related (56.4%), followed by diabetic nephropathy (12.3%). The mean haemoglobin levels were above 12 g/dl up to stage 3b and below 12 g/dl in stages 4 and 5. Macro-proteinuria was present in 42.3% of patients. Phosphate was generally less than 4 mg/dl, but in stage 5 the average phosphate levels were 4.47 mg/dl. LDL cholesterol levels > 100 mg/dl were found in slightly more than 50% of patients in all CKD stages except 1 and 2 combined, where they accounted for 67.1% of patients.

Cardiovascular diseases were the most common co-morbidities, with a frequency growing with higher renal functional impairment that exceeded 70% in Stages 4 and 5. The prevalence of diabetes was around 35% in all stages.

The mean baseline eGFR at the first visit was characterized in 2005–2016 by a shift towards higher renal function levels (Fig. 1), indicating that more patients in the early CKD stages were enrolled in the more recent years.

Follow-up and outcomes

At 31 December 2017 patients were followed up for a median time of 40.9 months (Table 3), ranging from 16.3 (stage 5) to 53.7 months (stage 3b). Fewer than 5% of patients were lost to follow-up, while 10.6% reached RRT and 27.8% died. The mean annual eGFR loss was − 0.34 ml, with varying magnitudes of change depending on the baseline eGFR level. While patients entering the project with a more preserved renal function (stages 1–3a) had the fastest declining slopes, those entering in stages 4 and 5 displayed a flat trajectory (Fig. 2). The mean change of eGFR was unrelated to the year of enrolment in the PIRP project and was associated with the length of follow-up, after adjusting for age, gender, type of nephropathy, proteinuria, diabetes, CV comorbidities, baseline levels of eGFR stage, phosphates and systolic pressure. For each year of follow-up, PIRP patients had a mean eGFR reduction of − 0.832 ml/min/1.73 m^2 (95% CI − 1.032, − 0.631; $p < 0.001$) (Fig. 3).

RRT initiation was common for patients who entered in stage 5 (42.6%), while death occurred more frequently in CKD-EPI 4 patients (39.6%). The main causes of death were cardiovascular diseases (43.5%) and neoplasm (21.6%). The crude rate of dialysis inception decreased over time and reached a plateau around 2.7 per 100 PIRP patients (Fig. 4). The inspection of this figure suggests that at the beginning of the project nephrologists probably enrolled patients already followed in pre-dialysis outpatient clinics and who were therefore more likely to start dialysis in the short term. The subsequent progressive reduction in the rates of PIRP patients reaching dialysis is mirrored by the trend of the incidence rate of dialysis in the adult population of the Emilia-Romagna region, that

Table 2 PIRP patients' baseline characteristics by CKD-EPI stage at first visit

	Total	CKD1 + CKD2	CKD3		CKD4	CKD5
			CKD3a	CKD3b		
N. patients, n (%)	25257 (100.0)	1272 (5.0)	3890 (15.4)	9121 (36.1)	8967 (35.5)	2007 (8.0)
Males, n (%)	16450 (65.1)	937 (73.7)	3238 (83.2)	6239 (68.4)	5045 (56.3)	991 (49.4)
Age at baseline, mean ± sd	72.5 ± 12.2	55.8 ± 15.7	67.6 ± 11.4	73.2 ± 10.4	75.9 ± 11.0	74.6 ± 12.5
Diagnosis of nephropathy, n (%)						
Hypertensive	14245 (56.4)	355 (27.9)	2145 (55.1)	5544 (60.8)	5230 (58.3)	971 (48.4)
Diabetic	3099 (12.3)	235 (18.5)	419 (10.8)	1000 (11.0)	1144 (12.8)	301 (15.0)
Unknown cause	2750 (10.9)	153 (12.0)	445 (11.4)	963 (10.6)	975 (10.9)	214 (10.7)
Single kidney	1741 (6.9)	92 (7.2)	342 (8.8)	656 (7.2)	543 (6.1)	108 (5.4)
Glomerulonephritis	1137 (4.5)	259 (20.4)	201 (5.2)	287 (3.1)	278 (3.1)	112 (5.6)
Polycystic kidney	1045 (4.1)	77 (6.1)	142 (3.7)	289 (3.2)	368 (4.1)	169 (8.4)
Pyelonephritis	870 (3.4)	59 (4.6)	140 (3.6)	264 (2.9)	318 (3.6)	89 (4.4)
Other nephropathies	353 (1.4)	42 (3.3)	55 (1.4)	111 (1.2)	103 (1.1)	42 (2.1)
Haemoglobin, g/dl mean ± sd	12.48 ± 1.87	13.91 ± 1.71	13.66 ± 1.74	12.74 ± 1.76	11.81 ± 1.64	11.11 ± 1.48
Presence of proteinuria, n (%)[a]	7151 (42.3)	475 (53.7)	926 (33.7)	2080 (33.8)	2767 (47.1)	903 (73.9)
eGFR (CKD-EPI), mean ± sd	34.1 ± 15.8	76.6 ± 16.3	50.9 ± 4.1	36.8 ± 4.2	23.1 ± 4.2	11.4 ± 2.6
PO_4, mg/dl mean ± sd[b]	3.63 ± 0.79	3.35 ± 0.62	3.25 ± 0.61	3.40 ± 0.63	3.75 ± 0.73	4.47 ± 0.96
Uric acid, mg/dl mean ± sd[c]	6.49 ± 1.88	5.86 ± 1.51	6.39 ± 1.59	6.51 ± 1.75	6.63 ± 2.08	6.34 ± 2.07
LDL COL > 100 mg/dl, n (%)[d]	3826 (53.6)	255 (67.1)	742 (56.7)	1434 (52.7)	1193 (51.0)	202 (51.4)
Diabetes, n (%)	9014 (35.7)	441 (34.8)	1304 (33.6)	3269 (35.9)	3304 (36.9)	696 (34.7)
Cardio-vascular co-morbidity, n (%)[e]	16056 (63.6)	405 (31.8)	1892 (48.6)	5758 (63.1)	6539 (72.9)	1462 (72.8)

[a]Missing data: n = 8371, 33.1%

[b]Missing data: n = 11,557, 45.8%

[c]Missing data: n = 5266, 20.8%

[d]Missing data: n = 18,115, 71.7%

[e]At least one hospital admission for cardio-vascular disease from 2000 to July 2017

decreased by more than 20 × million population in the decade 2006–2016, corresponding to around 100 cases (Table 4).

The percentage of patients with at least one hospital admission was 58.3% and as expected, this figure increased with the severity of illness. The percentage of patients with a medical admission was approximately twice that of surgical admissions, with the exception of stages 3b and 4 in which non-surgical admission were three to four times higher than surgical admissions. The percentage of patients with CV-related admissions was about one-half of the percentage with total admission.

Concerning pharmacological treatments, at the last recorded visit the frequency of drugs used approximately doubled with respect to their use before participating the PIRP project for all drugs except for RAS inhibitor drugs which were already frequently prescribed. Diuretics, statins, allopurinol, β-blockers and RAS inhibitors were used on average by more than 40% of patients (combinations included).

Discussion

The PIRP project is a unique long-standing collaborative experience between primary care physicians and nephrologists operating in a large Italian region (Emilia-Romagna) with the aim to identify and treat patients with chronic kidney disease. The network created by the project has enhanced the focus on this chronic disease, leading to improved identification and monitoring of patients over time. The effects of the closer and joint monitoring of CKD patients by GPs and nephrologists are becoming apparent in terms of stabilization of their mean annual GFR decline, which allows most patients of all levels of the disease to have a long follow-up. In comparison with other European CKD cohorts, PIRP showed one of the lowest adjusted mean annual decline of eGFR [18]. However, the more relevant result observed after the start of the PIRP project is the reduction in the number of patients that annually start RRT, which decreased of more than 20

Table 3 Follow-up and outcomes of PIRP patients by CKD-EPI stage at first visit

	Total	CKD1 + CKD2	CKD3		CKD4	CKD5
			CKD3a	CKD3b		
Follow-up in months; median(range)[a]	40.9 (0–164.9)	50.3 (0–164.9)	53.7 (0–163.9)	47.2 (0–164.8)	36.6 (0–164.1)	16.3 (0–140.3)
Number of visits; mean ± sd	4.0 ± 4.1	3.5 ± 3.8	3.4 ± 3.6	3.8 ± 3.9	4.5 ± 4.6	4.0 ± 4.2
eGFR at last visit, mean ± sd[b]	29.8 ± 16.8	64.7 ± 24.2	44.4 ± 14.0	33.0 ± 11.8	21.5 ± 9.8	11.5 ± 6.7
Absolute eGFR change, mean ± sd[b]	− 3.3 ± 11.3	− 10.7 ± 19.4	− 6.4 ± 13.6	− 3.7 ± 11.1	− 1.6 ± 9.2	− 0.15 ± 6.7
Annual eGFR change, mean ± sd[b]	− 0.34 ± 16.7	− 4.13 ± 17.9	− 2.07 ± 15.2	− 0.45 ± 15.1	0.75 ± 18.7	0.09 ± 14.7
Patients with hospital admissions after entering PIRP, n (%)	17011 (67.3)	622 (48.6)	2121 (54.5)	5920 (64.9)	6781 (75.6)	1567 (78.1)
Percentage of hospitalized patients at 3 years of follow-up, %	58.3	39.2	43.7	55.0	66.7	76.2
Percentage of patients with a surgical admission at 3 years of follow-up, %	30.1	21.4	26.0	29.2	31.5	41.7
Percentage of patients with a non-surgical admission at 3 years of follow-up, %	46.6	28.1	31.2	43.0	56.9	58.2
Percentage of patients with a CVD-related admission at 3 years of follow-up, %	35.8	14.2	22.7	33.6	45.3	42.9
Lost to follow-up, n (%)	1097 (4.3)	154 (12.1)	237 (6.1)	426 (4.6)	241 (2.7)	41 (2.0)
RRT initiation, n (%)[c]	2669 (10.6)	30 (2.4)	83 (2.1)	445 (4.9)	1257 (14.0)	854 (42.6)
Time to RRT in months; median (range)[c]	30.1 (0.1–147.4)	51.2 (12.2–103.9)	65.1 (3.7–137.7)	55.4 (1.2–147.4)	34.9 (0.3–144.9)	11.9 (0.1–124.7)
eGFR at last visit of patients initiating RRT, mean ± sd[c,d]	10.3 ± 5.5	11.8 ± 5.9	13.9 ± 8.0	13.1 ± 8.6	10.9 ± 5.1	8.3 ± 2.8
Annual eGFR change of patients initiating RRT, mean ± sd[c,d]	− 6.3 ± 11.9	− 19.6 ± 19.3	− 14.6 ± 24.4	− 9.0 ± 19.1	− 6.1 ± 8.3	− 4.1 ± 8.5
Deaths, n (%)[e]	7031 (27.8)	97 (7.6)	484 (12.4)	2256 (24.7)	3552 (39.6)	642 (32.0)
Time to death in months; median (range)[e]	33.1 (0.1–151.8)	41.7 (0.1–130.8)	43.3 (0.4–148.4)	39.3 (0.1–149.4)	30.9 (0.1–151.8)	17.9 (0.1–121.3)
Causes of death, n (%)[f]						
Cardio-vascular diseases	2994 (43.5)	34 (37.3)	185 (38.9)	944 (42.7)	1572 (45.0)	259 (42.1)
Cancer	1493 (21.7)	24 (26.4)	160 (33.6)	557 (25.2)	660 (18.9)	92 (15.0)
Respiratory system diseases	533 (7.7)	2 (2.2)	33 (6.9)	167 (7.6)	297 (8.5)	34 (5.5)
Genitourinary system diseases	462 (6.7)	5 (5.5)	15 (3.2)	87 (3.9)	260 (7.5)	95 (15.4)
Endocrine and metabolic diseases	452 (6.6)	12 (13.2)	19 (4.0)	135 (6.1)	227 (6.5)	59 (9.6)
Infectious diseases	233 (3.4)	5 (5.5)	13 (2.7)	81 (3.7)	115 (3.3)	19 (3.1)
Other diseases or traumatisms	716 (10.4)	9 (9.9)	51 (10.7)	240 (10.8)	359 (10.3)	57 (9.3)

[a]Time from first visit to exit or to 31.12.2017

[b]Only patients with at least 2 visits (n = 16,471)

[c]Information on RRT updated at 31.12.2016

[d]Only patients with less than 1 year between their last visit and date of RRT initiation

[e]Information on mortality updated to 30.06.2017; it does not include deaths after RRT or loss to follow-up

[f]Does not include deaths after RRT or loss to follow-up; missing data: n = 150, 2.1%

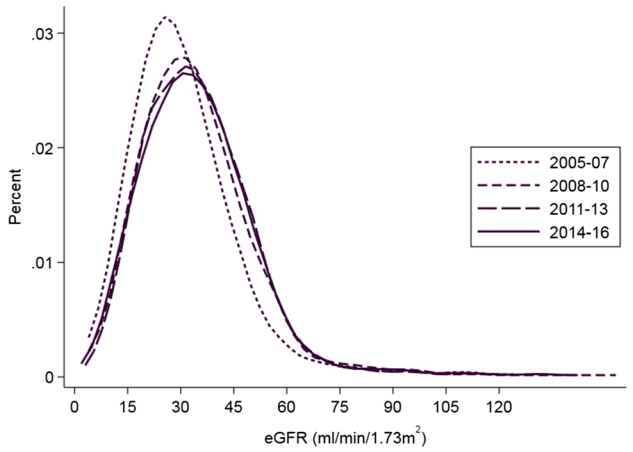

Fig. 2 Baseline average eGFR of patients who entered the PIRP project by 3-years periods

× million population, (approximately 100 subjects) from 2006 to 2016. The percentage of patients reaching RRT (10.6%) is much lower than that of an English cohort with a similar median follow-up time, in which 18% of patients arrived at dialysis over a 3.5-year period [19]. We argue that the sensitization of GP to the importance of early referral has allowed to improve the CKD prognosis and to delay the RRT inception.

Some other noteworthy strengths of the PIRP project are that: patients were referred in the large majority by the GPs working in the Emilia-Romagna region; the PIRP database is linked with the administrative regional databases of mortality, renal replacement therapy and hospital discharges to retrieve the outcomes of interest, and uses clinical lab data from all laboratories in Emilia-Romagna, allowing to track the course of renal function and of other biochemical parameters using high-quality data. Lastly, the PIRP project is open to international collaborations, in which study registries are compared for research purposes [18].

To our knowledge, the main prospective cohort studies on CKD patients currently include the CRIC study [20], the KEEP study [21], the AASK study [22] (a study focused on African-American patients) in the United States, the CKD-JAC study in Japan [23], the GCKD study in Germany [24], the MAURO study in the Calabria region of Italy [25]. However, these studies are research projects rather than public health programmes designed to improve the identification and adequate treatment of CKD on a large scale. The PIRP project should then be considered as a innovative experience of a regional community project aimed mainly to the prevention of endpoints for CKD patients that collected a large amount of data available for research projects. As a matter of fact, with more than 25,000 patients the PIRP database is the largest cohort of CKD patients in Europe [18]. However, because the PIRP is not an epidemiological study, it has a

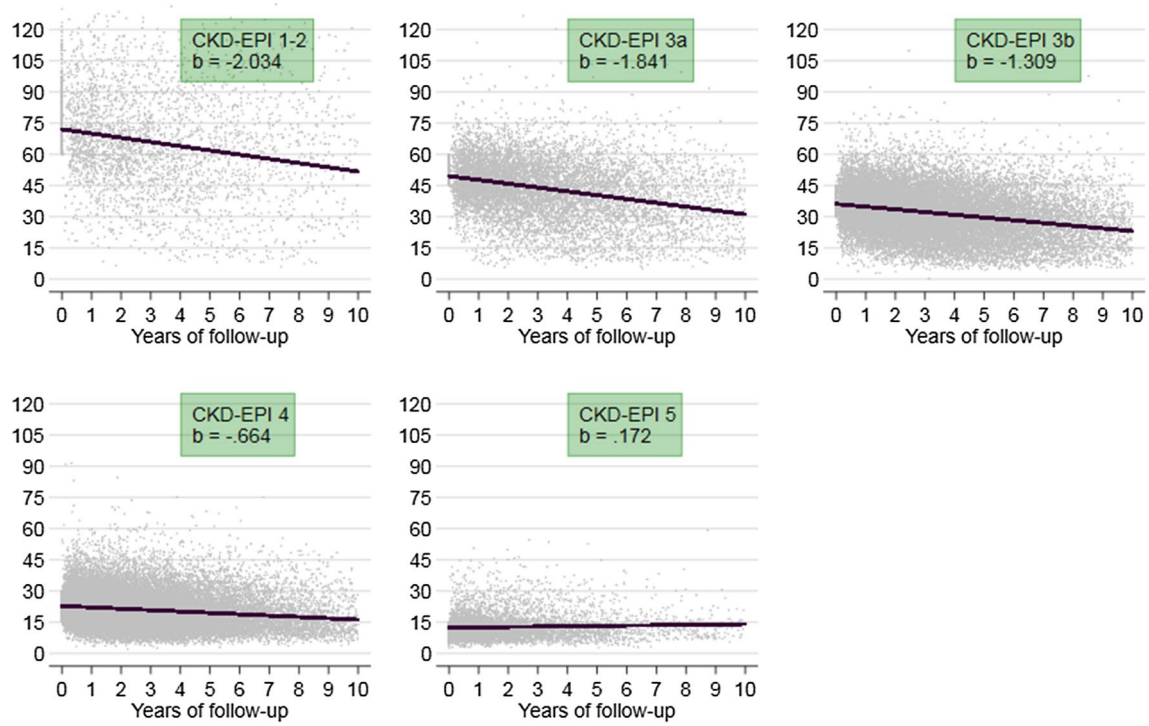

Fig. 3 Individual eGFR variations up to 10 years of follow-up of PIRP patients with estimated linear trend, by CKD stage at baseline. Patients with at least 2 visits

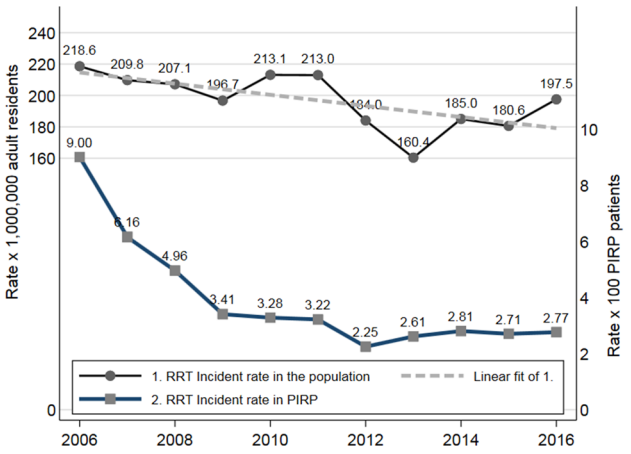

Fig. 4 Number of dialysis incident patients per million residents in Emilia Romagna, linear fit of dialysis incident patients trend and crude rate of RRT inception among patients followed in the PIRP project in the years 2006–2016

low proportion of prevalent CKD patients when compared to ad-hoc Italian surveys like the CARHES [2] and the INCIPE [3].

Moreover, considering the importance of genetic and environmental factors in the progression of CKD to ESKD, a program involving a large population of CKD patients from Southern Europe could provide extremely important data for this geographical area. CKD population living in this area cannot be assimilated to the North American CKD populations from which the most recent predictive models and algorithms have been developed [26, 27]. Those models cannot be generalized without a local validation that takes into account the specificities of the Italian population in terms of health care organization, lifestyles and clinical characteristics. The PIRP database can be effectively used for this purpose, because it is a large longitudinal cohort of CKD patients that could allow to identify the risk factors affecting the CKD progression rate. Some of these risk factors, namely baseline eGFR, proteinuria, phosphates, male gender and diabetes have been identified as associated with faster CKD progression and mortality in our previous studies conducted on PIRP patients, which are summarized below.

A study carried out on 1716 who entered the project between 2004 and 2007 [16] showed that patients with phosphate levels ≥ 4.3 mg/dl have a more than twofold risk of starting dialysis or dying (hazard ratio 2.04; 95% CI [1.44, 2.90]) compared with those with phosphate levels < 4.3 mg/dl. Notably, the magnitude of the risk associated with hyperphosphatemia varied depending on age, sex, diabetes, and CKD stage.

In a second study [17] we sought to identify CKD patient subgroups with differential renal function decline using classification tree analysis (CTA). The study included 2265

Table 4 Use of drugs in PIRP patients before enrolment and at last visit, by CKD-EPI stage at first visit

	Total		CKD1 + CKD2		CKD3				CKD4		CKD5	
					CKD3a		CKD3b					
	Before PIRP	Last visit	Before PIRP	Last visit	Before PIRP	Last visit	Before PIRP	Last visit	Before PIRP	Last visit	Before PIRP	Last visit
RAS inhibitors, n (%)	7228 (33.6)	10068 (46.9)	330 (37.2)	517 (58.3)	1246 (37.9)	1874 (57.0)	2788 (35.4)	4139 (52.6)	2497 (32.1)	3127 (40.2)	367 (22.2)	411 (24.8)
Diuretics, n (%)	4902 (22.8)	10355 (48.2)	76 (8.6)	180 (20.3)	465 (14.1)	1042 (31.7)	1635 (20.8)	3644 (46.3)	2225 (28.6)	4472 (57.5)	501 (30.3)	1017 (61.5)
β-blockers, n (%)	4584 (21.3)	9044 (42.1)	120 (13.5)	280 (31.6)	690 (21.0)	1334 (40.6)	1694 (21.5)	3417 (43.4)	1726 (22.2)	3339 (42.9)	354 (21.4)	674 (40.7)
Anti-hypertensive, n (%)	4402 (20.5)	8345 (38.8)	121 (13.6)	283 (31.9)	591 (18.0)	1227 (37.3)	1460 (18.5)	2967 (37.7)	1735 (22.3)	3018 (38.8)	495 (29.9)	850 (51.4)
Chelates, n (%)	561 (2.6)	1437 (6.7)	7 (0.8)	16 (1.8)	32 (1.0)	86 (2.6)	105 (1.3)	284 (3.6)	226 (2.9)	616 (7.9)	191 (11.5)	435 (26.3)
Allopurinol, n (%)	4088 (19.0)	9040 (42.1)	80 (9.0)	244 (27.5)	499 (15.2)	1329 (40.4)	1442 (18.3)	3410 (43.3)	1680 (21.6)	3302 (42.4)	387 (23.4)	755 (45.6)
Erythropoiesis stimulating agents, n (%)	1574 (7.3)	4141 (19.3)	6 (0.7)	46 (5.2)	62 (1.9)	231 (7.0)	310 (3.9)	1044 (13.3)	836 (10.7)	2033 (26.1)	360 (21.8)	787 (47.6)
Statins, n (%)	4565 (21.2)	9957 (46.3)	182 (20.5)	435 (49.0)	780 (23.7)	1712 (52.0)	1769 (22.5)	3871 (49.2)	1582 (20.3)	3339 (42.9)	252 (15.2)	600 (36.3)

patients enrolled in PIRP from July 2004 to June 2010, with at least four serum creatinine measurements. The CTA procedure generated seven mutually exclusive groups with a differential annual GFR decline using 6 variables routinely collected at baseline (age, gender, baseline GFR, proteinuria, phosphate levels and diabetes). The slowest progression was found in males and females aged > 67 years without diabetes and proteinuria and fastest among patients with proteinuria and a baseline eGFR > 33.65 ml/min/1.73 m^2.

In a third study [5] we estimated the decrease in survival of CKD patients at 9 years compared to the general population using relative survival. Overall, CKD patients had a 30% lower survival than the general population matched by gender and age. Lower survival was associated with cardiovascular comorbidities, proteinuria, diabetes, anaemia and high phosphate levels. In advanced CKD stages, it was also associated with male gender, older age and dialysis inception.

Because of its nature as a clinical continuous quality improvement project, PIRP has also several shortcomings: (1) it does not provide epidemiological data at population level, because only subjects referred by their GP participated in the project. However, because GPs have been trained and provided with the tools to identify CKD patients, it is very likely that under-representation could be circumscribed to the lowest levels of the disease. (2) The project is carried out only in one Italian region, which is however densely populated and has been exposed in the last decades to intense migration (particularly from Southern Italy), that mitigated its genetic and cultural specificity. (3) The laboratory data are not centralized, thus a certain variability in data from different laboratories cannot be ruled out. (4) Lastly, although efforts have been made to share CKD treatment strategies with GPs and other specialists, no evidence is available about variability in practice among individuals and among Nephrology units.

Despite these weaknesses, the other side of the coin is that the approach underlying the PIRP project represents the "real world" clinical practice for CKD in our region. The nephrologist-GP integrated approach might be considered as an advantage compared to exclusive management by nephrologists, of GPs or other specialists that might lack the approach to the course of kidney disease as a continuum. Furthermore, while in Italy data regarding ESKD patients on RRT are available with good quality by means of the RIDT registry [28], the PIRP project is one of the few sources providing insights on patients in pre-terminal CKD.

In conclusion, the PIRP project has assembled a large cohort, representative of the whole population of CKD patients in the Emilia-Romagna region, in which the benefits of a closer and joint monitoring of CKD patients by GPs and nephrologists are becoming apparent in terms of reduction in the mean GFR decline and by the decrease in the overall number of patients who started dialysis. Information regarding the estimated glomerular filtration rate decline over time, hospitalizations, the number of patients initiating dialysis is available to the political stakeholders for planning and optimizing resources at the regional level. Furthermore the knowledge about the risk factors for CKD progression and cardiovascular events obtained by analyzing data collected at baseline and follow-up will allow planning new therapeutic strategies to delay or prevent the rapid decline of renal function.

Compliance with ethical standards

Ethical statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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