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TITOLO TESI

USE OF ELECTRONIC HEALTH DATA FOR THE IDENTIFICATION OF CASES AND FOR THE EVALUATION OF HEALTHCARE CONSUMPTIONS AND CHRONIC KIDNEY DISEASE COSTS

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ABSTRACT

Introduction

Chronic kidney disease (CKD) is a common condition characterized by a gradual loss of kidney function and consequently increasing costs associated with the disease.

Aims

The aim was to use administrative databases and a pathology registry to characterize CKD patient according to their stage and to evaluate the burden of disease; to identify incident patients on dialysis; to investigate the impact of COVID-19 on mortality in CKD patients.

Methods

Data from a regional pathology registry and administrative databases were used to classify CKD patients into different disease progression subgroups (CT-PIRP classification) using the following 6 variables: age, sex, diabetes, glomerular filtration rate, proteinuria, phosphate level and different CKD stages (3a, 3b, 4, 5). Healthcare consumptions and costs were evaluated. Incident chronic dialysis patients were defined those seen regularly in outpatient clinics. The incidence and mortality of COVID-19 among CKD patients were estimated.

Results

The study cohort includes 7737 CKD patients, aged 73.2±11.6 years, 64.5% males, mostly stage 4 (3136, 40.5%) and 3b (2799, 36.2%). Average annual costs were significantly higher for CT-PIRP groups 2 and 3 (€7239 and €8825 respectively) and more than twofold higher for CKD stage 5 (€7,993) compared to stage 3a (€3,973).

Both algorithms used to identify incident chronic dialysis patients had high sensitivity, 90.8% and 88.4%, high positive predictive value (84.0% and 82.0%) and high agreement (77.4% and 74.1%).

The incidence of COVID-19 infection was 4.16%. COVID-19 hospitalized patients were the 95.5%, those on home isolation were the 3.6% and the 0.9% were asymptomatic. Compared to those without COVID-19, the overall excess mortality ranged between 34.4% and 56.3%.

Conclusion

Administrative databases are a powerful tool to describe the burden of CKD disease, in order to assess the interventions aimed at reducing the impact of CKD and improving the quality of care of CKD patients.

1 Introduction

Chronic kidney disease (CKD) is a very common condition, projected to become the fifth leading cause of lost life years worldwide by 2040 (1).

In Italy, its prevalence is estimated at 7.1% among people aged 35 to 79 (2) and it is expected to increase due to aging and risk factors. However, the nephrological prevention activities, the increased availability of diagnostic and therapeutic strategies and the early treatment of these patients are improving the prognosis of CKD, allowing a delayed progression to end-stage renal failure and a delay in initiation of replacement treatment (3,4).

The annual total cost of CKD in Italy has been estimated in 2,5 billion euros in 2011, which is approximately 2.0% of all health care spending in that year. More than half of this amount was spent on renal replacement therapy for minority (2%) of people with CKD that progresses to kidney failure.

In the last decades a large amount of information has been collected through the electronic health records (EHRs).

Health care data and their integration with demographic data constitute a powerful tool to conduct population-based epidemiological studies. When the research focus is on the course and the management chronic diseases, health care data linked with pathology registries may offer unique opportunities to trace the health services utilization and costs of each patient over time.

In Emilia-Romagna region, the problem of chronic kidney disease has been constantly present in the health planning strategies, and big efforts has been made towards identifying the best organizational solutions to promote prevention and appropriate care. In particular, the regional project Prevention of Progression of Renal Disease (PIRP), established in 2004, has accelerated the early recognition of the disease and the implementation of primary prevention strategies and monitoring of patients being treated. The project has the following aims:

- to delay the progression of chronic kidney disease towards end-stage renal disease (ESRD);
- to prevent the onset and reduce the burden of cardiovascular complications;
- to provide an appropriate, effective and efficient continuity of care of CKD patients based on outpatient care;
- to promote the integration between general practitioners and nephrologists of the management of CKD patients in order to reduce hospitalizations.

2. Aims of the study

The goal of the study is to use administrative databases and a pathology registry for 3 different applications: to characterize CKD patient subgroups at different risk of progression to end-stage renal failure and with different costs for quality of care assessment and health care planning; to identify incident patients on dialysis; to investigate the impact of COVID-19 on mortality in CKD patients.

3. Data sources & data warehouse

All Italian citizens have equal access to healthcare services as part of the National Health System (NHS). Computerised information systems of healthcare utilisation databases have been created within each of the 21 Italian regions to meet information needs of the NHS, principally, for the reimbursement of the healthcare services provided to the population (art.50 l. 24 November 2003 n.326) and to improve the healthcare quality as well as the clinical governance of local health services. All the electronic information is collected by Ministry of Health in a data warehouse (DWH) to implement an assessment model called Healthcare Network Monitoring System (MRA system). This system aims at capturing comprehensive information on the facilities that are part of the regional healthcare network of services. The MRA System enables the depiction, through appropriate geo-referencing tools, of the distribution of facilities and production factors active in the territory and enables, consequently, to effectively support both the definition of health policies and healthcare planning, as well as the planning of infrastructure investments at a local and regional level.

Moreover, the data collected by the New Italian Information technology System (NSIS) meet the monitoring and control requirements of the SSN with appropriate levels of accuracy, reliability and timeliness. The data collected through the DWH of Healthcare Information, in compliance with privacy laws and regulations applied to the processing of confidential data, may be used for improving healthcare quality and for clinical governance.

Emilia-Romagna has developed its own DHW that encompasses all the services delivered in the region to the citizens, organized into 27 databases, the most important being the following:

1) Hospital discharge records, including information on admission and discharge date, primary diagnosis, up to five coexisting conditions and procedures coded according to the International Classification of Diseases, 9th Revision (ICD-9) Clinical Modification classification system (http://icd9.chrisendres.com/);
2) Outpatient specialty services, including laboratory tests, specialty and rehabilitation visits. This information is collected through the Health Insurance Card System pursuant to article

50, Law 326/2003 and is systematically sent to the NSIS, pursuant to paragraph 10 of the same article 50. The Emilia-Romagna is collecting these data since 2008 (Circolare n. 9 del 28/11/2008);

3) Pharmaceutical prescriptions reimbursed by the NHS, coded according to the Anatomical Therapeutic Chemical (ATC) classification system (https://www.whocc.no/atc_ddd_index/);(D.M. 4 febbraio 2009)
4) Nursing homes for the elderly;
5) Emergency care;
6) Pharmaceutical prescriptions provided by the hospital;
7) Drug addiction care;
8) Mental health care delivered to adults patients.

3.1 Record linkage

Record linkage between databases is performed by means of the identification (progpaz) code assigned to each NHS beneficiary. The main challenge of record linkage is to establish whether records from different sources concern the same person. If there is no unique identifier across the data sources, a set of variables (or fields/attributes) that exist in all records can be used to assist in the decision process. The variables used for linking can be referred to as linkage variables, while the set of all these variables together is called a linkage key: each variable provides a piece of information, and together they form well-defined information about a specific person (or subject, or entity in a more general sense).

3.2 Pseudonymization

Data privacy is a prerequisite for any data warehouse (DWH), but especially for research that requires record-linkage. The DWH healthcare system uses authorisation policies to enable healthcare providers to access required patients' data. Ensuring patients' privacy means preventing unauthorised users from accessing this data.

Each person in Italy has a health card. The Health Card is issued to all Italian citizens entitled to the services provided by the National Health Service (SSN). The Health Card-CNS is free, is normally valid for 6 years or equal to the duration of the residence permit and, upon expiry of the ST, it is sent by the Ministry of Economy and Finance to all citizens assisted by the Service. National health.

The health card is necessary when the citizen goes to the doctor or paediatrician, collects a medicine at the pharmacy, books a visit to an analysis laboratory, undergoes a specialist visit in a hospital or at a Local Heath Unit(ASL) and, in any case, every time it needs it to certify your tax code.

The Health Card is produced automatically when the ASL communicates the assistance data to the Health Card System; the shipment is made to the address of residence reported, at the time of production, in the database of the Tax Register.

The pseudonymization consist in creating a random code for each Health card. This guarantees the accountability in the DWH. This code, in DWH of Emilia-Romagna, is called *progpaz.*

4. Applications

4.1 The costs of CKD patients

4.1.1 Background

CKD has as a strong impact on healthcare expenditure. Dialysis and transplant costs account for up to 3% of the annual health budget in high-income countries (5). In a study conducted in Tuscany on 484 patients, the direct annual healthcare costs of a patient with CKD were estimated at € 3,978 for stage 4 and € 5,529 for stage 5 (6). For stages 3a / b, the estimate of annual direct health costs provided by a study conducted on the whole national territory (7) is € 890. Direct medical costs increase in the presence of comorbidities such as diabetes, cardiovascular disease, anaemia and secondary hyperparathyroidism, as evidenced in studies conducted in different countries (8-11).

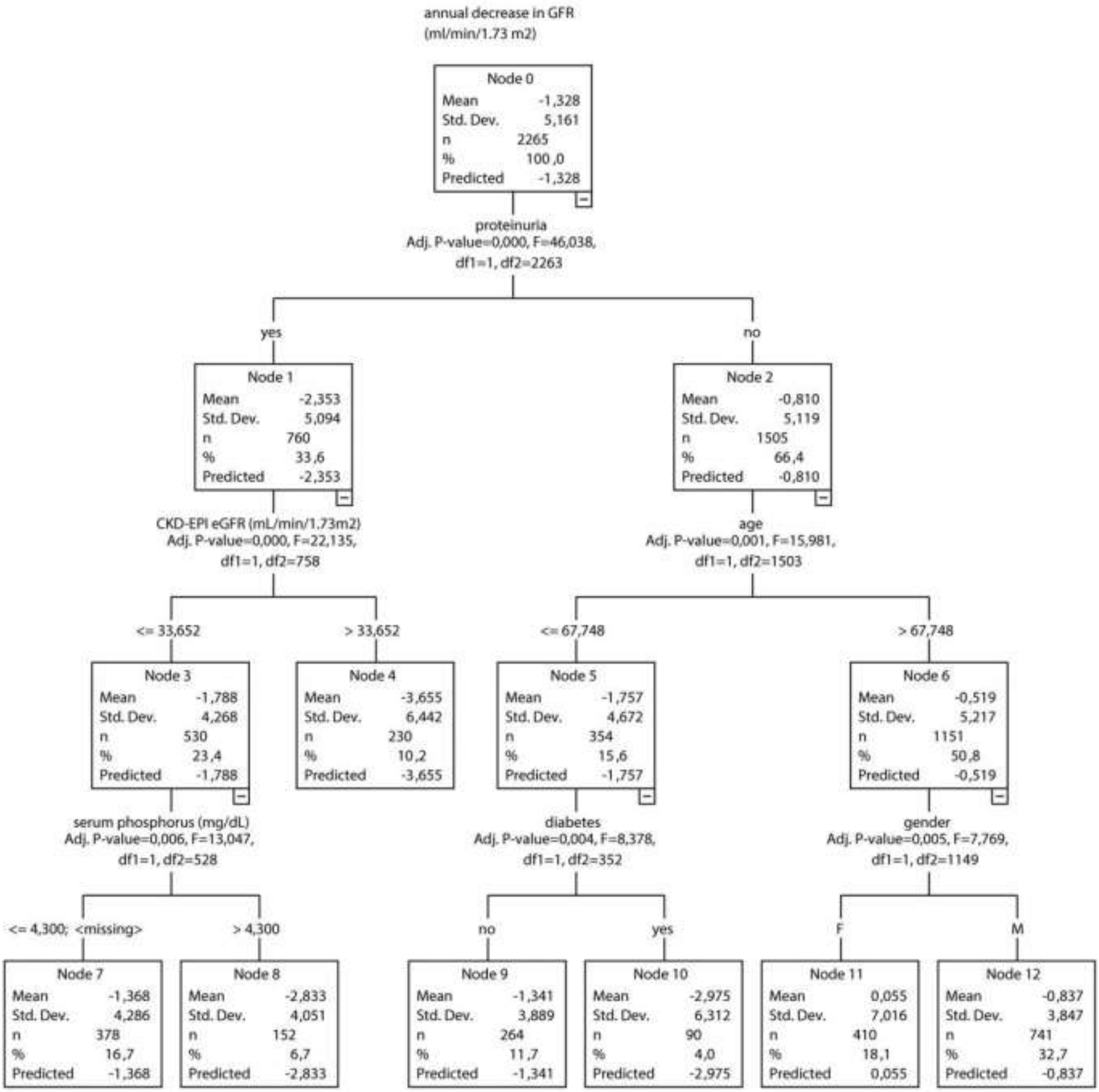
According to the estimate provided by Cicchetti et al. (7), if the prevention and nephrological care of CKD patients allowed to delay the progression from stage 3 to stage 4 for at least 5 years for 10% of Italian patients, the savings that the National Health System (NHS) could get it would amount to around 1.4 billion euros. Furthermore, since the annual cost to the NHS of a patient on dialysis treatment is about € 52,830 per year, if it were possible to delay the entry of dialysis by 5 years for 50% of patients entering stage 5 (about 4,500 patients per year), a saving of an additional 1.1 billion euros would be achieved.

Slowing down the loss of kidney function is therefore a priority, both in terms of quality of life of people with IRC, and in terms of sustainability of the health system (12).

4.1.2 Methods

This observational study has a retrospective cohort design. Patients "with structural or functional anomalies present for at least three months with implications for health" entering in the PIRP from 2007 to 2014 were extracted from the PIRP registry.

Patients were classified into subgroups with different disease progression using an algorithm developed and validated on two cohorts drawn from the PIRP registry (13,14). The algorithm, derived from a tree classification model, is based on 6 variables that are easily collected during the routine visits of patients with CKD: age, sex, diabetes (yes/no), glomerular filtration rate, proteinuria (yes/no), phosphate levels. CT-PIRP subgroups proved to be useful to predict renal function decline, mortality and end-stage renal failure (14).



Graph 1. Classification tree with 7 independent subgroups of patients with a different annual GFR decline, derived from (13)

In addition, patients were stratified according to 4 CKD stages (3a, 3b, 4, 5) defined by the KDIGO classification, which correspond to the following GFR ranges: 45-59, 30-44, 15-30, <15 ml/min/1.73 m2.

The primary outcomes were collected in the 4 years following entry into PIRP and included:

1) Healthcare consumptions (laboratory tests, nephrological, cardiological, endocrinological visits, hospitalizations and drugs);

2) Direct medical costs, estimated from the perspective of the NHS using a bottom-up approach. Types of medical services included hospitalizations, outpatient services and prescription drugs. To compute the total costs of each patient, the unit cost (tariff) of each medical service was multiplied by the number of units/services provided. For hospitalization costs we used the DRG tariffs, for outpatient specialist services the Regional Nomenclator and for drugs the unit costs of the prescribed packs.

The study protocol was approved by the Independent Ethics Committee of the Larger Emilia Center Area (CE-AVEC) on 19/6/2019, protocol n. 396/2019/Oss/AOUBo.

4.1.3 Data sources

The data for the present study were obtained through linkage of the individual records of the PIRP registry with administrative databases. Specifically, the comorbidities in the 2 years prior to entry into the PIRP were obtained by linking the PIRP registry with regional hospital discharge registers (International Classification of Diseases, Ninth Revision, Clinical Modification - ICD-9-CM) and Pharmaceutical Prescriptions Database (Anatomical Therapeutic Chemical Classification System Code-V.2013 - ATC). We used a weighted summary score (M-CDS, Iommi et al, 2020) to quantify the burden of comorbidities. Health care consumptions and direct medical costs were retrieved from Hospital Discharge Records, Outpatient Specialty Visits and Pharmaceutical Prescriptions Database.

4.1.4 Statistical Analysis

The demographic and clinical characteristics of patients, their costs and outcomes were summarized using the mean and standard deviation for continuous variables with a normal distribution, median and interquartile range for asymmetric continuous variables and for ordinal variables, absolute and percentage frequencies for categorical variables.

Mixed effects models were built to analyze the direct medical costs over follow-up as a function of 2 patient classifications, one based on CT-PIRP classification into 7 mutually exclusive groups and one on CKD stage.

In the first model, we used patients’ CT-PIRP classification into groups as between-subject effect, and the follow-up year and the interaction between CT-PIRP classification and year as within-subject effects. The calendar year of entry into PIRP and the local health authority of residence were also included as covariates to adjust the between groups comparisons for a possible cohort effect and for organizational characteristics.

In the second model, we used patients' classification into CKD stage as between-subject effect, and the follow-up year and the interaction between the CKD stage and year as within-subject effects. The MCS score, calendar year and local health authority of residence were included as potential confounders.

Data were modelled using the negative binomial function, which is suitable to represent the frequency distribution of costs, characterized by a marked positive asymmetry (few patients with very high costs). The goodness of fit of the predictive models based on the two types of stratification was compared using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). These indices have no predefined cut-offs and can only be interpreted when comparing two different models. Lower indices denote better model fit.

4.1.5 Results

Demographic and clinical characteristics of the study population

The cohort analysed consisted of 7,737 patients (*table 1*), who were followed up for 4 years, or until the exit from the PIRP for dialysis, death or loss at follow-up.

Table 1. Demographic and clinical characteristics of the study population

	N	%
Gender		
Female	2746	35.5%
Male	4991	64.5%
Age (mean ± DS, median)	73.2±11.6	
CKD stage		
3a	1105	14.3%
3b	2799	36.2%
4	3136	40.5%
5	697	9.0%
Multisource Comorbidity Score (MCS)		
0-4	2174	28.1%
5-9	2539	32.8%
10-14	1722	22.3%
15-19	747	9.7%
20+	555	7.2%
MCS (mean ± SD, median)	8.9±6.8	8
CT-PIRP groups		

1. proteinuria, eGFR >33	927	12.0%
2. proteinuria, eGFR≤33, PO_4≤4.3	1552	20.1%
3. proteinuria eGFR≤33, PO_4>4.3	553	7.1%
4. non diabetic, ≤67 years	671	8.7%
5. diabetic, ≤67 years	199	2.6%
6. female, >67 years	1478	19.1%
7. male, >67 years	2357	30.5%

Healthcare consumptions

As to hospitalization rates, a 10% decrease was observed over the 4 years, from 68.4% to 61.6%, 59.0%, and 58.3%. In hospitalized patients, the median length of stay was 10 days in the first 3 years and 11 in the 4th year.

Table 2. Descriptive statistics of the specialty outpatient visits delivered to the study cohort in the four years of follow-up.

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Total**
	Mean, median [min,max]				
All outpatient services	15.4, 13 [0-155]	13.8, 11 [0-170]	13.6, 11 [0-176]	13.6, 10 [0-181]	14.2,11 [0-181]
Nephrological visits	2.4, 2 [0-46]	1.8, 1 [0-80]	1.8, 1 [0-138]	2, 1 [0-155]	2, 1 [0-155]
Cardiological visits	0.9, 0 [0-42]	0.8, 0 [0-42]	0.8, 0 [0-36]	0.7, 0 [0-35]	0.8, 0 [0-42]
Endocrinological visits	0.7 ,0 [0-32]	0.6, 0 [0-31]	0.6, 0 [0-14]	0.5, 0 [0-22]	0.6, 0 [0-32]
Diagnostic visits	4.3, 3 [0-38]	3.8,3 [0-33]	3.6, 3 [0-43]	3.4, 2 [0-65]	3.8, 3 [0-65]
Laboratory tests	61.3, 50 [0-816]	55.7, 45 [0-1003]	53.5, 42 [0-1359]	52.7, 39 [0-1636]	56, 44 [0-1636]
Rehabilitative outpatient services	0.2, 0 [0-32]	0.2, 0 [0-51]	0.2,0 [0-102]	0.1, 0 [0-39]	0.2, 0 [0-102]
Therapeutic outpatient services	1.3, 0 [0-263]	1.7, 0 [0-317]	2.8, 0 [0-516]	3.8, 0 [0-635]	2.3, 0 [0-635]

As shown in *table 2*, examination of specialty outpatient services reveals a decrease in nephrological visits, from a median of 2 visits in the first year to a median of 1 visit in the following years and in parallel a reduction in laboratory tests from 50 to 39 with a change of the intensity of nephrological follow-up varied according to the CKD stage.

Concerning drug consumption, we focused on the most common categories of prescriptions for CKD, which include antidiabetic agents (ATC=A10), lipid-lowering agents (ATC=C10), anti-hypertensives and cardiac therapies (beta-blockers, ace inhibitors, statins, antiarrhythmics and others, for the complete list, see Appendix 1). In the overall sample, anti-hypertensives and cardiac therapies accounted for 74.8% of prescriptions, lipid-lowering agents for 15.7% and anti-diabetics for 9.5%. The number of prescriptions of anti-hypertensives and cardiac therapies decreased over time across CKD stages, differently from anti-diabetics and lipid-lowering, that remained almost stable.

Costs

In the study cohort, unadjusted direct mean medical costs were € 5,310 (median € 2,139; IQR [€ 1,156-€ 5,729]) in the first year, € 5,598 (median € 1,980; IQR [€1,026-€5,586]) in the second year, € 5,797 (median € 1,898, IQR [€912-€5,530]) in the third year and € 6,223 (median € 1,819; IQR [€813-€5,742]) in the fourth year. The sum of costs over the four years was € 164,338,254.

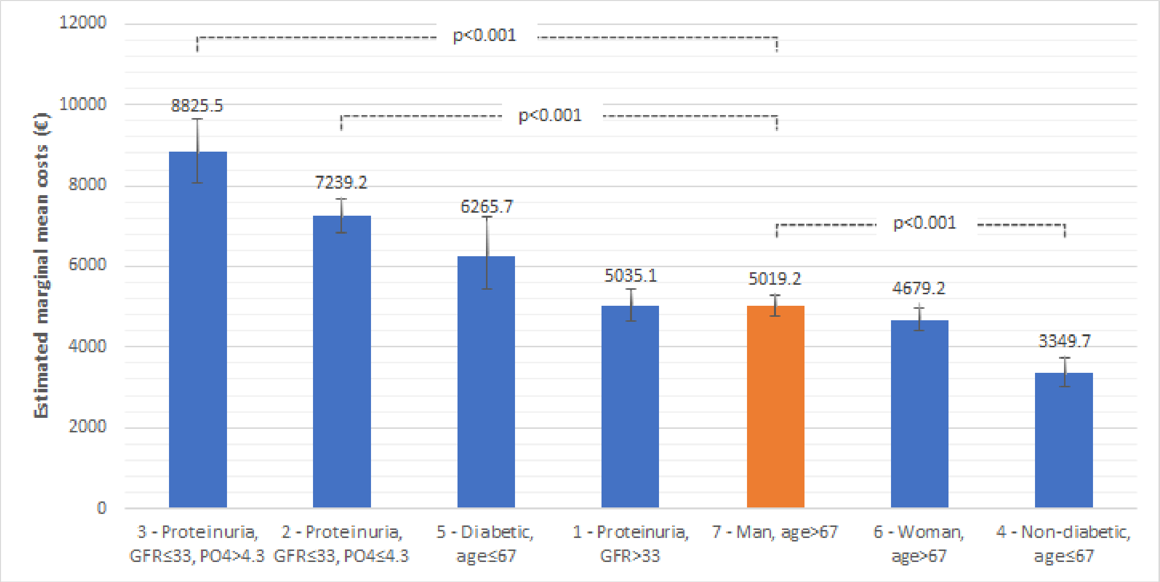
In the first mixed-effect model, in which patients were classified into the 7 CT-PIRP groups, estimated annual mean costs over the 4 years of follow-up exhibited a significant variability among groups (figure 3a), ranging from € 3,350 in non-diabetic patients aged<67 (group 5) to € 8,825 in patients with proteinuria, reduced renal function and increased phosphate levels (group 3). Compared with group 7 (men, age> 67 years, non-proteinuric and non-diabetic, mean cost € 5,019), the two groups of proteinuric patients (2 and 3) with low renal function had significantly (p<0.001) higher annual costs, while the proteinurics with partially preserved renal function (GFR> 33 mg/min/1.73 m2) had similar costs (€ 5,035). Group 4, that was significantly less costly than 7, (mean cost € 3,350; p<0.001), included patients <67 years of age, non-diabetics.

Moreover, the estimated costs of the CT-PIRP groups presented distinctive patterns over time . In group 2, with low renal function and low phosphate levels, costs increased by € 2,000 euros in the 3rd and 4th year from baseline, while in patients with diabetes (group 5) the peak of costs was found in the 2nd year. Vice versa, group 4 (non-diabetic) tended to have stable costs over time.

Notably, the local health authority of residence accounted significantly for the variability of direct medical costs, while the follow-up year and the calendar year of entry into the cohort did not. The fit indices of this model were AIC = 106,942.6 and BIC = 106,975.5.

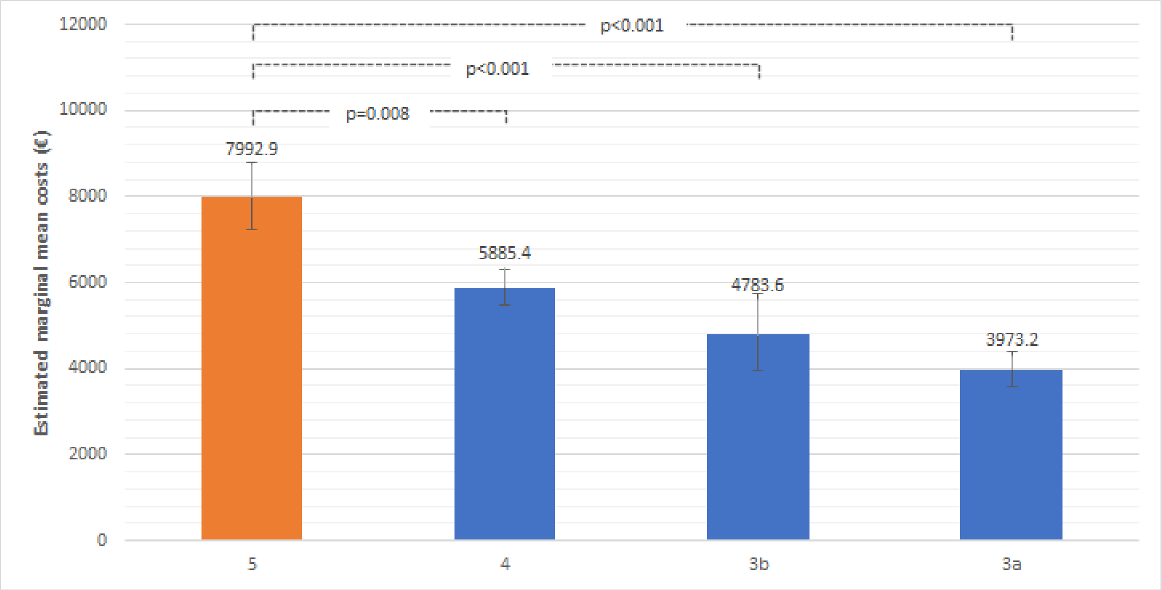
In the second model, estimating mean costs by CKD stage, mean annual costs were more than twofold for CKD stage 5 (€ 7,993) as compared to stage 3a (€ 3,973) and were € 4,784 for stage 3b and € 5,885 for stage 4 (figure 3b). The temporal trend of costs showed a linear growth over time for stages 3b (from € 4,222 to 5,330) and 4 (from € 5,244 to € 6,625), while for stage 3a the costs remained almost stable in the 4 years of follow-up. In stage 5, costs slightly increased from € 7,918 in the first year to € 8,264 in the 4th year (figure 4b). All the covariates included in the model, i.e. the local health authority of residence, the year of follow-up and the calendar year of entry into the cohort, accounted significantly for the variability of direct medical costs. The goodness of fit indices of the model were AIC = 107,132 and BIC = 107,165, indicative of a slightly worse fit to the data compared to the first model.

Figure 3a. Estimated annual mean costs* in the 7 CT-PIRP groups over the 4 years of follow-up, sorted in decreasing order. Group 7, including 30.5% of patients, is the reference group.



*Adjusted for Local Health Authority of residence and year of entry into PIRP program.

Figure 3b. Estimated annual mean costs* by CKD stage over the 4 years of follow-up. CKD stage 5, including 9% of patients, is the reference group.



*Adjusted for Local Health Authority of residence, year of entry into PIRP program and MCS comorbidity score.

4.1.6 Discussion

This study estimates the healthcare consumptions and the direct medical costs of CKD patients enrolled in the PIRP project between 2007 and 2014. We ruled out on purpose dialysis patients because the costs of dialytic therapy are particularly high and can distort the relationship between resource consumption and the health needs of CKD patients in conservative therapy.

Assuming a CKD incidence of 7% in the age range 35-79 (2) (CARHES Study), we can quantify the total amount of annual direct costs of conservative treatment for CKD patients resident in Emilia-Romagna region as of 1st January 2020 in 1,064 million euros.

As to overall per capita annual direct medical costs, our results (mean € 5,310; median € 2,139; IQR [1,156-5,729] in the first year) are partly consistent with existing studies carried out in other countries. Manns et al. (15) report comparable costs for Canada in terms of order of magnitude of the median (Can$ 3,672; IQR [1,496-10,221]), while Small et al. (16) using US data from the Medical Expenditure panel survey, indicate markedly higher median direct medical costs of $12,877 (IQR [5031-19,710]) for non-dialysis dependent patients.

Our findings indicate an increasing gradient of costs among baseline stages of kidney function, and a different trend over follow-up, after controlling for demographics, comorbidities and the local health authority of residence. In particular, costs were stable over time in CKD stage 3a patients, exhibited a marked increase over time in CKD stage 3b and 4 patients, and a slight increase in CKD stage 5 patients. This is consistent with the expected differential CKD progression in the 4 stages, that yields rapidly rising costs. Kuehn (17) reported medical costs of $ 20,500 for stage 3 CKD and $ 46,100 for stage 4/5 CKD.

However, the presence of accelerating factors such as proteinuria, high serum phosphorus level and complications, especially cardiovascular diseases and diabetes, makes the clinical picture more complex and requires a greater use of resources.

In our study, the estimated annual costs of patients with proteinuria and decreased renal function (GFR≤33 ml/min/1.73 m2) were the highest, and the presence of serum phosphorus levels >4.3 mg/dl increased the mean expenditure by 21.9% (€ 8825 vs. € 7239). This is consistent with the observation that moderately increased serum phosphorus levels are associated with faster progression and poorer outcomes (18).

Comorbid diabetes generates additional complications and accelerates renal dysfunction, leading to extra costs. Cortaredona and Ventelou (19) report an estimated healthcare expenditure of € 8,323 euro (95% CI [7,090- 9,556]) for CKD patients without comorbidities, that rises up to € 14,895 (95% CI [12,638- 17,153]) in the presence of diabetes. Our findings indicated that, among patients aged <67, the presence of diabetes is associated with a twofold healthcare expenditure (€ 6,265 vs. € 3,349).

Surprisingly, we found that the local health authority of residence is associated with differential costs, after adjusting for comorbidities and disease stage. This suggests that, despite the presence of an established regional kidney care and prevention program, local organizational factors play a key role in the management of CKD patients and should not be overlooked in cost analyses.

As to the patient classifications used to predict direct medical costs, we found that the CT-PIRP groups, combining demographic and clinical characteristics, have a better performance that the CKD stages.

In conclusion, our study indicates that CKD accounts for a substantial economic burden during conservative treatment and that costs exhibit large variations depending on the presence of comorbid conditions, illness stage and patients' age. When the CKD progresses to the dialytic phase, in another Italian study, per patient costs have been estimated to raise at €38,821 in the first year of dialysis (20).

Notably, the economic burden of CKD is similar to that of COPD, a chronic condition with a slightly higher estimated prevalence (21) and adjusted annual direct costs for GOLD grade 1 to 4 COPD that amount to € 3,809 [3,691–3,935], € 4,284 [4,176–4,394], € 5,548 [5,328–5,774], and € 8,309 [7,583-9,065] (23).

These results should be interpreted in light of strengths and limitations.

One important strength of the study is that the PIRP database was linked with the administrative regional databases, and uses clinical lab data from all laboratories in Emilia-Romagna, allowing to track the course of renal function and the outcomes using high-quality data.

As to the limitations, study patients are included in a prevention program and their medical costs may be on average higher than those of patients receiving usual care, although in the long term a reduction in direct health care costs is expected as a result of the slower progression of the disease and the delay of end stage renal failure (7). Second, we did not estimate the indirect costs for patients and caregivers. In Italy, information on productivity losses and out-of-pocket expenditure is not available at the patient level, and more efforts should be made to acquire these data, as social costs associated with chronic kidney disease are substantial. Third, patients included in the PIRP program are resident in Emilia-Romagna Region and may be affected by the local health care organization. Therefore, generalization to other regions or countries should be done with caution.

Fourth, we estimated annual costs using baseline classifications of patients (CKD stage or CT-PIRP group) and did not incorporate the CKD progression in the models because we were interested in comparing the predictive ability of these two classifications.

Despite these limitations, our findings can be used by stakeholders to estimate the cost of CKD care across relevant subgroups of CKD patients and to predict the health expenditure that will be required based on expected increases in the prevalence of CKD. Moreover, our results can be used to estimate the cost savings that can be obtained through the implementation of interventions that slow or prevent kidney function decline.

4.2 Developing and validating an algorithm to identify incident chronic dialysis patients using administrative data

4.2.1 Background

Implementing and regularly maintaining a regional dialysis registry would require a large amount of dedicated human resources. In Italy, only 8 out of regions out of 21 have actually developed a registry of dialysis patients. One way to overcome this problem is to exploit the data recorded in the official administrative databases and create a regional registry by means of an automated algorithm but there is no single algorithm definition. This study aims to develop and test a novel algorithm that identifies incident dialysis patients taking advantage of data from the hospital discharges and outpatient specialty databases. The algorithm was validated against the gold standard represented by the dialysis registry of the Emilia-Romagna region. This algorithm relies on ICD9-CM coding and can be easily adapted to be utilized in other regions and countries, where it may be used to implement a new registry of chronic dialysis patients or improve the quality of existing registries.

4.2.2 Data

The data for the study were obtained by searching the hospital discharge records and the outpatient specialty visits databases (ASV) for the years 2013-2015. administrative databases of Emilia-Romagna. The Emilia-Romagna regional Dialysis Registry (ERDR, established in 1994) was used as the gold standard to evaluate the accuracy of the two algorithms.

The ASV database contains records regarding each hemodialysis session or one monthly summary record for peritoneal dialysis; in both cases, data on the type of service delivered (laboratory test, specialty service, rehabilitation service), the medical discipline related to the service, the date of delivery are present.

4.2.3 Methods

The study proposed two different algorithms designed to identify the incident chronic dialysis patients in a selected time period (the index period) using data obtained from the regional hospital discharge records (HDR) and ambulatory specialty visits (ASV) databases. The algorithms require all dialysis events recorded from 1 year before the starting date to 1 year after the ending date of the index period. While the starting date of dialysis is searched in both databases, the first algorithm defines as chronic dialysis patients those who are seen regularly in outpatient clinics, and therefore searches for previous and subsequent dialysis events only in the ASV database; the second algorithm considers also dialysis treatments provided during hospitalizations, and thus uses data from both the ASV and the HDR databases to define a chronic dialysis patient. A variation of

algorithm 1 in which the index date is retrieved only from ASV records was also tested, to address situations in which only ASV data are available.
The two algorithms used the same inclusion criteria, as follow:

- in HDR, at least one admission in the index period with ICD9-CM main or secondary diagnosis codes 585.6 (end stage renal disease, excluding admissions aimed to create the arteriovenous or peritoneal fistula, identified by 39.27, 39.29 or 54.93 codes as the only dialysis-related procedure code), V45.1 (renal dialysis status), or V56.0-V56.8 (dialysis encounter). In this case, the admission date was used to set the dialysis date;
- or, in HDR, at least one admission with any procedure code ICD9-CM 39.95 (hemodialysis) or 54.98 (peritoneal dialysis) In this case, the date of the procedure was used to set the dialysis date; when more than one dialysis procedure was found, the earliest date was used. If the HDR record included both diagnosis and procedure codes related to dialysis, the procedure date was selected;
- or, in ASV, at least one hemodialysis (codes 39.95.1–39.95.9) or at least one peritoneal dialysis (codes 54.98.1 or 54.98.2) in the index year.

For each patient, the date of the first dialysis (index date) was defined as the earliest among the dates of visits and hospital admissions of 2014. The following exclusion criteria were implemented:

- patients not residing in the Emilia-Romagna region: they were excluded if at least one record from the HDR and ASV databases in the index period indicated a different region of residence;
- prevalent cases: patients were excluded if at least one hemodialysis or peritoneal dialysis was found in the 365 days before the index date;
- non-chronic dialysis patients: patients were excluded if, within 1 year following the index date, less than 30 days passed between the index date and the last dialysis date, or less than 90 days for patients who initiated dialysis for acute kidney injury (AKI, primary or secondary diagnosis code ICD9-CM 584.x found in the index dialysis admission or in admissions occurred less than 90 days before the index date). This criterion allows to exclude patients who died, or recovered, or were transferred to a nephrology unit of another region shortly after dialysis initiation;

- patients who died during the hospitalization in which the first dialytic treatment was provided. Only algorithm 2 used this criterion.

Sensitivity analyses were performed for both algorithms by using 60 and 90 days after the index date as thresholds to define non-chronic dialysis patients. The algorithms were developed using Stata 15.1 and SAS Enterprise Guide 7.1.

4.2.4 Gold standard

The Emilia-Romagna regional Dialysis Registry (ERDR) was used as the reference source to evaluate the accuracy of the two algorithms. The ERDR is part of the Italian Dialysis Registry network, which in turn feeds the ERA-EDTA Dialysis Registry; as such it is the official source of epidemiological information about chronic dialysis in the Emilia-Romagna region. Incident cases in the ERDR are patients living in the Emilia-Romagna region who initiate dialysis for the first time according to the intention-to-treat approach. The dialysis inception date reported in the ERDR is assigned by the nephrologist in charge, and is the date in which the patient started being considered as chronic. Patients who stop dialysis because of transplantation are maintained in the registry as “transplanted patients” (hence, they are not included in the population of prevalent dialysis patients) and if they subsequently reinitiate dialysis, they will be considered as new entries for that year. Patients starting dialysis following an AKI and not chronicized, as well as guests (patients temporarily treated with dialysis in a regional clinic but living elsewhere, in Italy or abroad) are not added to the ERDR. The registry is updated yearly by transferring data from the information systems of nephrology units, checked for data quality by the nephrologist in charge of the registry (EM) and uploaded on a dedicated website (https://www.regdial.it). In 2014 all but one of the local nephrology units could automatically transfer data from their patients’ management information systems to the ERDR, therefore widely reducing the possible mistakes due to manual data transcription. However, the ERDR is regularly monitored and revised for inconsistencies and missing data.

The comparison between the algorithms and the ERDR was made by calculating only percentage agreement, sensitivity and positive predictive value (PPV), because the ERDR does not contain subjects without dialysis.

4.2.5 Results

The novel algorithm #1 identified 680 incident chronic dialysis patients and the algorithm #2 676 incident chronic dialysis patients. The patients identified by both algorithms were 631. The ERDR included 625 incident patients in 2014 after removing those treated in the two local health authorities with incomplete data. Cases recorded in the ERDR and missed by the algorithms were respectively 58 and 72. Algorithm 1 showed sensitivity = 90.8% and PPV = 84.0% and algorithm 2 had a slightly lower performance (sensitivity =88.5% and PPV = 82.0%). Algorithm 2 was less accurate mostly because it identified more chronic incident in dialysis patients unknown to ERDR (68 vs. 39) on the basis of occasional hospital admissions while not having had any dialysis related specialty visit in the year following the index date. The estimated incidence rate of dialysis inception per million regional population was 168 for ERDR, 182 for algorithm 1 and 181 for algorithm 2. The algorithm that used only ASV data was very similar to algorithm 1 in terms of PPV (83.8%) and inferior for agreement and sensitivity. Sensitivity analyses confirmed that Algorithm 1 with threshold for chronicity at 30 days provided the best performance; all algorithms' variations displayed very good sensitivity, while PPV generally was around 5% lower.

4.2.6 Discussion

We provide two algorithms that identify with good accuracy incident chronic dialysis patients from the administrative databases of hospital discharges and outpatient visits. The algorithm that identifies patients as chronic dialysis incidents if they attended ambulatory specialty visits after the first dialysis is to be preferred, because it is more accurate. These algorithms may be useful to create regional registries of chronic dialysis patients or to improve the accuracy of existing registries. As they are derived from administrative databases using ICD9-CM codes, with the necessary adaptations they can be used in many regional or national settings and can easily be linked to other data sources, representing a valuable tool for clinical and epidemiological studies. The performance of our algorithms should be further validated using data from other regions.

4.3 Impact of SARS-CoV-2 on mortality in CKD patients

4.3.1 Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness named coronavirus disease 2019, or COVID-19. Although pulmonary involvement and respiratory failure have been recognized as the main features of COVID-19, renal involvement, defined both as urinary abnormalities and changes in kidney function, has been described among patients with COVID-19 and it might be present in up to 75% of cases [23]. In patients with COVID-19, abnormal kidney function may be a consequence of hemodynamic alterations, enhanced inflammatory status, coagulation abnormalities, organ cross-talk or of direct renal localization of SARS-CoV-2 [24, 25]. Receptors that mediate virus internalization, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) [26] are abundant in renal tissue. Therefore, it has been hypothesized that SARS-CoV-2 presents a specific renal tropism, which could constitute the biological basis of the common kidney injury in patients affected by COVID-19 [27].

The aim of this study is to estimate the survival of CKD patients during the COVID-19 outbreak by stage, age, BMI classes, AKI, non-invasive mechanical ventilation and to provide an estimate of the excess mortality experienced by CKD patients during the COVID-19 outbreak.

4.3.2 Data sources

Data were extracted from the PIRP registry, the Regional Mortality Registry and the Prevention Service Registry.

The study population consists of 5308 patients recruited in the PIRP project from 1.4.2004 to 31.12.2019, who were still alive as of 1.01.2020 and were resident in the Romagna Local Health Authority.

Patients were identified as SARS-CoV-2 infected if:

- They had a hospitalization in which COVID-19 was diagnosed
- They had been treated for COVID-19 even without a positive swab
- They were recorded in the database of the Prevention Service including swab-positive subjects even if not hospitalized

SARS-cov-2 infected subjects were searched over the period 1.01 - 31.07.2020.

The comorbidities were identified using the MCS algorithm (Corrao et al., 2017) applied to the data extracted from HDR and the pharmaceutical prescriptions database for the years 2018-19.

4.3.3 Statistical Analysis

Patients survival in 2020 was estimated using KM curves and compared among groups using log-rank test.

In order to investigate the impact of SARS-CoV-2 infection, mortality rates in the year 2020 were computed for the periods January-February, March, April, May, June and July, and compared with those of the corresponding periods of the years 2015-2019. To allow for possible changes in the structure of the PIRP population, mortality rates were adjusted for age and sex, using the prevalence by gender and age as of 1.1.2015. The excess mortality was calculated as (TMort2020 / TMort201x) -1. Negative values indicate a lower mortality in 2020, positive values a higher mortality. For instance, an excess mortality of 44.3 indicates that mortality is increased by 44.3%.

4.3.4 Results

The study population included 5308 patients, 65.5% male, with a mean age 75.3 years, SD=12.3. The incidence of SARS-CoV-2 infection was 4.16% (n=221). Patients hospitalized with COVID-19 were 211 (95.5%), those with COVID-19 on home isolation were 8 (3.6%) and 2 (0.9%) were asymptomatic.

Crude mortality rates for the period January 1st-July 31st, 2020 ranged from 5.92% to 7.29% in the Romagna provinces and the adjusted mortality rate for Romagna was 5.91%. The overall excess mortality ranged between 34.4% and 56.3% in the months of March, April and May 2020 (Tables 1,2, Fig.1) compared to the year 2019. Two remarkable peaks in the excess mortality of PIRP patients were found in Ravenna in the months of April and June-July 2020 (fig.1), in which no excess mortality was observed in the population. In Rimini, a peak in excess mortality in the month of March was observed in the population and in CKD patients, while the second peak of May involved only CKD patients.

When we focused on the characteristics associated with the survival of CKD patients, we found that survival significantly with increasing age (log-rank test=12.45, p=0.014, fig. 3), but did not differ by BMI classes (log-rank test=2.86, p=0.414), CKD stage (log-rank test=0.09, p=0.761, fig. 2), or the presence of AKI (log-rank test=2.64, p=0.104, fig. 5). Patients admitted to ICU had a lower survival (log-rank=8.90, p=0.003), but no difference was found concerning non-invasive mechanical ventilation (log-rank=1.76, p=0.184) (figures 6-7).

Figures 2-7. Kaplan-Meier survival estimates of patients in the first 90 days from hospital admission or ascertained positivity to SARS-CoV-2 by 2) CKD stage, 3) age group, 4) BMI class, 5) AKI vs. no AKI, 6) ICU admission, 7) non-invasive mechanical ventilation.

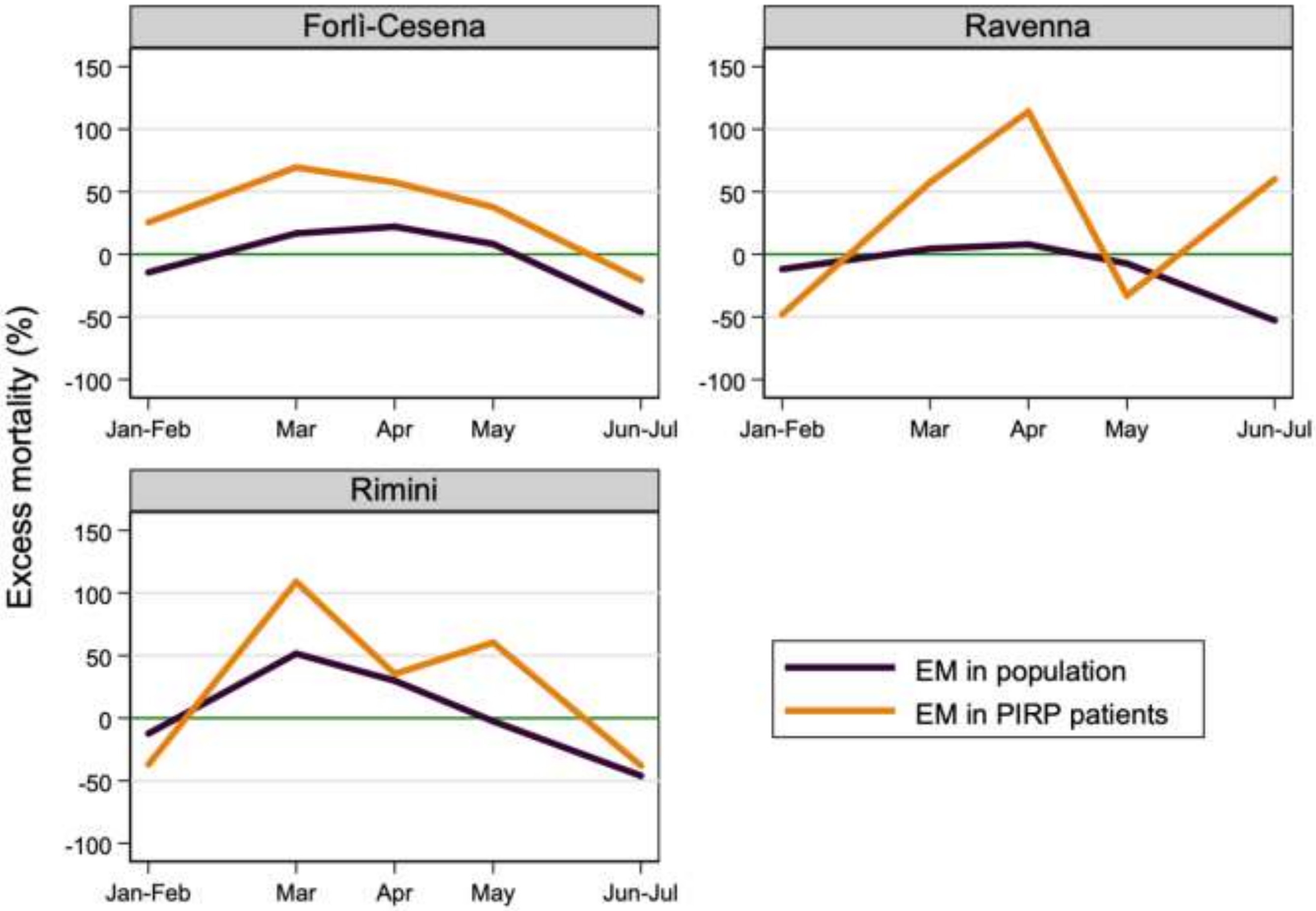
Table 1. Excess mortality in Romagna local health authority by months

	Adjusted mortality rates X 100						**Excess mortality (in 2020 compared with single year)**				
PERIOD	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**2015**	**2016**	**2017**	**2018**	**2019**
January - February	1.796	1.625	1.850	2.077	1.689	1.478	-17.7	-9.1	-20.1	-28.9	-12.5
March	0.671	0.533	0.938	0.852	0.867	1.355	102.0	154.1	44.5	59.1	56.3
April	0.649	0.529	0.955	0.561	0.761	1.053	62.3	99.1	10.3	87.8	38.4
May	0.736	0.530	0.578	0.490	0.581	0.781	6.2	47.6	35.2	59.4	34.4
June-July	1.320	1.298	1.263	1.147	1.205	1.244	-5.8	-4.1	-1.6	8.5	3.2
January - July	5.063	4.474	5.544	5.074	5.040	5.911	16.8	32.1	6.6	16.5	17.3

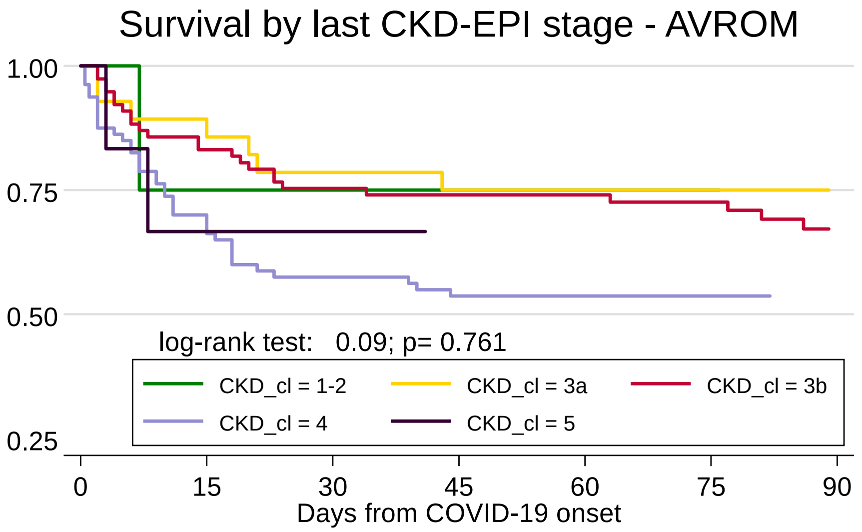
Table 2. Excess mortality in the Romagna provinces

		Adjusted mortality rates X 100							Excess mortality in 2020 compared with single year					
PERIOD	**AREA**	**mar-15**	**mar-16**	**mar-17**	**mar-18**	**mar-19**	**mar-20**	**MAR1519**	**2015**	**2016**	**2017**	**2018**	**2019**	**'15-'19**
January-February	Ravenna	2.064	2.226	2.176	2.709	2.632	1.231	2.361	-40.4	-44.7	-43.4	-54.6	-53.2	-47.9
March	Ravenna	0.344	0.406	1.447	0.816	0.97	1.255	0.797	264.7	208.7	-13.3	53.7	29.4	57.5
April	Ravenna	0.688	0.808	1.352	0.534	0.528	1.675	0.782	143.4	107.3	23.9	213.4	217.3	114.2
May	Ravenna	0.688	0.411	0.9	0.543	0.926	0.464	0.694	-32.5	12.9	-48.4	-14.5	-49.8	-33
June-July	Ravenna	1.376	0.908	0.757	1.536	1.334	1.893	1.182	37.6	108.6	150	23.2	42	60.1
January-July	Ravenna	5.046	4.759	6.534	6.041	6.162	6.518	5.708	29.2	37	-0.2	7.9	5.8	14.2
January-February	Forlì-Cesena	1.774	1.605	1.728	2.139	1.508	2.198	1.751	23.9	36.9	27.2	2.7	45.7	25.5
March	Forlì-Cesena	0.863	0.471	1.025	0.877	0.941	1.416	0.835	64.1	200.8	38.2	61.5	50.5	69.6
April	Forlì-Cesena	0.719	0.283	0.769	0.505	0.941	1.014	0.644	41	258.2	31.8	100.6	7.7	57.5
May	Forlì-Cesena	0.911	0.773	0.54	0.48	0.533	0.892	0.648	-2.1	15.3	65.1	85.7	67.2	37.7
June-July	Forlì-Cesena	1.294	1.35	1.535	1.137	1.131	1.026	1.29	-20.8	-24.1	-33.2	-9.8	-9.3	-20.5
January-July	Forlì-Cesena	5.417	4.435	5.597	5.094	5.017	6.545	5.112	20.8	47.6	16.9	28.5	30.5	28
January-February	Rimini	1.711	1.488	1.811	1.792	1.693	1.071	1.699	-37.4	-28.1	-40.9	-40.3	-36.8	-37
March	Rimini	0.611	0.617	0.618	0.839	0.754	1.438	0.688	135.2	133.2	132.7	71.4	90.7	109
April	Rimini	0.55	0.609	0.994	0.585	0.705	0.932	0.689	69.4	53.1	-6.3	59.4	32.1	35.3
May	Rimini	0.55	0.325	0.567	0.543	0.417	0.771	0.481	40.1	137.2	35.9	41.9	85	60.4
June-July	Rimini	0.856	0.653	0.596	0.528	0.684	0.412	0.663	-51.9	-36.9	-30.9	-22.1	-39.8	-37.9
January-July	Rimini	4.707	4.348	5.057	4.736	4.764	5.451	4.722	15.8	25.4	7.8	15.1	14.4	15.4

Figure 1. Excess mortality (%) in the population (black line) and in PIRP patients (orange line) from January to July 2020 in the three provinces of the Romagna Local Health Authority.

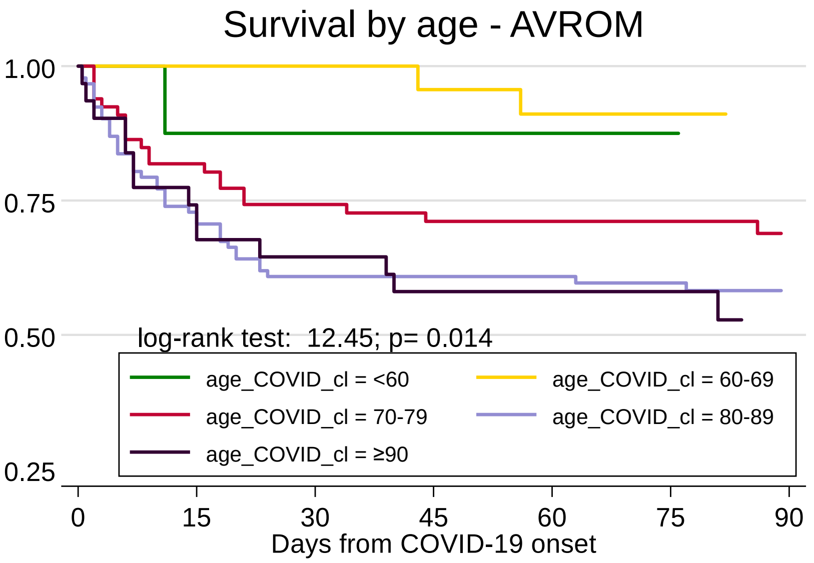


Figures 2-6. Kaplan-Meier survival estimates by PIRP patients' characteristics.

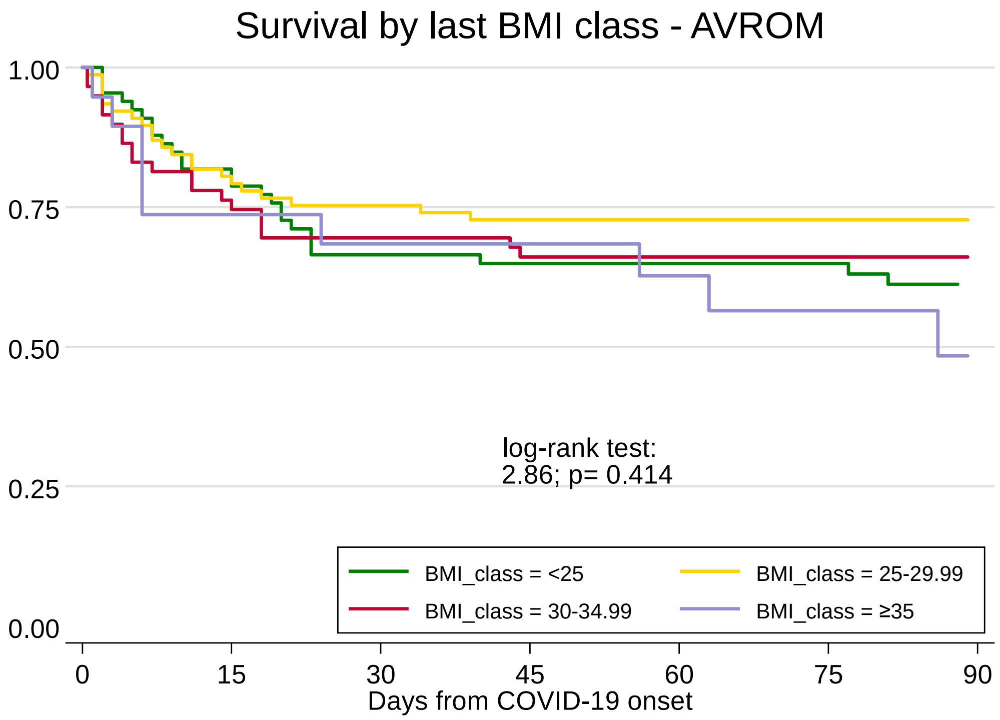


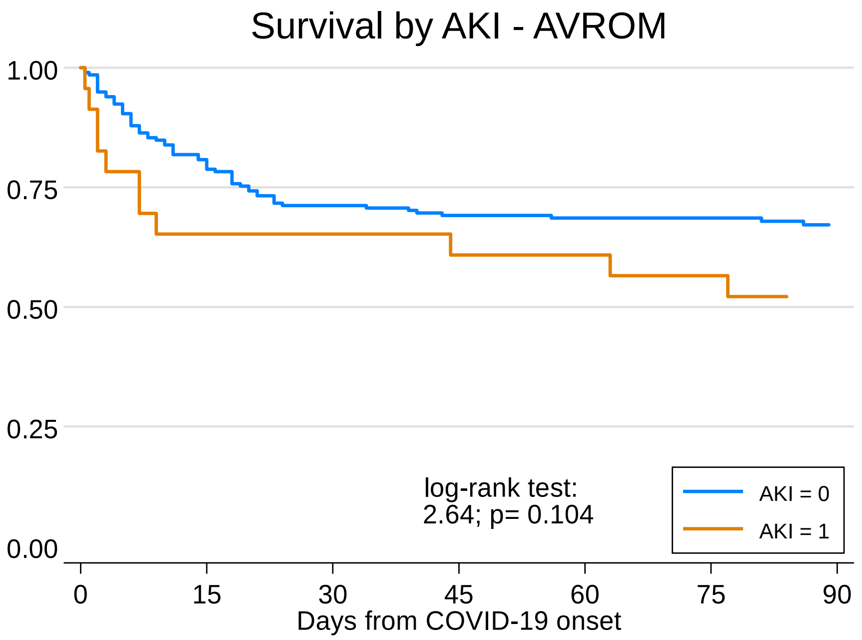
Number at risk													
CKD_cl = 1-2	4	(1)	3	(0)	3	(0)	3	(0)	3	(0)	3	(0)	2
CKD_cl = 3a	28	(3)	25	(3)	22	(1)	21	(0)	18	(0)	18	(0)	15
CKD_cl = 3b	77	(13)	64	(6)	58	(1)	56	(0)	54	(1)	43	(3)	31
CKD_cl = 4	80	(24)	56	(10)	45	(3)	42	(0)	39	(0)	31	(0)	25
CKD_cl = 5	6	(2)	4	(0)	4	(0)	3	(0)	3	(0)	3	(0)	3

excluding patients on dialysis or tx



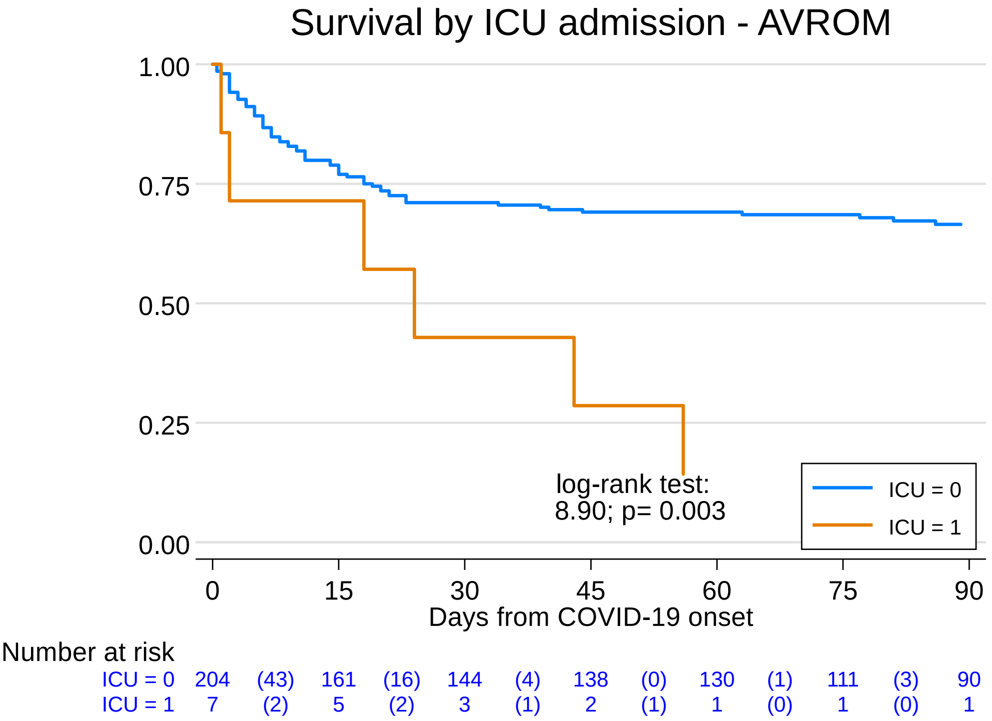
Number at risk													
age_COVID_cl = <60	8	(1)	7	(0)	7	(0)	7	(0)	7	(0)	7	(0)	6
age_COVID_cl = 60-69	24	(0)	24	(0)	23	(1)	22	(1)	20	(0)	18	(0)	17
age_COVID_cl = 70-79	66	(12)	54	(5)	48	(2)	45	(0)	42	(0)	36	(1)	30
age_COVID_cl = 80-89	92	(25)	67	(11)	56	(0)	55	(0)	51	(1)	43	(1)	36
age_COVID_cl = ≥90	31	(8)	23	(3)	20	(2)	18	(0)	18	(0)	15	(1)	8





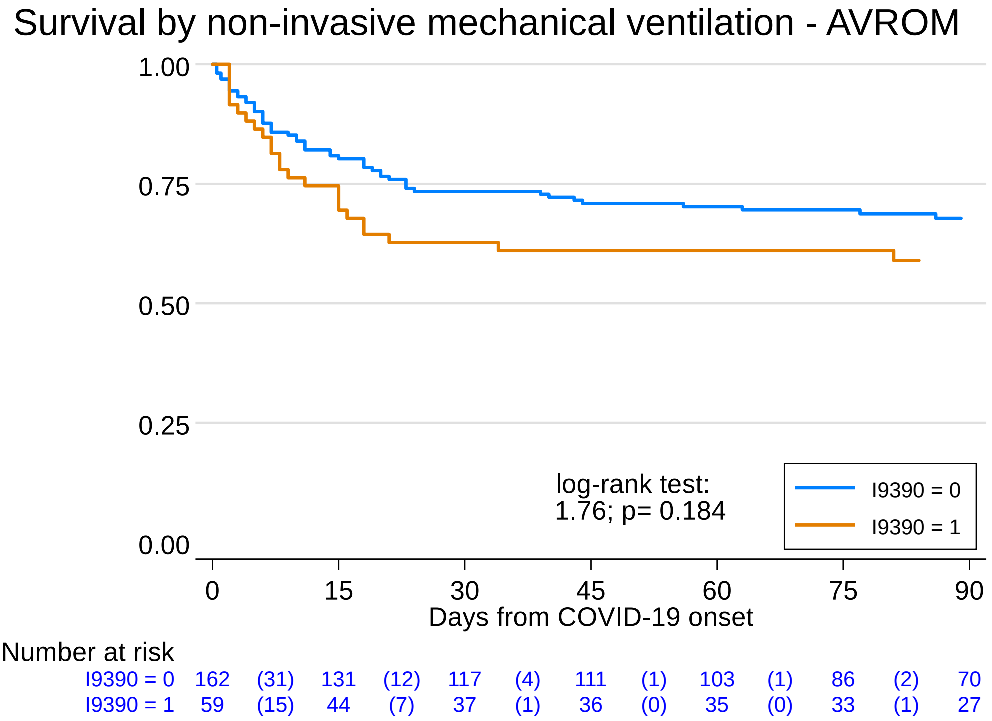
Number at risk

AKI = 0	198	(38)	160	(19)	139	(4)	133	(1)	124	(0)	106	(2)	87
AKI = 1	23	(8)	15	(0)	15	(1)	14	(0)	14	(1)	13	(1)	10


Survival by ICU admission - AVROM

Number at risk

ICU = 0	204	(43)	161	(16)	144	(4)	138	(0)	130	(1)	111	(3)	90
ICU = 1	7	(2)	5	(2)	3	(1)	2	(1)	1	(0)	1	(0)	1


Survival by non-invasive mechanical ventilation - AVROM

Number at risk

I9390 = 0	162	(31)	131	(12)	117	(4)	111	(1)	103	(1)	86	(2)	70
I9390 = 1	59	(15)	44	(7)	37	(1)	36	(0)	35	(0)	33	(1)	27

4.3.6 Discussion

This research provides evidence on the excess mortality of PIRP patients during the COVID-19 pandemic compared with the population living in the same catchment area and on the demographic and clinical correlates of mortality. Evidence on the association of patients' characteristics with mortality is inconclusive because of small number of patients in the subgroups and of the death events. Large, multicenter, prospective studies with a long-term follow-up are needed to better clarify the impact of renal damage not only during, but also after SARS-CoV-2 infection.

5.0 Discussion

To develop health policies useful for the management of CKD, it is necessary to know the prevalence, incidence, and progression of the disease and its related costs.

The alternative to developing a customized data collection system is to use available data sources: *health administrative data* (EAD). These datasets are useful for understanding the functioning of the SSN services and to support decision. Each hospital and local health unit produces a large amount of data and each of them has its own information system, more or less organized. The main role of the information system is to provide reliable, aggregated and easy-to-manage information. Information management is an important activity for everyone and particularly complex for those who perform managerial functions.

Moreover, large administrative datasets have recently become a rich source for research studies in several disciplines of medicine as EAD became more widely used. The combination of electronically extracted clinical data with traditional administrative datasets holds significant promise for providing increased value to researchers without the unnecessary burden of chart abstraction. Such databases are less expensive compared with large prospective clinical cohort studies while providing rich, individual data. In the presence of a universal healthcare system, these data sources reliably reflect health-related conditions at a population level, by gathering widespread information at an individual level. The presence of the same patient identifier code (ID code) in all databases allows the *record linkage* between them generating a population database. Technically, using a population database in Italy allowed to follow an individual from birth to death through the archives of the NHS. EADs have long been used consistently worldwide for epidemiological purposes, especially to identify acute and chronic health conditions. This is possible through disease-specific case-identification algorithms, that combine information coded in multiple EADs. EADs are often reliable when identifying subjects affected by acute health conditions, even when there is only one contact with the healthcare system (e.g., a diagnosis of acute myocardial infarction in the hospital discharge record database), while identifying subjects affected by chronic conditions usually requires multiple contacts with the healthcare system, over a longer time span. The importance of having accurate algorithms has been increasingly emphasized, to avoid possible misclassification bias and to improve the quality of research, especially in terms of internal validity of methods and generalizability. According to the specific study designs and objectives (e.g., definition of cohorts, exposures or outcomes), any characteristic of the algorithm can be modified to increase the expected sensitivity, specificity, or positive predictive value (PPV), tailored according to the specific research needs. For instance, high sensitivity might be preferred when estimating prevalence, while in order to avoid case misclassification, high specificity and PPV might be required when enrolling cohorts or analyzing the effects of specific exposure. The second application showed a new algorithm to identify incident chronic dialysis patients using administrative data. The algorithm is easy to implement because it needs as input data taken from the hospital discharge records and outpatient specialty visits databases and apply inclusion and exclusion criteria based on ICD-9 CM codes. In addition, this algorithm proved to have good accuracy, sensitivity = 90.8% and PPV = 84.0%.

Administrative databases are also increasingly used for comorbidity detection and to estimate patterns of utilization and cost of diseases. Stratification based on the presence of some concomitant diseases can be used to guide decisions about the follow-up schedule, treatments to slow progression of kidney disease, prevent its complications and to begin planning for dialysis and transplantation. Besides, the EAD, using the record linkage, can offer a wide range of information related to comorbidities, detected through the presence of a hospitalization discharge diagnosis ICD-9-CM code or disease-specific pharmaceutical prescriptions. The first application indicates that CKD accounts for a substantial economic burden during conservative treatment and that costs exhibit large variations depending on the presence of comorbid conditions, illness stage and patients' age, ranging from €5,310 to €6,233 in the four follow-up years.

Moreover, the availability of updated and ready to use databases allows to constantly monitor the evolution of specific diseases and the response of healthcare organization to COVID-19 pandemic. The third application evaluated incidence and outcomes of chronic kidney disease patients during the pandemic. It showed that the overall excess mortality ranged between 34.4% and 56.3% in the months of March, April and May 2020.

There are several limitations of EAD. EAD do not contain detailed clinical information, so that the presence of comorbid diseases can only be estimated by using information about pharmacological prescriptions, combined with hospital discharge records.

As regards the use of EAD to estimate health expenditure, the EAD contains the services provided by the national health service (SSN), while private ones as well as indirect costs and information on productivity losses and out-of-pocket expenditure are not available. Moreover, it should be noted that the EAD contains the reimbursement rates and not the actual costs. The SSN guarantees the provision of health services included in the essential levels of assistance (Lea) through the activity of public providers (health and hospital companies, university-hospital companies, public IRCCS), private individuals (private IRCSS, classified hospitals and "PRESIDI") and accredited private individuals, within specific agreements with Regions and Companies. The use of the tariffs is to ensure homogeneous coverage of costs.

Despite these limitations, our findings can be used by stakeholders to estimate the cost of CKD care across relevant subgroups of CKD patients and to predict the health expenditure that will be required based on expected increases in the prevalence of CKD. Moreover, our results can be used to estimate the cost savings that can be obtained through the implementation of interventions that slow or prevent kidney function decline.

Finally, the EAD offer the opportunity to identify the disease burden, adverse outcomes and care gaps—all useful for setting policy goals and improving the quality of care. Moreover, such databases could be used to measure the impact of interventions aimed at reducing the burden of CKD and its consequences, thereby producing generalizable evidence.

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