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ORIGINAL RESEARCH ARTICLE

Healthcare of patients with immunoglobulin A nephropathy through a retrospective observational study of Italian administrative data

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ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is a rare disease poorly described in real-world settings. This observational retrospective study aimed to assess the direct healthcare burden of new IgAN patients on the Italian National Healthcare Service (SSN).

Methods: From the Fondazione Ricerca e Salute's database (administrative healthcare data of ~5.5 million inhabitants/year), inpatients with new potential in-hospital biopsy-verified IgAN from 2016 to 2019 were identified. Dispensations of IgAN-recommended and other drugs, kidney replacement therapies (KRT), hospital and emergency department (ED) admissions, local outpatient specialist care, and related direct costs were assessed throughout a 3-year follow-up.

Results: New IgAN patients (n = 292) were identified (incidence/year: 1.25/100 000 inhabitants); 64% of patients were male; the median age was 41 (27; 57) years. Annual consumption of most healthcare resources decreased from Year 1 to 3: from 90% to 84% of patients received ≥1 IgAN-recommended drug; from 100% (due to selection criteria) to 15% of patients underwent overnight hospitalizations; from 8% to 3% patients underwent day hospitalizations; from 31% to 21% patients underwent ≥1 ED access; from 87% to 85% patients received local outpatient specialist services. Of all patients, 2–4% were treated with KRT, and ~91% received other drugs. The per capita mean total annual cost was €7441 in Year 1 (hospitalizations accounting for 73% due to selection criteria), €3497 in Year 2, and €3243 in Year 3 (drugs accounting for 51%, mostly attributable to other drugs).

Conclusion: This real-world study shows a substantial direct healthcare burden for new IgAN patients arising from IgAN-specific care and comorbidities.

Keywords: Comorbidity, Delivery of health care, Health care costs, Immunoglobulin A nephropathy, Pharmaceutical services

Introduction

Immunoglobulin A nephropathy (IgAN) is a rare disease that, by accumulating IgA-containing immune complexes in the kidney glomeruli, leads to chronic kidney inflammation (1). IgAN is the most common primary glomerulonephritis worldwide (2). Kidney biopsy is currently the only way to confirm the diagnosis (3,4). The reported incidence and prevalence rates vary greatly across Europe and worldwide, given the highly variable clinical presentation of IgAN that also includes asymptomatic cases, and information still mainly comes from registries of patients with biopsy-verified IgAN (1–3). Based on the Italian Registry of Renal Biopsies from 1996 to 2000, the annual incidence of IgAN in patients of all ages was 0.84/100,000 (3). According to a more recent study of native kidney biopsies in adults from a northeastern Italian area, IgAN incidence was 1.22/100,000, and this rate was almost constant from 1998 to 2010 (5). Despite the still limited studies looking at the different stages of life, differences between pediatric and adult IgAN exist and are still unclear (3,6); indeed, IgAN is more common in adults, where

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it presents a more severe disease and often progresses to kidney failure (KF) within 20 years from diagnosis.

IgAN is often a progressive disease associated with proteinuria, hypertension, kidney injury, upper respiratory tract infections, and inflammatory bowel diseases (IBD), and its prognosis is worst among older patients who are generally diagnosed with advanced kidney disease stage (2,3,6). The progression of IgAN is generally slow, but its clinical course varies widely, with up to 40-50% of patients requiring kidney replacement therapy (KRT) (i.e., dialysis/kidney transplantation) within 20 years from diagnosis (2,7-9). If disease progression cannot be efficiently slowed or prevented with current treatments, KF can occur at a relatively young age, with a substantial impact on quality of life (QoL), daily living, and ability to work (1,2,8-10).

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for the management of glomerular diseases recommend supportive care (SC) as first-line treatment, including renin-angiotensin system inhibitors (RASIs), blood pressure control, cardiovascular disease management and lifestyle modification (4). Other options, such as corticosteroids, non-steroidal immunosuppressive agents, and tonsillectomy, are controversial and recommended only for selected cases (4,11,12). Recently, new therapeutic strategies have been authorized by the European Medicines Agency (EMA) (i.e., enteric-coated budesonide and sparsentan), and research is underway for non-immunosuppressive and immunosuppressive drugs (4,13). As of now, among the most recent EMA authorizations, sparsentan and enteric-coated budesonide have entered the Italian market in 2024 and are reimbursed by the Italian National Healthcare Service (Servizio Sanitario Nazionale - SSN) for treating patients with IgAN at high risk of progressive kidney function decline (14,15). Specifically, sparsentan is supplied through the principle of compassionate use; that is, the way the SSN reimburses orphan drugs until safety and efficacy evidence is provided to release Italian marketing authorization (16). Therefore, to date, in Italy, there remain unmet clinical needs in terms of reducing proteinuria, long-term stabilization of kidney function, and a significant risk of toxicity associated with corticosteroid therapy (17). Moreover, evidence on the burden of illness, healthcare resource utilization, and economic impact of IgAN is still limited and heterogeneous, highlighting the need for more real-world studies (1,18).

This observational retrospective study of Italian administrative healthcare data aimed to identify patients potentially affected by IgAN and to describe their clinical characteristics, overall survival, and impact on the SSN in terms of healthcare resource consumptions and related direct costs in a 3-year follow-up.

Methods

Data source

The Fondazione Ricerca e Salute (ReS) database collects and integrates the administrative healthcare data that Italian Local and Regional Healthcare Authorities are obliged to provide annually to the Italian Ministry of Health for reimbursement purposes because SSN provides universal coverage. The ReS database includes information from 5.7 million inhabitants per year (from 2014 to 2022), representing ~9% of the Italian population. Its distribution by age group is consistent with that obtained by the Italian Institute of Statistics (Fig. S1) (19). More information about Fondazione ReS and its database is available in the Supplementary file.

Data were anonymized at source and provided in aggregated form according to European Regulations 2014/536 (20) and 2016/679 (21), as agreed by the regional/local authorities that own the data. Informed consent was waived according to the specific Italian Privacy Authority's provision (22). Ethical approval was waived according to the European Regulation 2014/536 (20); moreover, it is not required by the most recent national legislation on observational studies, which requires the Ethic Committee's positive opinion only for prospective observational studies, without reference to retrospective ones (23).

Study cohort identification

From the total population available in the ReS database from 2016 to 2019 (4-year accrual period), individuals with an analyzable 2-year lookback period were selected. Among these, patients potentially affected by IgAN were identified based on an algorithm combining in-hospital codes for the diagnosis of glomerulonephritis and the procedure of kidney biopsy in the same hospital discharge form (Table S1) because a specific diagnosis code for IgAN is lacking in the Italian version of the ICD-9-CM. The date of the first in-hospital potential identification of IgAN (i.e., glomerulonephritis and kidney biopsy) was considered as the index date. Patients with the same selection codes for 24 months preceding the index date were excluded in order to analyze only potential incident patients. Patients with in-hospital diagnosis codes identifying other nephropathies within 12 months following the index date were excluded to reduce the possibility of including patients diagnosed with other forms of primary and secondary glomerulonephritis; moreover, patients supplied with insulin in the lookback period were excluded because of the data potentially being affected by diabetic nephritis at accrual (Table S1). Because of the difficulty of identifying IgAN in real-world clinical practice and the limitations that affect administrative health data, the proposed algorithm has finally identified a study cohort that is mainly, but not exclusively, composed of patients with IgAN.

Demographics and clinical characteristics

At baseline (i.e., index date and 2-year lookback period; Figure S2), patients were characterized by sex, age, and frequency of analyzable relevant comorbidities (Table S2), namely arterial hypertension, dyslipidemias, chronic obstructive airway diseases, neoplasia, thyroid diseases, diabetes mellitus (DM), depression, chronic liver diseases, coronary artery disease, IBDs, rheumatoid arthritis, cerebrovascular diseases, heart failure, and arrhythmias. Prevalence rates of arterial hypertension, dyslipidemias, DM, and IBDs were also assessed throughout the 3-year follow-up period in case they may have been diagnosed after the IgAN identification.

The all-cause mortality was assessed by calculating the overall survival (OS) throughout the 3 years from the index date. The 3-year OS was estimated through the Kaplan–Meier estimator.

Healthcare resource utilization analyses

The study cohort was observed for 3 years following the index date (Years 1,2, and 3; Fig. S2). Each follow-up year was analyzed separately, considering the number of living patients at the beginning of each period and not withdrawn from the database, to provide the following information:

- drugs recommended for IgAN (Table S3) and other drugs dispensed, according to the KDIGO guidelines (4);
- annual frequency of KRT (Table S3);
- annual overnight and day hospitalizations, and emergency department (ED) accesses;
- local outpatient specialist services (i.e., diagnostics, invasive/non-invasive procedures), with a focus on some specific procedures (Table S3); per capita mean annual direct healthcare costs reimbursed by the SSN, which were provided by single cost items (i.e., pharmaceuticals, hospitalizations, local outpatient specialist services) and resulting from the integration of all administrative healthcare databases.

Direct healthcare costs were assessed annually as follows:

- pharmaceutical expenses derived from drugs dispensed by community and hospital pharmacies and reimbursed by the SSN (inclusive of value-added tax), which were split into IgAN-recommended and other drugs;
- in-hospital expenses were calculated through the diagnosis-related group classification (DRG) system tariffs, where each DRG code corresponded to all in-hospital care (from admission to discharge) in their entirety and complexity, without distinguishing single performed services. This item was split into overnight and day hospitalizations;
- costs for local outpatient specialist care were assessed through the current national fees listed in the 2017 version of the Italian "Nomenclatore tariffario" (24) and were split into dialysis treatments and other services.

Statistical analyses

Continuous variables are described as means ± standard deviation and median (interquartile range). Categorical variables are provided using frequencies and percentages within each category. Data extraction was performed using Oracle SQL Developer, Italian version 18.1.0.095 (Redwood City, CA, USA). Descriptive statistics were performed using Microsoft Excel Office 365 (MicroSoft Company, Redmond, WA, USA). Survival analysis was conducted using RStudio software (version 2022.07.2; Boston, MA, USA), an integrated development environment for the R programming language.

Results

Demographics and clinical characteristics

During the 4-year accrual period, 292 new patients potentially affected by IgAN were identified in the ReS database (Figure 1). The mean annual incidence was 1.25 new patients potentially affected by IgAN per 100,000 inhabitants.

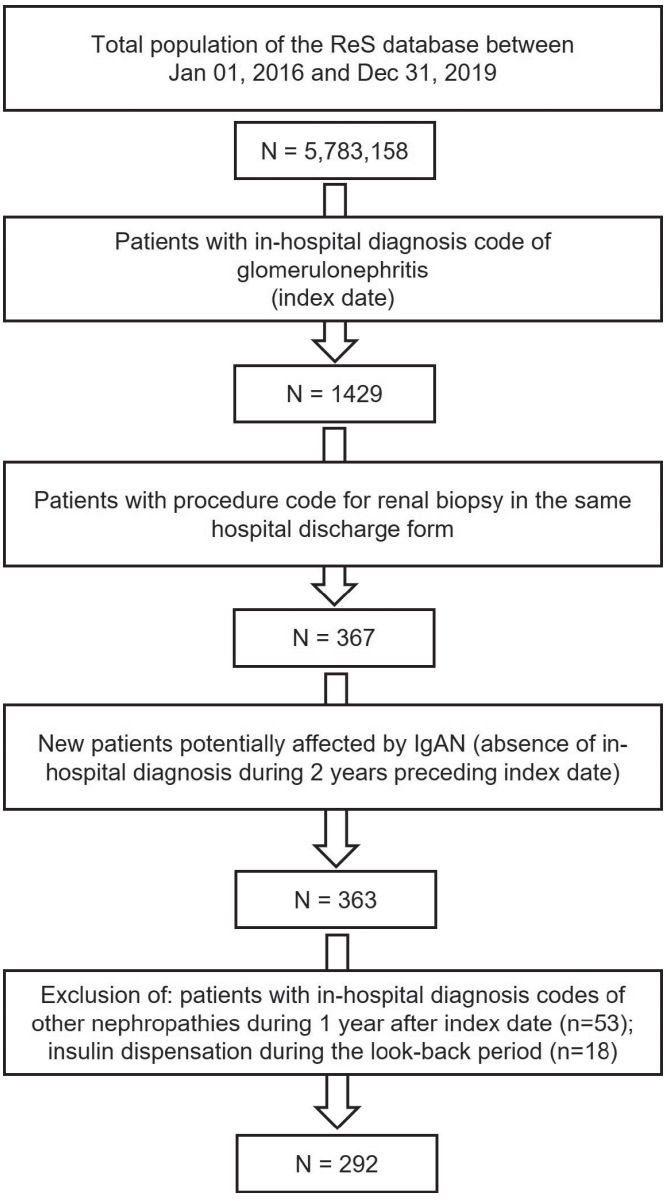

FIGURE 1 - Identification of patients with a new potential diagnosis of IgAN from 2016 to 2019 within the ReS database.

Males comprise 64% of the study cohort, and the median age at onset was 41 years (27; 57) (Table 1). At least one relevant comorbidity was identified in 68.2% of patients; notably, more than half of the cohort presented with arterial hypertension, 19.9% with dyslipidemia, and 13.7% with chronic obstructive airway diseases (Table 1).

The analysis of all-cause mortality revealed a favorable 3-year survival rate of 97.2% (95% CI: 94.4-98.6) in study patients. The mean age of patients who died for all causes during the 3-year observation period was 71.6 years.

TABLE 1 - Demographics and clinical characteristics of the study population of patients with a new potential identification of immunoglobulin A nephropathy from 2016 to 2019, at the baseline

Category	Patients with a new potential identification of IgAN (N = 292)
Males (n; n/N%)	188; 64.4
Mean age (standard deviation)	41 (19)
Median age (Q1; Q3)	41 (27; 57)
Distribution by age group, years (n; n/N%)	
<18	47; 16.1
18-29	40; 13.7
30-39	48; 16.4
40-49	54; 18.5
50-59	47; 16.1
60-69	40; 13.7
70-79	12; 4.1
≥80	4; 1.4
Comorbidities at baseline (n; n/N%)	
Arterial hypertension	163; 55.8
Dyslipidemia	58; 19.9
Chronic obstructive airway diseases	40; 13.7
Cancer	31; 10.6
Thyroid diseases	25; 8.6
Diabetes mellitus	20; 6.8
Depression	15; 5.1
Chronic liver diseases	13; 4.5
Coronary artery disease	12; 4.1
Inflammatory bowel disease	9; 3.1
Rheumatoid arthritis	5; 1.7
Cerebrovascular diseases	4; 1.4
Heart failure	3; 1.0
Arrhythmias	3; 1.0

Healthcare resource utilization analyses

At least one IgAN-recommended drug was dispensed to 89.7% of patients during Year 1 (Table 2). The treatment rate dropped by 4.2 percentage points in Year 2 and by a further 1.6 points in Year 3. The most frequently dispensed drugs in Year 1 were angiotensin-converting enzyme inhibitors (ACEIs; 63.0% of patients) and corticosteroids for systemic use (58.2%). Their utilization rates dropped to 56.2% and 32.8%, respectively, in Year 3 (Table 2). Other drugs were dispensed to ~91% of patients throughout the 3-year follow-up; proton pump inhibitors, vitamin D analogs, and penicillins (including β-lactamase inhibitors) were the most frequent.

During Year 1, given the criteria on which the identification algorithm was based, the entire study cohort was admitted to overnight hospitalization at least once (Table 3). Overall, 1.4 hospitalizations per patient were recorded, with an average stay of 9.6 days. About 8% of the cohort was admitted for day hospitalizations. At least one access to the ED occurred in 30.8% of patients. Chronic kidney disease (CKD) was the most common cause of admissions to hospital and ED; notably, 67.8% and 2.7% of patients were admitted to overnight and day hospitalizations, respectively, because of KF diagnosis.

During Year 2, 20.5% of the analyzable patients were admitted to at least one overnight hospitalization for an average stay of 9 days (Table 3). Again, KF was the most frequent cause of hospitalization, followed by diffuse diseases of connective tissue. The rate of day hospitalizations halved compared to Year 1, and 21.2% of patients were admitted to the ED at least once: causes were decreasingly related to renal diseases.

During Year 3, the rate of patients admitted to overnight hospitalizations at least once decreased by 5.2 percentage points compared to the previous year (Table 3). KF and diffuse diseases of connective tissue remained the leading causes of hospitalization, and the average stay was 9.2 days. Day hospitalizations occurred for 2.6% of patients, while ED access remained at 21.5% of patients.

At least one procedure of hemodialysis, peritoneal dialysis, or kidney transplantation was performed in 1.7%, 2.5%, and 3.6% of patients during follow-up Years 1, 2, and 3, respectively (Table 4). Patients treated with dialysis (performed only as local outpatient specialist services) doubled throughout the follow-up (i.e., from five to 10 patients), while one patient underwent transplantation each year. The mean annual costs per patient treated with KRT were €18,742 in Year 1, €10,053 in Year 2, and €11,369 in Year 3 (Table 4).

At least one local outpatient specialist service (Table 5) was provided to 86.6% of patients during both Years 1 and 2 and to 84.7% of patients in Year 3. During Year 1, at least one laboratory test was performed for 76.4% of patients, 78.9% of whom had required urinalysis; at least one unspecified examination occurred for 53.8% of patients, 31.8% of whom were specifically visited by a nephrologist; only three patients (1%) received at least one steroid injection. Throughout the follow-up, the prevalence of local outpatient specialist care performance, other than dialysis treatments, did not differ much from the above findings.

The mean total annual direct healthcare costs per study patient were €7441 (including in-hospital costs at the index date), €3497, and €3243 in Years 1,2, and 3, respectively (Table 6). Hospitalizations formed the bulk of the mean total cost at Year 1 (72.6%) due to being the main identification criterion of the study cohort, then declined to 33.7%. Pharmacologic treatments accounted for 45.6% and 51.4% of the average total costs in Years 2 and 3, respectively, with other drugs as the leading cost drivers. The economic impact of local outpatient specialist care increased from 7.4% to 14.9% of the average total costs from Years 1 to 3.

TABLE 2 - The therapeutic approach to the study population of patients with a new potential identification of IgAN from 2016 to 2019, during the 3-year follow-up and by year of follow-up

Drugs recommended for treating IgAN	Patients treated (n; n/N%)		
	Follow-up Year 1 (N = 292)	Follow-up Year 2 (N = 283)	Follow-up Year 3 (N = 274)
At least one dispensation	262; 89.7	242; 85.5	230; 83.9
Angiotensin-converting enzyme inhibitors	184; 63.0	168; 59.4	154; 56.2
Corticosteroids for systemic use	170; 58.2	107; 37.8	90; 32.8
Oral therapy	166; 56.8	101; 35.7	88; 32.1
Intravenous therapy	10; 3.4	12; 4.2	8; 2.9
Angiotensin II receptor blockers	85; 29.1	85; 30.0	81; 29.6
Immunosuppressants	50; 17.1	52; 18.4	44; 16.1
Mycophenolic acid	24; 8.2	27; 9.5	21; 7.7
Ciclosporin	12; 4.1	11; 3.9	7; 2.6
Tacrolimus	9; 3.1	10; 3.5	10; 3.6
Azathioprine	8; 2.7	9; 3.2	5; 1.8
Methotrexate	4; 1.4	3; 1.1	3; 1.1
Everolimus	2; 0.7	2; 0.7	2; 0.7
Golimumab	2; 0.7	3; 1.1	2; 0.7
Belimumab	1; 0.3	3; 1.1	3; 1.1
Etanercept	1; 0.3	1; 0.4	1; 0.4
Vedolizumab	1; 0.3	–	1; 0.4
Thalidomide	1; 0.3	1; 0.4	–
Ustekinumab	1; 0.3	1; 0.4	1; 0.4
Certolizumab pegol	1; 0.3	1; 0.4	1; 0.4
Adalimumab	–	2; 0.7	1; 0.4
Lenalidomide	–	1; 0.4	1; 0.4
Sirolimus	–	–	1; 0.4
Sodium-glucose co-transporter 2 inhibitors	2; 0.7	2; 0.7	3; 1.1
Rituximab	–	2; 0.7	1; 0.4
Other agents acting on the renin-angiotensin system	1; 0.3	1; 0.4	1; 0.4

Discussion

This was an observational retrospective cohort study of a large Italian administrative healthcare database collecting data from over 5 million inhabitants, representing ~9% of the Italian population cared for by the SSN in real-world inpatient and outpatient settings. This is one of the very few published real-world analyses of patients potentially affected by IgAN (18). Most knowledge about the epidemiology and management of IgAN comes from studies of patients with biopsy-verified IgAN diagnosis, which is still the most used and recommended way of disease confirmation, especially in Western countries (1). However, reported incidence and prevalence rates of biopsy-verified IgAN are likely to be underestimated, as well as their economic and care burdens, and their comparison is often difficult when coming from different data sources, populations, geographical contexts, and health system organizations (3,18). IgAN is a highly variable disease for many reasons, including kidney biopsy policies that can vary across the country, both between regions and reference centers, which makes the definition of a true incidence challenging (2,3). This variability should be partly prevented in universal coverage healthcare systems, such as the SSN. However, the integration between findings that come from different data sources, including larger and heterogeneous population-based and cross-sectional studies, such as those of administrative healthcare databases, is necessary to improve the understanding of the real-world impact and unmet needs of patients potentially affected by IgAN.

This study found a possible mean annual incidence of 1.25/100,000 inhabitants in Italy across all age groups. This

TABLE 3 - Rates of overnight hospitalizations during the 3-year follow-up and by follow-up year. Causes of hospitalization were listed in descending order by the primary diagnosis in the hospital discharge form according to ICD-9-CM codes

Cause of overnight hospitalization	Patients hospitalized (n; n/N%)		
	Follow-up Year 1 (N = 292)	Follow-up Year 2 (N = 283)	Follow-up Year 3 (N = 274)
At least one overnight hospitalization	292; 100.0	58; 20.5	42; 15.3
Chronic renal failure	198; 67.8	17; 6.0	15; 5.5
Chronic glomerulonephritis	56; 19.2	1; 0.4	2; 0.7
Acute renal failure	22; 7.5	2; 0.7	2; 0.7
Diffuse diseases of connective tissue	8; 2.7	4; 1.4	3; 1.1
Purpura and other hemorrhagic conditions	7; 2.4	2; 0.7	–
Acute glomerulonephritis	8; 2.7	–	–

ICD-9-CM: international classification of diseases, ninth version, clinical modification.

TABLE 4 - Rates of performed kidney replacement therapies (i.e., hemodialysis, peritoneal dialysis, kidney transplantation) in terms of proportion of patients treated, and the mean cost per patient treated and per capita, during the 3 years of follow-up and by follow-up year

Kidney replacement therapy (KRT)	Patients (n; n/N%)	Mean cost per treated patient (€)	Mean cost per capita (€; % on total cost)
Follow-up Year 1 (N = 292)			
Hemodialysis	4; 1.4	12 911	177; 55.1
Peritoneal dialysis	1; 0.3	3 625	12; 3.7
Kidney transplantation	1; 0.3	38 441	132; 41.1
At least one KRT	5; 1.7	18 742	321; 100.0
Follow-up Year 2 (N = 283)			
Hemodialysis	6; 2.1	5 322	113; 45.4
Peritoneal dialysis	–	–	–
Kidney transplantation	1; 0.4	38 441	136; 54.6
At least one KRT	7; 2.5	10 053	249; 100.0
Follow-up Year 3 (N = 274)			
Hemodialysis	10; 8.2	7 401	270; 65.1
Peritoneal dialysis	–	–	–
Kidney transplantation	1; 0.4	39 684	145; 34.9
At least one KRT	10; 3.6	11 369	415; 100.0

incidence is slightly higher than the older (from 1996 to 2000) published annual national incidence in Italy of 0.84/100,000 (3) but closer to the most recent incidence found in a northeastern Italian adult population (mean age 50.4 ± 17.7 years) with native kidney biopsies of 1.22/100,000 (2,3,5). The incidence found in this study could be underestimated by the inclusion of only in-hospital kidney biopsies; nevertheless, despite the exclusion of outpatients, it was necessary to associate it with the in-hospital glomerulonephritis diagnosis and make the algorithm more accurate. An overestimation could also have occurred because some patients with other forms of primary and secondary glomerulonephritis could not be accurately excluded. Ultimately, the study cohort should be considered as mainly, but not necessarily exclusively, composed of patients affected by IgAN.

In line with reported evidence that, in Europe, males are twice more likely than females to develop IgAN (2,6) and that IgAN is more common in adults than in children (3,6,8), this study found a male:female ratio of 1.8:1, and a median age of 41 (27; 57) years at index date.

IgAN is associated with a shortened life in up to 40-50% of patients who progress to KF within 20 years from diagnosis or earlier (2,3,7,9,10). The most excess mortality risk emerges following KF (9,10). There is still an important knowledge

TABLE 5 - Rates of the most frequent performed local outpatient specialist services during the 3-year follow-up and by follow-up year, in descending order by main grouping of services

Local outpatient specialist service (main grouping)	Patients (n; n/N%)		
	Follow-up Year 1 (N = 292)	Follow-up Year 2 (N = 283)	Follow-up Year 3 (N = 274)
At least one outpatient specialist service	253; 86.6	245; 86.6	232; 84.7
Laboratory test	223; 76.4	220; 77.7	200; 73.0
Urinalysis	176; 60.3	173; 61.1	156; 56.9
Creatinine clearance	104; 35.6	100; 35.3	91; 33.2
Urine protein electrophoresis	7; 2.4	6; 2.1	6; 2.2
General visit	157; 53.8	170; 60.1	156; 56.9
Nephrological visit	50; 17.1	50; 17.7	57; 20.8
Diagnostic imaging – abdomen	44; 15.1	32; 11.3	48; 17.5
Electrocardiogram	35; 12.0	34; 12.0	34; 12.4
Circulatory system examination	28; 9.6	24; 8.5	21; 7.7
Diagnostic imaging – thorax	28; 9.6	28; 9.9	24; 8.8
Diagnostic imaging – lower limb	21; 7.2	20; 7.1	15; 5.5
Diagnostic imaging – cardiology	19; 6.5	18; 6.4	23; 8.4
Oculist examination	19; 6.5	22; 7.8	18; 6.6
Diagnostic imaging – musculoskeletal	17; 5.8	14; 4.9	15; 5.5
Ear, nose, and throat surgery	11; 3.8	7; 2.5	16; 5.8
Diagnostic - spinal column	9; 3.1	13; 4.6	18; 6.6

TABLE 6 - Average annual healthcare costs directly reimbursed by the Italian National Healthcare Service for the healthcare of each patient with a new potential identification of IgAN from 2016 to 2019, during the 3 years of follow-up and by follow-up year

Cost item	Per capita mean annual cost (€; % of total expenditure)		
	Follow-up Year 1 (N = 292)	Follow-up Year 2 (N = 283)	Follow-up Year 3 (N = 274)
Total expenditure	7441; 100.0	3497; 100.0	3243; 100.0
Pharmaceuticals	1492; 20.0	1596; 45.6	1668; 51.4
Drugs recommended for IgAN	547; 7.4	640; 18.3	716; 22.1
Other drugs	945; 12.7	956; 27.3	953; 29.4
Hospitalizations	5399; 72.6	1502; 43.0	1093; 33.7
Overnight hospitalization with kidney transplantation	132; 1.7	136; 3.9	145; 4.5
Overnight hospitalization without kidney transplantation	5116; 68.7	1310; 37.5	932; 28.7
Day hospitalizations	152; 2.0	57; 1.6	16; 0.5
Local outpatient specialist care	549; 7.4	398; 11.4	482; 14.9
Dialysis	189; 2.5	113; 3.2	270; 8.3
Other specialist services	360; 4.8	285; 8.2	212; 6.5

gap in mortality rates across different geographical areas (9). In Italy, specific studies on long-term mortality rates in IgAN patients are still lacking, as well as on the elderly who frequently have poorer prognosis because diagnosis occurs at advanced kidney disease (3,9). This study found a favorable survival rate at 3 years of 97.2%. By comparison, and despite different follow-up periods, the survival rates in Europe were 87.4% at 20 years in Norway, 91.3% at 10 years in Sweden, 93% at 1 year, and 84% at 5 years in Romania (9,25,26). The mean age of the eight patients who died for all causes

throughout the 3-year follow-up was 71.6 years, which is significantly older than survivors and is as expected (3,9,26).

Making a prognosis is also a challenge, both in children and in adults (4,27). Overall, among factors to be considered in the International IgAN Prediction Tool, older age and comorbidities affecting kidney function and being clearly associated with poor prognosis (i.e., obesity, proteinuria, arterial hypertension, dyslipidemia) are worth discussing within this study (2,10,27). As in this study, 19% of patients were 60 years and older, and arterial hypertension and dyslipidemia were found in 56% and 20%, respectively, at baseline. Given the young median age of the study cohort, we considered that these diseases, which are more frequently diagnosed in older people, could be evaluated following the IgAN identification. Indeed, a further analysis showed that rates of patients diagnosed with arterial hypertension and dyslipidemia from baseline throughout the follow-up were 87% and 34%, respectively. The same reasoning was applied for DM, which was found in 6.8% of patients at baseline and in 12.3% from baseline throughout the follow-up.

IgAN often comes with asymptomatic microscopic hematuria, but some symptomatic cases suffering from macroscopic hematuria present with upper respiratory tract infections or IBDs (i.e., celiac disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome), which are probably involved in the IgAN pathogenesis as well as part of the gastrointestinal complications reported by 17% of patients with IgAN in Europe (2). The following findings suggest evidence of this mucosa–kidney crosstalk: at baseline, 3% of patients were affected by IBD; throughout the follow-up, at least 15% of patients were treated with different systemic antibacterials that are frequently, but often inappropriately, prescribed by Italian practitioners to treat upper respiratory infections (28).

Over 50% of adult patients are diagnosed with CKD with more severe clinicopathology (e.g., high level of proteinuria, extensive tissue damage at biopsy) and may have worse outcomes than if diagnosis and treatment had started earlier (8). Moreover, up to 40–50% of patients who progress to KF within 20 years from diagnosis require KRT (8). Patients requiring KRT and their caregivers must face a worsening of QoL, daily living and ability to work, and a high risk of relapse after transplantation (1,29). The rate of patients treated with KRT found in this study was very low, though it doubled from Year 1 (1.7% of patients) to Year 3 (3.6%) (6,9). Without knowing the other baseline values useful to assess CKD stages, we cannot assess the timing of disease progression in these patients.

Screening and management strategies differ across countries and between regions and reference centers of the same country. The KDIGO guidelines make some standard recommendations for adult patients, which are also listed based on specific geographic conditions (4). Nevertheless, an update is required to include novel therapies and diagnostics, as well as a detailed pediatric section, since a missed diagnosis in childhood could mean a delayed diagnosis in adulthood (6).

Despite significant, but still incomplete, advances in understanding IgAN etiopathology, the therapy has not changed in the last 30 years, with very few targeted treatments variously authorized and used worldwide (13). The primary goal is to delay IgAN progression, which is typically addressed through SC. According to KDIGO guidelines (4), after the prognosis assessment, adults with biopsy-verified IgAN should receive SC. This includes RASIs (i.e., ACEIs and angiotensin receptor blockers [ARBs] as the most studied) (12) as much as can be tolerated or allowed, blood pressure control, cardiovascular risk minimization, and adherence to lifestyle advice. RASIs should be prescribed regardless of arterial hypertension when proteinuria is >0.5 g/day. ACEIs and ARBs were the most dispensed drugs received by the study patients (i.e., ≥56% and ≥29%, respectively) throughout follow-up. If proteinuria exceeds 0.75–1 g/day, despite at least 3 months of optimized SC, the risk of progressive loss of kidney function increases and may be treated with glucocorticoids for 6 months, or the patient may be recruited into a clinical trial. Notwithstanding, there is a need to limit both the dosage and duration of steroid treatments due to the imbalance between their effectiveness and safety, even in short-term usage (13). Although IgAN is an immune-mediated disease, immunosuppressive treatments are recommended only for its rapid-progressive forms and secondary to SC (11,13). The KDIGO guidelines, therefore, recommend special attention in prescribing immunotherapy when glomerular filtration rate (GFR) is <50 mL/min/1.73 m^2 and to avoid systemic corticosteroids in case of GFR <30 mL/min/1.73 m^2, DM, obesity, untreated latent infections, active peptic ulcer disease, severe osteoporosis, or uncontrolled psychiatric conditions (4,13). Systemic corticosteroids, mostly in oral formulations, were dispensed to 58% of patients during Year 1; this proportion was reduced by 25% in Year 3. Around 17% of the study cohort was treated with non-steroid immunosuppressive agents throughout follow-up.

Despite the available therapies, the possibility of refractory IgAN is not uncommon, though not explicitly stated by KDIGO guidelines (13). If proteinuria remains elevated, strategies for personalizing treatments of IgAN include the optimization of SC, increasing RASIs to the maximum tolerated dose, and adding sodium-glucose cotransporter-2 inhibitors (13,30). For patients at high risk of progression and if enrollment in a clinical trial is not possible, sparsentan, a dual endothelin-angiotensin receptor antagonist, and enteric-coated budesonide, a novel way of delivering corticosteroids to the terminal ileum, have been recently authorized by EMA and are dispensed in Italy under the SSN (14,15,30). Other promising experimental treatments that specifically target pathways or molecules implicated in the IgAN pathogenesis are under investigation as new treatments and are needed to treat patients at high risk of progression (13,31).

IgAN has been demonstrated as having a substantial humanistic and economic burden, though evidence on patients' healthcare resource utilization and costs is scarce and highly heterogeneous, making comparisons between studies very difficult (1,17,18,32). Notwithstanding, since many patients progress to KF within 20 years from diagnosis, a 3-year follow-up from the potential identification of IgAN is not enough to reliably appreciate the long-term burden of IgAN. Nevertheless, some findings deserve discussion in light of previously published evidence. This study found a

reduction of all elements of direct healthcare resource consumption except for dialysis procedures throughout follow-up, which is in line with some literature (1,18). Similar to the few published studies, overnight hospitalizations were the most common type of hospital admissions; specifically, our study cohort was identified by an in-hospital diagnosis of glomerulonephritis and biopsy procedure codes; therefore, inevitably, all patients were admitted to an overnight hospitalization in Year 1 (1,17,18). Moreover, low frequencies of day hospital and ED admissions found soon after the index date (8% and 31%, respectively, in Year 1) were reduced throughout follow-up (3% and 21%, respectively, in Year 3), which is similar to rates reported in China, where proportions of IgAN patients among hospitalized patients with primary glomerular nephropathy reduced from 19.0% in 2010 to 10.6% in 2015 (1,17).

As regards the direct economic burden, costs for hospitalizations decreased over the 3-year follow-up, but costs for local outpatient specialist care, especially dialysis, increased during follow-up, suggesting that, in Italy, the healthcare setting of IgAN patients move from hospitalization to day-care/local outpatient care centers, especially if they progress to higher CKD stages, as shown by Lerma et al. in the USA (17). As regards pharmaceuticals, the immunosuppressive drug cost for IgAN has been demonstrated not to change over time due to the constant high use of steroids, especially in the case of refractory IgAN (32). Conversely, our study reported a slight increase in the per capita mean annual expenditure for drugs recommended for IgAN, probably due to the use of high-cost recent biologic therapies (e.g., rituximab), but also arising from the potential progression of disease with time, as supposed by Lerma et al. (17). Also, costs for other drugs and in-hospital kidney transplantation increased, which could account for the progression to higher CKD stages throughout follow-up. Overall, the slightly higher costs for KRTs, despite little increase across the short timeframe of 3 years of observation, suggest that prevention and delay in progression to KF may lead to potential healthcare cost savings (32). Moreover, given the elevated burden that patients with refractory IgAN must face, it could be assumed that if health policy improves access to novel high-cost target therapies, this cost may be balanced not only by improved health-related (HR) QoL but also by significant direct healthcare cost savings (32).

The real-world evidence that includes administrative data has already been validated as support in guiding clinical decisions and the proper allocation of economic and professional resources, with the further aim of improving access to novel, efficient, and safe treatments earlier during the care pathway for chronic diseases (33,34). Similarly, findings from real-world evidence should be systematically used to reach the above aims for the management of rare diseases, such as IgAN, that need to be treated early to slow the decline in HRQoL and to prevent the progression to KF (35).

Strengths and limitations

The ReS database (~9% of the Italian population) has been considered representative of the whole Italian population because the SSN is a universal coverage health system. Hence, findings about new patients potentially affected by IgAN from the perspective of the SSN, which includes both real-world inpatient and outpatient settings, can be extrapolated to the whole Italian population. The universal coverage of the SSN should avoid any extreme differences between Italian regions, but it is worth considering the absence of a specific diagnosis code for IgAN and the potential different policies regulating the use of biopsy beyond genetic, environmental, socioeconomic, and geographical etiopathogenetic factors.

Clinical information (e.g., GFR or general practitioner examination) and findings from diagnostic tests (e.g., hematuria, proteinuria) are not collected in Italian administrative healthcare databases; therefore, CKD stages or IgAN severity cannot be described. It is, however, possible that the study cohort included patients with moderate or advanced CKD, based on the frequent late diagnosis across Europe through kidney biopsy (2). Information about blood pressure control, cardiovascular risk minimization, and adherence to lifestyle advice, as well as data on the out-of-pocket purchase of low-cost drugs (e.g., equivalent RASIs), are lacking. Moreover, only dialyzes performed in public hospitals or specialist settings or those affiliated with SSN could be evaluated; despite the higher performance of home dialysis, home therapy is not a consolidated or identifiable item within the administrative database. Moreover, the drugs that we have categorized as recommended for IgAN are not exclusive to IgAN and can be dispensed for other concomitant diseases; therefore, their consumption could be slightly overestimated.

Overall, despite the unavailability of a cross-linkage with non-healthcare and indirect healthcare information, these findings are key to integrating the sparse existing literature about the burden of IgAN in Italy.

Conclusions

Through this retrospective observational study of the ReS database, we have presented an algorithm based on administrative healthcare data for the identification of patients with a new potential diagnosis of IgAN throughout a 4-year accrual period. The demographics and clinical characteristics, the healthcare resource utilization, and direct costs of the study patients throughout a 3-year follow-up have been presented from the perspective of the SSN. Despite the unavailability of a record linkage with clinical databases and registries, a significant humanistic and economic burden of disease has been found. Together with the minimal published and heterogeneous literature, our findings highlight the need for health policymakers to integrate real-world evidence into guiding clinical decisions, allocating proper economic and professional resources, and improving early access to novel, efficient, and safe treatments. A future analysis of the ReS database with a longer follow-up and a potential cross-linkage with clinical data will be even more useful and crucial for real-world-evidence-based practices with a long-term and more comprehensive view.

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Disclosures

Conflict of interests: LB reports no conflict of interests with any financial organization regarding the material discussed in the manuscript. GLM reports no conflict of interests with any financial organization regarding the material discussed in the manuscript. LD, GR, SC, ID, Leonardo D, CP, and NM are employees of Fondazione ReS and report no conflict of interests with any financial organization regarding the material discussed in the manuscript. AA and IE serve as consultants for Fondazione ReS and report no conflict of interests with any financial organization regarding the material discussed in the manuscript.

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Ethics approval and consent to participate: This was a retrospective, cohort, observational study. Fully anonymized data were extracted from the administrative databases of Italian Regional/Local Health Authorities, owners of the data. National legislation and institutional requirements do not require for ethical approval and consent to participate in this study, according to European Regulations 2014/536 (13) and 2016/679 (14), as agreed by the regional/local authorities that own the data.

Data availability statement: The datasets analyzed during the current study are not publicly available and are not available from the corresponding author on reasonable request because they are owned by the Italian Regional/Local Health Authorities who have not authorized Fondazione ReS to make them available.

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