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ORIGINAL RESEARCH

Immunoglobulin A Nephropathy Associated with Systemic Disease: Clinical Spectrum and Long-Term Kidney Outcomes in a Single-Center Cohort*

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ABSTRACT

Immunoglobulin A nephropathy diagnosed in a patient who already has a chronic systemic illness is conventionally reported as secondary disease, although for most associations the evidence for causation is limited and the clinical course is poorly characterized. We examined which systemic diseases accompany the nephropathy and how far they relate to long-term outcome. We reviewed 46 adults with biopsy-proven immunoglobulin A nephropathy and a systemic disease documented at or before biopsy at a single center between 1992 and 2023, grouped as gastrointestinal/liver, infection, rheumatologic or malignancy. The primary outcome was kidney replacement therapy. Median age was 40 years and median follow-up 10 years. Psoriasis was the most frequent associated diagnosis (12 patients, 26.1%); no difference from the rest of the cohort could be demonstrated in presentation, histology or outcome (KRT 4/12 vs 11/34, p=1.000; composite outcome 7/12 vs 17/34, p=0.742), although with 12 patients these estimates are imprecise. Patients with malignancy had a much lower estimated glomerular filtration rate (29.0 vs 90.0 mL/min/1.73 m^2, p<0.001), more nephritic syndrome (90.0% vs 13.0%, p<0.001) and more crescents (40.0% vs 8.7%, p=0.053). Overall, 15 patients (32.6%) required KRT, 10 (21.7%) died and 24 (52.2%) met the composite outcome. The 10-year cumulative incidence of KRT was 65.0% in the malignancy group against 4.3% in the rheumatologic group (p=0.016). Patients with psoriasis did not show more favorable outcomes than the rest of the cohort, although the size of this subgroup precludes a firm conclusion; since these patients are followed largely outside nephrology, periodic urinalysis might be considered, a suggestion drawn from a small single-center cohort rather than from tested evidence. The worst outcomes occurred in older patients presenting with advanced kidney impairment, most of whom had a malignancy, a group that may warrant closer nephrological follow-up.

Keywords: Glomerulonephritis; IGA. Psoriasis. Neoplasms. Kidney Failure. Chronic. Prognosis.

Sistemik Hastalıkla İlişkili İmmünoglobulin A Nefropatisi: Tek Merkez Kohortunda Klinik Spektrum ve Uzun Dönem Böbrek Sonlanımları

ÖZET

Kronik sistemik hastalığı bulunan bir hastada saptanan immünoglobulin A nefropatisi geleneksel olarak sekonder hastalık olarak tanımlanmaktadır. Ancak bu birlikteliklerin çoğunda nedenselliği destekleyen kanıtlar sınırlıdır ve hastaların klinik seyri yeterince tanımlanmamıştır. IgA nefropatisine eşlik eden sistemik hastalıkların dağılımını ve bu hastalıkların uzun dönem böbrek sonlanımlarıyla ilişkisini değerlendirmeyi amaçladık. Tek merkezde 1992-2023 yılları arasında böbrek biyopsisi ile immünoglobulin A nefropatisi tanısı alan ve biyopsi sırasında veya öncesinde sistemik hastalığı belgelenmiş 46 erişkin hasta geriye dönük olarak incelendi. Hastalar gastrointestinal/karaciğer, enfeksiyon, romatolojik ve malignite gruplarına ayrıldı. Primer sonlanım renal replasman tedavisiydi (RRT). Median yaş 40 yıl, median izlem süresi 10 yıldı. Psoriazis en sık eşlik eden tanıydı (12 hasta, %26,1); psoriazisli hastalar ile kohortun geri kalanı arasında başvuru özellikleri, histolojik bulgular veya klinik sonlanımlar açısından istatistiksel olarak anlamlı bir farklılık gösterilemedi (RRT 4/12 vs 11/34, p=1,000; kompozit sonlanım 7/12 vs. 17/34, p=0,742); ancak 12 hastalık bir alt grupta bu tahminlerin kesinliği düşüktür. Malignitesi olan hastalar daha düşük eGFR (29,0 vs 90,0 mL/dk/1,73 m², p<0,001), daha sık nefritik sendrom (%90,0 vs %13,0, p<0,001) ve daha sık kresent (%40,0 vs %8,7, p=0,053) ile başvurdu. Kohortta 15 hastada (%32,6) RRT gereksinimi gelişti, 10 hasta (%21,7) öldü ve 24 hasta (%52,2) kompozit sonlanıma ulaştı. On yıllık RRT kümülatif insidansı malignite grubunda %65,0, romatolojik grupta %4,3 idi (p=0,016). Psoriazisli hastaların kohortun geri kalanına göre daha iyi bir seyir izlediği gösterilemedi, ancak bu alt grubun küçüklüğü kesin bir yorumu engellemektedir; büyük ölçüde nefroloji dışında izlenen bu hastalarda aralıklı tam idrar tetkiki düşünülebilir. Bu öneri, tek merkezli ve küçük bir kohortun gözlemlerine dayanmakta olup prospektif olarak sınanmamıştır. En kötü sonlanımlar, başvuruda ileri derecede böbrek işlev bozukluğu bulunan ileri yaştaki hastalarda gözlendi ve bu hastaların çoğunda malignite mevcuttu; bu hasta grubunun nefrolojik açıdan daha yakın izlenmesi uygun olabilir.

Anahtar Kelimeler: Glomerülonefrit, IgA. Psoriazis. Neoplaziler. Böbrek Yetmezliği, Kronik. Prognoz.

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IgA nephropathy (IgAN) is the most frequently diagnosed primary glomerulonephritis in most biopsy registries, and Turkey is no exception: in the TSN-GOLD registry it accounted for a quarter of all primary glomerular disease and its share rose steadily over a decade[1]. The disease is driven by mesangial deposition of galactose-deficient IgA1 immune complexes and subsequent complement activation[2]. Its natural history is protracted but far from benign, with a substantial minority of patients reaching kidney failure within one to two decades of biopsy[3,4], and risk at the time of biopsy can now be estimated from routine clinical variables and the Oxford score[5].

A separate and much less well-characterized group is made up of patients in whom mesangial IgA deposition is found while a chronic systemic illness is already present. Such biopsies are customarily reported as secondary IgAN. The list of implicated conditions is long and keeps growing: cirrhosis and other chronic liver disease, inflammatory bowel disease and coeliac disease, chronic viral and mycobacterial infection, psoriasis and the spondyloarthritides, and solid and hematologic cancers, to which drug-induced forms have recently been added[6]. Liver disease is generally regarded as the commonest cause, and glomerular IgA can be demonstrated in the majority of cirrhotic patients who undergo biopsy, usually without any clinical manifestation at all[7].

The term 'secondary' carries an implication that is rarely tested. It asserts that the systemic disease produced the glomerular lesion, yet for most of the associations the supporting evidence consists of case reports, and the observation that would settle the question — remission of the nephropathy once the underlying disease is treated — is documented only occasionally. Both IgAN and the diseases in question are common, so simple coincidence is a serious alternative explanation. This is why several authors now prefer IgA-associated or concomitant nephropathy as the safer label, reserving secondary for cases in which the temporal course is convincing[6]. The distinction has practical consequences. If the nephropathy is truly secondary, treatment of the systemic disease is the priority and immunosuppression aimed at the kidney may be unnecessary or harmful; if the two are merely concurrent, the patient should be managed as any other person with IgAN, with the proviso that the systemic illness constrains what can safely be given.

Two of the associations deserve particular attention. The first is psoriasis. Population-based work has shown that psoriasis carries an increased risk of glomerulonephritis and of chronic kidney disease, and that the risk rises with the severity of the skin disease and with psoriatic arthritis[8]; a cohort drawn from more than eleven million electronic records found that the specific glomerular disease for which psoriatic patients are at increased risk is IgA nephropathy[9]. A recent series of 90 patients with IgAN and psoriasis reported that severe skin disease was accompanied by lower eGFR, heavier proteinuria, more tubulointerstitial damage, and more extensive crescent formation[10]. Despite this, psoriasis is still often listed as a minor entry among the causes of secondary IgAN, well behind liver disease.

The second is malignancy. Paraneoplastic glomerular disease is dominated by membranous nephropathy in solid tumors and by minimal change disease in Hodgkin lymphoma; IgAN is reported far less often and mainly as isolated cases[11,12]. Where it does occur, the accepted principle is that the glomerular lesion follows the tumor, so that treatment should be directed at the cancer and the kidney outcome depends on how well the tumor can be controlled[11]. Long-term outcome data for patients with concomitant IgAN and malignancy remain limited.

What is largely missing from the literature is information on how these patients actually fare. Series are small, follow-up is short, and we are not aware of a study that compares kidney outcomes across the different categories of associated disease within one cohort. We therefore reviewed nearly three decades of experience at our center with three aims: to establish which systemic diseases accompany IgAN in an unselected Turkish referral population; to compare the four main etiologic categories, and psoriasis in particular, with respect to presentation and long-term outcome; and to identify predictors of kidney failure and death.

Materials and Methods

Study Design and Patients

This was a retrospective observational cohort study conducted at a tertiary nephrology referral center. The departmental kidney biopsy archive was searched for all native biopsies reported between January 1992 and December 2023 in which mesangial IgA was the dominant or co-dominant immunoglobulin on immunofluorescence. Adults aged 18 years or over were eligible if a chronic systemic disease had been diagnosed before, or at the time of, the kidney biopsy. Patients with IgA vasculitis (Henoch-Schönlein purpura), lupus nephritis, or a biopsy in which another glomerular lesion accounted for the clinical picture were not included, nor were patients whose records did not allow follow-up beyond the biopsy. Forty-six patients met these criteria.

The study was approved by the Bursa Uludağ University Clinical Research Ethics Committee (decision number 2023-27/37, dated 12 December 2023) and was conducted in accordance with the Declaration of Helsinki. Because of the retrospective design and the fact that a number of patients had died or been lost to follow-up, the committee waived the requirement for individual informed consent.

Definitions and Variables

Demographic, clinical, laboratory, and histological data were abstracted from hospital records and biopsy reports by two of the investigators. Associated systemic diseases were assigned to one of four categories: gastrointestinal/liver disease, infection, rheumatologic or autoinflammatory disease, and malignancy. Where a patient carried more than one qualifying diagnosis, the condition judged clinically dominant at the time of biopsy determined the category. Clinical dominance was decided by consensus between two of the investigators from the hospital record, the disease that was active and under treatment at the time of biopsy, and to which the patient's systemic symptoms were attributable, being preferred to one that was quiescent, in long-standing remission, or an incidental comorbidity; where an active malignancy coexisted with a chronic rheumatologic disease, the malignancy was taken as dominant. Three patients with psoriasis were classified under another diagnosis on this basis and are identified in the footnote to Table II. Throughout this report the systemic illness is described as associated with the nephropathy rather than as its cause, and the term secondary is used only where the conventional nomenclature, or the usage of other authors, is being referred to. The individual diagnoses making up each category are listed in Table II.

Table I. Baseline characteristics and outcomes of the whole cohort.

Variable	All patients (n = 46)
Age at diagnosis, years	40.0 (31.0–48.0)
Male sex	25 (54.3)
Follow-up, years	10.0 (6.0–19.5)
Category of associated systemic disease	
Rheumatologic/autoinflammatory	23 (50.0)
Malignancy	10 (21.7)
Infection	7 (15.2)
Gastrointestinal/liver	6 (13.0)
Psoriasis (commonest single associated diagnosis)*	12 (26.1)
Clinical presentation	
Isolated hematuria	6 (13.0)
Non-nephrotic proteinuria with hematuria	20 (43.5)
Nephritic syndrome	15 (32.6)
Nephrotic syndrome	5 (10.9)
Hematuria (any)	46 (100)
Elevated serum IgA	11 (23.9)
Low serum C3	4 (8.7)
Mesangial C3 deposition on biopsy	16 (34.8)
Crescents on biopsy	8 (17.4)
Laboratory findings at diagnosis	
Serum albumin, g/dL	3.9 (3.5–4.1)
Proteinuria, mg/day	1467.5 (987.5–3218.0)
Proteinuria ≥ 3.5 g/day	8 (17.4)
Serum creatinine, mg/dL	1.2 (0.9–1.8)
eGFR, mL/min/1.73 m²	62.5 (40.8–92.2)
CKD stage at diagnosis	
Stage 1	13 (28.3)
Stage 2	11 (23.9)
Stage 3a	8 (17.4)
Stage 3b	8 (17.4)
Stage 4	2 (4.3)
Stage 5	4 (8.7)
Immunosuppressive treatment	
None	16 (34.8)
Directed at IgA nephropathy	23 (50.0)
Directed at the associated disease only	7 (15.2)
Outcomes	
Kidney replacement therapy	15 (32.6)
Maintenance dialysis	12 (26.1)
Kidney transplantation	3 (6.5)
≥ 50% decline in eGFR	17 (37.0)
Death (any cause)	10 (21.7)
Composite outcome	24 (52.2)

Values are median (interquartile range) or n (%). CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate. The composite outcome comprises kidney replacement therapy, a ≥ 50% decline in eGFR, or death. * Psoriasis is shown separately because it was the commonest single associated diagnosis; 11 of these patients fall within the rheumatologic category and 1 within the malignancy category, so this row overlaps with the categories above.

Table II. Systemic diagnoses within each etiologic category.

Category and diagnosis	n
Rheumatologic/autoinflammatory (n = 23)	
Psoriasis or psoriatic arthritis*	9
Ankylosing spondylitis	4
Spondyloarthritis, unclassified	2
Behçet disease†	2
Familial Mediterranean fever†	2
Rheumatoid arthritis	2
Gout	1
Reactive arthritis	1
Malignancy (n = 10)	
Breast carcinoma	2
Lung carcinoma	2
Laryngeal squamous cell carcinoma	1
Gastric carcinoma†	1
Bladder carcinoma	1
Prostate carcinoma	1
Renal cell carcinoma	1
Hodgkin lymphoma	1
Infection (n = 7)	
Chronic hepatitis B	3
Tuberculosis (pulmonary and nodal, urinary, other)	3
Infective endocarditis	1
Gastrointestinal/liver (n = 6)	
Liver cirrhosis (alcohol-related, hepatitis B-related, other)‡	3
Ulcerative colitis	1
Crohn disease	1
Chronic pancreatitis	1

Each patient is listed once, under the diagnosis judged clinically dominant at biopsy, so the psoriasis row does not capture every patient with psoriasis. Psoriasis was present in 12 patients (26.1% of the cohort) in all: the 9 in the psoriasis row (cutaneous psoriasis in 6, psoriatic arthritis in 3), 2 of the 3 patients marked † in the rheumatologic category (1 with Behçet disease and 1 with familial Mediterranean fever), and the 1 patient marked † in the malignancy category. Eleven of the 12 therefore fall within the rheumatologic category and 1 within the malignancy category. ‡ One of the three patients with cirrhosis was hepatitis B surface antigen positive.

Clinical presentation at biopsy was classified as isolated hematuria, non-nephrotic proteinuria with hematuria, nephritic syndrome, or nephrotic syndrome. Nephritic syndrome was defined as hematuria together with an acute or subacute loss of eGFR relative to the patient's baseline value, not attributable to another cause, and commonly accompanied by hypertension, edema, or oliguria. All 15 patients classified as nephritic had an eGFR below 60 mL/min/1.73 m² at biopsy (median 33.0). The category was assigned on the combination of hematuria with this loss of eGFR rather than on the degree of proteinuria, which varied widely in these patients. Nephrotic syndrome required proteinuria of 3.5 g/day or more with hypoalbuminemia and edema. Patients fulfilling the criteria for both a nephritic and a nephrotic presentation were classified as nephritic. Serum IgA and C3 were recorded as normal or abnormal according to the reference range of the laboratory at the time of measurement. Mesangial C3 deposition and the presence of crescents were taken from the original pathology report. Biopsies were reported by pathologists of our institution at the time of the procedure, according to the practice prevailing in that period; specimens were not retrieved and re-read by a single pathologist or by a central pathology committee for the purposes of this study, and no slides were re-scored. The Oxford (MEST-C) classification was consequently not applied systematically. It postdates a substantial part of the recruitment period and was not reported for the earlier biopsies, so M, E, S, T and C scores were not available for the cohort as a whole and could not be analyzed; crescents were therefore recorded only as present or absent, without the proportion of glomeruli involved.

Serum creatinine values recorded at biopsy and at last follow-up were used to recalculate the estimated GFR for all patients with the 2021 CKD-EPI creatinine equation, and CKD was staged by the KDIGO criteria. Proteinuria was expressed as mg per day. Renin-angiotensin system (RAS) blockade with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker was given as supportive treatment from the time of diagnosis to 42 of the 46 patients. RAS blockade was not initiated in the remaining four patients, all of whom had very advanced kidney dysfunction at biopsy. Its absence was therefore strongly associated with the severity of kidney dysfunction at presentation, making any association between RAS blockade and outcome highly susceptible to confounding by indication; RAS blockade was accordingly not examined as a determinant of outcome. Immunosuppressive treatment was categorized as none, treatment directed at the IgA nephropathy, or treatment given for the associated disease alone, and the individual agents used were recorded. The eGFR slope was calculated as the difference between the last and the baseline eGFR divided by the duration of follow-up in years.

Outcomes

The primary outcome was kidney replacement therapy (KRT), defined as the start of maintenance dialysis or pre-emptive kidney transplantation. Secondary outcomes were a decline of 50% or more from the baseline eGFR, death from any cause, and a composite of KRT, a ≥ 50% eGFR decline, and death. Follow-up ran from the date of biopsy to the last recorded clinic visit, death, or the start of KRT. In the three patients who underwent transplantation, the final eGFR reflects graft rather than native kidney function; these values were therefore excluded from analyses of native kidney function, while the patients themselves were counted as having reached the KRT endpoint.

Statistical Analysis

Normality was assessed with the Shapiro–Wilk test. Continuous variables are reported as median with interquartile range and were compared across the four categories of associated systemic disease with the Kruskal–Wallis test, and between patients with and without psoriasis with the Mann–Whitney U test. Categorical variables are given as counts with percentages and were compared with the Fisher–Freeman–Halton exact test, as appropriate for the small cell counts. For the comparison of patients with and without psoriasis, absolute risk differences are reported with 95% confidence intervals calculated by the Newcombe hybrid score method. To examine whether secular change across the recruitment period had influenced the findings, biopsies performed in 1992–2007 and in 2008–2023 were compared with the same tests (Table IV).

Because 10 of the 46 patients died, death was treated as a competing risk for kidney replacement therapy (KRT). The cumulative incidence of KRT was estimated with the Aalen–Johansen estimator, treating death before KRT as a competing event, rather than by one minus the Kaplan–Meier estimate. Differences between cumulative incidence functions were assessed with the Gray test. Cause-specific Cox proportional hazards models, with deaths censored, were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for KRT and for death. Hazard ratios for continuous predictors are expressed per clinically meaningful unit: per 1 g/dL decrease in serum albumin, per 10 mL/min/1.73 m² decrease in baseline eGFR, and per 10-year increase in age.

Multivariable models were kept deliberately small. Only 15 KRT events and 10 deaths occurred, and no death occurred in the infection group, so a four-level term for the associated disease would not converge in the mortality model. The rheumatologic and infection groups were therefore pooled as the reference category, and separate terms were fitted for malignancy and for gastrointestinal/liver disease. This pooling was driven by the observed event distribution rather than specified in advance. Neither multivariable model is intended as a prediction model or as confounder-adjusted definitive inference; with 15 KRT events and 10 deaths both are exploratory, and they are presented to show how the univariable estimates behave under minimal adjustment rather than to establish independent effects. Each model contained the two disease terms together with one additional predictor, so that three coefficients were estimated from 15 KRT events and from 10 deaths, giving 5.0 and 3.3 events per parameter respectively, well below the commonly cited rule-of-thumb of approximately 10 events per parameter. Crescents were chosen for KRT and proteinuria of 3.5 g/day or more for death because both are histological or clinical features that are not themselves part of the definition of the disease categories. Baseline eGFR, although a strong univariable predictor, differed by a factor of three across the categories and was therefore treated as collinear with the group term rather than as an adjustable confounder; a sensitivity model substituting baseline eGFR for crescents is reported alongside the main model.

All analyses were performed in R version 4.5.2 within RStudio, using the survival, cmprsk and ggplot2 packages. Two-sided p values below 0.05 were considered significant.

Results

Cohort Characteristics

Forty-six patients were included. The median age at biopsy was 40 years (31.0-48.0), 25 (54.3%) were men, and the median follow-up was 10.0 years (6.0-19.5). Rheumatologic and autoinflammatory conditions made up half the cohort (23 patients, 50.0%). Within that category, and indeed within the cohort as a whole, psoriasis in its cutaneous or arthropathic form was by far the commonest single diagnosis: 12 patients (26.1% of the cohort) had psoriasis, 11 of them in the rheumatologic category and one in the malignancy category. Malignancy was next (10, 21.7%), followed by chronic infection (7, 15.2%) and gastrointestinal or liver disease (6, 13.0%). Full characteristics are shown in Table I.

Hematuria was present in every patient. The commonest presentation was non-nephrotic proteinuria with hematuria (20, 43.5%), followed by a nephritic syndrome (15, 32.6%); only 5 patients (10.9%) presented with nephrotic syndrome. Median proteinuria at biopsy was 1467.5 mg/day (987.5-3218.0) and 8 patients (17.4%) had proteinuria of 3.5 g/day or more. Median eGFR was 62.5 mL/min/1.73 m² (40.8-92.2), and 22 patients (47.8%) already had stage 3 or worse CKD when the diagnosis was made.

Serum IgA was raised in only 11 patients (23.9%) and serum C3 was low in 4 (8.7%). Mesangial C3 deposition was reported in 16 biopsies (34.8%) and crescents in 8 (17.4%). Forty-two of the 46 patients (91.3%) received RAS blockade; the four who did not receive it had an eGFR of 4, 6, 11 and 15 mL/min/1.73 m² at biopsy, three of them had a malignancy and one psoriasis, and all four reached kidney replacement therapy. Twenty-three patients (50.0%) received immunosuppression intended for the nephropathy, 7 (15.2%) were treated for the associated disease only, and 16 (34.8%) received no immunosuppression at all. Among the 23 treated for the nephropathy the agents were recorded in 22: corticosteroids were given to 21, alone in 10 patients and combined with cyclophosphamide in 4, with

mycophenolate mofetil or azathioprine in 3, with a calcineurin inhibitor in 1, and with two or more further agents in 3; the remaining patient received mycophenolate mofetil without corticosteroids. Across the whole cohort mycophenolate mofetil or azathioprine was used in 7 patients, cyclophosphamide in 6, and a calcineurin inhibitor in 3. The proportion given immunosuppression for the nephropathy did not differ between the four categories of associated disease (p = 0.518), although the agents chosen did: cyclophosphamide was used in 3 of the 7 treated patients with malignancy, consistent with their nephritic presentation and advanced kidney impairment at biopsy, against 2 of the 11 treated patients in the rheumatologic group. In each of the three it was given for rapidly progressive nephropathy and could not be continued beyond one or two pulses because of the malignancy.

Table III. Presentation and outcomes according to the category of associated systemic disease.

Variable	Gastrointestinal/liver (n = 6)	Infection (n = 7)	Rheumatologic (n = 23)	Malignancy (n = 10)	p
Age at diagnosis, years	44.5 (41.8–58.5)	31.0 (30.5–43.0)	38.0 (29.5–44.0)	53.5 (44.2–60.2)	0.044
Male sex	5 (83.3)	4 (57.1)	11 (47.8)	5 (50.0)	0.484
Follow-up, years	8.5 (6.5–9.8)	18.0 (11.0–26.0)	15.0 (8.5–20.0)	5.0 (3.2–7.5)	0.017
Serum albumin, g/dL	3.6 (2.5–3.9)	4.3 (3.9–4.5)	3.9 (3.6–4.1)	3.7 (3.5–4.0)	0.073
Proteinuria, mg/day	2450 (1485–3213)	1090 (1040–2150)	1250 (830–2650)	2608 (1295–4375)	0.364
Proteinuria ≥ 3.5 g/day	1 (16.7)	0 (0.0)	3 (13.0)	4 (40.0)	0.163
Serum creatinine, mg/dL	1.7 (1.3–1.8)	1.2 (1.0–1.4)	1.0 (0.8–1.2)	2.4 (1.6–4.1)	0.002
eGFR, mL/min/1.73 m²	47.0 (44.2–55.0)	83.0 (57.0–85.5)	90.0 (58.0–107.0)	29.0 (13.2–41.8)	< 0.001
CKD stage ≥ 3	5 (83.3)	2 (28.6)	6 (26.1)	9 (90.0)	< 0.001
Nephritic syndrome at presentation	2 (33.3)	1 (14.3)	3 (13.0)	9 (90.0)	< 0.001
Crescents on biopsy	2 (33.3)	0 (0.0)	2 (8.7)	4 (40.0)	0.053
Elevated serum IgA	1 (16.7)	2 (28.6)	7 (30.4)	1 (10.0)	0.670
Mesangial C3 deposition	3 (50.0)	1 (14.3)	10 (43.5)	2 (20.0)	0.358
Immunosuppression for IgA nephropathy	2 (33.3)	3 (42.9)	11 (47.8)	7 (70.0)	0.518
Kidney replacement therapy	2 (33.3)	2 (28.6)	4 (17.4)	7 (70.0)	0.030
Death (any cause)	3 (50.0)	0 (0.0)	2 (8.7)	5 (50.0)	0.006
Composite outcome	4 (66.7)	2 (28.6)	10 (43.5)	8 (80.0)	0.123

Values are median (interquartile range) or n (%). p values are from the Kruskal-Wallis test for continuous variables and from the Fisher–Freeman–Halton exact test for categorical variables. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Table IV. Baseline characteristics and outcomes according to the calendar period of biopsy.

Variable	1992–2007 (n = 18)	2008–2023 (n = 28)	p
Age at diagnosis, years	32.0 (26.8–40.5)	45.0 (37.2–56.2)	0.005
Male sex	8 (44.4)	17 (60.7)	0.367
Follow-up, years	20.5 (12.0–23.8)	8.0 (5.0–13.2)	< 0.001
Category of associated systemic disease			**0.250**
Rheumatologic/autoinflammatory	8 (44.4)	15 (53.6)	
Malignancy	4 (22.2)	6 (21.4)	
Infection	5 (27.8)	2 (7.1)	
Gastrointestinal/liver	1 (5.6)	5 (17.9)	
Psoriasis	3 (16.7)	9 (32.1)	0.315
Serum albumin, g/dL	4.0 (3.8–4.5)	3.8 (3.4–3.9)	0.019
Proteinuria, mg/day	1160 (380–2950)	1875 (1098–3288)	0.065
Proteinuria ≥ 3.5 g/day	3 (16.7)	5 (17.9)	1.000
Serum creatinine, mg/dL	1.1 (0.9–1.6)	1.3 (1.0–1.9)	0.245
eGFR, mL/min/1.73 m²	85.5 (48.2–97.2)	54.5 (39.5–84.2)	0.173
CKD stage ≥ 3	6 (33.3)	16 (57.1)	0.140
Nephritic syndrome at presentation	5 (27.8)	10 (35.7)	0.749
Isolated hematuria at presentation	5 (27.8)	1 (3.6)	0.028
Crescents on biopsy	3 (16.7)	5 (17.9)	1.000
Mesangial C3 deposition	6 (33.3)	10 (35.7)	1.000
Elevated serum IgA	7 (38.9)	4 (14.3)	0.080
RAS blockade	16 (88.9)	26 (92.9)	0.639
Immunosuppression for IgA nephropathy	8 (44.4)	15 (53.6)	0.763
Kidney replacement therapy	6 (33.3)	9 (32.1)	1.000
Death (any cause)	5 (27.8)	5 (17.9)	0.480
Composite outcome	9 (50.0)	15 (53.6)	1.000

Values are median (interquartile range) or n (%). p values are from the Mann–Whitney U test for continuous variables, from the Fisher exact test for binary variables, and from the Fisher–Freeman–Halton exact test for the 4 × 2 comparison of disease categories. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate. All eGFR values were recalculated from the recorded serum creatinine with the 2021 CKD-EPI equation, so kidney function is expressed on the same scale in both periods.

Biopsies were divided into 18 (39.1%) performed in 1992–2007 (earliest 1994) and 28 (60.9%) in 2008–2023 (Table IV). Patients biopsied in the later period were older (median 45.0 vs 32.0 years, p = 0.005) and had a slightly lower serum albumin (3.8 vs 4.0 g/dL, p = 0.019), and their follow-up was necessarily shorter (8.0 vs 20.5 years, p < 0.001). Isolated hematuria as the presenting picture was largely confined to the earlier period (5 of 18 vs 1 of 28). The distribution of the four categories of associated disease, the frequency of crescents (16.7% vs 17.9%), of proteinuria ≥ 3.5 g/day, of mesangial C3 deposition, the proportion given immunosuppression for the nephropathy, and the rates of KRT (33.3% vs 32.1%) and of death did not differ appreciably between the two periods (all p > 0.1).

Patients With Psoriasis

Psoriasis was the commonest single associated diagnosis in the cohort. No difference could be

demonstrated between these 12 patients and the remaining 34 in their presentation (nephritic syndrome 25.0% vs 35.3%, p = 0.723), in baseline eGFR (78.0 vs 59.5 mL/min/1.73 m², p = 0.745), in proteinuria (1577.5 vs 1340.0 mg/day, p = 0.812), in the frequency of crescents (8.3% vs 20.6%, p = 0.660), of an elevated serum IgA (33.3% vs 20.6%, p = 0.441) or of mesangial C3 deposition (41.7% vs 32.4%, p = 0.726), or in the treatment they received (immunosuppression for the nephropathy 41.7% vs 52.9%, p = 0.738). Their outcomes were also similar: 4 (33.3%) reached KRT against 11 of 34 (32.4%, p = 1.000), and 7 (58.3%) against 17 (50.0%, p = 0.742) met the composite outcome. Three of the four patients in the rheumatologic category who progressed to KRT had psoriasis. With only 12 patients with psoriasis these estimates are imprecise. The absolute risk difference was +1.0 percentage point for KRT (95% CI −24.8 to +31.6) and +8.3 percentage points for the composite outcome (95% CI −22.5 to +35.8). These wide confidence intervals do not exclude clinically meaningful differences in either direction, so what the comparisons show is that no difference could be demonstrated, not that the two groups are alike; the figures are presented as descriptive only.

Differences Between Categories of Associated Disease

The four groups differed considerably at presentation (Table III). Patients with malignancy were the oldest (median 53.5 years) and those with infection the youngest (31.0 years, p = 0.044). The gradient in kidney function was steeper still: median eGFR was 29.0 mL/min/1.73 m² in the malignancy group and 47.0 in the gastrointestinal/liver group, against 83.0 and 90.0 in the infection and rheumatologic groups respectively (p < 0.001), and stage 3 or worse CKD was present in 9 of 10 patients with malignancy compared with 6 of 23 with rheumatologic disease (p < 0.001). Nine of the 10 patients in the malignancy group presented with a nephritic syndrome, against 3 of 23 in the rheumatologic group (p < 0.001), and crescents were numerically more frequent in the malignancy group (40.0% vs 8.7% in the rheumatologic group, p = 0.053).

Serological and immunofluorescence findings, by contrast, did not separate the groups. Neither an elevated serum IgA (p = 0.670) nor mesangial C3 deposition (p = 0.358) differed significantly between categories, and the proportion of patients given immunosuppression for the nephropathy was similar throughout (p = 0.518). Median follow-up was shortest in the malignancy group (5.0 years) and longest in the infection group (18.0 years, p = 0.017).

Kidney Outcomes

Fifteen patients (32.6%) reached KRT — 12 started maintenance dialysis and 3 were transplanted — at a median of 8 years from biopsy. Seventeen (37.0%) had an eGFR decline of at least 50%, and 24 (52.2%) met the composite outcome. The median eGFR slope for the cohort was −1.5 mL/min/1.73 m² per year (−3.8 to 0.1).

With death treated as a competing risk, the cumulative incidence of KRT for the whole cohort was 13.2% at 5 years and 18.1% at 10 years, but the average conceals a wide spread between the groups (Figure 1). At 10 years the cumulative incidence was 4.3% in the rheumatologic group and 0% in the infection group, against 16.7% in the gastrointestinal/liver group and 65.0% in the malignancy group (Gray test p = 0.016). Accounting for death changed these estimates materially only in the malignancy group, where one minus the Kaplan-Meier estimate would have given 70.8% rather than 65.0%. Crescents and heavy proteinuria separated the curves equally clearly: the 10-year cumulative incidence of KRT was 50.0% with crescents against 11.1% without (p = 0.002), and 62.5% with proteinuria of 3.5 g/day or more against 8.4% below that threshold (p < 0.001) (Figures 2a and 2b). These long-term estimates rest on very few patients and the tails of the curves are correspondingly unstable: in Figure 1 only 2 patients with gastrointestinal/liver disease and 2 with malignancy were still at risk at 10 years, and none of the former beyond 15 years, while in Figure 2 only 2 patients with crescents and 1 patient with proteinuria ≥ 3.5 g/day remained at risk at 15 years.

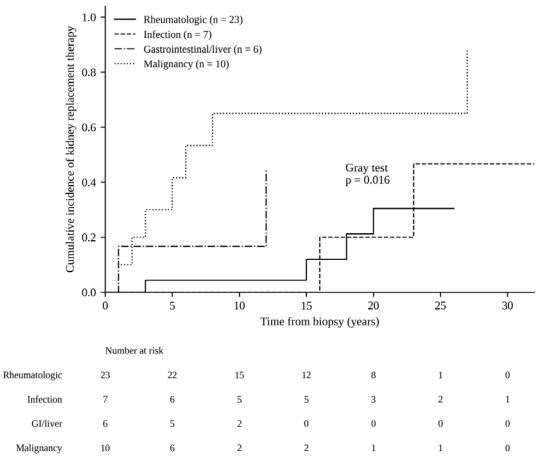


Figure 1:

Cumulative incidence of kidney replacement therapy according to the category of associated systemic disease, estimated with death treated as a competing risk. Differences between cumulative incidence functions were assessed with the Gray test. Numbers at risk are given below the horizontal axis. Estimates toward the end of follow-up rest on very few patients at risk, particularly in the smaller categories: no patient with gastrointestinal/liver disease remained at risk beyond 15 years and only one patient with malignancy beyond 20 years, so the later parts of these curves should be interpreted with caution.

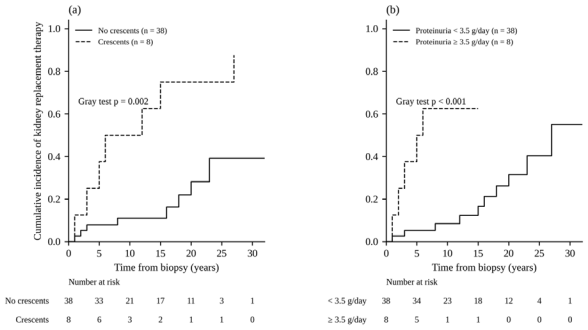


Figure 2:

Cumulative incidence of kidney replacement therapy, with death treated as a competing risk, according to (a) the presence of crescents on the diagnostic biopsy and (b) proteinuria of 3.5 g/day or more at diagnosis. Numbers at risk are given below the horizontal axis. As in Figure 1, few patients remained at risk in the later years — 2 patients with crescents and 1 patient with proteinuria ≥ 3.5 g/day at 15 years — and the corresponding parts of the curves are imprecise.

On univariable cause-specific Cox regression (Table V), crescents carried a hazard ratio of 5.69 (2.01-16.12) and proteinuria ≥ 3.5 g/day one of 8.50 (2.36-30.64). Each 1 g/dL fall in serum albumin was associated with an HR of 4.12 (1.96-8.67) and each 10 mL/min/1.73 m² fall in baseline eGFR with an HR of 1.38 (1.14-1.66). Taking the rheumatologic and infection groups together as reference, malignancy carried an HR of 6.51 (2.11-20.06) and gastrointestinal/liver disease one of 4.39 (0.79-24.29). In the exploratory multivariable model no term reached statistical significance: the HR for malignancy fell to 3.57 (0.80-15.90) and that for crescents to 2.48 (0.62-9.95). With 15 events this model is underpowered, and the loss of significance should not be read as evidence of no effect. In a sensitivity model in which baseline eGFR replaced crescents (Model B, Table V), eGFR itself remained associated with KRT (HR 1.28 per 10 mL/min/1.73 m² lower, 1.01-1.62) while the term for malignancy fell further, to 2.16 (0.50-9.26) — the behavior expected when a covariate that largely defines the difference between the groups is entered alongside the group term.

Mortality

Ten patients (21.7%) died during follow-up. Deaths were concentrated in two groups: 5 of the 10 patients with malignancy and 3 of the 6 with liver or gastrointestinal disease died, against 2 of 23 in the rheumatologic group and none in the infection group (p = 0.009). On univariable analysis (Table VI), proteinuria ≥ 3.5 g/day (HR 11.03, 2.85-42.78), crescents (4.48, 1.25-16.04), lower serum albumin, and lower baseline eGFR were all associated with death, as were malignancy (15.61, 2.94-82.98) and gastrointestinal/liver disease (11.70, 1.84-74.21) relative to the pooled reference. All three terms retained large point estimates in the multivariable model — proteinuria ≥ 3.5 g/day 14.76 (2.36-92.09), gastrointestinal/liver disease 23.44 (2.92-188.29), and malignancy 9.76 (1.62-58.79) — but with 10 deaths and a reference category containing only 2 of them, the confidence intervals span more than an order of magnitude. These estimates indicate the direction of an association and should not be read as independent effects.

Table V. Predictors of kidney replacement therapy.

Variable	No KRT (n = 31)	KRT (n = 15)	Univariable HR (95% CI); p	Model A HR (95% CI); p	Model B HR (95% CI); p
Crescents on biopsy	1 (3.2)	7 (46.7)	5.69 (2.01–16.12); 0.001	2.48 (0.62–9.95); 0.201	—
Baseline eGFR, mL/min/1.73 m²‡	78 (50–97)	43 (20–64)	1.38 (1.14–1.66); < 0.001	—	1.28 (1.01–1.62); 0.039
Proteinuria ≥ 3.5 g/day	3 (9.7)	5 (33.3)	8.50 (2.36–30.64); 0.001	—	—
Serum albumin, g/dL†	3.9 (3.8–4.3)	3.6 (3.1–4.0)	4.12 (1.96–8.67); < 0.001	—	—
Age, years§	39 (31–46)	45 (32–56)	1.51 (0.99–2.30); 0.054	—	—
Male sex	16 (51.6)	9 (60.0)	2.17 (0.71–6.63); 0.175	—	—
Mesangial C3 deposition	9 (29.0)	7 (46.7)	1.95 (0.68–5.58); 0.211	—	—
Associated disease category¶					
Malignancy	3 (9.7)	7 (46.7)	6.51 (2.11–20.06); 0.001	3.57 (0.80–15.90); 0.095	2.16 (0.50–9.26); 0.299
Gastrointestinal/liver	4 (12.9)	2 (13.3)	4.39 (0.79–24.29); 0.090	3.08 (0.51–18.60); 0.219	2.51 (0.45–13.98); 0.295

Values in the descriptive columns are median (interquartile range) or n (%). Hazard ratios are from cause-specific Cox models in which deaths were treated as censoring events. Model A contained malignancy, gastrointestinal/liver disease and crescents; Model B was a sensitivity analysis in which baseline eGFR replaced crescents. Both models are exploratory. CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; KRT: kidney replacement therapy. † HR expressed per 1 g/dL decrease. ‡ HR expressed per 10 mL/min/1.73 m² decrease. § HR expressed per 10-year increase. ¶ Reference category comprises the rheumatologic and infection groups combined; these were pooled because no death occurred in the infection group and a four-level term would not converge in the mortality model, and the same specification was retained here for consistency.

Discussion and Conclusion

Two findings stand out from this cohort. Psoriasis, rather than liver disease, was the systemic illness most often found alongside IgA nephropathy, accounting for a quarter of the series. Malignancy, which comprised a fifth of the cohort, was associated with the poorest kidney and patient outcomes. Over a median follow-up of ten years, half of the cohort reached the composite endpoint and one-third required

kidney replacement therapy, indicating a substantial long-term disease burden in patients with systemic disease-associated IgAN. All-cause mortality was 21.7%, higher than that reported in a single-center primary IgAN cohort with comparable follow-up[13], although differences in age and associated disease burden preclude direct comparison. A propensity-matched Romanian series that posed the same associated-or-secondary question reported a closely similar mortality of 19% in its secondary group, against 3% in primary disease, while the composite kidney endpoint did not differ significantly between the two[14]; our figures are consistent with that pattern. The composition of the two cohorts differs, however: theirs was dominated by chronic hepatitis B and alcoholic cirrhosis, contained no malignancy and no inflammatory bowel disease, and was followed for a median of under three years, whereas half of our patients had a rheumatologic condition and the median follow-up was ten years. One observation is shared: in their series the autoimmune subgroup had the lowest risk of reaching the endpoint, as our rheumatologic group did here. Their worst subgroup was viral infection, whereas our infection group fared comparatively well, but both series contain too few patients in these strata for the discrepancy to be interpreted.

Table VI. Predictors of all-cause death.

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Proteinuria ≥ 3.5 g/day	11.03 (2.85–42.78)	< 0.001	14.76 (2.36–92.09)	0.004
Crescents on biopsy	4.48 (1.25–16.04)	0.021	—	—
Serum albumin†	2.96 (1.29–6.80)	0.011	—	—
Baseline eGFR‡	1.39 (1.10–1.74)	0.005	—	—
Age§	1.53 (0.92–2.53)	0.099	—	—
Male sex	2.41 (0.62–9.35)	0.204	—	—
Mesangial C3 deposition	1.19 (0.33–4.21)	0.792	—	—
Associated disease category¶				
Malignancy	15.61 (2.94–82.98)	0.001	9.76 (1.62–58.79)	0.013
Gastrointestinal/liver	11.70 (1.84–74.21)	0.009	23.44 (2.92–188.29)	0.003

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio. † HR expressed per 1 g/dL decrease. ‡ HR expressed per 10 mL/min/1.73 m² decrease. § HR expressed per 10-year increase. ¶ Reference category comprises the rheumatologic and infection groups combined; no death occurred in the infection group, so a separate term for it was not estimable. The multivariable model contained malignancy, gastrointestinal/liver disease, and proteinuria ≥ 3.5 g/day, and with only 10 deaths its estimates are exploratory.

The frequency of psoriasis in our series is higher than its prominence in most reviews of secondary IgAN would suggest, but it fits the epidemiological data well. Psoriasis is associated with an increased incidence of glomerulonephritis and chronic kidney disease that rises with disease severity and with articular involvement[8] and when the analysis is taken down to the level of specific glomerular diagnoses, IgA nephropathy is the disease driving the excess[9]. Shared mucosal and interleukin-17-related immune mechanisms provide a plausible route[15] and psoriatic skin and joint disease are common enough in a nephrology referral population for the association to be encountered regularly. Whether the relationship is causal in any individual patient remains unresolved, but the practical point does not depend on resolving it.

That practical point is that we found no clear evidence that psoriasis-associated IgAN follows a more favorable course than the remainder of the cohort. None of the comparisons we made could demonstrate a difference, and a third of these patients still reached kidney replacement therapy. With 12 patients this is an absence of a demonstrable difference rather than evidence of equivalence: the confidence intervals around the absolute risk differences span roughly 25 percentage points in favor of the psoriasis group to roughly 32 against it, so effects of moderate and even of substantial size cannot be excluded. Three of the four patients in the rheumatologic category who progressed to KRT had psoriasis. This matters because the association is easy to read as incidental and therefore benign, and the temptation is to attribute the urinary abnormality to the skin disease and observe. Our data give no support to that stance, and they are consistent with the Chinese series in which severe psoriasis was accompanied by lower eGFR, heavier proteinuria, and more crescents at biopsy[10]. Because psoriasis is managed largely outside nephrology, it is tempting to suggest that periodic urinalysis and creatinine measurement might be considered in these patients, particularly in severe or arthropathic disease, as a low-cost way of finding the nephropathy earlier than we did. We would emphasize that this is a hypothesis generated by a small, single-center, retrospective series and not a recommendation: no screening strategy was tested here, we have no data on the interval at which such testing would be worthwhile or on what it would yield, and evidence adequate to support a recommendation would have to come from a prospective study in an unselected psoriasis population. New hematuria or new proteinuria may warrant nephrological assessment rather than observation alone; a third of our psoriasis patients eventually required kidney replacement therapy, although with 12 patients that proportion is itself imprecise. We did not test either strategy and this remains a suggestion drawn from the pattern of our cases.

The malignancy group told the opposite story. The 10-year cumulative incidence of kidney replacement therapy was 65.0% in this group against 4.3% in the rheumatologic group, and half of these patients died.

The direction is broadly consistent with observations from paraneoplastic glomerular disease[11,12], although a causal relationship between malignancy and IgA nephropathy cannot be established from our data. Our contribution is quantitative rather than conceptual, since dedicated long-term outcome data on malignancy-associated IgAN remain very limited and much of the available evidence comes from case reports[6].

The malignancy group presented with a distinctly more severe renal phenotype: an acute nephritic syndrome in nine of the ten, crescents in four, heavy proteinuria, and a median eGFR of 29 mL/min/1.73 m². They also reached kidney replacement therapy quickly, at 1, 2, 3, 5, 6, 8 and 27 years, against 3, 15, 18 and 20 years in the rheumatologic group. What our data cannot do is separate the contribution of the malignancy itself from that of the severity with which these patients presented, because the two are almost completely collinear in a group of ten. Malignancy should therefore be read as marking a severe, frequently crescentic phenotype rather than as an independent determinant of outcome; establishing the latter would require the interval between the cancer diagnosis and the kidney biopsy, and the tumor stage at biopsy, neither of which we were able to retrieve reliably. Whether the reverse inference holds — that an older patient presenting with newly diagnosed IgA nephropathy and advanced kidney impairment should prompt a search for an occult malignancy — is a question our design cannot answer, because a cancer diagnosis at or before biopsy was an entry criterion. The combination we observed is at least compatible with that possibility, and it would be a straightforward hypothesis to test in an unselected biopsy series.

Nothing in the routine work-up helped us decide whether any given association was causal. Serum IgA was raised in fewer than a quarter of patients and did not differ across the four categories, and neither did mesangial C3 deposition. Mesangial C3 has been shown to track progression in primary IgAN[16], yet here it predicted neither kidney failure nor death, and our figure of 34.8% is well below the proportions usually reported in primary disease. This is worth stating because an elevated serum IgA is sometimes taken as a pointer toward a secondary form. Techniques that might make the distinction — staining for galactose-deficient IgA1 with the KM55 monoclonal antibody, for instance — were not available across a cohort assembled over three decades[6]. Given that and given how common both IgAN and psoriasis or a first cancer are, we think the neutral term IgA-associated nephropathy is preferable for most of these patients, with secondary reserved for the minority in whom the temporal course is genuinely persuasive. The only study to have compared the two categories with propensity matching reached the same conclusion from the opposite direction: kidney endpoints were indistinguishable between primary and secondary disease, and the authors argued that the term associated describes the relationship better than secondary[14].

The remaining categories were small but nevertheless informative. Liver disease is the classical secondary form, and mesangial IgA can be demonstrated in most cirrhotic patients who are biopsied, attributed to impaired hepatic clearance of IgA immune complexes and to portosystemic shunting[7]. Three of our six gastrointestinal and liver patients died, an outcome that almost certainly reflects the liver disease rather than the kidney; the very large hazard ratio for mortality in this group should be read in that light rather than as a statement about glomerular injury. For inflammatory bowel disease the mechanistic case is stronger still, with shared genome-wide risk loci in mucosal immune pathways, and a Swedish population-based cohort has shown that inflammatory bowel disease is both more frequent in IgAN and predictive of progression to kidney failure[17]; only two of our patients had inflammatory bowel disease, so we can add nothing to that literature.

Our histological and clinical predictors were the familiar ones. Crescents were associated with a more than fivefold higher hazard of KRT on univariable analysis, directionally consistent with the work that led to the addition of the C lesion to the Oxford classification[18,19] and with the multicenter study of crescents in primary IgAN.[20] Our point estimate is considerably larger than the pooled hazard ratio reported in primary disease,[21] most likely because crescents in this cohort clustered in patients who were already in advanced kidney failure at biopsy; consistent with that, the association weakened once disease category was taken into account. Proteinuria of 3.5 g/day or more predicted both KRT and death, which is unsurprising given the central place of proteinuria in every IgAN risk model[5] and the increasingly strict targets set out in the 2025 KDIGO guideline[22].

This study has clear limitations. It is retrospective and drawn from a single center, and with 46 patients, 15 KRT events, and 10 deaths, the multivariable models are underpowered; several confidence intervals span more than an order of magnitude and should not be quoted as effect estimates. Expressed formally, each multivariable model estimated three coefficients, from 15 events for KRT and from 10 for death, so that the number of events per parameter was 5.0 and 3.3, well below the commonly cited rule-of-thumb of approximately 10; both models are accordingly exposed to overfitting and to unstable and potentially biased coefficient estimates, and we present them only to show how the univariable estimates behave under minimal adjustment. The psoriasis comparison, in

particular, rests on a subgroup of 12 patients and the confidence intervals around its risk differences are wide enough to include clinically meaningful effects in either direction. The pooling of the rheumatologic and infection groups into a single reference category was a response to the absence of deaths in the infection group rather than a pre-specified choice, and the mortality model in particular rests on a reference category containing only two events; both multivariable models should be regarded as exploratory and neither supports a claim of independent effect. We also lacked a contemporaneous cohort of primary IgA nephropathy from the same center, so nothing here constitutes a direct comparison between primary and associated disease; statements about the primary form are drawn from the published literature. Death was handled as a competing risk for KRT, but only in the estimation of cumulative incidence and in the use of cause-specific Cox models; a Fine-Gray subdistribution model, which would estimate the effect of a covariate on the cumulative incidence directly, was not fitted, and with 15 events it would in any case have been unstable. Follow-up duration was recorded to the nearest year, so the survival estimates are necessarily coarse. Psoriasis severity was not scored, which prevented us from testing the severity gradient reported elsewhere[8,10]. Published risk-prediction tools could not be applied either, since they were derived in primary IgAN and exclude patients with the degree of kidney impairment seen in our malignancy group[5]. Full MEST-C scoring was unavailable for the older biopsies, so the prognostic information carried by the M, E, S, T and C lesions is missing from this analysis, and testing for galactose-deficient IgA1 was not performed. Biopsies were not re-read centrally for the purposes of the study, so the histological variables carry whatever interobserver variation existed between the pathologists reporting over three decades; this applies particularly to mesangial C3, the frequency of which here (34.8%) is lower than is usually reported in primary disease. A further consequence of the long recruitment window is that diagnostic thresholds, treatment practice and the equations used to estimate GFR all changed over the period. We addressed the last of these directly by recalculating every eGFR from the recorded creatinine with the 2021 CKD-EPI equation, so that kidney function is expressed on a single scale throughout, and RAS blockade, which was given to all but four patients and in similar proportions in the two periods (88.9% and 92.9%, $p = 0.639$), cannot have differed systematically between eras in its presence although it may well have differed in dose and in the agents used. The comparison of the two calendar periods (Table IV) showed the differences in age and in follow-up duration that would be expected, but no appreciable difference in the distribution of associated diseases, in histological severity, in the use of immunosuppression, or in the rate of KRT, which did not reveal evidence that secular change was a major driver of our findings, although meaningful period effects cannot be excluded in a comparison of 18 with 28 patients.

In this long-term single-center cohort, psoriasis was the systemic disease most often found alongside IgA nephropathy, and we found no clear evidence that its course was more favorable than that of the cohort as a whole; a third of these patients reached kidney replacement therapy. Malignancy, by contrast, defined the group with the worst kidney and patient outcomes, in a direction consistent with what is known about paraneoplastic glomerular disease. Adverse outcomes were associated with kidney function, proteinuria, and crescents at biopsy, together with the nature of the associated illness, and not with any marker that identified the association as causal. We therefore suggest that IgA-associated nephropathy is the more honest description for most such patients, that psoriasis should not be dismissed as an incidental association, and that an abnormal urinalysis in a patient with cancer or chronic liver disease warrants consideration of nephrological evaluation, with kidney biopsy where clinically appropriate.

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Researcher Contribution Statement

Idea and design: A.Y.; Data collection and processing: S.E.G.B., F.N.E.Ö.; Analysis and interpretation of data: F.Ç.H., S.E.G.B.; Patient follow-up: S.E.G.B., M.S., A.İ.Ç., H.S.K., C.B.G., A.O., A.E., M.Y., K.D., M.G., A.Y.; Writing of significant parts of the article: S.E.G.B.; Critical review and editing: A.Y., M.G., K.D., M.Y., A.E., A.O., C.B.G., M.S., A.İ.Ç., H.S.K.

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The authors of the article have no conflict of interest declarations.

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