

Örebro Studies in Medicine 330



Johanna Rehnberg

IgA Nephropathy: Comorbidities and Prognosis

- Registry-based Studies

Author: Johanna Rehnberg

Title: IgA Nephropathy: Comorbidities and Prognosis - Registry-based Studies

Publisher: Örebro University, 2025
www.oru.se/publikationer

Print: Örebro University, Reprö 08/2025

ISSN: 1652-4063

ISBN: 978-91-7529-676-0 (print)

ISBN: 978-91-7529-677-7 (pdf)

Abstract

Johanna Rehnberg 2025: IgA Nephropathy; Comorbidities and Prognosis-Registry-based Studies.

This thesis investigates the associations between IgA nephropathy (IgAN), a common form of primary glomerulonephritis, and several health outcomes including inflammatory bowel disease (IBD), cancer, infections, and the reliability of biopsy data from the Swedish Renal Registry (SRR).

In a population-based cohort study of 3,963 IgAN patients and 19,978 controls, IgAN was linked to a significantly higher risk of both future and preceding IBD diagnoses. IBD also increased the risk of developing end-stage renal disease (ESRD) in IgAN patients, underscoring the importance of monitoring gastrointestinal comorbidities in this population.

Another cohort study of 3,882 IgAN patients examined the association between IgAN and cancer. An elevated cancer risk was identified, but only in patients who progressed to ESRD, suggesting that the increased cancer incidence is related to advanced kidney disease rather than IgAN itself.

A third study explored the frequency of infections in IgAN patients, revealing a higher incidence of infections and increased antimicrobial use compared to both the general population and sibling controls. The study highlighted a marked risk of sepsis, emphasizing the need for proactive infection prevention in IgAN management.

Finally, validation of biopsy data from the SRR demonstrated a high positive predictive value (95%) for IgAN diagnosis. This reinforces the reliability of the SRR as a valuable tool for future research on IgAN.

Together, these findings contribute to a deeper understanding of IgAN's broader clinical implications, and the potential risks associated with its progression.

Keywords: IgA Nephropathy, Epidemiology, Comorbidities

”Man ångrar aldrig ett dopp”

- En vis person med IgA-nefropati

Table of Contents

Thesis at a glance	12
LIST OF STUDIES	13
ABBREVIATIONS.....	14
INTRODUCTION	16
IgA Nephropathy	16
History.....	16
Clinical Presentation.....	16
Pathogenesis.....	17
Diagnosing IgAN.....	18
Epidemiology.....	20
Treatment	22
Prognosis	28
Inflammatory Bowel disease	29
Cancer in Chronic kidney disease	30
Infections and IgAN.....	31
The Swedish Renal Registry.....	32
AIMS OF THE THESIS.....	33
General aim	33
All studies.....	33
MATERIALS AND METHODS	34
Exposure; IgA Nephropathy cohort (Paper I-II and IV)	34
Validation cohort (Paper III)	34
Reference Individuals	35
The Total Population Register.....	35
Exclusion criterion	35
Follow-Up (Paper I-II and IV).....	36
Registries; Outcome and Covariates (Paper I-II and IV)	36
The National Patient Register	36
The Swedish Cancer Register	37
The National Prescribed Drug Register	37
LISA	38
Statistical methods.....	38
Cox Regression.....	38
Logistic Regression.....	38

Linear Regression	39
Paper I.....	39
Paper II.....	40
Paper III.....	40
Paper IV.....	41
ETHICS	43
RESULTS	45
Paper I.....	45
Risk of IBD in IgAN	45
Incidence and Absolute Excess Risk	45
Analyses by type of IBD	46
Risk of having an IBD diagnosis before IgAN	46
Risk of ESRD.....	46
Paper II	49
Risk of cancer in IgAN.....	49
Incidence and Absolute Excess risk	49
Cancer risk according to kidney function	50
Site-specific cancer	52
Cancer risk before IgAN diagnosis	52
Paper III.....	53
Characteristics	53
Positive Predictive Value (PPV) for IgAN diagnosis.....	53
Biopsy findings	54
Completeness.....	54
Paper IV.....	56
Risk of infections (Linear regression)	56
Subtypes of infections	56
Increased antimicrobial prescription.....	57
Risk of infections (Cox Regression)	58
Incidence and Absolute Excess risk	58
Risk of infections before IgAN diagnosis	59
DISCUSSION	60
Main Findings	60
Paper I.....	60
Paper II.....	61
Paper IV.....	62
Methodological considerations (Paper I, II and IV)	63

Validity and Generalizability.....	63
Power, Bias and Limitations.....	64
Validation Study (Paper III)	66
Clinical Implications	67
CONCLUSIONS	69
POPULÄRVETENSKAPLIG SAMMANFATTNING.....	70
ACKNOWLEDGEMENTS	72
REFERENCES.....	73

Thesis at a glance

	QUESTION	METHOD	RESULTS	CONCLUSION
Paper I	Is there an association between IBD and IgAN, and is IBD a risk factor for progression to ESRD?	Cox and Logistic regressions on registered based data on 3,963 IgAN patients and 19,978 reference individuals.	Significantly higher aHR and OR for IBD before and after IgAN diagnosis, and for risk of ESRD in patients with both diagnoses.	Patients with IgAN have an increased risk of IBD both before and after IgAN diagnosis, and IBD is associated with a higher risk of ESRD.
Paper II	Is there an increased risk of cancer in patients with IgAN?	Cox regressions on registered based data on 3,882 IgAN patients and 19,341 reference individuals.	No significant difference in aHR in non-ESRD patients with IgAN. Increasingly higher aHR in patients with ESRD and kidney transplant.	There was no support for IgAN as a risk factor for cancer or as a paramalignant condition. Cancer risk increases with kidney function loss.
Paper III	Validation of the biopsy data registered in the SRR for IgAN diagnosis.	Medical chart review of 142 randomly selected patients registered in the SRR after having undergone a kidney biopsy diagnosed with IgAN.	A histological and clinical diagnosis of IgAN was confirmed in 132 of 139 patients. In 3 patients data was missing or duplicated.	The PPV of a correct diagnosis of IgAN was 95% (95% CI 90-98%).
Paper IV	Is there an increased risk of primary infections in patients with IgAN?	Linear and Cox-regressions on registered based data on 2,406 IgAN patients and 11,609 reference individuals.	Significant association of cumulative infection incidence and increased antimicrobial prescription in patients with IgAN.	There was an increased risk of infections and more frequent prescriptions of antimicrobial treatment in patients with IgAN compared to the general population and to their siblings.

List of studies

- I. Inflammatory bowel disease is more common in patients with IgA nephropathy and predicts progression of ESKD: A Swedish population-based cohort study. *J Am Soc Nephrol*. 2021 Feb;32(2):411-423.
- II. Cancer risk in patients with IgA nephropathy: A Swedish population-based study. *Nephrol Dial Transplant*. 2022 Mar 25;37(4):749-759.
- III. Validation of IgA Nephropathy diagnosis in the Swedish Renal Registry. *BMC Nephrol*. 2024 Mar 4;25(1):78.
- IV. IgA Nephropathy and the Risk of Primary Infections: A Swedish population-based study. *Am J Nephrol*. 2025 Mar 4:1-12.

Reprints were made with permission from the respective publishers.

Abbreviations

ACEi	Angiotensin-converting enzyme-inhibitor
AER	Absolute excess risk
aHR	adjusted Hazard ratio
ARB	Angiotensin receptor blocker
CD	Crohn 's disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
eGFR	Estimated glomerular function
ENT	Ear, Nose and Throat
ERA	Endothelin receptor antagonists
ESKD	End stage kidney disease (US)
ESRD	End stage renal disease (Eur)
GALT	Gut-associated lymphoid tissue
GI-tract	Gastrointestinal tract
HIV	Human immunodeficiency virus
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Disease
IgAN	IgA nephropathy
IgAV	IgA vasculitis
IR	Incidence rate
KDIGO	Kidney Disease: Improving global outcomes
MRA	Mineralocorticoid receptor antagonists
NALT	Nasopharynx-associated lymphoid tissue
NMSC	Non-melanoma skin cancer
NPR	National Patient Register
TPR	Total Population Register
OR	Odds ratio
PIN	Personal identity number
PPV	Positive Predictive Value
RAASi	Renin-Angiotensin-Aldosterone system-inhibitor
RRT	Renal replacement treatment
SGLT2	Sodium-glucose transporter-2
SKR	Sveriges Kommuner och Regioner

SNOMED	Systematized Nomenclature of Medicine
SNR	Svenskt Njurregister (Sve)
SRR	Swedish Renal Registry (Eng)
UC	Ulcerative colitis
UTI	Urinary tract infection

LISA: The Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies

Introduction

IgA Nephropathy

History

IgA Nephropathy (IgAN) was first discovered and described in 1968 by French nephrologist Jean Berger and his colleague Nicole Hinglais (1), following their use of immunofluorescence technique to detect intercapillary IgA deposits in kidney specimen. Although initially considered a relatively benign condition, the application of this diagnostic method to a growing number of patients revealed that IgAN is a progressive kidney disorder. Today, it is recognized as the most common form of glomerulonephritis worldwide and the main cause for the need of renal replacement therapy (RRT)(2,3).

Clinical Presentation

IgAN affects both sexes in a male:female approximately 1:1 in Asia with a higher male proportion reported in Northern Europe and America. The disease is typically diagnosed in early to mid-adulthood, with greater incidence in children compared to elderly adults(3,4).

Clinical manifestations of IgAN are highly variable, ranging from acute kidney failure, macroscopic haematuria, hypertension, chronic kidney function decline and significant proteinuria to an asymptomatic presentation detectable only through urinary dipstick testing. It's not seldom discovered in association with respiratory- och GI-tract infections, which may trigger episodes of macroscopic hematuria and increased proteinuria (3,5,6).

There is a systemic variant of IgAN known as IgA vasculitis (IgAV), formerly referred to as Henoch-Schönlein purpura. In addition to kidney involvement, IgAV causes inflammation of small blood vessels, leading to palpable purpura most commonly on the lower extremities. Skin biopsy in such cases typically reveals leukocytoclastic vasculitis with IgA deposition. Some patients may experience abdominal pain, arthralgia and myalgia. The presence of purpura is the primary diagnostic criterion for IgAV. This condition is more common in children and generally has a favorable prognosis. Both isolated cutaneous vasculitis and IgAN can develop to systemic IgAV(2,3,7,8).

Pathogenesis

The pathogenesis of IgAN is still not fully understood, but research supports the involvement of multifactorial genetic and environmental factors. Mucosal infections have been recognized as potential contributors to the development of aberrant IgA antibody production (9,10).

Immunohistological examination of kidney specimens with IgAN typically reveals IgA deposits in the glomerular mesangium. A central finding is that the deposited IgA is exclusively of the IgA1 subclass, characterized by aberrant galactosylation, specifically galactose-deficient IgA1 (Gd-IgA1). Gd-IgA1 tends to form larger immune complexes, which allows them to evade normal catabolism in the liver.

Normally, circulating IgA1 is produced and secreted by B-lymphocytes in the bone marrow. In contrast, Gd-IgA1 appears to be synthesized by peripheral B-lymphocytes in the mucosa-associated lymphoid tissue, such as the tonsils and Peyer's patches in the intestinal mucosa (11–13).

It remains unclear how Gd-IgA1 enters the circulation. One theory suggests that IgA1-producing B cells migrate to the bone marrow due to altered expression of target receptors ('homing receptors') on the cell surface. Another hypothesis is that mucosal antigen stimulation leads to increased reactivity of local B cells, which overproduce IgA1 that subsequently enters the circulation. Elevated levels of Gd-IgA1 has also been found in healthy relatives of IgAN patients, indicating that its presence alone is not sufficient to cause the disease (11–13).

The galactose deficiency in Gd-IgA1 exposes specific glycan residues in the antibody's hinge region, which can be targeted by IgG antibodies. This leads to the formation of Gd-IgA1-IgG immune complexes. These complexes have been detected in patients with IgAN and are associated with an increased risk of disease progression, the need of dialysis, and mortality(11–16).

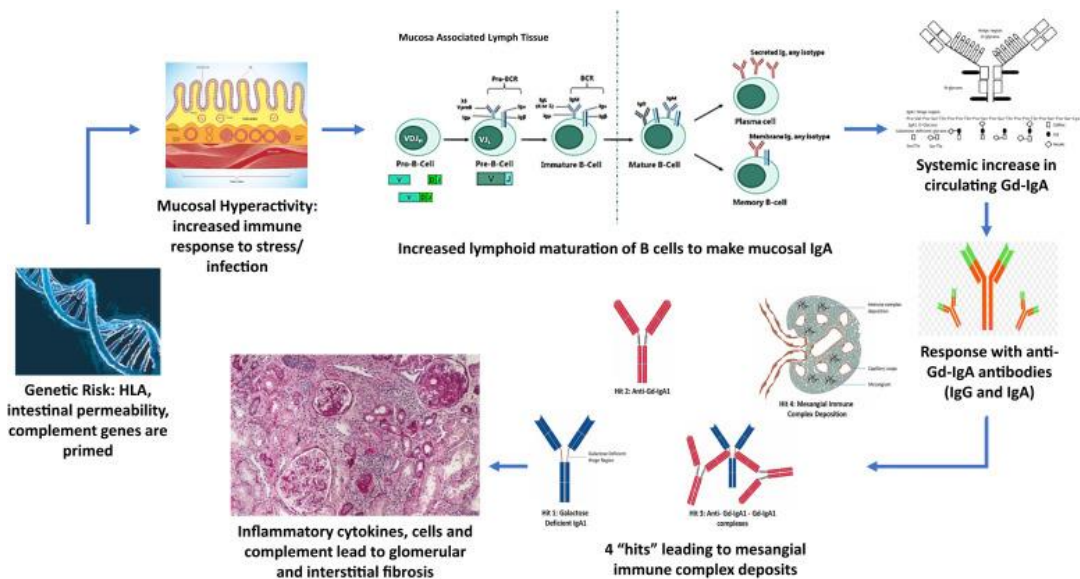


Figure 1. Schematic diagram of the pathogenesis. Caster DJ, Lafayette RA. The Treatment of Primary IgA Nephropathy: Change, Change, Change. Am J Kidney Dis.

Ig-Gd-IgA1 complexes entrapped in the glomerular mesangium trigger a local immune response and activation of the complement system, leading to mesangial matrix expansion, hypercellularity and the deposition of C3, IgM and/or IgG. The ratio of Gd-IgA1 to plasma levels of complement factor C3 has been associated with progression of IgAN. In aggressive disease, light microscope reveal the glomerular scarring and crescent formation due to infiltration of inflammatory cells into Bowman’s capsule (3,11,12,17,18).

It is shown that IgA-deposits in kidneys from subclinical IgAN-donors are cleared from the glomerular mesangium within weeks after transplantation into non-IgAN recipients. This supports the theory that the initiating cause of IgAN is extra-renal(3,11).

Diagnosing IgAN

There are currently no established pathognomonic biomarkers for IgAN in serum or urine, hence diagnosing IgAN requires kidney biopsy. The hallmark of IgAN in the biopsy specimen is the presence IgA deposits, identified using immunofluorescence. These deposits are primarily located in the mesangium

and are often dominant or co-dominant with C3. IgG or IgM can also be present, and in some cases C1q can be detected as well. The light microscopy also shows findings such as mesangial hypercellularity or proliferation (most common), endocapillary hypercellularity, sclerosis and, in severe cases, crescent formations (3,11,17,19).

Other kidney diseases, such as lupus nephritis associated with systemic lupus erythematosus (SLE), may also exhibit IgA deposition. However, SLE can usually be differentiated by its characteristic “full-house” immunofluorescence pattern, which include positive staining for IgG, IgA, IgM, C1q, and C3(20).

Additionally, IgA deposits can occur in non-kidney conditions, such as liver diseases and viral infections like HIV and hepatitis. In these cases, IgA is often found alongside IgM and/or C3 in equal staining intensity, and the deposits may be present not only in the mesangium but also along capillary walls. Such cases are sometimes referred to as Secondary IgAN, though this classification remains a topic of debate. Post-infectious glomerulonephritis can also feature IgAN deposits, but usually accompanied by a higher ratio of C3 (21).

Although there are some clear distinctions between IgAN and the above-mentioned examples characterized by IgA depositions, the absence of strict histopathological criteria, such as mesangial proliferation, for diagnosis raises questions about the pathological threshold for defining disease. In a study of 756 Finnish trauma victims, latent mesangial IgA depositions were found in 6.9% of the cases(22), and in a Japanese study, 16.6 % of 510 healthy living or deceased kidney donors had latent IgA depositions(23). These findings suggests that IgA deposition alone may not be sufficient to define a disease state, and that an additional trigger may be required to drive progression to overt IgAN. Thus, there could be a potential risk for overdiagnosis patients presenting only with isolated microhematuria and/or minimal proteinuria. Biomarkers such Gd-IgA1 or immune complex Gd-IgA1-IgG would perhaps better reflect significant disease, but unfortunately these biomarkers are not available for routine clinical use.

The assessment of biopsy material is nowadays commonly classified using the Oxford classification, which is based on the histopathological features of IgAN. The system is known as the MEST-C score and includes mesangial hypercellularity(M), endocapillary hypercellularity (E), segmental glomerulo-

sclerosis (S) and tubular/interstitial atrophy (T) and crescents (C). The prognostic value of this scoring system has been validated in several studies, including the European VALIGA cohort. The E score appears to provide less prognostic information compared to a positive T score, which reflects irreversible damage and is associated with a high risk of progression, or a positive C score, which is a sign of a rapidly progressive course(24–26).

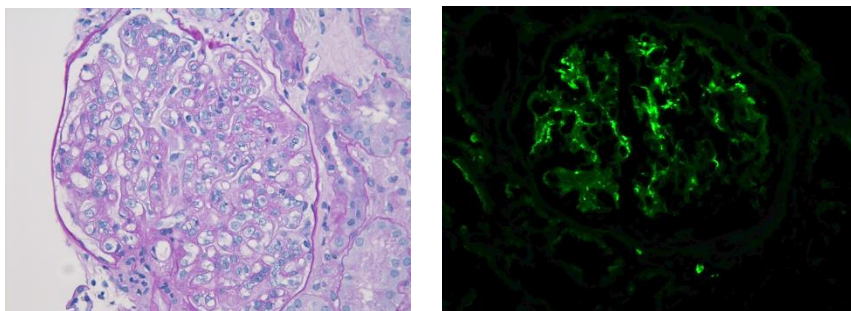


Figure 2 A and B. A: Glomerulus with endocapillary hypercellularity. B: Immunofluorescence staining for IgAN primarily in the mesangium. www.renalfellow.org/2019/07/29/kidney-biopsy-of-the-month-iga-nephropathy/

Epidemiology

IgAN is diagnosed worldwide, but its incidence shows considerable geographic variation. It is the most common among individuals of Asian and Caucasian descent, with particularly high prevalence reported in East Asia, Europe, Australia and the US. In contrast, IgAN is rarely observed in individuals of African descent or in African Americans(3,6,27).

A 2017 systematic review by McGrogan *et al.* estimated the global incidence of IgAN in adults to be at least 2.5/100.000/year (28). Individual studies report varying incidence rates: European studies have shown incidence of 3 to 19 cases per million people per year(4), while the US reports approximately 12 per million people per year in the USA(29) and Australia 105 per million people (30). In Japan, the pediatric incidence reported at 45 per million children year(31) .

A genome-wide association study (GWAS) it was found that the genetic risk of developing IgAN mirrors this geographic distribution, with risk increasing with greater genetic distance from the African continent (6).

The true incidence and prevalence of IgAN are difficult to determine. The disease can be entirely asymptomatic and thus remain undetected without action such as population-wide screening, as is done in Japan(32). The hidden burden of asymptomatic and slowly progressive IgAN is highlighted in the previously mentioned studies from Finland and Japan. When adding mesangial changes their numbers of possible IgAN was still 1.3% and 3.9% respectively(22,23).

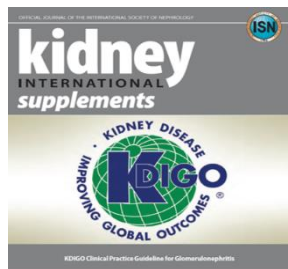
But even when IgAN is discovered, or suspected, the biopsy practices vary significantly in between countries, both in terms of access to kidney biopsy or the appropriate technique for evaluation and the nephrologist's attitude toward the necessity of performing a biopsy in mild cases or in elderly patients(4,28). The high incidence reported in the Australian study(30) was noted by the authors and may be influenced by a substantially higher overall rate of kidney biopsies performed compared to other studies. In their data, IgAN was identified in 34.1 % all biopsies, somewhat higher than for example the figure by the Swedish Renal Registry (SRR) where IgAN accounted for 21.1% of all registered biopsies in their most recent report(33). This association between IgAN (or all glomerulonephritis) incidence and total biopsy rate in a country is highlighted in a review by Fiorentino *et al.* (27).

A Scottish study reported support for a higher incidence of IgAN in socioeconomically deprived areas(34). The underlying reasons for this association are unclear and an interesting area for further investigations.

There may be a hereditary genetic predisposition to developing IgAN. Studies have suggested that up to 15% of patients with IgAN have at least 2 family members with the same condition (35,36).

Treatment

Kidney Disease: Improving Global Outcomes (KDIGO) is an international network organization that develops evidence-based clinical guidelines in kidney disease. There are treatment guidelines for Chronic Kidney Disease (CKD) management in general from 2024(37), and for IgAN specifically from 2021(38) where the latter one is currently under revision(39). Treatment strategies for IgAN are undergoing big changes based on new research and clinical experiences from the last years(40,41).



PREVENTION OF NEHPRON LOSS

Blood pressure

There is no curative treatment for IgAN. Instead, the control of hypertension and reduction of proteinuria are the pillar stones of patient care. Target blood pressure in patients with proteinuria is generally $<130/80$ mmHg and should advantageously be treated to even lower levels ($\leq 120/80$) in IgAN patients if significant protein leakage(3,17,38,42).

Renin-Angiotensin-Aldosterone system-inhibitors (RAASi)

The use of Renin-Angiotensin-Aldosterone system-inhibitors (RAASi) is central in the management of IgAN, irrespectively of hypertension or not. RAASi therapy, which includes angiotensin converting enzyme inhibitors (ACEi) and angiotensin-II-receptor blockers (ARB), has been shown to reduce proteinuria, slow the progression of CKD and protect long-term kidney function (3,17,37,49). The use of dual RAASi is not recommended due to increased risk of adverse effect such as hyperkalemia and acute kidney injury, without evidence of additional clinical benefit(43).

Mineralocorticoid receptor antagonists (MRAs)

In patients receiving RAASi, a phenomenon known as “aldosterone breakthrough” may occur, in which aldosterone levels rise despite ongoing RAAS inhibition. This limits the full therapeutic effect of RAAS blockade and has become an area of increasing clinical interest in recent years. Aldosterone breakthrough is thought to contribute to continued inflammation, fibrosis and proteinuria in CKD, underscoring the potential role of mineralocorticoid receptor antagonists (MRAs) as an adjunctive treatment. There are currently

two classes of MRAs in clinical use, steroidal MRA (e.g. spironolactone and eplerenone) and non-steroidal MRA (e.g. finerenone). While finerenone has demonstrated beneficial effects in patients with diabetic kidney disease, larger-scale studies in non-diabetic kidney diseases are lacking(44–46).

Sodium-glucose transporter-2-inhibitors

The drug class Sodium-glucose transporter-2-inhibitors (SGLT2-i) was initially used as a purely anti-diabetic treatment, lowering blood sugar levels by inhibiting reabsorption of glucose in the kidney tubules by blocking the sodium-glucose transporter-2. After safety studies showed a surprisingly positive effect on cardiovascular protection, several studies have followed and demonstrated both cardio- and renal protective effects. SGLT2-i and CKD studies have shown reduced proteinuria and decline in eGFR loss(47,48) including subgroup analysis in IgAN specifically (49), as well as lower rates of cardiovascular disease and all-cause mortality in patients with and without diabetes (47,48). SGLT2-i are now recommended to all IgAN patients with risk of progressive kidney function loss over time (39).

Since cardiac tissue doesn't express SGLT2 channels, the underlying mechanisms for these protective effects have been discussed and investigated. Increased myocardial ketone utilization over glucose, hemodynamic adjustments by enhanced diuresis/natriuresis, and vascular function appear to be the some of the main underlying mechanisms on the heart. On the kidney, an important mechanism of the SGLT2-inhibitors is the reduction in vasodilation of afferent arteriole reducing intra-glomerular pressure. An additional observed consequence with using SGLT2-inhibitors are antifibrotic effects due to reduction of inflammation and oxidative stress(50).

Endothelin receptor antagonists

Endothelin A is a vasoactive peptide, that in animal models has shown to increase cell injury, proteinuria, inflammation and fibrosis in CKD(51). Using endothelin receptor antagonists (ERA) have shown to decrease or reverse this kind of kidney injuries in both diabetic and non-diabetic CKD (52–54), including a small group of patients with IgAN although the result in that cohort was very varying(55). A problem with the ERA's has been fluid retention, which could be decreased, and also enhancing the overall effect, by adding SGLT2i(56).

Sparsentan is a dual ERA and ARB (57), and after a positive interim showing significant reduction in proteinuria, it was approved by the US Food and Drug Administration (FDA)(58). It is recommended in the revised KDIGO guidelines to IgAN patients with proteinuria and high risk of progressive function loss(39).

REDUCTION OF INFLAMMATORY DRIVE

Corticosteroids

Systemic glucocorticoids are effective anti-inflammatory drugs. Since Pozzi's first trial, along with subsequent follow-up studies and meta-analyses, suggesting that corticosteroids could reduce proteinuria and improve kidney survival in IgAN (59–62) it has been commonly recommended. However, more recent studies have not demonstrated these beneficial effects in patients without significant proteinuria(63). Moreover, the German study STOP-IgAN trial found no reduction in eGFR decline either from corticosteroid monotherapy in patients with $eGFR \geq 60 \text{ mL/min/1.73m}^2$ or from a combination of corticosteroids, cyclophosphamide and azathioprine in patients with $eGFR < 60 \text{ mL/min/1.73m}^2$. Although there was a temporary reduction in proteinuria, the treatment was associated with significant adverse effects(64). Similarly, the TESTING study which randomized patients to receive steroids or placebo alongside standardized supportive care, also highlighted severe, sometimes fatal, adverse effects associated with high-dose steroid therapy, without a clear long-term benefit for kidney function preservation(65). The TESTING study was temporarily halted due to the safety concerns but later resumed using a reduced-dose steroid regimen along with antimicrobial prophylaxis. The modified regimen was associated with lower a lower risk of GFFR decline and death due to kidney disease, while also resulting in fewer serious adverse event. These results form the basis for the KDIGO recommendation for patients with persisting proteinuria and $eGFR > 30 \text{ mL/min/1.73m}^2$ in settings where topical steroid nefecon (see next section) is not available. The guidelines suggest methylprednisolone at a maximum dose of 32 mg/day for 2 months, followed by tapering by 4 mg/day each month, for a total treatment duration of 6-9 months. This regimen should be accompanied by antimicrobial prophylaxis, gastroprotection and bone protection.

Hence, due to the undesirable effects of systemic corticosteroid treatment, such as metabolic side effects and increased susceptibility to infections, the risk-benefit ratio must be carefully evaluated before prescribing them. While

there may be short-term benefits, systemic corticosteroids should not be used in all cases of IgAN. Before starting treatment, patients should be screened for latent infections and assessed for diabetes risk, with a goal of using the lowest effective dosage.

Topical steroids

An appealing alternative to systemic corticosteroids is topical steroids, and more specifically the relatively new targeted-release formula of budesonide (nefecon). It acts directly in the distal ileum and proximal colon, where a large portion of the Peyer's patches are located and where the production of the aberrant IgA1 is thought to occur. The drug undergoes extensive first-pass metabolism by the liver, which significantly reduces systemic exposure.

In the NEFIGAN study, nefeccon was evaluated as an add-on to RAASi and showed a significant reduction in proteinuria, with a sustained effect even after treatment cessation, without the typical corticosteroid-related side effects(66,67). In a retrospective study, Ismail et al. compared regular budesonid (budenofalk) with systemic corticosteroids and found that budesonid was effective, if not more so, in reducing proteinuria and slowing GFR decline(68). After the phase 3 NefigArd study demonstrated that patients treated with nefeccon for 9 months significantly reduced their proteinuria within the first year(69), the current KDIGO recommendation suggests that patients at risk of progressive kidney function loss should be treated with the nefeccon for a 9-months course. It is likely that patients will require repeated courses or may need to remain on a lower maintenance dose(39).

Immunosuppressive treatment

In patients with severe and progressive disease with crescents in the histological specimen a combination of corticosteroids and cyclophosphamide followed by azathioprine can be considered as studies have shown some improvement in kidney survival, even if side effects were noted(38,42,70).

Treatment with T and B lymphocyte suppressive Mycophenolate mofetil (MMF) has shown positive outcomes in Asian studies, but the results have been less convincing in European trials(71–73). As a result, MMF is not currently recommended, except in Chinese patients where it may be used as a glucocorticoid-sparing option(38,42,74,75). Although, a recent and larger study, even if still Chinese, demonstrated again that patients with eGFR 30–60 ml/min/1.73m², proteinuria >0.75 g/day, or persistent hypertension despite

maximum tolerated supportive care, including RAASi, experienced reduced CKD progression and proteinuria when treated with MMF(76).

Calcineurin inhibitors are currently not recommended, although a meta-analysis suggested that tacrolimus may reduce proteinuria when used in combination with corticosteroids(38,77).

New drugs targeting complement system and antibody production

Mesangial complement C3 deposits, reflecting alternative and possibly lectin pathway activation has inspired studies on the effect of complement system inhibitors. Iptacopan is an oral inhibitor of the alternative complement pathway that selectively binds to factor B, thereby preventing the formation of C3 and C5 convertases and the downstream activation of inflammatory mediators. In a Phase 2 trial (APPLAUSE-IgAN II), treatment with iptacopan as an add-on to RAS inhibitors resulted in a significant, dose-dependent reduction in proteinuria (38.3% relative to placebo)(78). Based on a pre-specified interim analysis of the Phase 3 APPLAUSE-IgAN study, which assessed proteinuria reduction at 9 months compared to placebo, the U.S. Food and Drug Administration (FDA) granted accelerated approval for the drug last year(79). Studies on the C5a receptor inhibitor Avacopan is also currently ongoing(80).

The B-lymphocyte CD20-antigen antibody rituximab has been used in cases of severe active disease but has not shown beneficial effects, and is therefore not currently recommended in guidelines(38,81,82). Clinical trials targeting B cell(CD38+) activating cytokines APRIL and BAFF is ongoing(83).

Tonsillectomy

Tonsillectomy was once commonly used, particularly in Asia, for IgAN patients with recurrent tonsillitis and episodes of macroscopic hematuria. While it is recommended, either alone or in combination with corticosteroids, in Japanese guidelines, it is not endorsed as a standard treatment in the KDIGO guidelines due to a lack of confirmatory studies outside of Japan(3,38,39).

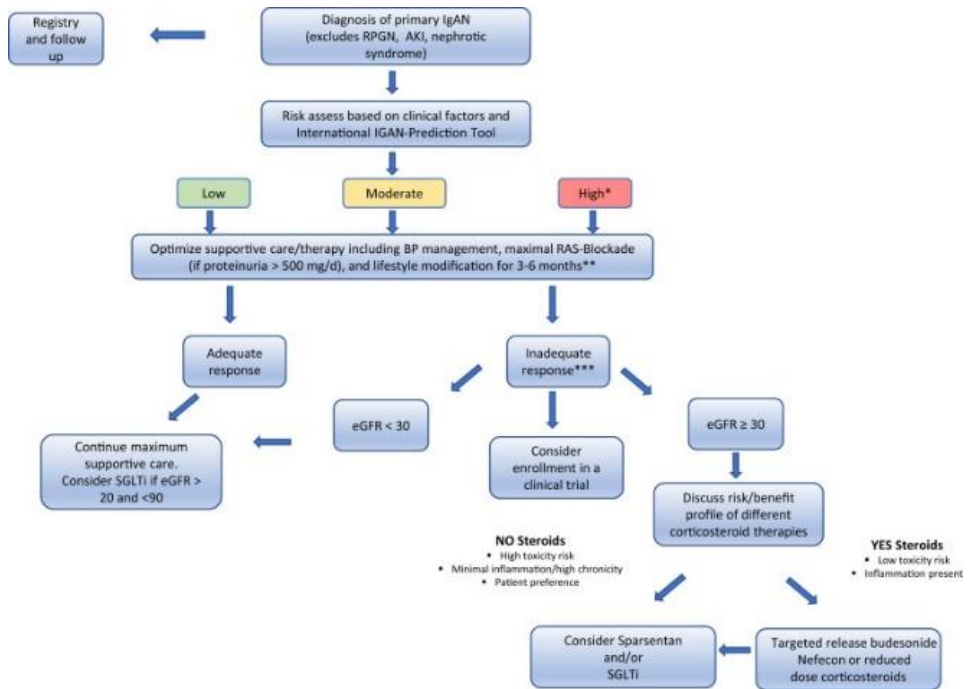


Figure 3. Flow chart of treatment options. Caster DJ, Lafayette RA. The Treatment of Primary IgA Nephropathy: Change, Change, Change. Am J Kidney Dis.

SUPPORTIVE TREATMENT

Statins

Treatment with statins is recommended to all patients ≥ 50 years with CKD stage 3, irrespectively of underlying kidney disease (84) and studies have indicated that statins can reduced proteinuria, although not effectively slow the progression of GFR decline (85). In some small studies statins have been described to have beneficial effect specifically on IgAN (86,87).

Lifestyle

In addition to medical treatment, weight control, dietary salt restriction, avoidance of high-protein diet, regular exercise and smoking cessation are of high importance for reducing the risk of progression of IgAN and managing CKD in general(23,38,74,88–91).

A study with gluten-free diet did not show any beneficial effects for the general IgAN patient(92).

Fish oil/Omega-3 was previously recommended, but upon review of earlier studies, there is now insufficient evidence to support its use, was been removed from guidelines (38).

Prognosis

Approximately 30-40% of IgAN patients will progress to end-stage renal disease (ESRD) within 20-30 years of diagnosis with consequent need of dialysis treatment or kidney transplantation(5,93). A recent British study showed that nearly all patients with an eGFR < 60 mL/min/1.73 m² and proteinuria > 0.5 g/day were expected to progress to ESRD, regardless of their age at diagnosis (94).

As previously mentioned, the reduction in proteinuria, achieved through the use of RAAS inhibitors and effective blood pressure controls, is a key prognostic factor for preserving kidney function. A reduced eGFR at the time of diagnosis is also a significant negative prognostic factor (95).

A risk prediction tool for IgAN was developed by Barbour et al(96) and further validated in an Asian-Caucasian cohort by Zhang et al(97). This tool integrates clinical data, use of immunosuppressive treatment, and histopathological findings based on the MEST-C score. It has demonstrated superior prognostic accuracy compared to models based solely on clinical or histological parameters.

Familial forms of IgAN has shown to have a worse kidney survival than the sporadic form(98,99).

Pregnancy may be a risk factor for disease progression in women with IgAN. Women with a preserved GFR and absent or low-grade proteinuria have lower risk of progression, however Su *et al.* reported accelerated progression even in cases with moderate kidney impairment (eGFR <60mL/min/1.73m²). A recent study also found that pregnant women with IgAN are at increased risk of preeclampsia and preterm birth, highlighting the need for close monitoring during the pregnancy(100,101).

IgAN is known to recur in donor kidneys following transplantation in approximately 30-60% of cases and represents an significant cause of graft loss over time (11,102,103). In a study investigating long-term outcome of kidney transplantation in patients with glomerulonephritis, short-term graft survival was

comparable to grafts in recipients with non-recurrent autosomal dominant polycystic kidney disease (ADPKD), but survival curves began to deviate after approximately 10 years, presumably because of the impact of disease recurrence. No difference in graft survival were observed between recipients of living versus deceased donors. This suggests that the cautious approach towards blood-related donors to IgAN patients, due to concerns for increased risk of recurrence, may not be necessary (104). This topic was also addressed in the Japanese study of latent IgA depositions in donors, which found no increased risk of IgA depositions in donors who were blood-related to the patient with IgAN compared to non-related donors(23).

A Swedish study found no increase in mortality among IgAN patients until the onset of ESRD. Furthermore, there was some evidence suggesting that patients with IgAN may have a better survival prognosis compared to ESRD patients with other underlying kidney disease(105).

Children with IgAN are generally considered to have a better prognosis, and remissions are not uncommon, but there are only a few studies on remission in adults. In a Japanese study of 62 adult patients with a baseline GFR of 75 ml/min who had received conservative treatment for at least 5 years, were investigated, 30.6% achieved remission of both hematuria and proteinuria. This finding highlights the heterogeneity of the disease and underscores the importance of individualized assessment (106).

Inflammatory Bowel disease

Inflammatory bowel disease (IBD) is an autoimmune condition characterized by chronic or relapsing flares of inflammatory activity in the gastrointestinal tract. The two most common subtypes are ulcerative colitis and Crohn's disease. The pathogenesis is still not completely understood, but abnormal T-cells in genetically susceptible persons are probably central. It is foremost prevalent in the western world, but incidence is increasing also in the developing countries(107,108). Extra-intestinal manifestations are common, including kidney manifestations (due to e.g. nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, amyloidosis, dehydration and adverse drug effects) in 4-23% of the IBD patients(109), and Vajravelu *et al.* showed in 2019 that 5.1% of the patients with IBD developed ESRD(110).

The fact that IgA antibodies are produced mainly by the mucosal tissue has led to that the gut-renal connection in IgAN has long been discussed and multiple case reports have described correlations between inflammatory activity in IBD and progression in IgAN(107,111–114). What the mechanisms linking the conditions together are, is still to be unraveled but some pathophysiological steps are suggested to be involved; i) abnormal T-cells that stimulates the bone marrow to produce IgA1 antibodies (114–116). This is supported by the findings already in 1987 of increased levels of IgA1-producing cells in colonic tissue in IBD patients(117). ii) raised levels of the cytokine IL-17, that has been showed to promote inflammation in both the intestinal mucosa in CD patients and in the tubular epithelial cells in IgAN patients (118,119). iii) common genetic factors, especially HLA-DR1(113,114), and more recent genetic studies have found shared risk loci between IgAN and IBD, and new risk loci associated to IgAN. Most of these loci were shared with other autoimmune conditions, mainly associated with IBD and to the maintenance of the intestinal barrier(120,121).

No major epidemiological studies on the association between IgAN and IBD had been published before ours. Two previous studies had retrospectively reviewed kidney biopsy specimen from a general population, and patient charts from an IBD cohort. They both found a significantly higher prevalence of IgAN in patients with IBD than in non-IBD patients(108,122).

Cancer in Chronic kidney disease

Patients with advanced chronic kidney failure regardless of etiology have been reported to have an increased risk of cancer in several studies (123–127). Proposed mechanisms are i) the uremic toxins' impairing effect of the immune system with chronic inflammation and oxidative stress driving cancerogenic transformations in the compromised immune system with reduced ability to detect and destroy cancer cells (128–130), ii) endothelial cell injury facilitating cancer cell invasion (131), iii) activation of the renin-angiotensin system impelling tissue angiogenesis and cellular proliferation(132,133) and iv) abnormalities in the vitamin-D metabolism that may influence oxidative stress and cell apoptosis(134–136). Recent studies have implied an increased risk also in early stage CKD (126,137–140) as well as in patients with proteinuria(126,141), but reports are not fully concordant.

The Stockholm Creatinine Measurements (SCREAM) study has explored the association on cancer risk and creatinine levels. The authors found a moderate

U-shaped correlation and the association was regardless of kidney disease etiology. They concluded that in the case of CDK, the increased cancer risk can partly be due to reversed causality because of extended health care surveillance(140). Previous studies regarding glomerular kidney disorders (such as IgAN) have reported associations with cancer, and have also been regarded as potential paramalignant conditions(142–145). Several malignancies have been indicated to be specifically related to IgAN. Most often suggested is renal cell carcinoma(146–148), but also lung cancer(149), larynx(150), esophagus(151), cutaneous T-cell lymphoma(152), Hodgkin's(153–155) and non-Hodgkin's(156) lymphoma are mentioned. Mustonen *et al* (150) theorized on that the connection in some cases could be that tumors in the respiratory tract, oral cavity, and nasopharynx invades the mucosal barrier leading to increased circulating IgA-levels and glomerular depositions.

Most of the above-mentioned studies are small or elementary case reports lacking statistical significance. Two bigger and fairly recent studies by Heaf *et al.* (157) and Ryu *et al* (158) examined the association on having a cancer diagnosis after a kidney biopsy-proven glomerulonephritis. Heaf *et al.* reported an increased risk mainly within one year after the kidney diagnosis, and Ryu *et al.* described a three-times higher risk of a cancer diagnosis within the first month of follow up in patients > 50 years (157,158). In these studies, IgAN were either underrepresented in cancer cases or not studied exclusively.

Cancer risk in patients with kidney transplants is widely accepted to be increased with more than three times the risk compared to the general population, even after excluding the most frequently occurring non-melanoma skin cancer (NMSC) (124,125,159). This is recognized as a consequence of the long-term use of immunosuppressive medications, which, given improved graft and patient survival time, could impose an even larger long-term risk for both patients and the health care system(125,160,161).

Infections and IgAN

Since IgA antibodies are mainly produced by the mucosal associated lymphoid tissue the relationship between the mucosal immune system and IgAN has been considered since the disease was first identified by Berger *et al.*(1). The IgAN pathogenesis is still not fully understood, but research support multifactorial genetic and environmental factors to be involved, and the role of mucosal infections as a potential contributor in the development of the aberrant IgA1 antibody production has been recognized(9,10).

The nasopharynx-associated lymphoid tissue (NALT) and the gut-associated lymphoid (GALT) are the first line of defense from foreign antigens entering our body, and in some IgAN patients gastrointestinal and/or upper respiratory infections can aggravate the disease with episodic macrohematuria and/or increased proteinuria(3). Coincidentally, these kinds of infections are the same that patients with selective IgA deficiency show a higher frequency of(162). At the same time, ESRD also leads to an impaired immunosystem with high prevalence of infections regardless of the underlying kidney disorder(163).

The Swedish Renal Registry

The Swedish Renal Register (SRR) is a national quality register monitoring adults (≥ 18 years) with CKD in Sweden. It was launched in 2007 when three existing registers (Swedish Registry of Renal Replacement Therapy, SRAU, founded in 1991; the Swedish Dialysis Database, SDDDB and The Chronic Kidney Disease Registry) were merged.



All Swedish nephrology departments report to the SRR. The registry contains information including information on primary kidney diagnosis, kidney function, modality and timing of RRT, laboratory values, blood pressure and medication. The registry collects data longitudinally, allowing follow-up throughout the complete patient trajectory (164).

In 2015, a separate module was added to collect data on native kidney biopsies. This includes biopsy indication, procedure-related complications, and histological diagnoses.

Annual reports are published and available to both clinicians and the public.

Aims of the thesis

General aim

Being the most common primary glomerulonephritis, our studies are relevant to many nephrology patients and aim to answer important questions about risk of comorbidities and malignancies. The studies may merit implementations of systematic screening and the tailoring of more personalized follow-up, which in turn could improve the usage of both the patients' and the health care system's resources and time.

All studies

Paper I: Although long discussed and with many case reports suggesting association between IgAN and IBD, there was no previous large-scale epidemiological study. In our first paper, we aimed to examine the association between IgAN and IBD, and to evaluate if concomitant disease is a risk factor for progression.

Paper II: Glomerular kidney disease is acknowledged to be associated with malignancies and been proposed to be paramalignant condition. IgAN is a subgroup of glomerular kidney disease but has not been studied exclusively or in big cohorts regarding this association. The aim of our second study was to examine the risk of *any* and/or *site-specific* cancer in patients with IgAN, and whether there was any support for IgAN being a paramalignant condition.

Paper III: Sweden is internationally well-known for our unique population-based registries. Continuous validation of these registries is an important feature necessary to ensure reliable data and lay the foundation of good epidemiological data for research purposes. This study aimed to validate the biopsy data and more specifically IgAN diagnoses in the Swedish Renal Registry (SRR).

Paper IV: In the last study the aim was to further investigate the connection between the mucosal associated lymphoid tissue and the altered immune system status in IgAN, by exploring if an IgAN diagnosis is associated with an increased risk of infections or antimicrobial prescriptions. The secondary aim was to classify the most common subtypes of infections in IgAN.

Materials and Methods

Exposure; IgA Nephropathy cohort (Paper I-II and IV)

We defined IgAN as having a recorded kidney biopsy confirming the diagnosis. The database we used contained patients that underwent a biopsy between 1974-2011 in Sweden, evaluated at any of the four pathology departments that in that time examined all kidney biopsy specimen in Sweden (Stockholm, Gothenburg, Malmö/Lund and Linköping). Patient charts were reviewed manually or ascertained by the local IT departments that searched biopsy records for the IgAN Systematized Nomenclature of Medicine Clinical Term (SNOMED) code D67300(165).

Since the database was set up, Jarrick *et al.* has manually validated a random subset of SNOMED codes against patient charts and biopsy records(166). They found that 121 out of 127 patients with the IgAN diagnosis also had a clinically confirmed diagnosis with classic symptoms such as hypertension, hematuria, and a decrease in kidney function; rendering a positive predictive value (PPV) of 95% (95%CI 92-99%). Typical IgAN deposits were reported in 97% of the biopsy records (n=123), mesangial hypercellularity in 76% (n=96), and C3 deposits in 89% (n=113).

Approximately one third in the database constitutes of women, which can be stated as representative for the condition. Two thirds of the cohort were between 18-59 years old, with almost the same distribution of the rest between age categories < 18 years and > 60 years. The patients were equally divided in the study entry year categories, and >50% had a follow up period exceeding 10 years. The majority (>70%) had an educational level higher than compulsory school (>9 years).

In Paper IV, we included patients diagnosed from 1997 onwards, as this was the year ICD-10 was introduced in the NPR. Additionally, data on day surgeries began to be recorded that year.

Validation cohort (Paper III)

The biopsy data in the SRR contains detailed medical information from performed biopsies including the pathology diagnosis (classified according to SNOMED; Systemized Nomenclature of Medicine(165)). Some 563 patients had an IgAN or IgAV diagnosis after a renal biopsy performed 2015-2019.

We requested a random sample of 25% (142 of total 563) of these patients. The patients were selected by enrolling every fourth registered case chronologically. After being provided with the personal identity number (PIN) of selected patients, as well as extracts from the SRR and information on the primary caregiver, we requested original biopsy records and patient charts from relevant departments. Using this information, we were able to review the histological descriptions in the biopsy reports and examine if clinical symptoms and laboratory measurements were consistent with an IgAN diagnosis, and with the registered data in the SRR.

Reference Individuals

In Paper I, II and IV the government agency Statistics Sweden identified up to five reference individuals for each patient diagnosed with IgAN from the Total Population Register.

The Total Population Register

The Total Population Register (TPR) is a register maintained by the Swedish Tax Agency containing data on the birth, death, family, marital status, and migration on the entire Swedish population, residents and citizens(167).

The reference individuals were matched for age, sex, calendar year, and county of residence at the time of the kidney biopsy. The reason for choosing 5 controls was that matching in 1:4 has been stated optimal in terms of statistics but that using more controls may be beneficial to keep statistical power over time in a prospective study if controls are lost during follow-up(168).

Exclusion criterion

Regarding the IgAN patients, there was no exclusion criterion except that the patients did not have the studied outcome before the start of follow up in the main analyses in Paper I-II.

In Paper IV, there were additional exclusion criteria such as a record of organ transplant, human immunodeficiency virus (HIV) or immunodeficiency before study follow up. Since ESRD, regardless of underlying cause, leads to impaired function of the immune system with elevated risk of infections(163), patients who had ESRD at the time of biopsy were also excluded. Individuals

who developed any of the mentioned conditions including ESRD during follow up were censored at first occurrence in the National Patient Register (NPR).

There were no exclusion criteria pertaining to the reference individuals except that they were not previously diagnosed with IgAN at the time of matching, hence the control cohort contained a random selection of the general population with or without chronic diseases.

Reference individuals with the studied outcome (Paper I and II) at the start of follow up were excluded in the main analyses. In Paper IV, the same exclusion criteria applied for the reference individuals as for the IgAN patients stated above.

Follow-Up (Paper I-II and IV)

Follow up started on the day of kidney biopsy/IgAN diagnosis and corresponding date for reference individuals. Follow up ended with event (Paper I: **IBD-diagnosis**; Paper II: **Cancer diagnosis**), death, migration or on the 31st of December 2015.

Registries; Outcome and Covariates (Paper I-II and IV)

Since 1947 all permanent residents in Sweden have their unique personal identity number (PIN)(169). Through the PIN, patient data can be found and obtained from medical records and other national and regional registers.

The National Patient Register

The National Patient Register (NPR) is a national medical register established in 1964 and maintained by the National Board of Health and Welfare in Sweden. The register contains diagnoses and data from all specialized medical care such as hospitalizations and non-primary care outpatients visits, without any Swedish resident being lost to follow-up(170).

In the NPR we obtained our outcome for Paper I; an IBD diagnosis. For IBD diagnosis the validity in the register is high. The positive predictive value for having ≥ 2 IBD diagnoses was 93% for years 1987 and onwards despite that the diagnostic requirements changed(171). In the NPR we also got information on comorbidity (hypertension, heart failure and diabetes).

In Paper II we used codes in the NPR for smoking, tobacco use and/or chronic obstructive pulmonary disease (COPD). These variables were used as a proxy for smoking. Albeit the information probably being incomplete, smoking is such an important risk factor for cancer development, hence an attempt to adjust for it was mandatory and we do believe that we captured the most severe long-term smokers.

In Paper IV we obtained data from the register on numbers of primary infections during the follow up period, and diabetes mellitus diagnosis for adjustment.

The Swedish Cancer Register

The Swedish Cancer Register was founded in 1958 and receives data from more than 96% of all malignancies each year, and 99% of all cancers are morphologically verified(172). The reporting physicians use the International Classification of Diseases (ICD)-10 code, and the Cancer Register then centrally supplements these data with the corresponding ICD-7 code(173).

From this register we obtained the outcome for Paper II; first cancer diagnosis. We have primarily used the ICD-7 codes and then converted them to ICD-9/10 codes.

The National Prescribed Drug Register

The National Prescribed Drug Register was established in 2005 and provides the basis for the official statistics about all prescribed drugs dispensed at pharmacies in Sweden. The register is administered by the National Board of Health and Welfare with the purpose of increasing patient safety in the pharmaceutical area. The register can be linked to other health data registers, and data can be used by both independent researchers as well as the pharmaceutical industry. The register is updated monthly with new data from the Swedish eHealth Agency based on the billing of the pharmacies. Drugs administered at hospital settings or nursing homes are not included in the register, nor are vaccines and over-the-counter medicines. The register contains information about patients' gender, age and place of residence; products' ATC codes, strengths and pack sizes; prescription details; prescriber (not name or specific workplace); and costs(174).

Information from this register was used in Paper IV for data on prescription of antimicrobial medications and systemic glucocorticoids.

LISA

The Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) is a database kept by the Statistic Sweden where they collect data on residents' education, employment, and income. We used register data on patients' highest educational level(175) as a proxy for socioeconomic status, which is acknowledge as a risk factor for several other conditions(176). The education levels were categorized according to length (≤ 9 years compulsory school, 10-12 years, ≥ 13 years/university and Unknown. We used the highest level available during follow-up and for children we used their parents'. Data from the register was used in Paper I, II and IV.

Statistical methods

Cox Regression

Cox regression (Proportional hazards regression) is a statistical technique to analyze time-to-event data. The method is semi-parametric and can investigate the effect of several covariables, both continuous and binary, upon time to a specified outcome/event. It is also called a survival analysis, since in the begin of the method's use the outcome was usually death in advanced diseases such as cancer. The model provides an estimate of the Hazard ratio (HR) and confidence intervals (CI). HR is the ratio between the hazard rate in the exposed vs the unexposed group, given that they meet the assumption that the hazards are proportional (risk of outcome does not vary) throughout the follow up period. In internally stratified Cox regression models the cases are only compared with their own reference individuals. This is to maintain the matching design throughout the analysis.

Logistic Regression

Logistic regression models predict a dependent variable/outcome by analyzing the relationship between independent variables. The model does not consider any time to event as the above-described method. The outcome is always binary, but the covariates can be continuous, categorical, or binary. This method is practical to use when you wish to adjust for several parameters, compared to a χ^2 test. The model provides Odds Ratios (OR) adjusted for the covariates and CI. Logistic regressions can also be performed internally stratified, only comparing cases with its reference individuals. This is done to exclude the impact of the matching variables and is then called *Conditional Logistic regression*.

Linear Regression

A linear regression model is used to determine the relationship between a dependent variable (y) and one or more independent variables (x). Both dependent and independent variables must be quantitative, and categorical variables need to be recoded to binary variables or other types of contrast variables. For each value of the independent variable, the distribution of the dependent variable must be normal. The analysis estimates a linear equation and its coefficients by various mathematical techniques, usually the “least squares” method to find the line that best fits the data by minimizing the overall error between the observed and predicted values. With the value of the coefficient, the linear regression model can then be used to make predictions for new data based on the given values of the independent variables.

Paper I

In Paper I we performed:

- I) Cox Regression (internally stratified) on risk of IBD/UC/CD/IBD Unspecified between IgAN patients and reference individuals, matched on sex, age and county and additionally adjusted for educational level.
 - Sensitivity analyses restricting reference individuals to those who had at least one entry in the NPR (to secure that we compare individuals that are familiar to the health care system), and restricting IBD patients to those with ≥ 2 diagnoses in the NPR(171).
 - To mitigate ascertainment bias we performed one analysis excluding first year of follow up, and separate analyses on restricted follow up (1,5,10 years) to explore the association over time.
- II) Logistic regression for OR on future IgAN according to IBD status adjusted for age, sex, calendar year and education.
- III) Cox Regression models on risk of ESRD according to IBD status:
 - 1) IBD status at baseline
 - 2) IBD status ever during follow up
 - 3) IBD status as a time-varying covariate

The reason for not treating IBD as a time-varying covariate in the 2) model is that it is not unusual with a diagnostic delay in both IgAN and IBD, hence an exact diagnosis date is not always representative for when exposure starts. All three analyses were adjusted for birth year, sex, calendar year, education, *hypertension*, *heart failure* and *diabetes*.

IV) Logistic Regression with the same adjustments as above, for OR on ESRD according to IBD status.

Paper II

In Paper II we performed:

- I) Cox Regression (internally stratified) on risk of cancer diagnosis between IgAN patients and reference individuals, matched for sex, age, calendar year and county and additionally adjusted for *smoking* and education level. - A sensitivity analysis to mitigate ascertainment bias excluding first year of follow up was performed. In a second sensitivity analysis we wanted to evaluate if there was any support for IgAN being a paramalignant condition by restricting follow up to only the first year after IgAN diagnosis.
- II) Cox Regression on the risk of cancer according to kidney function:
 - 1) IgAN patients that never reached or had the outcome before reaching ESRD (date of ESRD censoring event for both cases and reference individuals).
 - 2) IgAN patients with ESRD (date of ESRD as start of follow up for both cases and reference individuals).
 - 3) IgAN patients that had not yet started on dialysis treatment or received a kidney transplantation (date of ESRD as start of follow up, and dialysis treatment or transplantation censoring event).
 - 4) IgAN patients with kidney transplants (date of transplantation as start of follow up both cases and reference individuals).

We restricted analysis 4) to patients with a kidney transplantation since the immunosuppressive medications are considered a further risk for cancer development. Also, it is well known that NMSC is commonly occurring in these patients, hence we therefore analyzed cancer risk excluding NMSC in all subgroups.

- III) Conditional Logistic regression to assess OR of cancer diagnosis prior to IgAN. This was not run in strata, but instead adjusted for age, sex, calendar year, county, proxy for *smoking*, and education level.

Paper III

In Paper III we performed:

We used similar criteria as Jarrick et al (166) in their previous validation of IgAN diagnosis from Swedish biopsy charts, but chose to divide patients into four, instead of three, categories:

- i) Confirmed IgAN: required mesangial IgA deposits in biopsy record, IgAN as primary biopsy diagnosis, IgAN stated in patient chart, and no data or clinical presentation contradicting IgAN.
- ii) Likely IgAN: required mesangial IgA deposits in biopsy record, and either IgAN as primary biopsy diagnosis or IgAN stated in the patient chart, and no data or clinical presentation contradicting IgAN.
- iii) IgAN as Secondary diagnosis: above-mentioned histological requirements for IgAN are met, but IgAN is not likely to be responsible for the main clinical presentation or reason of decline in renal function.
- iv) Not IgAN: when neither clinical nor histological requirements are met.

All patient charts and biopsy reports were reviewed according to a standardized template. We assessed clinical presentation, comorbidities, medications, and laboratory parameters available from the year of the biopsy and one year after the time of biopsy, to differentiate from other plausible diagnoses.

We classified immunofluorescence staining for IgA, C3 and C1q positive if the biopsy chart stated it as weak, moderate or strong, but as negative if reported as just traces.

We calculated a positive predictive value (PPV) with 95% confidence interval for IgAN diagnosis, merging categories i-ii, but we also provide data when including IgAN as secondary diagnosis (categories i-iii).

Paper IV

In Paper IV we performed:

- I) Linear regressions adjusted for sex, educational attainment and *diabetes* with i) total number of infections registered in the NPR, ii) subtypes and iii) antimicrobial treatments registered in the Prescribed Drug Registry as the outcomes.
- Sensitivity analyses were made comparing IgAN patients to their siblings for the same outcomes, to control for shared genetic and environmental factors.
- II) Cox regression (internally stratified) adjusted for educational attainment and *diabetes* with the same outcome as above.
- In the Cox regressions sibling analyses were not run in strata (since siblings may not share age, sex and residency), but adjusted at baseline for age, sex, educational level and *diabetes*.
 - A subgroup analysis on the risk of different subtypes of infections excluding those with prior *corticosteroid prescription* and further censoring at first corticosteroid prescription during follow-up was also added.
- III) Linear regression of previously registered infection types (registered in the NPR from January 1st of 1997 until date of IgAN diagnosis/corresponding date in reference individuals), adjusted for sex, age, education and *diabetes*.

Ethics

The studies for Paper I-II+IV were approved by the Stockholm Ethical Review Board/Etikprövningsnämnden (22 January 2014, approval number 2013/2095-31/2).

Study III was approved by the Stockholm Ethical Review Authority/Etikprövningsmyndigheten (31st of January 2022, approval number 2021-066629-01).

In strictly register-based studies informed consent is not mandatory(177), and sometimes even advised against to avoid public concern.

The major ethical concerns in register-based studies are related to the data handling security, so we can secure the integrity and anonymity of the participants. We have only used pseudonymized data provided from Statistic Sweden, who also oversaw the deciphering code before it was destroyed in 2020. The original database with the IgAN patients is stored at the Karolinska Institute.

We have had no direct contact with the participants. The IgAN cohort is based on those who underwent a kidney biopsy between 1974-2011, reflecting the health care system's routines and the condition's prevalence in the population, hence we have not set up any further selection criteria that could have been discriminating on age or gender. We have only used secondary data from national mandatory registers, and by the "no opt out possibility" we are not only comparing subgroups with higher propensity of accepting being included in a study. Also, health care in Sweden is also almost entirely tax-financed and equally available for all socioeconomic subgroups.

Regarding Paper III, before entering data on patients in the SRR, informed consent is mandatory at each nephrology department. Validating this type of quality register is usually not regarded to be research, since it is demanded by Sveriges Kommuner och Regioner (SKR) to regularly secure the quality in regional registers, and for the use of the register data in future research. But since this study was part of a doctoral dissertation and international publication followed an ethical application was submitted.

Few studies are done on comorbidity in the world's most common primary kidney disease. Given the unique possibilities of epidemiological studies that the web of Swedish registers constitutes, it could be considered a missed ethical obligation not to pursue this line of research.

Results

Paper I

The study included 3,963 patients with IgAN and 19,978 reference individuals, followed for a median of 12.6 years with >55% of the participants followed for more than 10 years. The cohorts consisted of approximately 30% women, about 10% of participants were younger than 18 years and 15% were older than 60. The participants were relatively evenly distributed across the entry year categories (1974-1994, 1995-2005, and 2006-2015). Regarding educational levels, approximately 20% had completed compulsory school, 45% had finished upper secondary school, and 30% had a university education, with 2% having unknown educational levels. In the IgAN cohort, 7.6% had diabetes, 36.7% had hypertension, and 4.8% had heart failure, compared to 5.6%, 12.6%, and 2.9% in the reference group, respectively.

Risk of IBD in IgAN

During the follow-up 196 out of our 3,963 IgAN patients (4.95%) were diagnosed with IBD, compared to 330 out of 19,978 (1.65%) of the reference individuals, corresponding to an adjusted hazard ratio (aHR) of 3.29 (95%CI 2.73-3.96). The risk increase was seen in all subgroup analyses (sex, age-groups, and calendar years).

In the sensitivity analyses restricting the reference individuals to those who had at least one previous entry in the NPR the aHR was 2.69 (95%CI 2.44-3.60) and restricting the patients to having ≥ 2 records of IBD the aHR was 2.64 (95%CI 2.03-3.42).

In analyses of different time periods, we could show that the association lasts overtime. The aHR was 4.18 (95%CI 2.22-7.85) for being diagnosed with IBD within the first year after an IgAN diagnosis, aHR 3.54 (95%CI 2.58-4.87) within 5 years and aHR of 3.56 (95%CI 2.81-4.52) within 10 years. When excluding the first year of follow-up, the aHR was 3.21 (95%CI 2.64-3.90).

Incidence and Absolute Excess Risk

The incidence rate of IBD in IgAN patients was 3.8 per 1000 person-years, compared to 1.2 per 1000 person-years in the reference individuals, resulting in a risk ratio of approximately 3.2:1. This corresponds to an absolute excess

risk (AER) of 2.6 additional cases of IBD per 100 IgAN patients followed for 10 years.

Analyses by type of IBD

Subgroup analyses showed a stronger association between IgAN and UC compared to IgAN and CD with aHR 2.60 (95%CI 1.70-3.97) vs 1.55 (95%CI 0.84-2.85). This was still consistent when restricting the analyzes to patients with ≥ 2 IBD diagnoses in the NPR; aHR-UC 2.65 (95%CI 1.71-4.11), aHR-CD 1.10 (95%CI 0.51-2.38) and aHR-IBD Unspecified 3.54 (95%CI 2.48-5.04).

Risk of having an IBD diagnosis before IgAN

In the conditional logistic regression analysis, we identified an OR of 2.37 (95%CI 1.87-3.01) for having an IBD diagnosis before being diagnosed with IgAN; 103 out of 4,066 (2.53%) IgAN vs 220 out of 20,198 (1.09%) reference individuals. On subgroup level the ORs were OR-UC 2.20 (95%CI 1.43-3.40), OR-CD 2.43 (95%CI 1.38-4.27) and OR-IBD Unspecified 2.41 (95%CI 1.74-3.33).

Risk of ESRD

A total of 299 IgAN patients were diagnosed with IBD, of whom 148 (50%) developed ESRD during follow-up, compared to 7 out of 550 (1.3%) reference individuals with IBD but without biopsy-proven IgAN. Among IgAN patients without IBD, 927 out of 3,767 progressed to ESRD, resulting in an odds ratio (OR) of 2.60 (95%CI 2.02-3.35) when comparing IgAN patients who were ever diagnosed with IBD to those who were never diagnosed with IBD. A Cox regression analysis of patients with or without IBD at baseline showed an aHR of 1.59 (95%CI 1.04-2.44) for reaching ESRD in the IBD group, and an aHR of 1.84 (95%CI 1.33-2.55) when treating IBD as a time-varying covariate.

Table 1BD

Any IBD	IgAN with IBD (of 3,963)	Controls with IBD (of 19,978)	IR IgAN with IBD	IR Controls with IBD	Adjusted HR*	Total number of follow up years IgAN	Total number of follow up years Controls	IgAN with IBD ≥2 diagnoses	Controls with IBD ≥2 diagnoses	Adjusted HR*
Total	196 (4.9%)	330 (1.7%)	3.8 (3.2-4.3)	1.2 (1.1-1.3)	3.29 (2.73-3.96)	51,883	277,103	91 (2.3%)	184 (0.9%)	2.64 (2.03-3.42)
Sex										
Female	59 (5.1%)	112 (1.9%)	3.8 (2.8-4.8)	1.4 (1.1-1.6)	2.84 (2.04-3.95)	15,588	81,210	26 (2.2%)	63 (1.1%)	2.14 (1.34-3.43)
Male	137 (4.9%)	218 (1.5%)	3.8 (3.1-4.4)	1.1 (1.0-1.6)	3.57 (2.85-4.49)	36,294	195,893	65 (2.3%)	121 (0.9%)	2.90 (2.12-3.99)
Age										
<18 years	10 (2.7%)	23 (1.2%)	1.9 (0.7-3.1)	0.9 (0.5-1.2)	2.41 (1.09-5.29)	5,186	26,820	5 (1.3%)	13 (0.7%)	1.97 (0.65-5.97)
18-39 years	80 (4.8%)	126 (1.5%)	3.2 (2.5-3.9)	1.0 (0.8-1.1)	3.30 (2.47-4.42)	25,210	129,015	46 (2.8%)	83 (1.0%)	2.81 (1.93-4.10)
40-59 years	71 (5.2%)	126 (1.8%)	4.1 (3.2-5.1)	1.4 (1.1-1.6)	3.03 (2.22-4.15)	17,175	92,356	25 (1.8%)	70 (1.0%)	1.84 (1.11-3.04)
≥60 years	35 (6.1%)	55 (1.9%)	8.1 (5.4-10.8)	1.9 (1.4-2.4)	4.56 (2.79-7.45)	4,309	28,912	15 (2.6%)	18 (0.6%)	6.57 (2.95-14.67)
Calendar year										
1974-1994	72 (6.8%)	137 (2.6%)	3.1 (2.4-3.8)	1.1 (0.9-1.3)	2.99 (2.20-4.06)	23,236	125,109	39 (3.7%)	73 (1.4%)	3.08 (2.03-4.68)
1995-2005	104 (6.3%)	152 (1.8%)	4.8 (3.9-5.7)	1.3 (1.1-1.5)	3.78 (2.91-4.92)	21,600	115,622	43 (2.6%)	86 (1.0%)	2.52 (1.73-3.67)
2006-2015	20 (1.6%)	41 (1.6%)	2.8 (1.6-4.1)	1.1 (0.8-1.5)	2.41 (1.39-4.20)	7,045	36,371	9 (0.7%)	25 (0.4%)	1.86 (0.84-4.10)
Education										
Compulsary school, ≤9 years	59 (6.7%)	70 (1.6%)	5.4 (4.0-6.8)	1.1 (0.9-1.4)	4.47 (2.66-7.53)	10,916	61,043	26 (2.9%)	38 (0.9%)	3.48 (1.69-7.19)
Upper secondary school, 1-3 years	90 (5.1%)	162 (1.8%)	3.8 (3.0-4.6)	1.3 (1.1-1.5)	2.82 (2.01-3.97)	23,714	126,862	51 (2.9%)	89 (1.0%)	2.74 (1.76-4.25)
University level	44 (3.5%)	92 (1.5%)	2.6 (1.9-3.4)	1.1 (0.8-1.3)	3.01 (1.72-5.26)	16,715	86,218	14 (1.1%)	56 (0.9%)	1.18 (0.51-2.72)
Unknown	3 (3.3%)	6 (1.3%)	5.6 (0.0-11.9)	2.0 (0.4-3.6)	3.25 (0.41-25.49)	536	2,979	(0.0%)	1 (0.2%)	N/A
Ulcerative colitis										
Total	34 (0.8%)	74 (0.4%)	0.6 (0.4-0.8)	0.3 (0.2-0.3)	2.60 (1.70-3.97)	53,751	280,268	32 (0.8%)	70 (0.3%)	2.65 (1.71-4.11)
Mb Crohn										
Total	14 (0.3%)	43 (0.2%)	0.3 (0.1-0.4)	0.2 (0.1-0.2)	1.55 (0.84-2.85)	54,050	280,708	8 (0.2%)	38 (0.2%)	1.10 (0.51-2.38)

IBD- Unclassified	IgAN with IBD-U	Controls with IBD-U	IR IgAN with IBD-U	IR Controls with IBD-U	Adjusted HR ^a	Total number of follow up years IgAN	Total number of follow up years Controls	IgAN with IBD-U ≥2 diagnoses	Controls with IBD-U ≥2 diagnoses	Adjusted HR ^a
Total	148 (3,7%)	213 (1,1%)	2,8 (2,4-3,3)	0,8 (0,7-0,9)	3,90 (3,11-4,87)	52,803	279,159	58 (1,4%)	82 (0,4%)	3,54 (2,48-5,04)
Risk of ESRD	Total (of 4,066)	ESRD	OR (95%CI)	HR; with or without IBD at baseline (95%CI)	HR; IBD ever during follow up (95%CI)	HR; IBD as a time-variant (95%CI)				
IgAN with IBD	299	148 (50%)	2,60 (2,02-3,35)	1,59 (1,04-2,44)	1,89 (1,50-2,37)	1,89 (1,33-2,55)				
IgAN no IBD	3,767	927 (25%)								
IBD no IgAN	550	7 (1,3%)								

^a Analyses run in strata of cases and 5 (sex, age, calendar-year and county) matched controls additionally adjusted for educational attainment.

IgAN: IgA nephropathy

IBD: Inflammatory bowel disease

UC: Ulcerative colitis

IBD-U: Inflammatory bowel disease unclassified

IR: Incidence rate

OR: Odds Ratio

HR: Hazard Ratio

ESRD: End stage renal disease

N/A: Not able to calculate

Paper II

Our study cohort included 3,882 patients with IgAN, of whom 1,117 (29%) were women. Two-thirds of the cohort were aged between 18 and 59, with similar proportions in the younger (<18 years) and older (>60 years) age categories. The cohort was evenly distributed across the study entry year categories, and over 50% had a follow-up period exceeding 10 years. The majority (76%) had an educational level beyond compulsory school (>9 years). In the IgAN group, 85 (2%) patients had a smoking or tobacco-related record in the NPR, compared to 621 (3%) of the reference individuals. A total of 1,014 (26%) IgAN patients developed ESRD during follow-up, and 793 (20%) received a kidney transplant. Among the reference individuals, 11 had ESRD at baseline, with an additional 33 developing ESRD during follow-up.

Risk of cancer in IgAN

In the IgAN cohort 488 out of 3,882 (12.6%) were diagnosed with cancer during follow up, compared to 1,783 out of the 19,341 (9.2%) reference individuals. This corresponds to an aHR of 1.70 (95%CI 1.52-1.89). When excluding the first year of follow-up the aHR was 1.41 (95%CI 0.91-2.20), and when restricting the analysis to all cancers but NMSC the association was weaker but still with an aHR of 1.31 (95%CI 1.16-1.48). The risk increase was shown in all subgroup analyses (sex, age and calendar year), except in the age category <18 years.

Incidence and Absolute Excess risk

The incidence rates for cancer (excluding NMSC) in the ESRD and transplantation groups were 14.0 and 13.6 per 1,000 person years, corresponding to an AER of 5.7 and 6.3 extra cases per 1,000 person years- or approximately 6 extra cases per 100 IgAN patients with ESRD per 10 years and >17 extra cases if including NMSC as well.

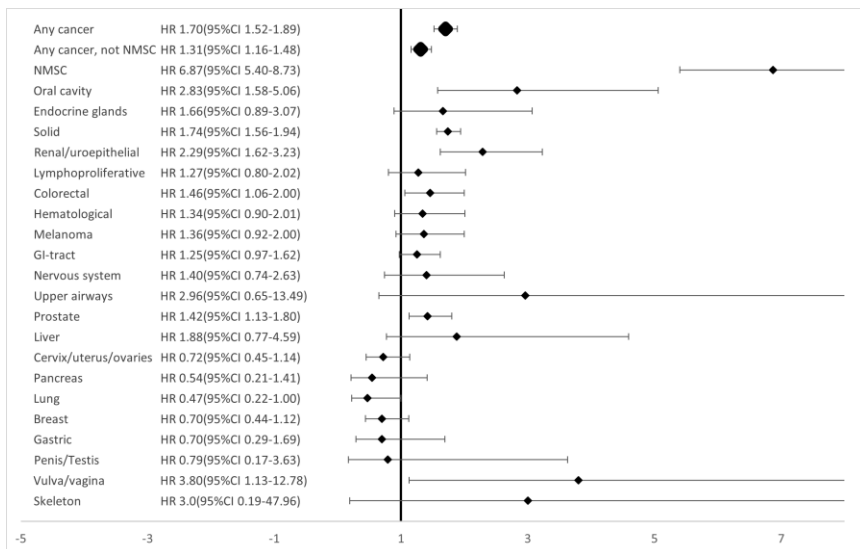


Figure 4. Risk of Cancer in IgAN. NMSC: Non-melanoma skin cancer, GI: Gastrointestinal, HR: Hazard Ratio

Cancer risk according to kidney function

We analyzed the risk of cancer according to kidney function and found that IgAN patients with *non-ESRD* had an aHR of 1.13 (95%CI 0.99-1.30) of any cancer, hence no difference compared to the reference individuals.

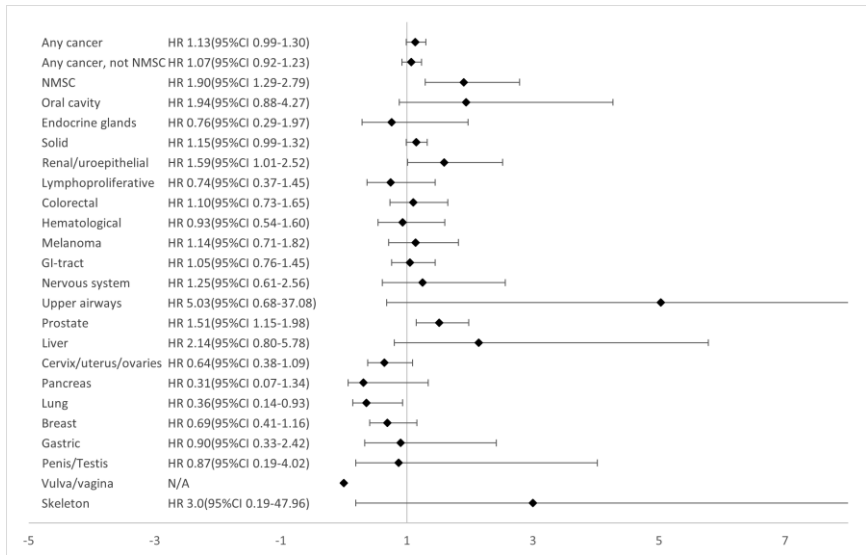


Figure 5. Risk of Cancer in non-ESRD IgAN patients. NMSC: non-melanoma skin cancer, GI: Gastrointestinal, HR: Hazard Ratio, CI: Confidence interval, N/A: Not able to calculate

IgAN patients *with* ESRD had an aHR of 4.01 (95%CI 3.33-4.82). In 327 patients that who had not started dialysis treatment nor received a kidney transplant 12 (3.7%) were diagnosed with cancer before starting on renal replacement therapy, yielding an aHR of 2.26 (95%CI 1.09-4.66).

When restricting that group to those who had received a *kidney transplant* the aHR was 4.46 (95%CI 3.64-5.46). When excluding NMSC in the transplantation group the aHR was 2.28 (95%CI 1.80-2.88).

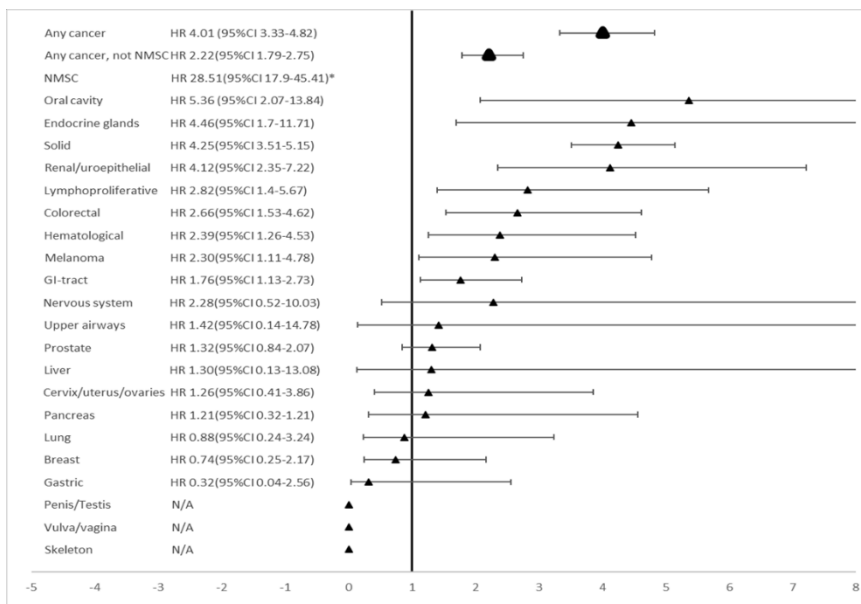


Figure 6. Risk of Cancer in IgAN patients with ESRD. NMSC: non-melanoma skin cancer, GI: Gastrointestinal, HR: Hazard Ratio, CI: Confidence Interval, N/A: Not able to calculate. * Not in graph

Site-specific cancer

NMSC was the site-specific cancer type with the strongest association both in the ESRD and transplantation group. Excluding NMSC almost halved the overall excess risk in those subgroups. Besides NMSC, cancer in the oral cavity, vulva/vagina and foremost renal malignancies were subtypes with the highest HRs in the ESRD and transplantation groups. NMSC, renal, colorectal, and oral cavity cancers also had the highest AER.

We did not identify an overall cancer risk increase in the non-ESRD patients, but they had a statistically significant higher risk of NMSC (aHR 1.90; 95%CI 1.29-2.79) and further for prostate and renal/uroepithelial cancers. The stratified analysis showed that this was confined to men > 60 years.

Cancer risk before IgAN diagnosis

The conditional logistic regression analysis on cancer risk before having an IgAN diagnosis showed an adjusted OR of 1.10 (95%CI 0.92-1.32), hence indicating that there was no increased risk nor any support for IgAN being a paramalignant condition.

Paper III

A total of 142 registrations/patients diagnosed with IgAN from 29 distinct nephrology units across Sweden were chosen in a random manner for the validation process. Upon reaching out to all primary healthcare providers, medical records were obtained from 140 individuals, accounting for 98.6% of the patients across 27 departments. One patient's biopsy record was duplicated in the SRR, and both registrations had been randomly chosen. Consequently, the ultimate count of patients subjected to review amounted to 139.

Characteristics

Categories i and ii

Among the 139 patients whose charts were validated 107 (77.0%) were identified as having Confirmed IgAN (category i). This classification was based on a clear and definitive diagnosis code in the biopsy chart along with explicit indications of IgAN in their medical records. Another subset of 25 patients (18.0%) fell under the classification of Likely IgAN (category ii). The rationale behind categorizing them as "Likely" instead of "Confirmed" was primarily due to limited material in the biopsy sample and/or unsuccessful immunofluorescence staining. Nevertheless, these patients possessed a distinct diagnosis statement and clinical symptoms consistent with IgAN as documented in their medical charts. In four out of the 25 patients, the registration pertained to their second (or subsequent) biopsy, providing further support for the diagnosis of IgAN.

Categories iii and iv

For four patients (2.9%), a different clinical condition, rather than IgA nephropathy (IgAN), was more likely to account for their symptoms or declining renal function, despite meeting the histological criteria for IgAN. We categorized these cases as having an IgAN as a Secondary diagnosis (category iii).

In three out of 139 patients (2.2%), IgAN was deemed an incorrect diagnosis, resulting in their classification as Not IgAN (category iv).

Positive Predictive Value (PPV) for IgAN diagnosis

Our examination of patient charts revealed that 132 out of 139 patients had both a clinical and histopathological diagnosis of IgAN/IgAV, yielding a PPV

of 95% (95% CI 90-98%). Additionally, if we extend the consideration to include IgAN/IgAV as a secondary diagnosis (category iii), the PPV increased even further to 98% (95% CI 93-99%).

Results after medical chart review						
	All patient	Confirmed IgAN	Likely IgAN	IgAN as Secondary diagnosis	Not IgAN	Missing or Duplicate data
n (%)	142	107 (75.4)	25 (17.6)	4 (2.8)	3 (2.1)	3 (2.1)
Age (median, years)	46	44	51	65.5	63	42
Male: n (%)	97 (68.3)	72 (67.3)	18 (72.0)	3 (75.0)	1 (33.3)	3 (100.0)
Calendar year						
2015	23	15	6	1	0	1
2016	26	20	4	1	1	0
2017	26	24	1	0	0	1
2018	33	26	5	1	1	0
2019	34	22	9	1	1	1

Table 1. Summary validation

Biopsy findings

The biopsy records indicated the presence of mesangial IgA deposits in all 132 (100%) patients with IgAN. Mesangial hypercellularity or proliferation was documented in 102 out of 132 patients (77.2%). Furthermore, immunofluorescence staining for C3 was found to be positive in 74.2% (98 out of 132) of cases. Additionally, previous studies have indicated that the classical complement pathway protein, C1q, could serve as a marker for more severe IgAN and correspondingly worse prognosis (178–180). In our cohort of patients undergoing review, C1q positivity was noted in 20.5% (27 out of 132) of all patients and in 11.1% (2 out of 18) of those categorized as having IgAV.

Completeness

The inclusion of biopsy data in the SRR commenced in 2015, and within the initial five years, their data completeness improved from 37% to 58%. This progress was determined by comparing the yearly assessment of kidney biopsies from pathology departments to the overall count of biopsy registrations.

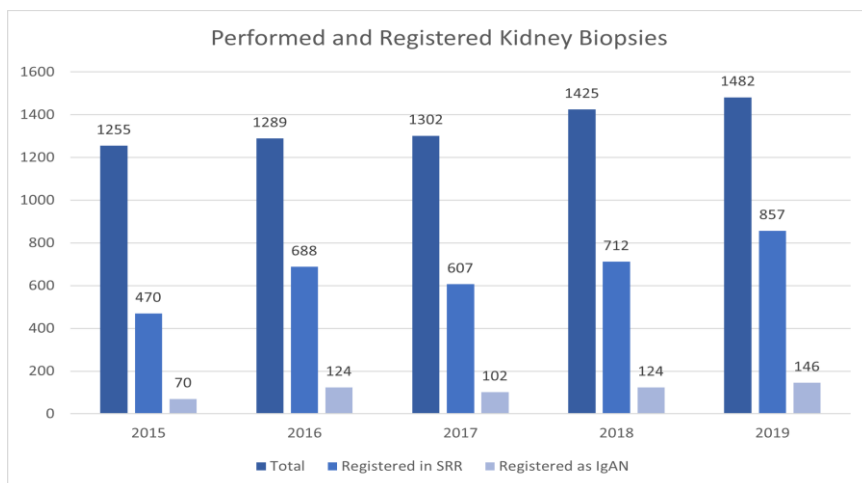


Figure 7. Completeness. SRR: Swedish Renal Registry. IgAN: IgA Nephropathy

Throughout these years, there was a slight rise in the overall number of kidney biopsies submitted for histopathological examination in Sweden, escalating from 1255 in 2015 to 1482 in 2019. However, the proportion of IgAN/IgAV diagnoses remained consistent, ranging between 15-18% during this entire period.

Paper IV

Our study cohort included a total of 2,406 patients with IgAN and 11,609 controls. Among the IgAN patients, 739 (31%) were women. Two-thirds of the patients were aged between 18 and 59 at diagnosis, with roughly equal numbers in the younger (<18 years) and older (≥ 60 years) age groups. Around 50% of the participants were included during the last study period (2006-2011), and the median follow-up time was 9.3 years. The majority (78%) had an educational level beyond compulsory school (≥ 10 years). In the IgAN cohort 121 (5.0%) had a diabetes diagnosis, compared to 233 (2.0%) of the reference individuals.

Risk of infections (Linear regression)

The linear regression analysis revealed a significant association between IgA nephropathy (IgAN) and the overall frequency of infections compared to reference individuals, with a coefficient of $\beta=0.44$ (95%CI 0.35-0.53). This suggests that each IgAN patient experienced, on average, 0.44 more infection episodes during follow-up. For women, the coefficient was $\beta=0.34$ (95%CI 0.18-0.50), and for men it was $\beta=0.48$ (95%CI 0.37-0.60). The highest association was observed in the youngest subgroup (<18 years, $\beta=0.62$; 95%CI 0.46-0.78), and the lowest in the 40-59 years subgroup ($\beta=0.34$; 95%CI 0.18-0.50).

A comparison between IgAN patients and their siblings also showed a statistically significant association with future infections, though with a lower coefficient ($\beta=0.36$; 95%CI 0.23-0.49). The values were $\beta=0.23$ (95%CI 0.05-0.41) for women and $\beta=0.42$ (95%CI 0.24-0.60) for men.

Subtypes of infections

The infectious subtypes most strongly associated with IgA nephropathy (IgAN) were urinary tract infections (UTIs) ($\beta=0.09$; 95%CI 0.07-0.11), musculoskeletal and connective tissue infections ($\beta=0.08$; 95%CI 0.05-0.12), ear, nose, and throat (ENT) infections ($\beta=0.07$; 95%CI 0.02-0.11), and gastrointestinal (GI) tract infections ($\beta=0.06$; 95%CI 0.03-0.09). Statistically significant associations were also observed for infections in the lower respiratory tract, skin, and mycoses, but no associations were found for central nervous system infections or infections caused by helminths and protozoans.

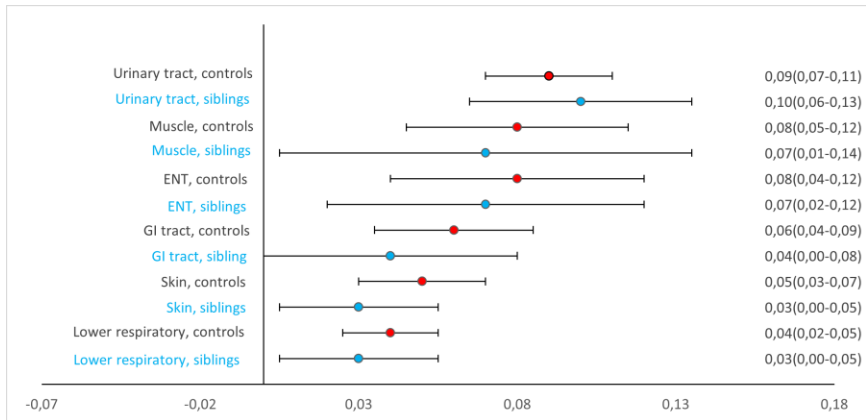


Figure 8. Subtypes of Infections; β -coefficient and 95% CI (linear regression). CI: Confidence Interval, Muscle: musculoskeletal, ENT: ear,nose and throat, GI: Gastrointestinal

In the sibling analysis, the subtypes with the strongest associations with IgAN were again UTIs ($\beta=0.10$; 95%CI 0.06-0.13), ENT infections ($\beta=0.07$; 95%CI 0.01-0.12), musculoskeletal infections ($\beta=0.07$; 95%CI 0.01-0.14), and GI tract infections ($\beta=0.04$; 95%CI 0.00-0.08).

Increased antimicrobial prescription

A significant association was observed for the frequency of prescribed antimicrobial agents compared to reference individuals, with a coefficient of $\beta=0.65$ (95%CI 0.49-0.80). For women, the coefficient was $\beta=0.89$ (95%CI 0.52-1.25), and for men, it was $\beta=0.54$ (95%CI 0.38-0.70). Similar results were found in the sibling analysis, with a coefficient of $\beta=0.47$ (95%CI 0.25-0.69). The highest association was seen for antibiotic prescriptions ($\beta=0.62$; 95%CI 0.47-0.76), with a corresponding estimate of $\beta=0.40$ (95%CI 0.19-0.61) in the sibling comparison.

Cox regression analysis showed an adjusted Hazard Ratio (aHR) of 1.49 (95%CI 1.40-1.58) for overall antimicrobial prescriptions and 1.48 (95%CI 1.39-1.58) for antibiotics, compared to reference individuals. When compared to siblings, the aHR was 1.27 (95%CI 1.17-1.38) for overall prescriptions and 1.26 (95%CI 1.16-1.37) for antibiotics.

Risk of infections (Cox Regression)

Cox regression analysis showed an increased risk of any infection, with an adjusted Hazard Ratio (aHR) of 2.02 (95%CI 1.85-2.20). The highest aHR was observed for sepsis (aHR 3.18; 95%CI 2.17-4.65), although all infection subtypes, except for central nervous system infections and those caused by helminths and protozoans, were significantly elevated. When compared to siblings, the aHR was 1.88 (95%CI 1.67-2.12) for any infection and 2.36 (95%CI 1.09-5.12) for sepsis. The highest aHRs in the sibling comparison were found for urinary tract infections (aHR 2.67; 95%CI 2.06-3.45) and mycoses (aHR 2.73; 95%CI: 1.83-4.08).

Prescription of Corticosteroids

During the follow-up, 793 (33%) of 2,406 IgAN patients were prescribed systemic corticosteroids, and 1,932 (17%) of the 11,609 reference individuals. When excluding those with a prescription of corticosteroids prior to study entry and censoring patients at the first registered corticosteroid prescription, the analysis showed similar estimates with an aHR 1.93 (95%CI 1.74-2.14) for any infection in the non-steroid group compared to 2.02 (95%CI 1.85-2.20) in the main analysis. Changes in aHRs were minor for all subtypes of infections.

Among those with a record of sepsis, only 2 (3%) of the 60 IgAN patients collected a corticosteroid prescription within 180 days before the sepsis diagnosis. The corresponding numbers for the reference group were 3 (2%) of 143 individuals. In the subgroup analysis excluding individuals at first corticosteroid prescription, the aHR for risk of sepsis was 2.90 (95%CI 1.78-4.70) as compared to 3.18 (95%CI 2.17-4.65) in the main analysis.

Incidence and Absolute Excess risk

The incidence rate of any infection in IgAN patients was 112 per 1000-person years compared to 52 for the reference individuals (ratio of 2.2:1) corresponding to an AER of 60 more infection episodes in 100 IgAN patients followed for 10 years, or one extra infection each year in 17 IgAN patients.

The incidence rate of sepsis during the follow up was 2.9 vs. 1.3 per 1 000 person-years respectively for IgAN patients and reference individuals. Hence,

the AER was 1.6 cases of sepsis per 100 patients followed for 10 years or equal to one extra case per 63 patients followed for 10 years.

Risk of infections before IgAN diagnosis

Linear regression analysis of previously recorded infections also showed a significant association ($\beta=0.53$; 95%CI 0.47-0.59), indicating an elevated risk even before time of diagnosis. This association was particularly strong in IgAN patients diagnosed in the most recent calendar period (2006-2011), who had a longer follow-up period (9-14 years), suggesting a persistently increased risk over time. The most common type of infection was urinary tract infection (UTI), with a coefficient of $\beta=0.25$ (95%CI 0.23-0.27).

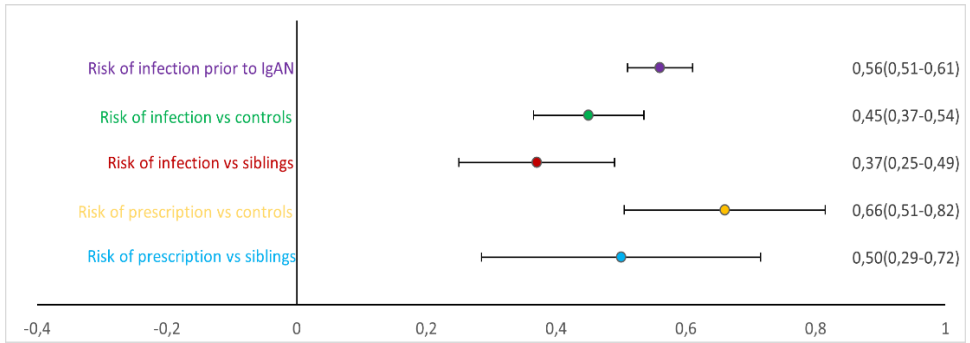


Figure 9. Summary main results, β -coefficients and 95%CI (linear regression). CI: Confidence interval.

Discussion

Main Findings

Paper I

Our study found a significant association between IBD and IgAN, both before and after IgAN diagnosis, and an increased risk of ESRD in IgAN patients with IBD compared to those without. Previous studies have shown that kidney manifestations, including nephrolithiasis, glomerulonephritis, and secondary amyloidosis, are common in IBD patients(107,109). Our results are in line with those of Ambruzs *et al.*'s review of kidney biopsy specimens that showed a three times higher prevalence of IgAN in IBD patients (24%) compared to non-IBD patients who underwent a kidney biopsy (8%)(108).

We identified 299 (7.4%) patients with IBD out of 4,066 IgAN patients, which aligns with or slightly exceeds findings from similar studies(181).

A study by Vajravelu *et al.* showed that 5.1% of IBD patients developed ESRD based on diagnostic criteria or estimated glomerular filtration rate(110). Our results showed a cumulative ESRD incidence of 50% in patients with IBD *and* IgAN, compared to only 1.3% in IBD patients without IgAN. In the group with IgAN without IBD the numbers were 927 of 3767 (25%).

The pathophysiological connection between IgAN and IBD remains unclear, but it is thought that abnormal T-cell responses and gut inflammation may trigger the production of aberrant IgA1 antibodies(114,116). Additionally, genetic factors like HLA-DR1(113,114) and raised cytokine levels, such as IL-17(118,119), may contribute to the shared inflammatory pathways in both diseases.

Studies have also highlighted the role of the mucosal immune system, with evidence that treatment targeting the ileocecal region in IgAN patients reduced proteinuria(66,67). This, combined with our results with a stronger association of ulcerative colitis (UC) with IgAN compared to Crohn's disease (CD), suggests that colonic inflammation may play a role in the development of glomerulonephritis. The chronic inflammation in the gastrointestinal mucosa may drive the production of the aberrantly glycosylated antibodies seen

in IgAN, contributing to the higher risk of ESRD in these patients. Other factors such as malnutrition and potentially nephrotoxic medications used in IBD treatment could also play a role.

Our results are supported by a subsequent Chinese genetic study (182) that found a significant positive causal effect of IBD (UC and CD) on IgAN risk but insufficient evidence for the causal effect of IgAN on IBD (UC, or CD).

Paper II

In our study, we found no evidence to support an increased risk of cancer before IgAN diagnosis, nor did we identify IgAN as a paramalignant condition. However, we observed an elevated cancer risk in IgAN patients who developed ESRD, particularly in those who had undergone kidney transplantation (aHR 4.46). Patients with ESRD without dialysis or transplant also had an increased risk (aHR 2.26), though this was lower than in transplant patients. The risk increase was primarily for NMSC and kidney cancer.

While earlier studies have suggested a link between cancer and IgAN(146–148,150–153,183), most of these were small or lacked statistical power. Unlike previous research(142–145,157,158), our results did not show a direct temporal relationship between IgAN and cancer diagnoses, nor an increased risk of cancer before IgAN diagnosis. This contrasts with some reports, such as Ryu *et al.*'s study(158), which found a higher cancer risk shortly after a kidney disease diagnosis. However, their findings in IgAN specifically were limited to only three cancer cases and thus lacked clinical significance. Heaf *et al.*(157) also investigated cancer incidence in patients with biopsy proven glomerulonephritis. Among 5,594 patients, they identified 911 cancer events, with the highest risk occurring primarily within one year before or after the glomerulonephritis diagnosis. However, IgAN patients were not studied separately but were grouped with more uncommon types of glomerulonephritis, so the findings cannot be fully generalized to the IgAN cohort.

Our findings of increased cancer risk in IgAN patients with ESRD, particularly for NMSC and kidney cancer, align with other studies that show a heightened cancer risk in kidney failure, regardless of underlying kidney disease(123–126,139). This suggests that impaired kidney function and also the supportive treatments(128,129,131–136,140), rather than IgAN itself, is likely responsible for the increased risk.

Xu *et al.* investigated the relationship between cancer risk and creatinine levels as part of the Stockholm Creatinine Measurements (SCREAM) project, which included data from 719,033 individuals over 40 years old with no prior history of cancer. They identified 64,319 cancer cases (9% of participants) and found a U-shaped association between kidney function decline and cancer risk. This association was modest and primarily driven by NMSC and urogenital cancers. They suggested that detection bias could partly account for the overestimation of cancer risk in CKD patients, particularly during the first year of follow-up(140). For IgAN patients without ESRD, we found no significant association with overall cancer risk, except for prostate, renal/uroepithelial cancer, and NMSC in older men. This may also be due to detection bias from more frequent healthcare visits and kidney screenings.

Immunosuppressive medications, especially in kidney transplant recipients, are likely to contribute to this elevated risk. Although we did not have sufficient data to assess the specific impact of medications, immunosuppression appears to be the main factor driving the increased cancer risk in the ESRD/transplant group.

There was little difference in cancer risk between ESRD patients and those who received a transplant, likely because the majority of ESRD patients in our study underwent transplantation (793 of 1,014). The most common cancer types were consistent with previous post-transplant studies, including NMSC, renal/uroepithelial, oral cavity, colorectal, and lymphoproliferative cancers(184).

Paper IV

Our study demonstrates an increased prevalence of infections and antibiotic prescriptions in IgAN patients compared to the general population and their siblings, both before and after IgAN diagnosis. Since our outcome was only based on hospital-based infections our risk estimates may primarily represent the risk of severe infection, but the concomitantly increased level of antimicrobial prescriptions likely reflects a truly increased frequency of infections as the prescription registry also contains all primary care prescriptions. Another important finding is the increased risk of sepsis, this has to our knowledge not been reported in IgAN previously, and warrants increased clinical awareness.

We are not aware of any other studies specifically addressing infection risk in IgAN patients with their known aberrant IgA1 antibody production, though

there are studies on IgA deficiency. While generally better tolerated than other antibody deficiencies, IgA deficiency still increases the risk of infections requiring hospitalization, particularly respiratory, gastrointestinal, ENT infections, UTIs, and sepsis(162,185–187), similar to the infection subtypes found in our study. Interestingly, in our analysis of infections before IgAN diagnosis, UTIs were most prominent, possibly due to misinterpretation of urinary dipsticks.

Both chronic kidney disease and proteinuria, with the associated loss of gamma globulins and complement factors, are recognized risk factors for infections(188–190). Previous research has shown that proteinuria increases infection risk, independent of kidney function(191,192). Although we do not have proteinuria data in our study, it likely contributes to the increased infection risk observed.

Corticosteroid treatment is another well-known risk factor for infections(64,65,193). In our cohort, 33% of patients were prescribed corticosteroids during follow-up, but only 3% had such prescriptions within 180 days of a sepsis diagnosis, compared to 2% of the reference group. Hence, corticosteroids are unlikely to be the sole explanation of the observed increased risk of sepsis in IgAN patients

Methodological considerations (Paper I, II and IV)

Validity and Generalizability

Our study cohort of biopsy verified IgAN patients was assembled through reports from pathology departments responsible for evaluating the biopsy specimens. Given that IgAN defined by characteristic histopathological features, a biopsy-confirmed diagnosis is generally considered reliable. To further validate the cohort, a journal review was performed on a randomly selected subset of patients, demonstrating a PPV of 95% of confirmed or likely IgAN. These findings support the high internal validity of the dataset and indicate that the correct population has been analyzed.

Most of our outcomes come from the NPR. The validity of the register is considered to be high. For IBD diagnosis the PPV value for having ≥ 2 IBD diagnoses was 93%, and other validation studies for different somatic disease the PPVs have been 87-99% (170,171).

The study cohort exclusively includes biopsy verified IgAN cases. As a result, individuals with a milder phenotype or subclinical disease not warranting biopsy were not included. While this does not compromise internal validity, it may limit the generalizability of the findings to a broader IgAN population. Although, our IgAN cohort consists of one third women and approximately 25% of the cohort developed ESRD, which is considered to be representative for the condition in general(3).

The Swedish population is predominantly of Caucasian descent, so the applicability of our results to other ethnic groups, particularly those of Asians or African descent, may be limited. Lastly, Sweden's publicly funded healthcare system and status as a high-income country could influence both access to care and long-term, making the transferability of results to settings with differing healthcare infrastructure and economic conditions.

Lastly, even if we found some statistically strong associations in our studies, studies with an observational design cannot establish causality.

Power, Bias and Limitations

Our large cohort comprising approximately 4,000 IgAN cases with 20,000 reference individuals provides substantial statistical power, hence a high ability to detect a true association when one exists (prevents type II errors). A large study also increases precision in estimates and narrows confidence intervals.

As observational studies cannot be randomized, there could be risk for systematic differences between groups (confounding) that can bias results. To address this, we have implemented matching and statistical adjustments. Matching should be performed on variables believed to influence both the likelihood of exposure (IgAN) and outcome. There is always a risk for overmatching, if chosen variables do not relate to the outcome, and thereby reducing the studies ability to detect meaningful associations. We sought to minimize bias and preserve statistical strength by only selecting key variables as sex, age, calendar year and residency, the latter two to ensure comparable access to healthcare and adherence to practice guidelines.

Even with high power and relevant matching, there is always a risk for other kinds of biases and study design limitations. **Selection bias** occurs when the participants included in a study are not representative of the target population, leading to systematic errors in the estimation of associations or outcomes. This

can result from how individuals are selected, lost to follow-up, or self-select into the study, potentially distorting the true relationship between exposure and outcome. Using data from our national mandatory registers without the option to “opt out” and virtually no loss of follow-up, we believe that this minimizes the risk of selection bias and strengthens our findings.

In our studies the risk of **ascertainment (or detection) bias** must also be considered. As IgAN patients are more likely to be followed and monitored in the health care system more symptoms may be followed up, investigated and diagnosed. As previously discussed, ascertainment bias may have influenced the result when we found an increased risk for prostate, renal/uroepithelial cancer, and NMSC in non-ESRD older men. To mitigate this bias in Paper I, we restricted one set of analysis to reference individuals with at least one entry in the NPR, and hence seen by a medical specialist during follow-up, to ensure that they were familiar to the healthcare system. This only slightly attenuated our association from aHR 3.29 to 2.96. In Paper I and II we performed analyses excluding the first year of follow-up, where ascertainment bias is most pronounced. This did not change our estimates more than marginally, and in Paper II we did *not* find an increased risk for any cancer diagnosis at all.

Another common bias is **misclassification bias**, where data is inaccurately interpreted or recorded, leading to individuals being wrongly categorized. In Paper IV, most infection types showed similar linear coefficients both before and after IgAN diagnosis with one exception: UTI being far more commonly diagnosed before IgAN diagnosis. This may reflect misclassification of pre-diagnosis protein/hematuria as UTI instead of IgAN.

Other limitations in Paper IV are that we did not have data on proteinuria levels, and we did not stratify for CKD stages due to lack of reliable data. Also, in Paper IV, a limitation is that our study does not include infections managed by primary care providers with the risk of missing outcomes, however, the data on antimicrobial prescriptions can be thought of as a proxy for diagnosed infections outside of hospital care, as it includes all primary care prescriptions.

Further, we did not include information on medications (except corticosteroids in Paper IV), comorbidity or other comorbidities than diabetes and ESRD in Paper IV. The ascertainment for smoking using proxy diagnoses (tobacco use and/or COPD) in Paper II is probably not complete.

There may always be residual **unmeasured confounders** in a study. In Paper IV we conducted sibling analyses to mitigate unmeasured *familial* confounding, and the results were consistent with those obtained when comparing with the general population.

The strengths of our studies (Paper I-II, IV) are the long follow up periods with more than 50% being followed for >10 years, the large size of a well-defined cohort, data from validated registers and robust statistical methods with consistent results in analyses including sensitivity and stratified analyses.

Validation Study (Paper III)

We found a high PPV for a histological IgAN diagnosis with a corresponding clinical IgAN diagnosis in patients registered in the SRR after having performed a kidney biopsy. Initially at 95%, the PPV rose to 98% when considering IgAN as a secondary kidney diagnosis. The clinical attributes of the individuals evaluated were in line with previous descriptions of IgAN patients, and our results are similar to those reported by Jarrick *et al.*, who also observed a PPV of 95% (95% CI 92-99%)(166).

Our validation study's strength is the high proportion (98%) of medical charts that were successfully obtained for comprehensive review. Secondly, the charts were sourced from a diverse array of Swedish nephrology clinics (n=29), thereby likely reducing potential selection bias; and thirdly, the detailed dataset encompassing laboratory results, original biopsy records, and medical charts allowed for a thorough evaluation of the patients' complete clinical profiles.

A limitation of the study is that we had to restrict the follow-up period to one year before and after diagnosis. Additionally, it's plausible that crucial information known to the treating physician might not have been documented in the available medical charts under review.

Clinical Implications

The risk of IBD in patients with IgAN

Our findings suggest an association between IBD and IgAN. Identification of IBD in IgAN patients may be useful for the risk prediction of ESRD. KDIGO guidelines(38) recommend the assessment of every biopsy-proven IgAN for causes of Secondary IgAN, such as IBD. Whether there is a different pathophysiological mechanism in primary IgAN compared to an IgAN driven by IBD was not within the scope of our study, however, systematic screening for IgAN and IBD (in terms of laboratory test for kidney disorder in gastroenterological departments, and increased awareness of signs and symptoms of IBD in nephrology departments) appears to be warranted, as well as extra surveillance in patients with both diagnoses. Further studies on pathophysiological mechanisms and whether optimized treatment for IBD improves prognosis in patients with IgAN are needed.

The risk of Cancer in patients with IgAN

Our study shows that IgAN does not seem to imply a higher risk of cancer, and that cancer screening is not needed in the average patient with IgAN. However, we did see a significant increase in cancer among men >60 years at diagnosis, so this subgroup may still merit surveillance.

With progressive disease the risk increases just as for any patient with kidney failure regardless of etiology. In patients with terminal kidney failure, especially those of high age, regular cancer screening should be advocated and directed questions recorded systematically to improve chances of an early detection of any future malignant condition (provided they are eligible for further interventions). Skin cancer surveillance should be performed routinely, especially in patients with a kidney transplant. Our results indicate approximately 6 extra cancer cases per 100 IgAN patients with ESRD per 10 years, or >17 extra cases if including NMSC as well.

Risk of Infections in patients with IgAN

Infections and antimicrobial prescriptions, especially antibiotics, were more common in IgAN patients than in matched reference individuals and siblings. We found an AER corresponding to one extra case of sepsis per 63 IgAN patients followed for 10 years. The increased risk of sepsis mandates clinical awareness to facilitate prevention with early antimicrobial treatment. The role

of proteinuria in the risk development should be considered and treated, and vaccination status for all patients should be discussed.

Validation study

Regarding the validation study, Sweden and the Nordic countries are globally renowned for their distinct population-based registries, encompassing compulsory nationwide healthcare databases and national quality registries like the SRR. Ongoing validation of these registries stands as a crucial aspect to ensure the accuracy and dependability of the data. Moreover, Swedish qualitative registers funded by taxes are obliged to regularly report internal quality validation to sustain their funding. Validating the globally common disease IgAN holds significant importance, as it paves the way for further research into the etiology and prognosis of patients with IgAN. The validation of the SRR, with a high PPV for biopsy-proven IgAN, strengthens it as a valuable resource of data in future IgAN research.

Conclusions

We found an association between IgAN and increased risk of IBD and demonstrated that concomitant diagnoses of IgAN and IBD were associated with future elevated risk ESRD. Common genetic and pathophysiological mechanisms are probable explanations.

We found no support for a higher risk of cancer preceding an IgAN diagnosis, or for IgAN acting as a paramalignant condition. We found an elevated risk for cancer in patients with IgAN, but this excess risk was confined only to those who developed ESRD and especially increased in patients with a kidney transplant. We do not interpret this association to be IgAN specific, but rather potentially linked to decline in kidney function and the impact of immunosuppressive treatments.

We found an increased incidence of infections and antibiotic prescriptions in IgAN patients compared to the general population and their siblings. The heightened susceptibility may be attributed to underlying immunological aberrations and proteinuria.

Our medical chart validation of the SRR established a high PPV (95%) for clinical IgAN in patients with an IgAN biopsy. Clinical characteristics of the evaluated patients were consistent with previous reports of IgAN patients.

Populärvetenskaplig sammanfattning

IgA-nefropati (IgAN) är världens vanligaste inflammatoriska njursjukdom. Sjukdomen drabbar båda könen och alla åldrar, även om det är något vanligare att diagnosticeras i yngre medelåldern. IgAN leder i 30-40% av fallen till terminal njursvikt med behov av dialys eller transplantation inom 20–30 år. Sjukdomen kan även återkomma i njurtransplantat. Den här avhandlingen syftar till att undersöka om patienter med IgAN har högre risk att drabbas av andra sjukdomar också och om samsjuklighet bidrar till sämre prognos.

I tre av de fyra forskningsprojekten använder vi oss av ett personregister innehållande 4096 individer med en biopsiverifierad IgAN-diagnos. Det finns inga specifika prover eller urinundersökningar för att ställa diagnosen, vilket innebär att en njurbiopsi krävs för att man ska vara helt säker. Personregistret sammanställdes av Welander *et al.* 2013 genom insamling av data från de fyra patologienheter som då bedömde njurbiopsier i Sverige. Biopsierna utfördes mellan åren 1974–2011. Registret har därefter kontrollerats genom journalgenomgångar av Jarrick *et al.* för att bekräfta att diagnosen var korrekt.

För varje individ med IgAN har Statistiska Centralbyrån identifierat 5 referensindivider med samma ålder och kön, som vi kan jämföra sjukdomshistoria med. Genom individernas personnummer har data länkats från Nationella Patient-, Cancer- och Läkemedelsregistret.

I den första studien undersöker vi sambandet mellan IgAN och inflammatorisk tarmsjukdom (IBD) och huruvida patienter med båda tillstånden har en sämre prognos vad gäller deras njursjukdom. Här såg vi att patienter med IgAN har en större risk att drabbas av IBD både före och efter sin IgAN-diagnos. De patienter som hade båda sjukdomarna hade tydlig ökad risk för att utveckla terminal njursvikt.

I den andra studien analyserar vi om patienter med IgAN har en ökad risk för cancer. Det har debatterats ifall en IgAN-diagnos skulle kunna vara ett så kallat *paramalignt fenomen*, alltså något som uppstår p.g.a att det finns en cancersjukdom i kroppen. Vi fann inget stöd för att patienter med IgAN hade en ökad risk för cancer, varken före eller efter de fått sin diagnos. Det verkar inte heller finnas belägg för att tillståndet skulle kunna härledas till redan befintlig can-

cer. Däremot såg vi att risken för cancer ökar i takt med försämrad njurfunktion. Det stämmer med tidigare studieresultat, och tros vara kopplat till njursvikten i sig oavsett bakomliggande orsak.

I den fjärde studien undersöker vi risken för primära infektioner hos IgAN patienter. Här kunde vi visa att de hade en högre frekvens av infektionsinsjuknanden samt även fler utskrivna recept mot bakteriella och andra mikrobiella tillstånd. Denna risk var förhöjd både när man jämförde patienterna med sina referensindivider och med deras egna syskon.

Den tredje studien är en validering av Svenskt Njurregister (SNR). I SNR registrerar samtliga njurkliniker i Sverige information om patienter med kronisk njursjukdom. År 2015 startade en ny del i registret, där kliniker lägger in information om genomförda diagnostiska njurbiopsier. En validering är en granskande genomgång och i vårt projekt granskade vi den nya biopsidelen för att se om införda uppgifter i SNR överensstämmer med patienternas kliniska verklighet. Regelbunden validering av nationella register är inte bara en kvalitetsförsäkran, utan även en förutsättning för att register som SNR ska få fortsatt skattefinansiering av Sveriges Kommuner och Regioner (SKR). Vi kunde konstatera att det var en hög grad av tillförlitlighet på den informationen som hade registrerats i SNR gällande genomförda biopsier och att det överensstämde med patienternas kliniska bild.

IgAN är en vanlig sjukdom med många nu drabbade individer och kommande i framtida generationer. Våra resultat skulle kunna leda till att man mer systematiskt och regelbundet gör riktade undersökningar mot förekomst av IBD. Å andra sidan verkar man kunna undvika onödiga utvidgade utredningar för cancer vid nydiagnostiserad IgAN. Detta kan bespara både sjukvårdens och patienternas tid och resurser. Vi kan också visa på att man bör vara observant på den ökade risken för infektioner hos patienter med IgAN och att man t.ex. ser över att de har fått sina rekommenderade vaccinationer.

Valideringen av SNR stärker registrets ställning som källa av pålitliga data för framtida forskning.

Acknowledgements

I would like to express my deepest gratitude to all those who have supported me and contributed to the completion of this work:

To my supervisors, Louise Emilsson and Jonas F. Ludvigsson, for their invaluable expertise, guidance, and, quite frankly, their seemingly supernatural abilities.

To my dear colleagues at the Nephrology Department, for their unwavering support and for going the extra mile at the clinic during my absences.

To my boss, Anna-Karin Larsson, for her constant encouragement and for making it possible to combine clinical duties with research.

To the Värmland and Örebro County Councils, for their generous financial support throughout the years.

To Kersti Theander at the Centrum för Klinisk Forskning, for encouraging me to take the first step on this journey.

To Anita Berglund and her team at SINGS, for providing a solid foundation upon which to build future research.

To Märten Segelmark, for his outstanding support both as an all-knowing nephrologist and as a co-author.

To Adina Symreng, Simon Jarrick, and Juan-Jesus Carrero, for their collaboration and contributions as co-authors.

To all the dedicated coworkers across clinics in Sweden who voluntarily contributed their time and effort to the validation study.

And finally, to my beloved family, who make everything easier and more joyful after a long day's work.

REFERENCES

1. Berger J, Hinglais N. [Intercapillary deposits of IgA-IgG]. *J Urol Nephrol (Paris)*. 1968;
2. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. *Quarterly Journal of Medicine*. 1987.
3. Donadio J V., Grande JP. IgA nephropathy. *New England Journal of Medicine*. 2002.
4. Willey CJ, Coppo R, Schaefer F, Mizerska-Wasiak M, Mathur M, Schultz MJ. The incidence and prevalence of IgA nephropathy in Europe. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2023 Sep;38(10):2340–9.
5. D'Amico G. Natural history of idiopathic IgA nephropathy and factors predictive of disease outcome. *Semin Nephrol*. 2004;
6. Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet*. 2012;8(6).
7. Lu S, Liu D, Xiao J, Cheng G, Zhang X, Liu Z, et al. Correlation Between Clinical and Pathological Characteristics of Henoch-Schönlein Purpura Nephritis in Adults. *Iran J Kidney Dis*. 2016 Jan;11(1):12–7.
8. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013 Jan;65(1):1–11.
9. Rollino C, Vischini G, Coppo R. IgA nephropathy and infections. *J Nephrol*. 2016;29(4):463–8.
10. He JW, Zhou XJ, Lv JC, Zhang H. Perspectives on how mucosal immune responses, infections and gut microbiome shape iga nephropathy and future therapies. *Theranostics*. 2020;10(25):11462–78.
11. Novak J, Moldoveanu Z, Julian BA, Raska M, Wyatt RJ, Suzuki Y, et al. Aberrant glycosylation of iga1 and anti-glycan antibodies in iga nephropathy: Role of mucosal immune system. In: *Advances in Oto-Rhino-Laryngology*. 2011.
12. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. *Kidney Int*. 2015 Nov;88(5):974–89.
13. Salvadori M, Rosso G. Update on immunoglobulin a nephropathy. Part II: Clinical, diagnostic and therapeutical aspects. *World J Nephrol*. 2016 Jan;5(1):6–19.

14. Barratt J, Rovin BH, Cattran D, Floege J, Lafayette R, Tesar V, et al. Why Target the Gut to Treat IgA Nephropathy? Vol. 5, *Kidney international reports*. United States; 2020. p. 1620–4.
15. Berthoux F, Suzuki H, Thibaudin L, Yanagawa H, Maillard N, Mariat C, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. *J Am Soc Nephrol*. 2012 Sep;23(9):1579–87.
16. Yanagawa H, Suzuki H, Suzuki Y, Kiryluk K, Gharavi AG, Matsuoka K, et al. A panel of serum biomarkers differentiates IgA nephropathy from other renal diseases. *PLoS One*. 2014;9(5):e98081.
17. Wyatt RJ, Julian BA. *Medical progress: IgA nephropathy*. New England Journal of Medicine. 2013.
18. Chen P, Yu G, Zhang X, Xie X, Wang J, Shi S, et al. Plasma Galactose-Deficient IgA1 and C3 and CKD Progression in IgA Nephropathy. *Clin J Am Soc Nephrol*. 2019 Oct;14(10):1458–65.
19. Welander A, Sundelin B, Fored M, Ludvigsson JF. Increased risk of IgA nephropathy among individuals with celiac disease. *J Clin Gastroenterol*. 2013;
20. Kudose S, Santoriello D, Bomback AS, Stokes MB, D’agati VD, Markowitz GS. Sensitivity and specificity of pathologic findings to diagnose lupus nephritis. *Clin J Am Soc Nephrol*. 2019;
21. Saha MK, Julian BA, Novak J, Rizk D V. Secondary IgA nephropathy. *Kidney International*. 2018.
22. Varis J, Rantala I, Pasternack A, Oksa H, Jäntti M, Paunu ES, et al. Immunoglobulin and complement deposition in glomeruli of 756 subjects who had committed suicide or met with a violent death. *J Clin Pathol*. 1993 Jul;46(7):607–10.
23. Suzuki K, Honda K, Tanabe K, Toma H, Nihei H, Yamaguchi Y. Incidence of latent mesangial IgA deposition in renal allograft donors in Japan. *Kidney Int*. 2003;
24. Roberts ISD, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: Pathology definitions, correlations, and reproducibility. *Kidney Int*. 2009;76(5):546–56.
25. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int*. 2014 Oct;86(4):828–36.
26. Lv J, Shi S, Xu D, Zhang H, Troyanov S, Cattran DC, et al. Evaluation of the Oxford Classification of IgA nephropathy: a systematic review and meta-analysis. *Am J kidney Dis Off J Natl*

- Kidney Found. 2013 Nov;62(5):891–9.
27. Fiorentino M, Bolignano D, Tesar V, Pisano A, Van Biesen W, D'Arrigo G, et al. Renal Biopsy in 2015--From Epidemiology to Evidence-Based Indications. *Am J Nephrol*. 2016;43(1):1–19.
 28. McGrogan A, Franssen CFM, De Vries CS. The incidence of primary glomerulonephritis worldwide: A systematic review of the literature. *Nephrology Dialysis Transplantation*. 2011.
 29. Wyatt RJ, Julian BA, Baehler RW, Stafford CC, Mcmorrow RG, Ferguson T, et al. Epidemiology of IgA nephropathy in central and eastern Kentucky for the period 1975 through 1994. *J Am Soc Nephrol*. 1998;
 30. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, et al. The incidence of biopsy-proven glomerulonephritis in Australia. *Nephrol Dial Transplant*. 2001;
 31. Utsunomiya Y, Koda T, Kado T, Okada S, Hayashi A, Kanzaki S, et al. Incidence of pediatric IgA nephropathy. *Pediatr Nephrol*. 2003 Jun;18(6):511–5.
 32. Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkinno H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. *Clin J Am Soc Nephrol*. 2007 Nov;2(6):1360–6.
 33. <https://www.medscinet.net/snr/rapporтерdocs/Svenskt%20Njurregi ster%20%C3%85rsrapport%202024.pdf> [Internet]. SNR2024.
 34. McQuarrie EP, Mackinnon B, McNeice V, Fox JG, Geddes CC. The incidence of biopsy-proven IgA nephropathy is associated with multiple socioeconomic deprivation. *Kidney Int*. 2014;
 35. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol*. 2011 Oct;22(10):1795–803.
 36. Scolari F, Amoroso A, Savoldi S, Mazzola G, Prati E, Valzorio B, et al. Familial clustering of IgA nephropathy: further evidence in an Italian population. *Am J kidney Dis Off J Natl Kidney Found*. 1999 May;33(5):857–65.
 37. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Vol. 105, *Kidney international*. United States; 2024. p. S117–314.
 38. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* [Internet]. 2021;100(4):S1–276. Available from: <https://kdigo.org/wp-content/uploads/2017/02/KDIGO-Glomerular-Diseases-Guideline-2021-English.pdf>

39. KDIGO IgA [Internet]. Available from: <https://kdigo.org/igan-igav-public-review-draft/>
40. Caster DJ, Lafayette RA. The Treatment of Primary IgA Nephropathy: Change, Change, Change. *Am J kidney Dis Off J Natl Kidney Found.* 2024 Feb;83(2):229–40.
41. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. *J Am Soc Nephrol.* 2024 Jan;35(1):103–16.
42. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. *Clin J Am Soc Nephrol.* 2017 Apr;12(4):677–86.
43. Lennartz DP, Seikrit C, Wied S, Fitzner C, Eitner F, Hilgers RD, et al. Single versus dual blockade of the renin-angiotensin system in patients with IgA nephropathy. *J Nephrol.* 2020 Dec;33(6):1231–9.
44. Zachariah T, Radhakrishnan J. Potential Role of Mineralocorticoid Receptor Antagonists in Nondiabetic Chronic Kidney Disease and Glomerular Disease. *Clin J Am Soc Nephrol.* 2024 Nov;19(11):1499–512.
45. Kim DL, Lee SE, Kim NH. Renal Protection of Mineralocorticoid Receptor Antagonist, Finerenone, in Diabetic Kidney Disease. *Endocrinol Metab (Seoul, Korea).* 2023 Feb;38(1):43–55.
46. Bombback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol.* 2007 Sep;3(9):486–92.
47. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2023 Jan;388(2):117–27.
48. Heerspink HJL, Stefánsson B V, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020 Oct;383(15):1436–46.
49. Wheeler DC, Toto RD, Stefánsson B V, Jongs N, Chertow GM, Greene T, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int.* 2021 Jul;100(1):215–24.
50. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, et al. An Overview of the Cardiorenal Protective Mechanisms of SGLT2 Inhibitors. *Int J Mol Sci.* 2022 Mar;23(7).
51. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int.* 2014 Nov;86(5):896–904.
52. Heerspink HJL, Parving HH, Andress DL, Bakris G, Correa-Rotter R, Hou FF, et al. Atrasentan and renal events in patients with type

- 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* (London, England). 2019 May;393(10184):1937–47.
53. Trachtman H, Nelson P, Adler S, Campbell KN, Chaudhuri A, Derebail VK, et al. DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS. *J Am Soc Nephrol*. 2018 Nov;29(11):2745–54.
 54. Smeijer JD, Kohan DE, Webb DJ, Dhaun N, Heerspink HJL. Endothelin receptor antagonists for the treatment of diabetic and nondiabetic chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2021 Jul;30(4):456–65.
 55. Dhaun N, MacIntyre IM, Kerr D, Melville V, Johnston NR, Haughe S, et al. Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertens* (Dallas, Tex 1979). 2011 Apr;57(4):772–9.
 56. Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. *Kidney Int*. 2021 Feb;99(2):346–9.
 57. Rovin BH, Barratt J, Heerspink HJL, Alpers CE, Bieler S, Chae DW, et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. *Lancet* (London, England). 2023 Dec;402(10417):2077–90.
 58. Heerspink HJL, Radhakrishnan J, Alpers CE, Barratt J, Bieler S, Diva U, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. *Lancet* (London, England). 2023 May;401(10388):1584–94.
 59. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet* (London, England). 1999 Mar;353(9156):883–7.
 60. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol*. 2004 Jan;15(1):157–63.
 61. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial*

Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2009 Dec;24(12):3694–701.

62. Tesar V, Troyanov S, Bellur S, Verhave JC, Cook HT, Feehally J, et al. Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study. *J Am Soc Nephrol*. 2015 Sep;26(9):2248–58.
63. Nagasawa Y, Yamamoto R, Shinzawa M, Shoji T, Hasuike Y, Nagatoya K, et al. Efficacy of corticosteroid therapy for IgA nephropathy patients stratified by kidney function and proteinuria. *Clin Exp Nephrol*. 2020 Oct;24(10):927–34.
64. Rauen T, Eitner F, Fitzner C, Sommerer C, Zeier M, Otte B, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med*. 2015 Dec;373(23):2225–36.
65. Wong MG, Lv J, Hladunewich MA, Jha V, Hooi LS, Monaghan H, et al. The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) Study: Trial Design and Baseline Characteristics. *Am J Nephrol*. 2021;52(10–11):827–36.
66. Smerud HK, Bárány P, Lindström K, Fernström A, Sandell A, Pählsson P, et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant*. 2011;
67. Fellström BC, Barratt J, Cook H, Coppo R, Feehally J, de Fijter JW, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet (London, England)*. 2017 May;389(10084):2117–27.
68. Ismail G, Oabrișcă B, Jurubiță R, Andronesi A, Sorohan B, Vornicu A, et al. Budesonide versus systemic corticosteroids in IgA Nephropathy: A retrospective, propensity-matched comparison. *Medicine (Baltimore)*. 2020 Jun;99(26):e21000.
69. Barratt J, Lafayette R, Kristensen J, Stone A, Cattran D, Floege J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NeflgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int*. 2023 Feb;103(2):391–402.
70. Ballardie FW, Roberts ISD. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol*. 2002 Jan;13(1):142–8.
71. Tang S, Leung JCK, Chan LYY, Lui YH, Tang CSO, Kan CH, et al. Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. *Kidney Int*. 2005 Aug;68(2):802–12.

72. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleggem J, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int.* 2004 May;65(5):1842–9.
73. Frisch G, Lin J, Rosenstock J, Markowitz G, D'Agati V, Radhakrishnan J, et al. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc.* 2005 Oct;20(10):2139–45.
74. Floege J, Rauen T, Tang SCW. Current treatment of IgA nephropathy. *Semin Immunopathol.* 2021 Oct;43(5):717–28.
75. Du B, Jia Y, Zhou W, Min X, Miao L, Cui W. Efficacy and safety of mycophenolate mofetil in patients with IgA nephropathy: an update meta-analysis. *BMC Nephrol.* 2017 Jul;18(1):245.
76. Hou FF, Xie D, Wang J, Xu X, Yang X, Ai J, et al. Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy: A Randomized Clinical Trial. *JAMA Netw open.* 2023 Feb;6(2):e2254054.
77. Zhang Y, Luo J, Hu B, Ma T. Efficacy and safety of tacrolimus combined with glucocorticoid treatment for IgA nephropathy: a meta-analysis. *J Int Med Res.* 2018 Aug;46(8):3236–50.
78. Perkovic V, Barratt J, Rovin B, Kashihara N, Maes B, Zhang H, et al. Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy. *N Engl J Med.* 2025 Feb;392(6):531–43.
79. Novartis. p. www.novartis.com/news/media-releases/novartis-rece.
80. Bruchfeld A, Magin H, Nachman P, Parikh S, Lafayette R, Potarca A, et al. C5a receptor inhibitor avacopan in immunoglobulin A nephropathy-an open-label pilot study. *Clin Kidney J.* 2022 May;15(5):922–8.
81. Lundberg S, Westergren E, Smolander J, Bruchfeld A. B cell-depleting therapy with rituximab or ofatumumab in immunoglobulin A nephropathy or vasculitis with nephritis. *Clin Kidney J.* 2017 Feb;10(1):20–6.
82. Lafayette RA, Canetta PA, Rovin BH, Appel GB, Novak J, Nath KA, et al. A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction. *J Am Soc Nephrol.* 2017 Apr;28(4):1306–13.
83. Selvaskandan H, Gonzalez-Martin G, Barratt J, Cheung CK. IgA nephropathy: an overview of drug treatments in clinical trials. *Expert Opin Investig Drugs.* 2022 Dec;31(12):1321–38.
84. Tonelli MA, Wanner C, Cass A, Garg AX, Holdaas H, Jardine AG,

- et al. Kidney Disease: Improving Global Outcomes (KDIGO) lipid work group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl.* 2013;3(3):1–315.
85. Zhang Z, Wu P, Zhang J, Wang S, Zhang G. The effect of statins on microalbuminuria, proteinuria, progression of kidney function, and all-cause mortality in patients with non-end stage chronic kidney disease: A meta-analysis. *Pharmacol Res.* 2016 Mar;105:74–83.
 86. Buemi M, Allegra A, Corica F, Aloisi C, Giacobbe M, Pettinato G, et al. Effect of fluvastatin on proteinuria in patients with immunoglobulin A nephropathy. *Clin Pharmacol Ther.* 2000 Apr;67(4):427–31.
 87. Moriyama T, Oshima Y, Tanaka K, Iwasaki C, Ochi A, Itabashi M, et al. Statins stabilize the renal function of IgA nephropathy. *Ren Fail.* 2014 Apr;36(3):356–60.
 88. Konishi Y, Nishiyama A, Morikawa T, Kitabayashi C, Shibata M, Hamada M, et al. Relationship between urinary angiotensinogen and salt sensitivity of blood pressure in patients with IgA nephropathy. *Hypertens (Dallas, Tex 1979).* 2011 Aug;58(2):205–11.
 89. Yamamoto R, Nagasawa Y, Shoji T, Iwatani H, Hamano T, Kawada N, et al. Cigarette smoking and progression of IgA nephropathy. *Am J kidney Dis Off J Natl Kidney Found.* 2010 Aug;56(2):313–24.
 90. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int.* 2007 Jan;71(2):159–66.
 91. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. *Adv Chronic Kidney Dis.* 2015 Jan;22(1):6–15.
 92. Coppo R, Roccatello D, Amore A, Quattrocchio G, Molino A, Gianoglio B, et al. Effects of a gluten-free diet in primary IgA nephropathy. *Clin Nephrol.* 1990 Feb;33(2):72–86.
 93. Lai KN, Tang SCW, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. *Nat Rev Dis Prim.* 2016 Feb;2:16001.
 94. Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem MA, et al. Long-Term Outcomes in IgA Nephropathy. *Clin J Am Soc Nephrol.* 2023 Jun;18(6):727–38.
 95. Lafayette RA, Kelepouris E. Immunoglobulin A Nephropathy: Advances in Understanding of Pathogenesis and Treatment. *Am J*

- Nephrol. 2018;47 Suppl 1:43–52.
96. Barbour SJ, Coppo R, Zhang H, Liu ZH, Suzuki Y, Matsuzaki K, et al. Evaluating a New International Risk-Prediction Tool in IgA Nephropathy. *JAMA Intern Med.* 2019 Jul;179(7):942–52.
 97. Zhang Y, Guo L, Wang Z, Wang J, Er L, Barbour SJ, et al. External Validation of International Risk-Prediction Models of IgA Nephropathy in an Asian-Caucasian Cohort. *Kidney Int reports.* 2020 Oct;5(10):1753–63.
 98. Schena FP, Cerullo G, Rossini M, Lanzilotta SG, D’Altri C, Manno C. Increased risk of end-stage renal disease in familial IgA nephropathy. *J Am Soc Nephrol.* 2002 Feb;13(2):453–60.
 99. Shi M, Yu S, Ouyang Y, Jin Y, Chen Z, Wei W, et al. Increased Lifetime Risk of ESRD in Familial IgA Nephropathy. *Kidney Int reports.* 2021 Jan;6(1):91–100.
 100. Simon Jarrick, Sigrid Lundberg, Olof Stephansson, Adina Symreng, matteo Bottai, Jonas Höijer J f L. Pregnancy outcomes in women with immunoglobulin A nephropathy: a nationwide population-based cohort study. 2021;Oct;34(5):1591–8.
 101. Su X, Lv J, Liu Y, Wang J, Ma X, Shi S, et al. Pregnancy and Kidney Outcomes in Patients With IgA Nephropathy: A Cohort Study. *Am J kidney Dis Off J Natl Kidney Found.* 2017 Aug;70(2):262–9.
 102. Moroni G, Belingeri M, Frontini G, Tamborini F, Messa P. Immunoglobulin A nephropathy. Recurrence after renal transplantation. *Frontiers in Immunology.* 2019.
 103. Garnier AS, Dureau A, Demiselle J, Croué A, Subra JF, Sayegh J, et al. Early post-transplant serum IgA level is associated with IgA nephropathy recurrence after kidney transplantation. *PLoS One.* 2018;
 104. Pippias M, Stel VS, Aresté-Fosalba N, Couchoud C, Fernandez-Fresnedo G, Finne P, et al. Long-term Kidney Transplant Outcomes in Primary Glomerulonephritis: Analysis From the ERA-EDTA Registry. *Transplantation.* 2016 Sep;100(9):1955–62.
 105. Jarrick S, Lundberg S, Welandar A, Carrero JJ, Höijer J, Bottai M, et al. Mortality in IgA nephropathy: A nationwide population-based cohort study. *J Am Soc Nephrol.* 2019;
 106. Sato H, Ichikawa D, Okada E, Suzuki T, Watanabe S, Shirai S, et al. Spontaneous remission in adult patients with IgA nephropathy treated with conservative therapy. *PLoS One.* 2021;16(5):e0251294.
 107. Park S, Chun J, Han K Do, Soh H, Choi K, Kim JH, et al. Increased end-stage renal disease risk in patients with

- inflammatory bowel disease: A nationwide population-based study. *World J Gastroenterol*. 2018;
108. Ambruzs JM, Walker PD, Larsen CP. The histopathologic spectrum of kidney biopsies in patients with inflammatory bowel disease. *Clin J Am Soc Nephrol*. 2014;
 109. Pardi D. Renal and Urologic Complications of Inflammatory Bowel Disease. *Am J Gastroenterol*. 1998;
 110. Vajravelu RK, Copelovitch L, Osterman MT, Scott FI, Mamtani R, Lewis JD, et al. Inflammatory Bowel Diseases Are Associated With an Increased Risk for Chronic Kidney Disease, Which Decreases With Age. *Clin Gastroenterol Hepatol*. 2019;
 111. Hirsch DJ, Jindal KK, Trillo A, Cohen AD. Acute Renal Failure in Crohn's Disease Due to IgA Nephropathy. *Am J Kidney Dis*. 1992;
 112. Filiopoulos V, Trompouki S, Hadjiyannakos D, Paraskevakou H, Kamperoglou D, Vlassopoulos D. IgA nephropathy in association with Crohn's disease: A case report and brief review of the literature. *Ren Fail*. 2010;
 113. Oikonomou K, Kapsoritakis A, Eleftheriadis T, Stefanidis I, Potamianos S. Renal manifestations and complications of inflammatory bowel disease. *Inflammatory Bowel Diseases*. 2011.
 114. Terasaka T, Uchida HA, Umebayashi R, Tsukamoto K, Tanaka K, Kitagawa M, et al. The possible involvement of intestine-derived IgA1: A case of IgA nephropathy associated with Crohn's disease. *BMC Nephrol*. 2016;
 115. Coppo R. The Gut-Renal Connection in IgA Nephropathy. *Seminars in Nephrology*. 2018.
 116. Trimarchi HM, Iotti A, Iotti R, Freixas EAR, Peters R. Immunoglobulin A Nephropathy and Ulcerative Colitis. *Am J Nephrol*. 2001;
 117. Kett K, Brandtzaeg P. Local IgA subclass alterations in ulcerative colitis and Crohn's disease of the colon. *Gut*. 1987;
 118. Choi JY, Yu CH, Jung HY, Jung MK, Kim YJ, Cho JH, et al. A case of rapidly progressive IgA nephropathy in a patient with exacerbation of Crohns disease. *BMC Nephrol*. 2012;
 119. Lin FJ, Jiang GR, Shan JP, Zhu C, Zou J, Wu XR. Imbalance of regulatory T cells to Th17 cells in IgA nephropathy. *Scand J Clin Lab Invest*. 2012;
 120. Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M, Verbitsky M, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet*. 2014;
 121. Shi D, Zhong Z, Wang M, Cai L, Fu D, Peng Y, et al.

- Identification of susceptibility locus shared by IgA nephropathy and inflammatory bowel disease in a Chinese Han population. *J Hum Genet.* 2020;
122. Elaziz MMA, Fayed A. Patterns of renal involvement in a cohort of patients with inflammatory bowel disease in Egypt. *Acta Gastroenterol Belg.* 2018;
 123. Matas AJ, Kjellstrand CM, Simmons RL, Buselmeier TJ, Najarian JS. INCREASED INCIDENCE OF MALIGNANCY DURING CHRONIC RENAL FAILURE. *Lancet.* 1975;
 124. Cengiz K. Increased incidence of neoplasia in chronic renal failure (20-year experience). *Int Urol Nephrol.* 2002;
 125. Vajdic CM, McDonald SP, McCredie MRE, Van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. *J Am Med Assoc.* 2006;
 126. Mok Y, Matsushita K, Ballew SH, Sang Y, Jung KJ, Lee S, et al. Kidney Function, Proteinuria, and Cancer Incidence: The Korean Heart Study. *Am J Kidney Dis.* 2017;
 127. Iff S, Craig JC, Turner R, Chapman JR, Wang JJ, Mitchell P, et al. Reduced estimated GFR and cancer mortality. *Am J Kidney Dis.* 2014;
 128. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int.* 2005;
 129. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002.
 130. Lawless MW, O'Byrne KJ, Gray SG. Targeting oxidative stress in cancer. *Expert Opinion on Therapeutic Targets.* 2010.
 131. Franses JW, Drosu NC, Gibson WJ, Chitalia VC, Edelman ER. Dysfunctional endothelial cells directly stimulate cancer inflammation and metastasis. *Int J Cancer.* 2013;
 132. Viazzi F, Bonino B, Cappadona F, Pontremoli R. Renin-angiotensin-aldosterone system blockade in chronic kidney disease: current strategies and a look ahead. *Internal and Emergency Medicine.* 2016.
 133. Ager EI, Neo J, Christophi C. The renin-angiotensin system and malignancy. *Carcinogenesis.* 2008.
 134. González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D Insufficiency and Deficiency in Chronic Kidney Disease. *Am J Nephrol.* 2004;
 135. Vandewalle B, Adenis A, Hornez L, Revillion F, Lefebvre J. 1,25-Dihydroxyvitamin D3 receptors in normal and malignant human colorectal tissues. *Cancer Lett.* 1994;
 136. Mawer EB, Walls J, Howell A, Davies M, Ratcliffe WA, Bundred

- NJ. Serum 1,25-dihydroxyvitamin D may be related inversely to disease activity in breast cancer patients with bone metastases. *J Clin Endocrinol Metab.* 1997;
137. Christensson A, Savage C, Sjoberg DD, Cronin AM, Frank O'Brien M, Lowrance W, et al. Association of cancer with moderately impaired renal function at baseline in a large, representative, population-based cohort followed for up to 30 years. *Int J Cancer.* 2013;
 138. Lowrance WT, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the risk of incident cancer. *J Am Soc Nephrol.* 2014;
 139. Wong G, Hayen A, Chapman JR, Webster AC, Jie JW, Mitchell P, et al. Association of CKD and cancer risk in older people. *J Am Soc Nephrol.* 2009;
 140. Xu H, Matsushita K, Su G, Trevisan M, Ärnlöv J, Barany P, et al. Estimated glomerular filtration rate and the risk of cancer. *Clin J Am Soc Nephrol.* 2019;
 141. Jørgensen L, Heuch I, Jenssen T, Jacobsen BK. Association of albuminuria and cancer incidence. *J Am Soc Nephrol.* 2008;
 142. Lee JC, Yamauchi H, Hopper J. The association of cancer and the nephrotic syndrome. *Ann Intern Med.* 1966;
 143. Lien YHH, Lai LW. Pathogenesis, diagnosis and management of paraneoplastic glomerulonephritis. *Nature Reviews Nephrology.* 2011.
 144. Pani A, Porta C, Cosmai L, Melis P, Floris M, Piras D, et al. Glomerular diseases and cancer: evaluation of underlying malignancy. *Journal of Nephrology.* 2016.
 145. Ronco PM. Paraneoplastic glomerulopathies: New insights into an old entity. *Kidney Int.* 1999;
 146. Tanaka K, Kanzaki H, Taguchi T. IgA glomerulonephritis in a patient with renal cell carcinoma. *Japanese J Nephrol.* 1991;
 147. Magyarlaki T, Kiss B, Buzogány I, Fazekas A, Sükösd F, Nagy J. Renal cell carcinoma and paraneoplastic IgA nephropathy. *Nephron.* 1999;
 148. Mimura I, Tojo A, Kinugasa S, Uozaki H, Fujita T. Renal cell carcinoma in association with IgA nephropathy in the elderly. *Am J Med Sci.* 2009;
 149. Paraneoplastic IgA nephritis as initial symptom of a bronchial carcinoma. *Lung Cancer.* 1997;
 150. Mustonen J, Pasternack A, Helin H. IgA mesangial nephropathy in neoplastic diseases. *Contrib Nephrol.* 1984;
 151. Lam KY, Law SYK, Chan KW, Yuen MC. Glomerulonephritis associated with basaloid squamous cell carcinoma of the

- oesophagus: A possible unusual paraneoplastic syndrome. *Scand J Urol Nephrol*. 1998;
152. Bajel A, Yin Lin M, Hill PA, Goodman D, McCormack C, Foley P, et al. IgA nephropathy associated with cutaneous T cell lymphoma. *Leukemia and Lymphoma*. 2009.
 153. Cherubini C, Barbera G, Di Giulio S, Muda AO, Faraggiana T. Lymphomas and IgA nephropathy [4]. *Nephrology Dialysis Transplantation*. 2001.
 154. Blanco P, Denisi R, Rispal P, Deminière C, Pellegrin JL, Leng B, et al. Henoch-Schonlein purpura associated with segmental and focal proliferative glomerulonephritis in a patient with Hodgkin's disease. *Nephrol Dial Transplant*. 1999;
 155. Bergmann J, Buchheidt D, Waldherr R, Maywald O, Van Der Woude FJ, Hehlmann R, et al. IgA nephropathy and Hodgkin's disease: A rare coincidence. Case report and literature review. *Am J Kidney Dis*. 2005;
 156. Zahner J, Bach D, Malms J, Schneider W, Diercks K, Grabensee B. [Glomerulonephritis and malignant lymphoma. Mostly men with low-grade lymphoma with various forms of glomerulonephritis]. *Med Klin*. 1997;
 157. Heaf JG, Hansen A, Laier GH. Quantification of cancer risk in glomerulonephritis. *BMC Nephrol*. 2018;
 158. Ryu J, Ryu HJ, Kim S, Chin HJ, Na KY, Chae DW, et al. Comparison of cancer prevalence between patients with glomerulonephritis and the general population at the time of kidney biopsy. *PLoS One*. 2019;
 159. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant*. 2004;
 160. Grulich AE, Vajdic CM. The epidemiology of cancers in human immunodeficiency virus infection and after organ transplantation. *Seminars in Oncology*. 2015.
 161. Krynitz B, Edgren G, Lindelöf B, Baecklund E, Brattström C, Wilczek H, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008 - A Swedish population-based study. *Int J Cancer*. 2013;
 162. Yel L. Selective IgA Deficiency. *J Clin Immunol*. 2010;30(1):10–6.
 163. Syed-ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. *Adv Chronic Kidney Dis* [Internet]. 2022;26(1):8–15. Available from: <https://doi.org/10.1053/j.ackd.2019.01.004>
 164. Emilsson L, Lindahl B, Köster M, Lambe M, Ludvigsson JF.

- Review of 103 Swedish Healthcare Quality Registries. *J Intern Med.* 2015;
165. SNOMED CT: The global language of Healthcare. Available from <http://www.ihtsdo.org/snomed-ct>. Accessed November 23 2021. No Title.
 166. Jarrick S, Lundberg S, Welander A, Fored CM, Ludvigsson JF. Clinical validation of immunoglobulin A nephropathy diagnosis in Swedish biopsy registers. *Clin Epidemiol.* 2017;
 167. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol.* 2016;
 168. Linden A, Samuels SJ. Using balance statistics to determine the optimal number of controls in matching studies. *J Eval Clin Pract.* 2013;
 169. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;
 170. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;
 171. Jakobsson GL, Sternegård E, Olén O, Myrelid P, Ljung R, Strid H, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scand J Gastroenterol.* 2017;
 172. Barlow L, Westergren K, Holmberg L, Tälback M. The completeness of the Swedish Cancer Register - A sample survey for year 1998. *Acta Oncol (Madr).* 2009;
 173. Socialstyrelsen. Cancer incidence in Sweden 2005. *Statistics: Health and Diseases 2007:3.* Stockholm, 2007.
 174. <https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-prescribed-drug-register/>.
 175. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *European Journal of Epidemiology.* 2019.
 176. Olén O, Bihagen E, Rasmussen F, Ludvigsson JF. Socioeconomic position and education in patients with coeliac disease. *Dig Liver Dis.* 2012;
 177. Ludvigsson JF, Håberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. *Clinical Epidemiology.* 2015.
 178. Lee HJ, Choi SY, Jeong KH, Sung JY, Moon SK, Moon JY, et al.

- Association of C1q deposition with renal outcomes in IgA nephropathy. *Clin Nephrol.* 2013;
179. Nasri H. Letter to the article: Association of C1q deposition with renal outcomes in IgA nephropathy *Clin Nephrol.* 2013; 80: 98-104. *Clinical Nephrology.* 2014.
 180. Tan L, Tang Y, Pei G, Zhong Z, Tan J, Zhou L, et al. A multicenter, prospective, observational study to determine association of mesangial C1q deposition with renal outcomes in IgA nephropathy. *Sci Rep [Internet].* 2021;11(1):1–10. Available from: <https://doi.org/10.1038/s41598-021-84715-7>
 181. Pohjonen J, Nurmi R, Metso M, Oksanen P, Huhtala H, Pörsti I, et al. Inflammatory bowel disease in patients undergoing renal biopsies. *Clin Kidney J.* 2019;
 182. Xiao M, Ran Y, Shao J, Lei Z, Chen Y, Li Y. Causal association between inflammatory bowel disease and IgA nephropathy: A bidirectional two-sample Mendelian randomization study. *Front Genet.* 2022;13:1002928.
 183. Moe SM, Baron JM, Coventry S, Dolan C, Umans JG. Glomerular Disease and Urinary Sézary Cells in Cutaneous T-Cell Lymphomas. *Am J Kidney Dis.* 1993;
 184. Benoni H, Eloranta S, Dahle DO, Svensson MHS, Nordin A, Carstens J, et al. Relative and absolute cancer risks among Nordic kidney transplant recipients—a population-based study. *Transpl Int.* 2020;
 185. Rawla P, Killeen RB, Joseph NI. Selective IgA Deficiency. In *Treasure Island (FL);* 2024.
 186. Ludvigsson JF, Neovius M, Hammarström L. Risk of Infections Among 2100 Individuals with IgA Deficiency: a Nationwide Cohort Study. *J Clin Immunol.* 2016 Feb;36(2):134–40.
 187. Furst DE. Serum immunoglobulins and risk of infection: how low can you go? *Semin Arthritis Rheum.* 2009 Aug;39(1):18–29.
 188. Claudio P, Gabriella M. Nephrotic syndrome: pathophysiology and consequences. *J Nephrol.* 2023 Nov;36(8):2179–90.
 189. Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J kidney Dis Off J Natl Kidney Found.* 2017 Jun;69(6):752–61.
 190. McDonald HI, Thomas SL, Millett ERC, Nitsch D. CKD and the risk of acute, community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using electronic health records. *Am J kidney Dis Off J Natl Kidney Found.* 2015 Jul;66(1):60–8.

191. Yang WS, Chang YC, Hsieh ML, Wang JL, Wu LC, Chang CH. Stratified risks of infection-related hospitalization in patients with chronic kidney disease - A prospective cohort study. *Sci Rep.* 2020 Mar;10(1):4475.
192. Glenn DA, Henderson CD, O'Shaughnessy M, Hu Y, Bomback A, Gibson K, et al. Infection-Related Acute Care Events among Patients with Glomerular Disease. *Clin J Am Soc Nephrol.* 2020 Dec;15(12):1749–61.
193. Rivedal M, Haaskjold YL, Eikrem Ø, Bjørneklett R, Marti HP, Knoop T. Use of corticosteroids in Norwegian patients with immunoglobulin a nephropathy progressing to end-stage kidney disease: a retrospective cohort study. *BMC Nephrol.* 2024 Jan;25(1):42.