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Article

IGA-Nephropathy in Northeastern Europe: Clinical and Morphological Presentation and Outcomes

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Abstract: Aim. The analysis of incidence, clinical and morphological manifestations, and the prognosis of IgA nephropathy in the Northeastern Europe (NEE). **Materials and methods.** We enrolled cases with primary IgA nephropathy (IgAN) from 2005 to 2020 in the single-center retrospective study. Demographic and clinical parameters, histology data, and the treatment were analyzed. The outcomes were the occurrence of complete (PR) or partial remission (CR), renal replacement therapy (RRT), eGFR<15 ml/min/1.73m² and eGFR decrease $\geq 50\%$. The composite endpoint included all renal outcomes and was used to evaluate the risk of IgAN progression and associated factors. **Results.** The incidence of IgAN cases was 23.6% of all indication biopsies and 41.2% of primary immune glomerulopathies. At the time of the kidney biopsy, the proteinuria was 2.5 (1.5-5.0) g/24h, eGFR - 69 \pm 32 ml/min/1.73 m². Proportions of cases with arterial hypertension and eGFR <60 ml / min / 1.73 m² were 75% and 36%, respectively. The prevalence of histological changes in accordance with the Oxford (MEST-C) classification was M1 - 40.5%, E1 - 22.9%, S1 - 70.2%, T1 - 22%, T2 - 9%, C1 - 16.7%, C2 - 4.4%. In the follow-up of 27 (11; 61) months, 6 deaths occurred (1.7%). The 10-year cumulative dialysis-free survival was 80% and progression-free survival was 56%. Remissions registered in 50% of cases, being more frequent in patients who received immunosuppression vs renoprotection (60% vs. 40%, p = 0.001). In multivariable Cox regression, the independent factors associated with the increased probability of IgAN progression were male gender, a younger age, higher blood pressure and hematuria, lower eGFR, interstitial fibrosis/ tubular atrophy ($\geq 50\%$), the presence of peritubular capillaritis and any crescents. Compared to the cohorts of other ethnic or geographical origin, IgAN in the studied cohort were found to have more severe clinical and morphological presentations and faster progression rate. **Conclusion.** Being the most common glomerulopathy in the NEE population, IgAN has more pronounced clinical and morphological presentations. Considering the distinctive features of the disease, further research is warranted in order to establish approaches for enhancing risk stratification and treatment efficacy.

Keywords: Immunoglobulin A nephropathy; Northeastern Europe; clinical manifestations; morphology; renal survival; progression; prognosis; associated factors

1. Introduction

Immunoglobulin A nephropathy (IgAN) is the most common immune glomerulopathy worldwide [1]. The disease represents specific damage to the kidney due to alterations in the mucosal immune response. A critical factor underlying the disease progression is the occurrence of minor molecular rearrangements within the hinge region of secretory immunoglobulin A1 (IgA1) [2,3]. These rearrangements result in a deficiency of galactosylation in the O-glycan structure, consequently causing conformational changes in the molecule and leading to the acquisition of autoantigenic properties [4]. A prerequisite for hyperproduction of galactose-deficient IgA1 (Gd-IgA1) is the activation of mucosa associated lymphoid tissue (MALT) immune response and impaired IgA1 secretion [5,6]. Increased circulating pool of Gd-IgA1 leads to the formation of immune complexes



(IC). The latter comprises anti-glycan autoantibodies represented by either class of immunoglobulin (IgG, IgA or IgM) targeting Gd-IgA1, and CD89 (Fc α RI) and complement [7,8]. Gd-IgA1-containing IC cannot undergo natural clearance in hepatocytes [9], leading to its glomerular deposition, mainly in the mesangial area. An interaction with CD71, transferrin receptor on mesangial cells, causes their proliferation with subsequent activation of the complement and inflammation, which associated with organ damage and formation of a typical morphological pattern of the disease [10,11].

The prevalence, clinical and morphologic manifestations, and prognosis of IgA-nephropathy have significant geographic and racial differences [12–16]. Long-term clinical observations of the course of IgA-nephropathy cases enabled us to assume that the disease in the Northeastern Europe (NEE) population may have considerable peculiarities of incidence, clinical and morphologic manifestations, and prognosis. To explore this hypothesis, we conducted the initial extensive large-scale study of IgAN in this specific geographical location.

2. Materials and Methods

2.1. Study design

Cases diagnosed with primary IgA nephropathy at the Renal Clinic of the Research Institute of Nephrology, Pavlov University in the period from 01.05.2005 to 01.08.2020, were enrolled in this retrospective single-centre cohort study with unrestricted criteria at entry. This clinic is a major renal centre serving Northwest Russia with a population of about 18 million since 1987. A brief scheme of the study design is presented in Figure 1.

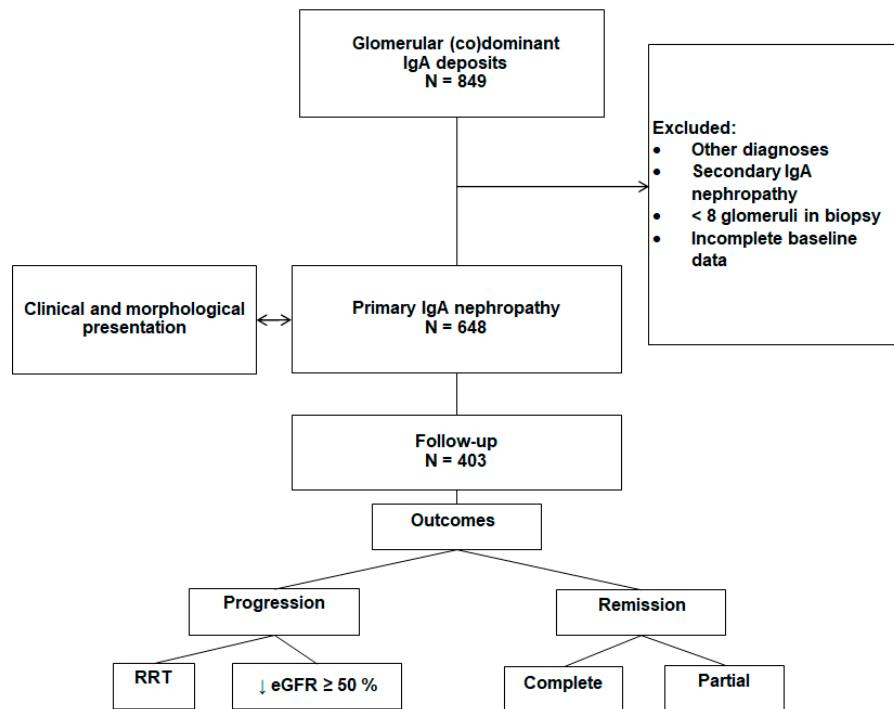


Figure 1. Study design and patient selection; IgA - immunoglobulin A, RRT - renal replacement therapy, ↓ eGFR – decreased estimated glomerular filtration rate.

2.2. Baseline data at the time of kidney biopsy

Demographic and clinical data

The following parameters were recorded at the time of diagnosis: sex, age, height, body mass index (BMI), estimated glomerular filtration rate (eGFR), erythrocyturia, daily proteinuria (DP),

serum albumin, total serum IgA, serum C3- and C4- complement fractions, systolic, diastolic and mean arterial blood pressure (ABP), and the presence of nephrotic syndrome (NS). NS was defined at DP >3.5 g/day and serum albumin <30 g/l. The clinically significant chronic infection of mucous membranes of various localizations was also recorded: upper and lower respiratory, gastrointestinal (GI), urinary and genital. We also collected the data on the clinical manifestations of the disease and the period elapsed until the verification of the diagnosis.

Histologic data

The light microscopy and immunomorphology data were analysed. For light microscopy, we used 4-6 μm thick tissue sections and standard stainings (PAS, trichome, haematoxylin-eosin and silver-methenamine) [17]. The prevalence of histologic changes of various structures within the area of the kidney biopsy specimen was evaluated. The global and segmental glomerular sclerosis, cellular, fibro-cellular and fibrous crescents were evaluated quantitatively (as a percentage of the total number of glomeruli in the biopsy specimen). We used a semi-quantitative assessment of interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation and peritubular capillaritis (PTC) (grade 0, <5%; grade 1, 6-24%; grade 2, 25-49%; grade 3, $\geq 50\%$). At immunofluorescence studies, the intensity of glomerular and extra glomerular deposits of immunoglobulins G, M, A, C3-component of complement (C3) and fibrinogen was also evaluated semi-quantitatively in scores from 0 to 3.

Histologic alterations were also evaluated according to the Oxford classification [18,19]: mesangial proliferation (M0, <50% of the tubules; M1, >50% or more), endocapillary proliferation (E0 - absent, E1 - present) and segmental sclerosis or adhesion of capillary loops to the tubular capsule (S0 - absent, S1 - present), tubular atrophy/interstitial fibrosis (T0, < 25% of cortical area; T1, 26-50% of cortical area; T2, > 50% of cortical area; cellular or fibro-cellular crescents (C0 - none; C1, < 25% of the tubules; C2, $\geq 25\%$ of the glomeruli).

2.3. Follow-up and outcomes

Dynamic clinical data

The changes in DP, erythrocyturia, serum albumin and eGFR were evaluated at follow-up.

Therapy

We registered the data on tonsillectomy and pharmacological therapies, including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and immunosuppressive therapies (IST) using corticosteroids, cyclosporine, cyclophosphamide (CP), mycophenolic acid (MMF), and azathioprine.

Outcomes

The outcomes were all-cause death, end-stage kidney disease (ESKD) with eGFR<15 ml/min/1.73 m^2 , start of renal replacement therapy (RRT), and decrease of eGFR $\geq 50\%$ of baseline. Disease progression was assessed by a composite endpoint that included all renal outcomes. At the end of follow-up, we assessed complete or partial remissions of the disease. Complete remission was defined as DP <0.5 g/day and erythrocyturia <5 cells in the field of view (FOV). Partial remission was defined as proteinuria decrease by >50% of the baseline level with its absolute value <3.5 g/day, provided that haematuria regressed by at least 70% from baseline.

2.4. Statistical analysis

Frequencies (fractions, percentages) were used for descriptive statistics of qualitative variables. Continuous variables were expressed as mean with its standard deviation ($M \pm SD$) or as median with interquartile range (Me (25%;75%)), depending on the variable distribution. Intergroup differences were evaluated using Student's t-test, Mann-Whitney U-test, Pearson's χ^2 test, and analysis of variance. Spearman's correlation analysis was used to assess the relationships between the study

parameters. The cumulative proportions of survivors who reached a particular outcome were calculated by the Kaplan-Meier method with the assessment of intergroup differences by the Mantel-Cox criterion. Cases that reached the outcome were included in the analysis as complete observations, and other cases were censored at the end of the observation period. Univariable and multivariable Cox regression models were used to analyze the associations of the studied parameters with the probability of outcome. For subsequent use in multiple regression, independent variables (baseline clinical and morphologic indices) were pre-selected in the univariable analysis. First, applying univariable Cox models, we selected clinical variables with a p-value <0.05 for the regression coefficient. Second, only these clinical variables were included in the multiple regression model to identify those independently associated with the probability of outcome. Next, we selected morphological indices by including each of them in a regression models adjusted for a set of previously identified independent clinical factors. Finally, we constructed a regression model by the inclusion of all pre-selected clinical and morphological variables. For the final model building, we used variable stepwise exclusion and bootstrapping procedures. Variables with skewed distribution could be logarithmically transformed before inclusion in the analysis. Differences, correlation, or regression coefficients were considered significant at p-values <0.05. Statistical analyses were performed using SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) and R programming software (version 4.3.1).

3. Results

The prevalence of IgAN cases among all indication biopsies and morphologically confirmed primary immune glomerulopathies was 23.6% and 41.2%, respectively.

3.1. Clinical presentation

The IgAN patients were predominantly of male sex and young in age, and the disease expectedly manifested with urinary abnormalities and/or episodes of macro haematuria. The median period from the first symptoms to kidney biopsy was 3.4 years. At the baseline, most of the patients had significant erythrocyturia and proteinuria. Nephrotic syndrome was registered in nearly every tenth case. One third of patients had eGFR level <60ml/min/1.73m². The serum complement and total IgA mainly corresponded to the reference values. A significant proportion of patients had clinically evident chronic mucosal inflammatory diseases. Arterial hypertension was also prevalent for the analysed cohort (Table 1).

Table 1. Baseline clinical data of IgA-nephropathy patients (n=648).

Indicator	Value*
Age, years	34±12
male gender, %	55
BMI, kg/m ²	25.5±5
Months from first IgAN manifestations to biopsy	41 (10;116)
Proteinuria, g/24h	2.5 (1.5-5.0)
Proteinuria >1 g/24h, %	76
Proteinuria>3.5 g/24h, %	30
Serum albumin, g/L	35.7±5.6
Nephrotic syndrome, %	9.3
Macrohematuria before biopsy, %	41
Erythrocyturia, cells per field of view	9 (4;19)
Creatinine, mmol/L	0.106 (0.082;0.140)
eGFR, ml/min/1.73 m ²	71±32
CKD stages 1/2/3AB/4/5, %	31/32/25/7/4
Total serum IgA, g/L	3.5±1.3
Serum IgA elevation, %	10.6

Serum C3, g/L	1.08±0.24
Serum C4, g/L	0.24±0.07
Mean ABP (maximal), mm Hg	116±20
Mean ABP (at admission), mm Hg	99±20
Arterial hypertension, %	75
Inflammatory diseases of upper respiratory tract, %	55
Tonsillitis, %	49
Inflammatory diseases of lower respiratory tract, %	8
Inflammatory diseases of gastrointestinal tract, %	48
Inflammatory diseases of lower urinary tract, %	10
Vaginitis/cervicitis, %	7**

Notes: BMI, body mass index; IgA-immunoglobulin A; C3-C3 complement fraction; C4-C4 complement fraction; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ABP, arterial blood pressure; GI tract, gastrointestinal tract; *values are presented as fractions/percentages or as mean with its standard deviation (M±SD), or as median with interquartile range (Me (25%;75%)); ** among females.

Histology of IgA nephropathy

Light microscopy showed a high prevalence of glomerular fibroplastic alterations, tubular atrophy and interstitial fibrosis. Among inflammatory lesions, diffuse mesangial proliferation was detected more frequently, followed by endocapillary hypercellularity and crescents. Among the histologic changes not included in the Oxford criteria, a significant incidence of interstitial infiltration and PTC was noticeable (Table 2).

Table 2. Prevalence of histological alterations.

Indices	Values*
<i>Oxford classification (MEST-C):</i>	
Mesangial proliferation (M1), %	40.5
Endocapillary hypercellularity (E1), %	22.9
Segmental sclerosis or adhesions (S1), %	70.2
Tubular atrophy/interstitial fibrosis (T1+T2), %	31
T0, %	69
T1, %	22
T2, %	9
Cellular/fibro-cellular crescents, %	16,7
C1, %	12,3
C2, %	4,4
<i>Other changes:</i>	
Global sclerosis, % of glomeruli	13 (5;30)
Segmental sclerosis, % of glomeruli	9 (0;17)
Fibrous crescents, %	7.7
Interstitial infiltration, %	50.5
>25% of interstitial area, %	14.8
Peritubular capillaritis, %	30.1

Notes: M1, mesangial proliferation ≥50% of the tubules; E1, presence of endocapillary proliferation; S1, presence of segmental sclerosis/adhesions; T1, tubular atrophy/interstitial fibrosis 26-50% of the cortical area, T2, tubular atrophy/interstitial fibrosis >50% of the cortical area; C1, cellular/fibro-cellular crescents <25%; C2, ≥25% of the glomeruli. * Values are presented as fractions/percentages or as medians with interquartile range (25%;75%).

Mesangial deposits of IgA and C3 could be combined with their deposits in the glomerular capillary walls and, less frequently, in small arteries and peritubular capillaries. Co-deposition of IgA and IgM was a typical finding in the study cohort, with a smaller proportion of cases having both

IgA and IgG positivity at immunofluorescence. Deposits of C3 and fibrinogen were infrequently found extraglomerularly (Table 3).

Table 3. Prevalence of deposits of immunoglobulins, C3 complement and fibrinogen in sub-structures of kidney (immunofluorescence).

Indices	Frequency, %
IgA in the mesangium	100.0
IgA n glomerular capillary wall	17.1
IgA in arteries	4.0
IgA in peritubular capillaries	5.7
IgM in mesangium	71.1
IgG in mesangium	9.6
C3 in mesangium	98.0
C3 in glomerular capillary wall	13.8
C3 in arteries	4.5
C3 in peritubular capillaries	6.6
Fibrinogen in mesangium	21.4
Fibrinogen n glomerular capillary wall	6.2
Fibrinogen in peritubular capillaries	12.2

Note: IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; C3, C3 complement fraction.

Clinical and morphologic correlations

Correlations between major clinical and histologic indices are represented in the Table 4. Haematuria, a typical clinical sign of the disease, was associated with histologic indices of active glomerular and interstitial inflammation. Proteinuria and eGFR had significant correlations with all major histologic alterations, both fibroplastic and inflammatory. Mean BP was positively associated with IFTA, endocapillary **hypercellularity**, interstitial inflammation, and PTC. The intensity of IgA and C3 deposits in glomerular capillary walls and peritubular vessels correlated with proteinuria, but not with haematuria (Table 4).

Table 4. Clinical and morphological correlations.

Histologic indices, units	Mean ABP	eGFR	Daily proteinuria	Hematuria
Global glomerular sclerosis, %	0.29 p<0.001	-0.47 p<0.001)	0.39 p <0.001	-0.03 NS
Segmental glomerular sclerosis, %	0.16 p <0.001	-0.20 p<0.001	0.35 p<0.001	0.00 NS
Crescents (any), %	0.04 NS	-0.10 p=0.024	0.25 p<0.001	0.15 p<0.001
Cellular/fibrocellular crescents, %	0.05 NS	-0.11 p<0.001	0.28 p<0.001	0.17 p<0.001
IFTA, grades	0.36 p<0.001	-0.57 p <0.001	0.39 p <0.001	-0.02 NS
Interstitial infiltration, grades	0.29 p<0.001	-0.51 p <0.001	0.35 p <0.001	0.118 p =0.005
Mesangium proliferation, grades	0.07 NS	-0.15 p <0.001	0.19 p <0.001	0.14 p =0.001
Endocapillary hypercellularity, no vs yes	0.15 p<0.001	-0.25 p<0.001	0.30 p<0.001	0.12 p=0.004
PTC, grades	0.20 p<0.001	-0.41 p<0.001	0.37 p<0.001	0.11 p=0.009

IgA glomerular capillaries, grades	0.13 p<0.001	-0.10 p=0.009	0.16 p <0.001	0.01 NS
IgA mesangium, grades	-0.12 p =0.002	0.06 NS	0.00 NS	0.04 NS
IgA peritubular capillaries, grades	0.07 NS	-0.20 p<0.001)	0.16 p<0.001	0.01 NS
IgM mesangium, grades	-0.04 NS	0.03 NS	0.12 p=0.002	0.01 NS
IgG mesangium, grades	-0.07 p=0.042	0.05 NS	-0.04 NS	-0.01 NS
C3 glomerular capillaries, grades	0.15 p<0.001	-0.11 p=0.005	0.18 p<0.001	0.02 NS
C3 mesangium, grades	-0.054 NS	0.01 NS	-0.01 NS	0.01 NS

Notes: IFTA, interstitial fibrosis and tubular atrophy; PTC, peritubular capillaritis; eGFR, estimated glomerular filtration rate; ABP, blood pressure; IgA, immunoglobulin A; C3, C3 complement fraction; IgM, immunoglobulin M; IgG, immunoglobulin G; NS, non-significant correlation at $p>0.05$; values are Spearman R (p-values).

3.2. Follow-up and outcomes

Overall and renal survival

Patients with follow-up differed significantly from cases without follow-up in a number of clinical and morphologic manifestations of IgAN: severity of proteinuria and haematuria, eGFR level, prevalence of NS, segmental glomerulosclerosis, endo- and extracapillary proliferation (Table S1).

The median follow-up period was 27 (11; 61) months. Median annual decrease in eGFR was -2.3 (-11.4; -1.9) ml/min/1.73m². A total of 6 all-cause deaths (1.7%) were registered. During the follow-up period, 72 patients (17.9%) reached the composite endpoint, of which dialysis was initiated in 47.2%. The cumulative dialysis-free and progression-free survival probabilities are shown on Figure 1 (A, B).

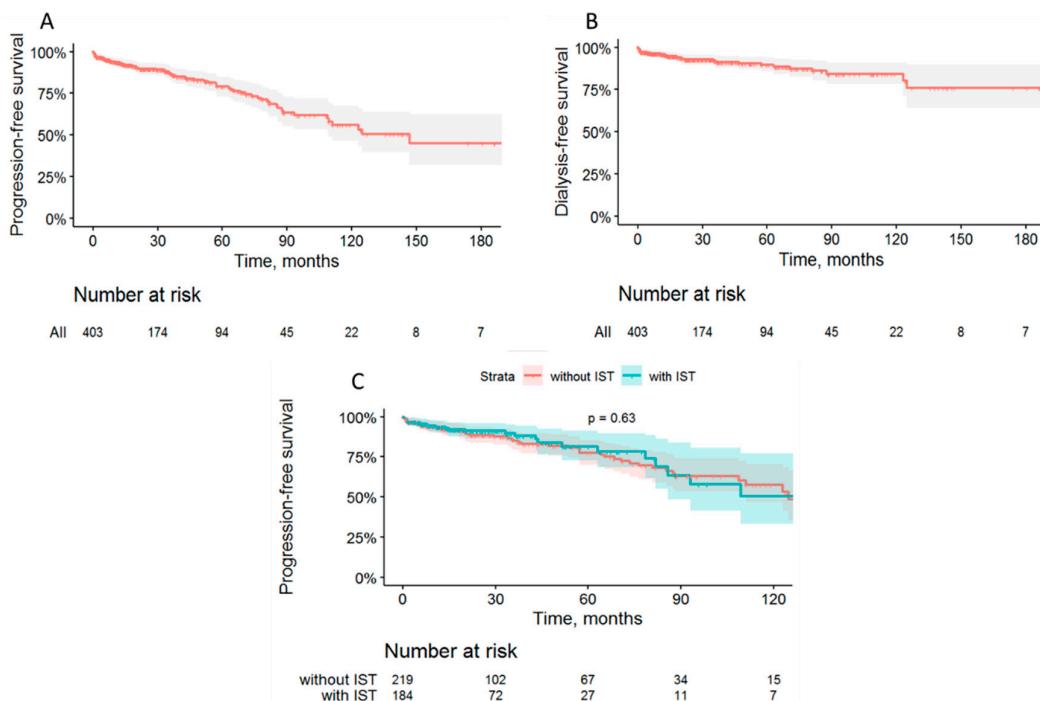


Figure 1. Cumulative renal survival: dialysis-free survival (A); progression-free survival (B); progression-free survival who received and not received immunosuppression (C); IST - immunosuppressive therapy.

Treatment and remissions

Most patients (95%) were treated with renin-angiotensin system blockers according to current guidelines [20]. IST was administered to 29% of patients. Steroids monotherapy or steroids in combination with other immunosuppressants, mainly cyclophosphamide, MMF and azathioprine, were used in 23% and 9% of patients, respectively. The proportion of cases on IST in those with follow-up (n=403) was 46% (steroids monotherapy - 31%, combined IST - 15%). By the end of follow-up, we registered remissions in 50% of cases: PR in 26%, CR in 24%. Remissions were observed more frequently in patients who received IST compared to those on symptomatic therapy (60% vs. 40%, p=0.001), including CR (31% and 16%) and PR (29% and 24%).

Notwithstanding a higher remission rate, renal survival did not differ between the groups of patients who did not receive and those who received IST (Figure 3C). However, the group of patients undergone IST had more pronounced clinical and morphologic manifestations of IgAN. These differences were related to proteinuria and NS, as well as fibrous and proliferative alterations of the glomeruli and interstitium (Table S2).

3.3. Factors associated with prognosis

Comparative analysis showed significant differences between cases with progression of IgA nephropathy compared with patients who did not reach the composite prognostic endpoint for many of the clinical and morphologic parameters studied (Table S3).

In a Cox regression model, including only clinical variables at the time of biopsy, sex, age, mean ABP, eGFR, and severity of haematuria were independently associated with the risk of IgAN progression. Among morphologic indices, severe IFTA (T2), PTC, interstitial infiltration, the presence of any crescents, and the proportion of global glomerulosclerosis were significantly associated with the probability of reaching the composite end-point. In the final model using both clinical and morphologic parameters, the independent factors associated with a negative prognosis were male sex, younger age, increased mean BP, lower eGFR, higher haematuria, IFTA ≥50%, severe PTC, and the presence of any crescents. No other parameters had an independent association with the risk of IgAN progression (Table 5).

Table 5. Clinical and histologic factors associated with the progression of IgA-nephropathy (Multivariable Cox regression models).

Models	Factors (unit change)	Exp β (95% CI)	P-value
Clinical parameters ^a	Age (1 year)	0.974 (0.949-0.999)	0.041
	Male sex (vs female)	1.956 (1.131-3.382)	0.016
	Mean BP maximal (1 mmHg)	1.015 (1.002-1.029)	0.025
	eGFR (1 ml/min/1.73m ²)	0.950 (0.937-0.963)	<0.001
	Ln (Hematuria) (1 unit)	1.406 (1.121-1.762)	0.003
	Ln (Proteinuria) (1 unit)	1.237 (0.893-1.714)	0.20
Morphological parameters	M (M1 vs M0) ^b	1.679 (0.984-2.864)	0.06

	E (E1 vs E0) ^b	0.920 (0.502-1.685)	0.67
	S (S1 vs S0) ^b	1.472 (0.746-2.905)	0.26
	T (T1 vs T0) ^b	1.021 (0.452-2.309)	0.95
	T (T2 vs T0) ^b	4.579 (1.835-11.462)	0.001
	C (C1 vs C0) ^b	1.851 (0.960-3.569)	0.07
	C (C2 vs C0) ^b	1.068 (0.400-2.855)	0.89
	Global glomerular sclerosis (1%) ^b	1.014 (1.001-1.027)	0.029
	Any crescents (vs no crescents) ^b	1.939 (1.110-3.389)	0.02
	Interstitial infiltration (1-24% vs 0%) ^b	1.418 (0.624-3.222)	0.40
	Interstitial infiltration ($\geq 25\%$ vs <25%) ^b	2.465 (1.097-5.539)	0.029
	PTC (moderate vs none) ^b	1.321 (0.630-2.770)	0.46
	PTC (severe vs none) ^b	2.590 (1.206-5.560)	0.015
Clinical and morphological parameters ^c	Age (1 year)	0.964 (0.939-0.990)	0.006
	Male gender (vs. female)	2.566 (1.448-4.548)	0.001
	eGFR (1 ml/min/1.73m ²)	0.966 (0.953-0.979)	<0.001
	Ln(Hematuria) (1 unit)	1.482 (1.166-1.884)	0.001
	Mean BP (maximal) (1 mm Hg)	1.024 (1.010-1.040)	0.001
	PTC (severe vs none/moderate)	2.422 (1.262-4.648)	0.008
	Tubular atrophy/interstitial fibrosis (T2 vs T0-1)	6.738 (3.542-12.817)	<0.001
	Any crescents (vs no crescents)	2.078 (1.200-3.596)	0.009

Note: ABP - blood pressure, eGFR - estimated glomerular filtration rate, M0 - mesangial proliferation <50%, M1 - mesangial proliferation ≥50%; E - endocapillary hypercellularity; E0 - no endocapillary hypercellularity, E1 - presence of endocapillary hypercellularity; S0 - no segmental sclerosis, S1 - presence of segmental sclerosis; T0 - tubular atrophy less than 25% of the cortical area, T1 - tubular atrophy/interstitial fibrosis 26-50% of the cortical area, T2 - tubular atrophy/interstitial fibrosis > 50% of the cortical area, C - cellular and fibrocellular crescents; C0 - no cellular and fibrocellular crescents, C1 - cellular and fibrocellular crescents <25%; C2 - >25% of tubules, PTC - peritubular capillaritis, CI - confidence interval. a - forced inclusion of variables with adjusted for immunosuppressive therapy - (forced inclusion of variables). b - adjusted for all clinical variables and immunosuppressive therapy. c - adjusted for all clinical and morphological variables and immunosuppressive therapy (backward stepwise regression).

4. Discussion

There is a notable disparity in the prevalence of IgAN among various regions and ethnicities, characterised by a geographical gradient from the Southwest to the Northeast [1,12,21,22]. The disease is most prevalent in people of East Asia ancestry (45–58% of primary glomerulonephritis), followed by Caucasians and relatively rare in individuals of African descent. It has been estimated to account for approximately 40% of all native biopsies in Japan, 25% in Europe, 12% in the USA and less than 5% in Central Africa [1,21–24].

Here, we present the first cohort study that has provided detailed information on the clinical, morphologic, and prognostic aspects of IgAN in NEE, assuming higher frequency and more severe course. Indeed, we demonstrated that IgAN was the most frequent variant of immune glomerulopathies and the most prevalent kidney disease by clinical and morphologic examination in this region. Moreover, the prevalence of IgAN in NEE seems to be ahead of most regions in Europe and America and comparable to Asian countries [1,16,21–23,25,26].

Clinical manifestations of IgAN were expectedly represented by a combination of proteinuria and haematuria. However, the studied IgAN cohort differed from the European and Asian cohorts in the severity of urine protein loss, renal dysfunction, and hypertension. Compared to European data, histologic lesions associated with active inflammation were also more pronounced in the study cohort [16] (Table S4).

Diagnosis of IgAN is established by the presence of immunoglobulin A1 (IgA1) as the dominant or co-dominant immunoglobulin in the glomerular mesangium [18,19]. While the mesangial IgA deposition is a defining disease feature, we found no associations of mesangial IgA staining with the clinical indices of the disease severity (see Table 4). One might suggest that distinct processes are being responsible for mesangial IgA deposition and glomerular inflammation.

Contrariwise, IgA deposits in the glomerular capillary walls, detected in one of six cases, correlated to proteinuria, ABP and eGFR levels, likely mirroring the course of more severe forms of the disease with the formation of a membranoproliferative pattern [32] and worse prognosis [33].

In addition, we found the significant prevalence of extra-glomerular changes in IgAN. In particular, the significance of interstitial inflammation and peritubular capillaritis was apparent. Both lesions closely correlated with hypertension, renal dysfunction, proteinuria and haematuria, the major clinical manifestations. The interaction of immunocytes with peritubular capillary walls, along with occasionally detectable deposits of IgA, C3, and fibrinogen may indicate that a proportion of IgAN cases had with histologic features of renal-limited interstitial vasculitis. Such patients may have an unfavourable prognosis, as PTC was identified as an independent factor associated with the higher probability of disease progression (see Table 5).

IgAN has often been considered a disease with a benign prognosis. Such perceptions have been largely based on large cohort studies conducted in Asia, where the 10- and 20-year renal survival rates in these studies are 82–84% and 64–70%, respectively [1,13–15,34,35]. Contrariwise, the pooled European data in multicenter retrospective VALIGA study [16] showed significantly lower survival rates (see Table S4), suggesting a less favourable course of the disease in the Caucasian population. Our data definitely showed that dialysis-free survival in the NEE population is lower than in Asian regions. A cumulative rate of disease progression (ESKD, RRT or decrease in eGFR>50%) was also inferior compared to the European population [16].

The likely explanation for such findings could be the delayed recognition of IgAN, acquiring a more pronounced glomerular and tubulointerstitial fibrotic lesions [21,22]. However, there were no apparent differences in the prevalence of glomerulosclerosis and IFTA in both cohorts (Table S4). Therefore, given the comparable treatment [16], these data could suggest a more aggressive course of the disease in the NEE region (Table S4). Therefore, given the comparable treatment [16], these data could suggest a more aggressive course of the disease in the NEE region.

Our study was also focused on the evaluation of clinical and morphologic factors associated with the IgAN outcomes. Among the major clinical indices, proteinuria is considered a significant predictor of IgAN prognosis and treatment [13,16]. However, in this study, baseline proteinuria was not an independent predictor of IgAN progression. One explanation could rely on the small

proportion of cases in our cohort with proteinuria <1 g/day known to be associated with a more favourable prognosis [38,39]. A link between proteinuria and the progression of IgAN is thought to be influenced by a range of histological alterations that also exhibit strong correlations with urinary protein loss (see Table 4).

In addition, baseline proteinuria and histologic indices of current disease activity can be modified by therapy [16,40,41]. Consequently, an average proteinuria during in follow-up period seems to be more important for predicting IgAN outcomes [16,42]. Next, in the patients with higher proteinuria, one can also assume that other clinical and morphologic parameters have a greater prognostic value. Particularly, this refers to haematuria that was independently related to IgA progression, consistent with prior data [42]. Judging by the close relationship with histologic and clinical activity indices (see Table 4), haematuria seemed to be a significant biomarker of disease activity, requiring clinical monitoring at the background of therapy.

In our study, the prognostic value of the Oxford classification indices (MEST-C [18,19]) differed significantly from the original data and the results of validation studies [35,43–48]. Of these, only IFTA was significantly associated with long-term prognosis in models adjusted for baseline clinical parameters and treatment. Consequently, we do not exclude that the MEST-C classification may be of limited use in patients with higher proteinuria levels, which exceeded 1 g/day in almost ¾ of cases of the entire cohort.

Like several other studies [49–51], we have found independent and significant associations with prognosis for some morphologic indices not included in the MEST-C classification. Among them, are PTC and the occurrence of any crescents in the renal biopsy. It is likely that further development of the MEST-C classification, along with clarification of the prognostic value of other histologic changes [52], will allow a more accurate assessment of IgAN prognosis. So far, our findings leave open the issue on the reliability of using MEST-C for predicting the IgAN outcomes [38,53–57] in the NEE population, requiring additional validation studies.

The substantial prevalence, severity of course and unfavourable prognosis of IgAN in NEE suggest the existence of predisposing specific, yet unknown, population-level factors. Future research should be focused on assessments of genetic predisposition and environmental factors, including dietary patterns and infections affecting the mucosal immune system [27–29,36,37].

This retrospective study was not designed to analyse the efficacy of currently recommended therapies [20]. As the natural evolution of clinical and morphologic manifestations of IgAN can be influenced by treatment [42,58–65], we accounted for treatment in the construction of regression models.

Almost half of the patients in the analyzed cohort received some variant of IST. In the analysis of outcomes and associated factors, there were no differences in renal survival between patients receiving symptomatic therapy alone (based on renin-angiotensin system blockers) and its combination with IST. The subgroup of patients receiving IST had significantly more severe clinical and morphological manifestations of IgA nephropathy, having a less favourable prognosis. These observations probably do not mirror the ineffectiveness of immunosuppression in IgAN, however, further studies appropriately designed for the high-risk disease are warranted.

Short-term efficacy of treatment is assessed by the development of remission, an important modifier of prognosis (39). Within the follow-up period, complete or partial remissions were reported in 50% of cases and occurred more frequently in patients on IST compared to symptomatic renoprotection. These data are consistent with the results of prospective studies, where remission rates on IST were only 25 - 62% (including complete remissions of 7.8 - 55.3%) [63–69]. Notably, we applied a more strict definition of remission, including the regress of haematuria beyond the fall in urine protein. Haematuria, a hallmark of IgAN, correlated mostly with active inflammatory lesions. The persistence of proteinuria may resulted from either active disease or glomerular and tubulointerstitial fibrosis. Haematuria can help to separate the latter cases, avoiding unnecessary IST. Moreover, urine blood cell count

Overall, the unsatisfactory remission rate in IgAN definitely calls for an intensification of research on approaches to therapy of IgAN. Beyond IST, these approaches should be focused on targeting the known nodal hits of the disease pathogenesis [27–29,59].

The main limitation of the study was its retrospective nature. This did not allow to determine causal relationships between clinical and morphologic parameters and disease outcomes. Next, patients with follow-up had more pronounced clinical and morphologic manifestations at the baseline. As a result, the renal survival may be underestimated, because it was estimated for a group of patients at higher risk of progression. Furthermore, the relatively small number of cases that reached the endpoint precluded multivariable analysis of potential prognostic predictors in groups with different therapies, which can significantly affect the prognostic impact of morphologic and clinical parameters [58]. However, to reduce potential bias, all prognostic models were adjusted for IST.

5. Conclusions

The present study showed that in NEE population IgAN is the most common glomerulopathy. The disease is characterized by more severe clinical and morphological manifestations and a faster progression compared to cohorts of other ethnicities or geographic regions. Considering specific features of a disease in NEE, additional research is required to ascertain approaches to the risk stratification and effective treatment.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. **Table S1.** Clinical and morphological data in patients with and without follow-up; Notes: ABP - arterial blood pressure; eGFR - estimated glomerular filtration rate; M1 - mesangial proliferation $\geq 50\%$; E1 - endocapillary hypercellularity; S1 - segmental sclerosis/adhesions; C1 - cellular/fibrocellular crescents $< 25\%$; C2 - cellular/fibrocellular crescents $\geq 25\%$; values are presented as fractions/percentages or as mean with its standard deviation ($M \pm SD$) or as median with interquartile range (25%;75%); **Table S2.** Clinical and demographic parameters in patients who received and not received immunosuppression in the follow-up period; Notes: ABP – arterial blood pressure; eGFR – estimated glomerular filtration rate; IgA – immunoglobulin A; RASB – renin-angiotensin system blockers; PTC – peritubular capillaritis; M1 – mesangial proliferation $\geq 50\%$; E1 – endocapillary hypercellularity; S1 – segmental sclerosis/adhesions; C1 – cellular/fibrocellular crescents $< 25\%$; C2 – cellular/fibrocellular crescents $\geq 25\%$; IST – immunosuppressive therapy; values are presented as fractions/percentages or as mean with its standard deviation ($M \pm SD$) or as median with interquartile range (25%;75%); **Table S3.** Clinical and morphological data in patients with and without progression of IgA-nephropathy; Note: BP – blood pressure, eGFR – estimated glomerular filtration rate, M1 – mesangial proliferation $\geq 50\%$; E1 – endocapillary hypercellularity; S1 – segmental sclerosis/adhesions; T1 – tubular atrophy/interstitial fibrosis 26–50% of the cortical area, T2 – tubular atrophy/interstitial fibrosis $> 50\%$ of the cortical area, C – cellular and fibrotic-cellular crescents; C1 – cellular/fibrotic-cellular crescents $< 25\%$; C2 – $> 25\%$ of the tubules, PTC – peritubular capillaritis; RASB – renin-angiotensin system blockers; values are presented as fractions/percentages or as mean with its standard deviation ($M \pm SD$) or as median with interquartile range (Me (25%;75%)); **Table S4.** Clinical and morphological presentation of IgAN in Northeastern Europe and other world regions; Note: eGFR – estimated glomerular filtration rate, ND – no data; values are presented as fractions/percentages or as mean with its standard deviation ($M \pm SD$) or as median with interquartile range (Me (25%;75%)); *, n=403; superscripts are references to original studies.

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