Diplomarbeit

The Prognostic Value of Crescents in IgA Nephropathy

An Observational Study

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1 Affirmation

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 02.09.2020 *Joel Johannes Schreiber eh*

2 Preamble

Der Blick durch das Mikroskop ist wie ein Blick in eine andere Welt…

3 Acknowledgments

Zu allererst möchte ich mich bei meiner Betreuerin Univ.-Ass.in Dr.in med.univ. Marion Pollheimer, für die ständige Unterstützung, die Beratung, die Expertise, die Mitbenutzung ihres Büros, das eigene Mikroskop und die vielen Tassen Kaffee bedanken. Du hattest immer ein offenes Ohr für meine Anliegen und standst mir immer mit Rat und Tat zur Seite. Dir verdanke ich auch die Faszination für dieses Thema, die Du durch deine Vorlesungen auf mich übertragen hast. Vielen Dank!

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Meinen Eltern und meiner Großmutter widme ich diese Arbeit!

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5 Glossary and Abbreviations

C

C1GalT1 ..... *core 1 beta 1,3-galactosyltransferase*
Cosmc ..... *core 1 β 3 GalT-specific molecular chaperone*

E

eGFR..... *estimated glomerular filtration rate*
ESKD ..... *end stage kidney disease*
ESRD .....*end stage renal disease*

G

GalNAc..... *N-acetylgalactosamine*

I

IgAN ..... *Immunoglobulin A Nephropathy*

M

MASP-2..... *mannan-binding lectin-associated serine protease-2*

P

PGD ..... *primary glomerular disease*
pmp .....*per million population years*

R

RAS.....*renin-angiotensin-aldosterone-system*
RAS-I..... *renin-angiotensin-aldosterone-system-inhibitor (blocker)*

T

tob ..... *time of biopsy*

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8 Zusammenfassung

Einleitung: Die IgA Nephritis (IgAN) ist die häufigste Glomerulonephritis weltweit. Die Inzidenz in der Gesamtbevölkerung beträgt ca. 2.5/100000/Jahr. Innerhalb von 10-20 Jahren nach Beginn der Erkrankung entwickeln ca. 20-40% der PatientInnen eine terminale Niereninsuffizienz. Die IgAN präsentiert sich klinisch durch unterschiedliche Symptome. Außerdem unterscheiden sich die Prävalenzen von Kontinent zu Kontinent. Durch die Evaluierung von Nierenbiopsien konnten fünf unspezifische Veränderungen beschrieben werden, die eine prognostische Aussagekraft bezüglich des Krankheitsverlaufes besitzen. Diese Veränderungen wurden zu der sogenannten modifizierten Oxford Klassifikation zusammengefasst. Diese beinhaltet mesangiale Hyperzellularität (M), endokapilläre Hyperzellularität (E) segmentale Sklerose (S), tubuläre Atrophie/interstitielle Fibrose (T) und extrakapilläre Proliferationen (C) (Halbmondbildung). Das Ziel dieser Studie war es, die prognostische Aussagekraft der histopathologischen Veränderungen, mit speziellem Augenmerk auf die Halbmonde, hinsichtlich des renalen Überlebens zu evaluieren.

Material und Methoden: Für diese retrospektive Studie wurden Daten von 205 IgAN PatientInnen, aus Südost-Österreich, im Zeitraum von 2002 bis 2018 gesammelt und statistisch analysiert. Die Prüfung auf Zusammenhänge zwischen histopathologischen Veränderungen und dem Nierenüberleben / der Nierenfunktion erfolgte mithilfe von Kreuztabellen, Chi-quadrat-Tests und binär logistischen Regressionsanalysen. Mit der Kaplan-Meier-Methode wurden Überlebenskurven für das Auftreten einer Niereninsuffizienz oder eines Nierenversagens erstellt. Mittels Log-Rank-Test wurden die Überlebensdaten zwischen den Gruppen verglichen. Die Endpunkte dieser Studie waren das Erreichen einer terminalen Niereninsuffizienz und/oder ein Abfall der geschätzten glomerulären Filtrationsrate (eGFR) von >50%.

Ergebnisse: PatientInnen mit tubulärer Atrophie/interstitieller Fibrose in >25% des renalen Cortex, zeigten einen signifikant schlechteren Krankheitsverlauf hinsichtlich beider Endpunkte kombiniert (*p-Wert<0.001*). Halbmondbildung allein zeigte sich ohne signifikante Aussagekraft hinsichtlich eines Nierenversagens und 50%

Abnahme der Nierenfunktion. Allerdings konnte ein signifikanter Effekt von Halbmonden in <25% der Glomerula hinsichtlich eines Nierenversagens gefunden werden, wenn die Analyse bezüglich der immunsuppressiven Therapie angepasst wurde (*p-Wert=0.001*). IgAN PatientInnen mit C1-Läsionen nahmen signifikant häufiger immunsuppressive (*p-Wert<0.001*) und antihypertensive (*p-Wert=0.039*) Medikamente ein. Fibrozelluläre (gemischt) und fibröse (alt) Halbmonde zeigten im Vergleich zu zelluären (frisch) Halbmonden einen signifikant schlechteren Einfluss auf das Auftreten eines Nierenversagens (*p-Wert=0.002*).

Diskussion: Wir konnten die Aussagekraft der T-Läsionen als verlässlichsten, histopathologischen Marker hinsichtlich des renalen Überlebens bestätigen. Für Halbmonde konnten wir nur einen signifikanten Effekt auf das Auftreten eines Nierenversagens beschreiben, nachdem die Analyse an die immunsuppressive Therapie angepasst wurde. Es müssen weitere repräsentative Studien durchgeführt werden, damit die unabhängige Aussagekraft von Halbmonden bestätigt werden kann.

9 Abstract

Introduction: Immunoglobulin A Nephropathy (IgAN) is the most common glomerular kidney disease in the world. The overall population incidence of IgAN is approximately 2.5/100000/year and in about 20-40% of the cases IgAN is reported to progress to end-stage kidney disease (ESKD) within 10 to 20 years from onset. IgAN shows highly variable and heterogeneous clinical symptoms as well as diverse rates of frequency in different continents. In kidney biopsies, five distinct features prognostic of disease progression and outcome, have been summarized as the modified Oxford Classification. These features are mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T) and glomerular crescent formation (C). Aim of this study was to validate the prognostic value of the histopathological features with special emphasis on crescentic lesions on renal survival.

Material and Methods: For this retrospective analysis data from 205 IgAN patients from Southeast Austria between 2002 and 2018 were collected and statistically analyzed. We performed cross tabulation, chi-squared tests and binary logistic regression analyses to determine the association between histopathological parameters and renal survival/function. Renal survival curves with the Kaplan-Meier method were generated and between-group survival was compared by using the log-rank test. The study endpoints are the onset of ESKD and/or 50% decline in estimated glomerular filtration rate (eGFR).

Results: Patients with tubular atrophy/interstitial fibrosis in >25% of cortical area showed a significantly adverse renal outcome concerning the combined event (*p-value<0.001*). Crescentic lesions did not prove to be a significant prognostic factor for renal failure and for 50% decline of renal function. When adjusted for immunosuppressive therapy however, crescentic lesions in <25% of glomeruli were predictive of renal failure (*p-value=0.001*). IgAN patients with C1 lesions more likely received immunosuppressive (*p-value<0.001*) and antihypertensive (*p-value=0.*039) treatment. Fibrocellular (mixed) and fibrous (old) crescents, proved to

have a significantly adverse impact on renal failure than cellular (fresh) crescents (*p-value=0.002*).

Discussion: We could validate the prognostic value of T lesions on renal survival as the most consistent marker. Crescentic lesions however, only were predictive of renal failure once adjusted for immunosuppression. Further representative studies need to be conducted to validate the independent prognostic value of crescentic lesions.

10 Introduction

Immunoglobulin A Nephropathy (IgAN) is described as the most common glomerular disease worldwide (1) and one of the most frequent reasons for the onset of chronic kidney disease. IgAN is reported to progress to end-stage kidney disease (ESKD) in approximately 20 to 40% of patients within 10 to 20 years from onset (2,3).

The etiopathogenesis of IgAN is complex and known to develop in a multi-hit process. Pathomechanistic factors contributing to disease initiation and progression include increased serum IgA levels, aberrantly glycosylated IgA1 antibodies, production of O-glycan-specific anti-IgA1-IgG-autoantibodies resulting in immunocomplex formation and deposition within the mesangium and the glomerular capillary cell walls, further leading to an inflammatory glomerular response and impairment of renal function (4). Patients with IgAN commonly show unspecific or mild clinical symptoms, often hampering clinical diagnosis and delaying medical treatment. IgAN may lead to a wide range of histopathological glomerular changes, reflecting the clinical diversity of disease, including hematuria, proteinuria, impaired glomerular filtration rate and arterial hypertension (2).

Most patients with IgAN show asymptomatic urinary abnormalities, such as microhematuria in 88%, macrohematuria in 43%, and proteinuria (5). Patients commonly develop proteinuria with >1g/d and show nephrotic range proteinuria (>3-3,5g/24h) in 10% of reported cases (5). Other symptoms may be lumbar or abdominal pain (30%) and hypertension (25%). In 7% of cases, acute renal failure is reported. In other cases, IgAN may cause chronic renal failure in 20-40% within 10-20 years (2,3,6). In addition, development of thrombotic microangiopathy is seen in 53% of the cases (5,7).

Kidney biopsy with histological Classification of IgAN is essential for diagnosing IgAN, evaluating disease severity and guiding appropriate therapeutic strategies (8). Histopathological glomerular changes are variable ranging from virtually normal histology with minimal mesangial hypercellularity to severe necrotizing, crescentic glomerulonephritis or advanced glomerulosclerosis and tubular atrophy (8). In 2009, the Oxford Classification of IgAN was developed by an

international working group using a retrospective study cohort of 265 adults and children with confirmed IgAN diagnosis in order to establish a consensus on identifying the specific pathologic features reliably predicting the risk of IgAN progression (1,8). The Oxford Classification for IgAN established four typical histopathological features, including mesangial (M) and endocapillary (E) hypercellularity, segmental glomerulosclerosis (S), and moderate to severe interstitial fibrosis and tubular atrophy (T), summarized as the so-called MEST score, as independent risk factors for poor renal outcome (1,8). The original Oxford Classification, however, does not account for the presence of glomerular crescents (9), as crescentic lesions lacked prognostic significance in the Oxford study cohort (8). Since 2017, an additional C-category in the original MEST score for the presence of glomerular crescents is recommended: C0 (no crescents), C1 (crescents in less than one fourth of glomeruli), and C2 (crescents in over one fourth of glomeruli), summarized as the modified MEST-C score. However, there are conflicting data on the prognostic value of glomerular crescent formation for renal outcome (9–12).

In the following years, further retrospective studies, review articles, and meta-analyses have been performed in order to test the prognostic impact of the Oxford Classification in different patient cohorts with different epidemiological background.

10.1 Epidemiology of IgAN

The overall population incidence for IgAN in adults is suggested to be 2.5/100000/year according to McGrogan et al (13). However, biopsy registry data tend to underestimate disease burden as patients with mild disease may not undergo biopsy, and in countries lacking screening programs disease may not be detected (14). Thus, the worldwide distribution of IgA Nephropathy shows highly variable geographic prevalence and incidence rates (15) attributable to several influencing factors. Systematic urine screening is not commonly practiced in many countries (15). In Asian countries, however, systematic urine screening is part of standard health check programs for all primary and secondary school students as well as for people attending the military in Japan (15). The number of performed renal biopsies due to asymptomatic urine abnormalities found in routine checkups

correlates with number of identified IgAN patients, as reflected by data from Japan: almost 50% of diagnosed IgAN cases are found after performing renal biopsy secondary to urine pathologies in the context of routine examination (15). General practitioners, especially in European and some Asian countries, tend to underestimate the clinical significance of persistent microscopic hematuria as well as low proteinuria, thus delaying IgAN diagnosis by a specialist (nephrologist) (15).

Kiryluk et al found five susceptibility gene loci in patients with IgAN contributing to disease development. Those loci were additionally associated with other autoimmune diseases, such as type I diabetes, multiple sclerosis and inflammatory bowel disease. These findings suggest an influence of genetic factors on regional and familial IgAN (16).

In addition, indications for a kidney biopsy vary substantially in different countries and reported prevalence rates vary according to how data have been determined, using biopsy registry data or registry data of dialysis patients (14).

10.1.1 Asia

The incidence and prevalence of IgAN is considered to be the highest in East Asian and Pacific Asian regions (14). China leads all Asian countries with IgAN frequencies of 54% of patients with a diagnosed primary glomerular disease (PGD) (17). Japan and Singapore follow China with 47% and 43% of PGD patients (15,18,19). Lower rates of IgAN frequencies among Asian countries were reported in Bangladesh, India, and United Arab Emirates with 7%, 6%, and 6% (15,20–22). In Japan and Singapore, incidence rates vary between 39-45 and 18 cases per million population years (pmp) (15,19,23). In Japanese children (age of 0-15 years), the frequency rate of IgAN was found to be 4.5 cases /100 000/year (24). In a large pediatric South Korean study, IgAN or Henoch-Schönlein nephritis was diagnosed in 85% of 662 evaluated kidney biopsies (25).

Interestingly, no differences in the proportion of Asian patients were found between female and male patients and age distribution peaked in the second and third decade of life (15).

10.1.2 Europe

Similar to Asia, incidence and prevalence rates vary in European countries. The highest rates are reported in France, Germany, Sweden, and the United Kingdom with 53%, 51%, 41%, and 39% of patients with a diagnosed PGD (15,26–29). These high numbers are based on strict indications for renal biopsy performance (15). Registry data show that a high percentage of biopsies already had signs of chronic renal insufficiency, suggesting that systematic urine analyses did not take place in routine practice. While the use of mass urinary screening programs was not common practice in most European countries, data from the UK showed that as physicians payed attention to asymptomatic urine abnormalities and consequently performed renal biopsies, the prevalence of IgAN increased from 4% to 38% (30,31). The lowest prevalence rates of PGD patients among European countries were found in Croatia, Macedonia and Serbia and Montenegro with 18%, 12%, and 8.5%, respectively (32–34). Age distribution among European countries shows a peak at 20 and 30-year-old individuals. In Europe, the male:female ratio varies between 2:1 to 6:1 (35).

10.1.3 North and South America

North and South America face a complex situation regarding IgAN epidemiology based on the heterogeneity of the population. While Caucasian Americans show prevalence rates of about 8%, prevalence rates for African Americans are only around 1% in North America (36). According to Schena et al, differences in epidemiologic parameters among ethnicities in North America might be explained by varying indications to perform renal biopsies and by different numbers of study cohorts (15). Age distribution among the United States shows a peak around the second and third decade of life in Caucasian Americans (15).

There is little data on the epidemiological situation of IgAN in South America. The lack of reported literature data can be explained by the fact that patients in South America are referred to nephrologists in already late and symptomatic stages (often with nephrotic symptoms). Hence, signs of progressive and advanced renal disease with focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis are often seen on histological renal biopsy examination (15).

10.1.4 Oceania

In Australia, reported prevalence rates are 34% of all patients with biopsy proven PGD (37). The indication for renal biopsy performance in Australia is equal to that in Japan including patients with persistent asymptomatic urinary abnormalities. This is comprehensible as renal replacement therapy registries in Australia show that IgAN is the most frequent cause of end stage renal disease (38). Prevalence rates of IgAN were found to be higher in populations with European ethnicity (24%) in comparison to indigenous population, such as the Aborigines (13%) (39). This could again be explained by different access to medical examination, diagnostics, and treatment for minorities as they live in remote areas with huge distances to the next appropriate institutions (15).

Interestingly, the numbers of IgAN cases in New Zeeland showed similar distribution between indigenous and nonindigenous populations with a higher frequency in non-indigenous patients (15). However, indigenous populations, mostly Polynesians (Maori), showed higher frequencies in general glomerular diseases (15). The overall frequency of IgAN in New Zeeland among patients with proven PGD was 16% as described by the New Zeeland Glomerulonephritis Study Group, in 1989 (15).

10.1.5 Africa

In Africa the primary indication to perform renal biopsy was nephrotic range proteinuria (15). Patients with microscopic hematuria or low proteinuria normally did not undergo biopsy. These factors contribute to very low numbers of frequency of IgAN in African populations with 0.7% and 5.8% as reported by Seedat et al in 1998 and Okpechi et al in 2011 (15,40,41).

10.2 Etiology and Pathogenesis

The etiopathogenesis of IgAN still remains an important topic of scientific research. Its underlying mechanisms responsible for disease initiation and progression are complex. Current understanding of mechanistic factors suggest that not only generic progression factors (e.g. arterial hypertension) but also genetic and environmental influences are involved in IgAN pathogenesis (4).

During the past decades, extensive scientific progress has been achieved in understanding the complex interplay of involved pathomechanisms. Major factors responsible for disease onset and progression include: (I) Elevated serum levels of poorly galactosylated IgA1, (II) formation of O-glycan-specific-anti-IgA1-IgG-autoantibodies directed against the poorly galactosylated regions, (III) formation of IgA1-IgG or IgA1-IgA immune complexes which are prone to mesangial deposition, (IV) mesangial immune complexes initiating the production of inflammatory cytokines and chemokines, (V) proinflammatory mediators support the onset of cellular proliferation, the production of extracellular matrix and finally lead to glomerular injury and renal function loss (4,42). Key steps in the pathogenesis of IgAN are shown in Figure 1.

10.2.1 Poorly galactosylated IgA1: Role and Origin

Human IgA consists of two subclasses: IgA1 and IgA2. IgA normally is secreted by subepithelial plasma cells onto mucosal surfaces, such as the nasal or the gastrointestinal mucosa, via transcytosis in dimeric form (42,43).

In IgAN, increased levels of poorly O-galactosylated IgA1 in both serum and glomerular immune deposits have been identified as a key factor in the etiopathogenesis of IgAN, as found in IgAN patients of different ethnic and geographic origin (42,44–49).

O-galactosylation of IgA1 molecules includes a complex sequence of enzymatic reactions: The hinge region of the α heavy chain of IgA1 contains an amino acid chain that is extended by 18 amino acids where O-glycans chains may attach to serine or threonine residues. Although there are up to nine possible serine/

threonine sites available for O-galactosylation in each α heavy chain, only between three and six sites may be occupied at any time. O-galactosylation of the hinge region is mediated by a group of enzymes through a series of stepwise co/post-translational modifications. This process is initiated by the addition of N-acetylgalactosamine (GalNAc) on the IgA1-hinge region by the activity of N-acetylgalactosaminyl-transferase (42). The addition of a galactose residue to the amino acid requires multiple enzymatic reactions (42). In the next step, core 1 beta 1,3-galactosyltransferase (C1GalT1) provides for the galactosylation reaction by ***β***-1,3-linking galactose to GalNAc forming a disaccharide (42). In order to prevent protein misfolding and to assure protein stability, an interaction between C1GalT1 and its molecular chaperone, core 1 ***β*** 3 GalT-specific molecular chaperone (Cosmc) is required (42). In the end the addition of sialic acid to either GalNAc or to the galactose unit can occur by sialylation through diverse sialytranferases.

The last step is crucial in the formation of poorly galactosylated IgA1 as it prevents the addition of galactose once bound to GalNAc (42). Poorly galactosylated IgA1 molecules are not only found in IgAN patients but are present to a much greater proportion of the IgA1 O-glycoform circulating pool in IgAN patients when compared to healthy individuals (42).

Abnormal generation of poorly O-galactosylated glycoforms cannot be attributed to just one defective enzyme or chaperon. However, it is more likely, that subpopulations of IgA1-commited plasma cells with differences in their activity and expression of the enzymes needed for IgA1 generation might be involved (42).

Yet not sufficiently elucidated but interestingly enough, genetic and epigenetic control mechanisms have been found to play role in IgAN. Associations between serum levels of poorly O-galactosylated IgA1 and a non-coding region of C1GALT1, the gene responsible for coding the galactosyltransferase C1GalT1 have been found. Most likely these genetic changes do not occur in all cells but affect certain microenvironments, like mucosal surfaces. However, this association does not seem to be specific for IgAN since it has been detected in healthy individuals and patients with membranous nephropathy, supporting the hypothesis that circulating levels of poorly O-galactosylated IgA1 are heritable and influenced by genetic variations within the C1GALT1 gene (42,50).

Epigenetic control by microRNAs of IgA1 O-galactosylation is considered to be involved in IgAN pathogenesis (42). Upregulation and overexpression of a specific micro RNA (miR-148b) in peripheral blood mononuclear cells has been associated with a decreased expression of C1GalT1 and production of poorly O-galactosylated IgA1 (42). A binding site for miR-148b has been identified within the recently identified C1GALT1 risk haplotype, underlying a role for miR-148b in IgAN (42,51). Susceptible gene loci in the major histocompatibility complex responsible for the gastrointestinal immune response with deletions in CFRH1, CFHR3 at chromosome 1q32 and a locus at chromosome 22q12 have been identified in genome wide association studies (42,52). Thus, the importance of the mucosal immune system as the source of poorly O-galactosylated IgA1 in IgAN is being increasingly discussed and referred to as the mucosal-kidney axis (43).

Further evidence supporting the importance of the mucosal-kidney axis is based on the typical clinical presentation of IgAN patients. IgAN patients with an upper respiratory tract infection develop visible hematuria during or short after the infection occurs (synpharyngitic hematuria) (42). Other studies show associations between IgAN patients and their predisposition to autoimmune diseases in which the mucosal immune system and an exaggerated immune response to mucosal antigens is involved, e.g. coeliac disease and inflammatory bowel disease (42).

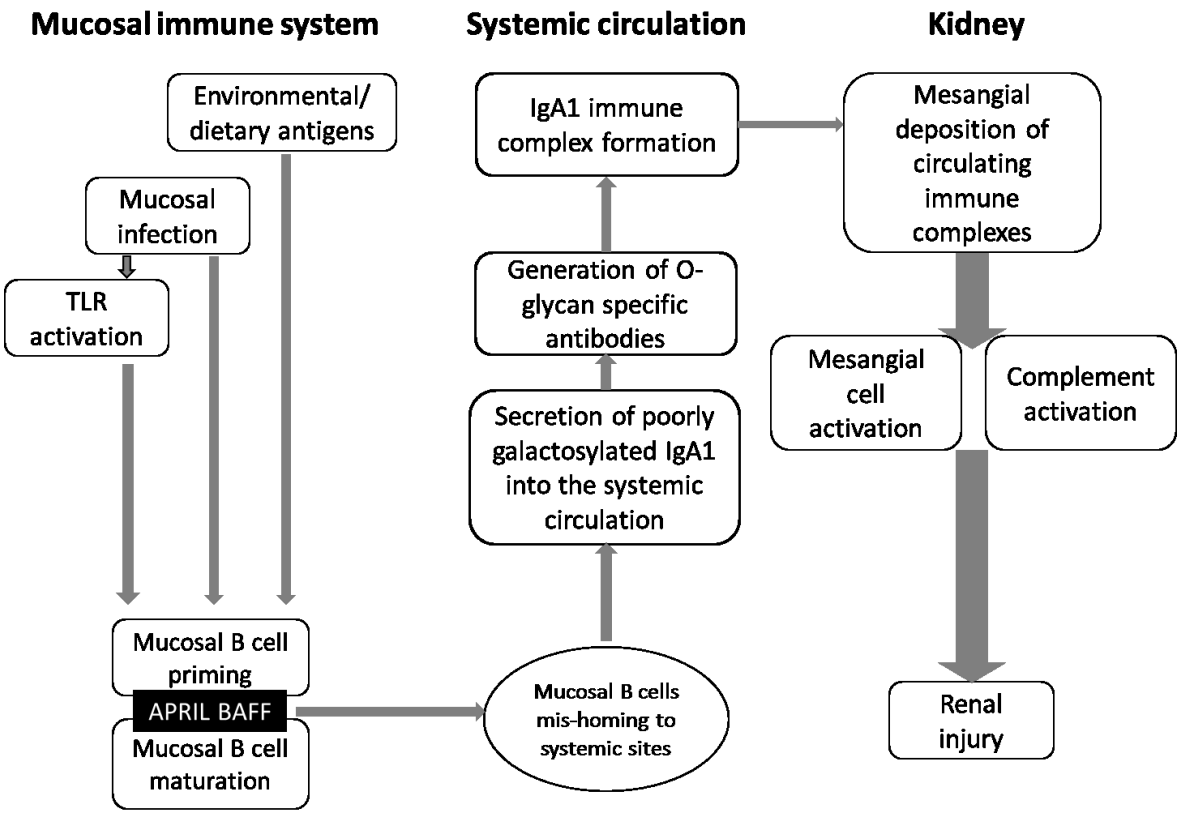


Figure 1: Key steps in the pathogenesis of IgAN (modified after Yeo SC et al. Pediatr Nephrol 2018)

10.2.2 Formation of O-glycan Specific Autoantibodies

Evaluation of glomerular depositions in patients with IgAN showed presence of immune complexes. As the sole presence of monomeric IgA1 is not able to initiate mesangial cell activation in *in vitro* experiments, formation of poorly O-galactosylated IgA1 molecules cannot be the only factor responsible for the disease initiation in IgAN (42,53). Thus, a major pathogenetic step in IgAN is the production of antibodies, IgA or IgG, against galactose-deficient sugar residues in poorly O-galactosylated IgA1. This process is assisted by toll-like receptors (TLRs), involved in response to the exposure to bacterial wall and viral envelope components, and in the polyclonal activation of B lymphocytes and immunoglobulin production (54–56). In the majority of cases, reported immune complexes consist of polymeric poorly O-galactosylated IgA1 as the substrate of immune complexes and O-glycan-specific autoantibodies.

Conformational changes of the IgA1 molecule (due to O-galactosylation of the hinge region) is likely to be the molecular trigger for specific O-glycan-specific

autoantibody production and recognition by serum antimicrobial antibodies that mistake the IgA1 hinge region O-glycans for bacterial or viral cell wall glycoprotein structures (molecular mimicry) (42). A proposed model of the pathogenetic mechanisms of immune complex formation is shown in Figure 2.

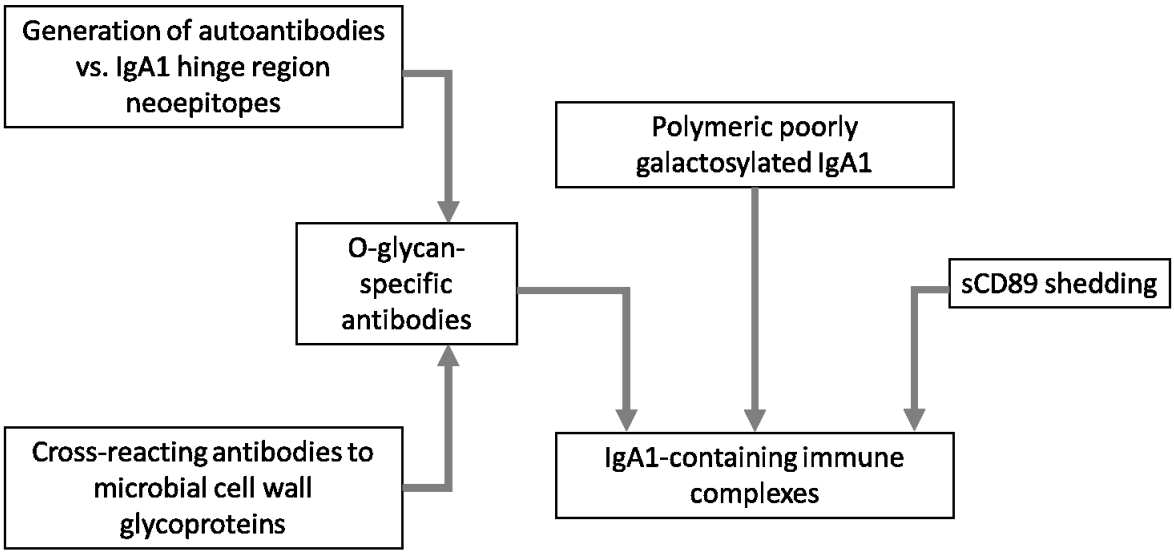


Figure 2: Pathogenesis of immune complex formation in patients with IgAN (modified after Yeo SC et al. Pediatr Nephrol 2018)

A strong association between the levels of O-glycan-specific autoantibodies in the serum and the disease activity and progressive kidney disease in IgAN has been found (42). Following the mucosal-kidney-axis, increased antimicrobial mucosal antibodies drive immune complex formation during mucosal infections in IgAN, resulting in a temporary flooding of the glomeruli with IgA immune complexes with severe glomerular inflammation and development of synpharyngitic hematuria (42).

10.2.3 Mesangial Immune Complex Deposits and Initiation of Glomerular Injury

Glomerular injury is triggered by the deposition of immune complexes in the glomerular mesangium in susceptible individuals. As described by Coppo et al already in 1993 and Kokubo et al in 1998, mesangial trapping and an increased affinity of poorly galactosylated IgA1 for extracellular matrix components, such as fibronectin and type IV collagen, are the main pathomechanistic factors in glomerular immune complex deposition (57,58). Once deposited, IgA1-containing immune complexes bind to and activate mesangial cells, cytokine release, such as IL-6, tumor necrosis factor-α and transforming growth factor-β and further promote an inflammatory response (42). Cellular proliferative changes, as reflected by the highly variable histopathological changes typically seen in IgAN, parallel these molecular processes, including mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis, and in severe cases glomerular crescent (1,59). Local proinflammatory cytokines and chemotactic mediators lead to recruitment of inflammatory cells, trigger glomerular cell proliferation, change podocyte gene expression and glomerular permeability, causing filtration of IgA immune complexes, podocyte damage, and segmental glomerulosclerosis (glomerulopodocytic crosstalk) (42,60–63). Glomerular-derived cytokines and filtered IgA1, have been shown to activate proximal tubule epithelial cells (glomerulotubular crosstalk), which in turn drives tubulointerstitial fibrosis (42,64).

Immunhistochemical/immunofluorescence findings support a role of the complement system in perpetuating glomerular injury in IgAN (65). The presence of glomerular complement component 3 (often in the same distribution as IgA) and absence of C1q suggest activation of the lectin and/or alternative pathways (42).

10.3 The Oxford Classification

Kidney biopsy with histopathological classification of IgAN remains the cornerstone for diagnosing IgAN, evaluating disease severity and guiding appropriate therapeutic strategies (8). In 2009, the International IgA Nephropathy Network and Renal Pathology Society published the Oxford Classification of IgAN developed in

a cohort of 265 adults and children of Caucasian and East Asian ethnicity with IgAN (1,59,66). In the original Oxford Classification, three reproducible histopathological variables were identified to be independently predictive of poor renal outcome: mesangial hypercellularity (M), segmental glomerulosclerosis (S), and interstitial fibrosis and tubular atrophy (T) (1,59,66). In patients with endocapillary hypercellularity (E), renal dysfunction was significantly lower in those receiving immunosuppressive therapy. Finally, the original Oxford Classification proposed four parameters, including mesangial (M) and endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and interstitial fibrosis and tubular atrophy (T), summarized as the so-called MEST score (1,59,66). Mesangial hypercellularity is defined as ≥3 cells per peripheral mesangial area (M) (67). Endocapillary hypercellularity (E) is defined as increased numbers of cells within the glomerular capillaries causing luminal narrowing (67). In the S category (S), the presence of segmental glomerular sclerosis should be assessed. In the T category (T), tubular atrophy/interstitial fibrosis in the cortical area should be determined as T1 when 26-50% is involved and as T2 in cases showing >50% of tubular atrophy/interstitial fibrosis (1,59,68).

The MEST scoring system offered the first opportunity to use histology to predict renal outcome independent of proteinuria, blood pressure and eGFR (1). In 2014, the association of M1, S1 and T1/2 with renal outcomes and the association of M1 and E with subsequent increase in proteinuria was further confirmed by the European Validation Study of the Oxford Classification of IgAN (VALIGA) study (68). However, in the original Oxford study cohort, only 265 adults and children of Caucasian and East Asian ethnicity were included, and the cohort was selected to be enriched for typical slowly progressive IgAN (1,66). Advanced cases with an estimated glomerular filtration rate (eGFR) <30 ml/in per 1.73 m^2, those with dominant glomerulosclerosis and interstitial fibrosis as well as rapidly progressive cases, in which crescents might more likely be predictive of outcome, were excluded from the study (1,66). Numerous validation studies proved the significant effect of the histopathological lesions on renal outcome (59,68). Notably, the T lesion was a more consistent predictor of renal outcome than M and S lesions when ESRD was evaluated (59).

The original Oxford Classification did not account for the presence of glomerular crescents, since in the original Oxford study (1) and in several validation studies with similarly restrictive entry criteria (69–72) crescents were not found to be an independent predictor of renal outcomes (9). Cellular glomerular crescents are defined by extracapillary cell proliferation of more than two cell layers with more than 50% of the lesion occupied by cells (8,67). In fibrocellular crescents, the extracapillary lesion comprises of cells and extracellular matrix with more than 50% cells and less than 90% matrix and in fibrous crescents more than 90% matrix is present (8,67). Thus, glomerular crescents can be sub-classified by their predominant components in cellular, fibrocellular or fibrous crescents (8,67), reflecting the dynamic process of glomerular crescent formation.

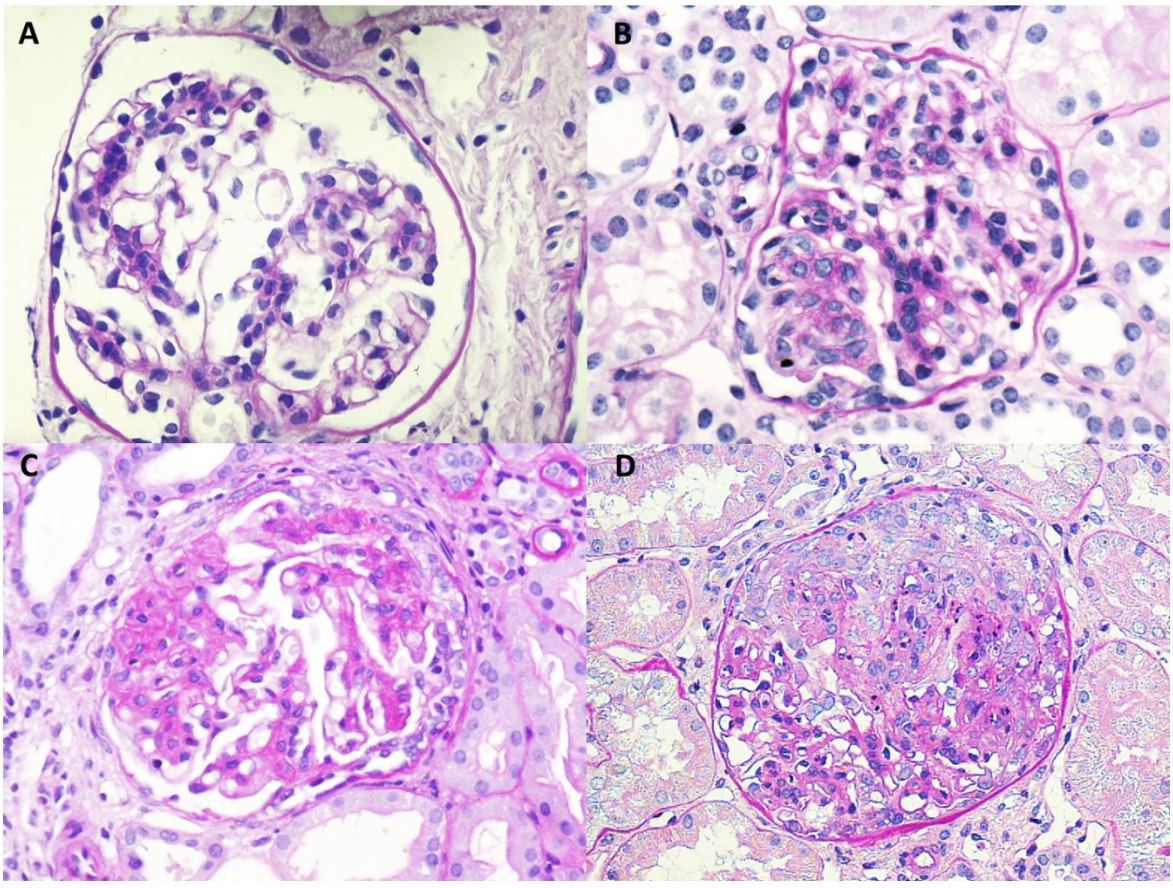


Figure 3: Representative images of glomerula showing A) mesangial hypercellularity (M1); B) endocapillary hypercellularity (E1); C) segmental glomerulosclerosis (S1); D) cellular crescent (C)

In the updated Oxford study, the presence of at least 25% of crescents (C1) was significantly predictive of poor renal outcome in patients not receiving immunosuppressive therapy, but not in patients under immunosuppression (59). The C2 category identified patients at risk of poor renal outcome regardless of

immunosuppressive therapy (59). Since 2017, an additional C-category in the original MEST score for the presence glomerular crescents is recommended: C0 (no crescents), C1 (crescents in less than one fourth of glomeruli), and C2 (crescents in over one fourth of glomeruli), summarized as the modified MEST-C score (9). Images of representative glomeruli showing histopathological changes typical of IgAN are shown in Figure 3. Figure 4 shows representative immunohistochemical staining pattern of IgA and c3c.

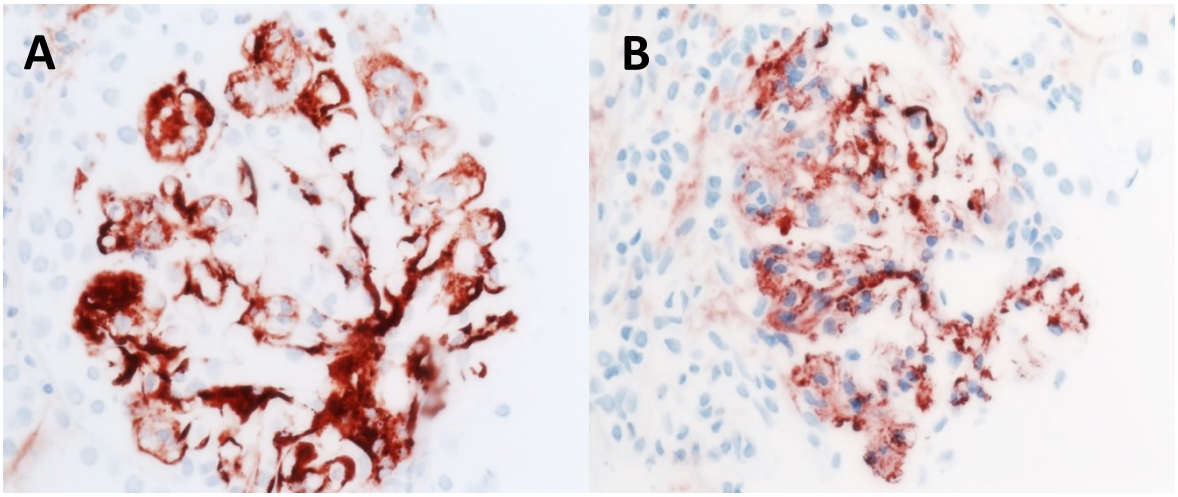


Figure 4: Representative images showing immunohistochemical staining with the antibody against IgA (A) and c3c (B). Note the granular staining pattern of IgA and c3c within the mesangium

10.4 Therapy and Future Therapeutic Approaches

The optimal therapeutic approach of IgA nephropathy is uncertain (73,74). However, the global nonprofit organization Kidney Disease Improving Global Outcomes (KDIGO) developed guidelines for the optimal treatment of patients with kidney diseases such as IgAN. They recommend two major approaches to treat IgAN. General interventions (not specific to IgAN) to slow progression include blood pressure control with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers in patients with proteinuria. Furthermore, they include lifestyle modifications, such as dietary sodium restriction, smoking cessation, and weight loss. The individual cardiovascular risk should additionally be assessed. Alternatively, therapy with glucocorticoids with or without other

immunosuppressive agents to treat the underlying inflammatory disease might be used (75). The general interventions are used in all patients at risk for progression (i.e. with proteinuria), while immunosuppressive therapy is used in selected patients.

According to a multi-center study, comparing the effects of immunosuppressive and supportive therapy, patients with high risk IgAN (e.g. eGFR<30ml/min/1,73m^2, diabetes, obesity (BMI>30kg/m^2), latent infections, secondary disease, active peptic ulceration, uncontrolled psychiatric illness, severe proteinuria, and hypertension) receiving additional immunosuppression did not show significant renal outcome but showed even adverse effects (76). Reducing obesity has been shown to contribute to ameliorate proteinuria in IgAN (77,78).

The use of immunosuppressive therapy is being controversially debated. Although early studies suggest the use of corticosteroids to improve clinical outcome (5,68,79,80), other studies underline the possible adverse effects of immunosuppressive agents (81). According to the VALIGA study, the use of corticosteroids reduces the risk of disease progression proportional to proteinuria (5,68). In severe cases most trials describe a beneficial effect of corticosteroids on renal survival, reduction in the risk of progressive renal dysfunction, and risk of renal failure (79–81). However, these studies reported certain confounding factors, mostly that the use of RAS blockage had not been conducted uniformly (79–81).

As the underlying pathomechanisms of IgAN are being more and more deciphered, future therapeutic approaches for IgAN are now being developed. In the NEFIGAN study, a novel targeted-release formulation of budesonide designed to deliver the drug to the distal ileum has been shown to reduce proteinuria in patients with IgA nephropathy when added to optimized RAS blockade. (82).

Two novel therapeutic agents interfering with cytokine signaling pathways are currently under clinical evaluation. Blisibimod, a selective peptibody antagonist of the cytokine B cell activating factor (BAFF), is under investigation in a phase 2, randomized, double-blind, placebo-controlled trial to test its protective effect on proteinuria aggravation when subcutaneously administered (ClinicalTrials.gov Identifier: NCT02062684). Atacicept is a humanized recombinant TACI-IgGFc fusion protein with anti-APRIL and anti-BAFF activity (75).

Toll-like receptor-9 (TLR-9) is thought to play a role in IgAN pathogenesis as its blockage via Hydroxychloroquine, a potent TLR-9 inhibitor, has shown to ameliorate proteinuria in IgAN patients (83–85).

Moreover, Fostamatinib as a selective spleen tyrosine kinase (Syk) inhibitor is effective in decreasing pro-inflammatory cytokine response, damage, and inflammation of the renal tissue (86,87). Autophosphorylation and transphosphorylation of SYK tyrosine residues, and subsequent activation of downstream targets has been detected in IgAN patients. Its upregulation apparently correlates with serum creatinine and histological lesions of disease activity in IgAN (ClinicalTrial.gov Identifier: NCT02112838) (88).

Furthermore, the impact of the complement system activation in IgAN can be targeted with Eculizumab, a monoclonal recombinant, fully humanized hybrid IgG2/IgG4 antibody, by binding complement C5 and hence interrupting the formation of the membrane attack complex (MAC) (42). Early initiation of Eculizumab in patients with progressive IgA nephropathy has been shown to have a beneficial effect on renal function and proteinuria by blocking complement-mediated renal inflammation (89,90).

Another possible therapeutic agent might be a monoclonal antibody against mannan-binding lectin-associated serine protease-2 (MASP-2) called OMS721. As MASP-2 acts as the effector enzyme of the lectin pathway of the complement system, its blockage might lead to amelioration of proteinuria in IgAN patients (42).

11 Aims of this Study

We aimed to validate the prognostic value of the different histopathological categories of the modified Oxford Classification (MEST-C score), with special emphasis on crescentic lesions, on renal survival in our IgAN study cohort. In addition, histological findings were correlated with available clinical data, such as proteinuria, hematuria, systolic as well as diastolic blood pressure, estimated glomerular filtration rate, and serum creatinine.

12 Materials and Methods

12.1 Ethic Statement

The study was approved by the local Ethics Committees (ethics approval IDs: 32-193 ex 19/20) in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

12.2 Study Cohort

From January 1st in 2002 to December 31st in 2018, 349 patients were diagnosed with IgA nephropathy via renal biopsy at the Institute of Pathology, Medical University of Graz. Patients under the age of 18 years, patients with Schoenlein-Henoch purpura and secondary causes of mesangial IgA deposition, such as IgA-dominant acute post-infectious glomerulonephritis and systemic lupus erythematosus, were excluded from this study (n=46). Patients with incomplete clinical follow-up data (n=31) or ongoing treatment in different clinical centers with insufficient available clinical data, were considered ineligible for further analyses (n=67).

We included patients regardless of their rate of clinical parameters, such as estimated glomerular filtration rate (eGFR) and creatinine at time of biopsy (tob) and after a minimum follow-up period of 12 months.

Cases with clear histopathological and immunohistochemical glomerular features diagnostic of IgAN, irrespective of the number of present glomeruli on biopsy examination, were included into the analyses. Overall, a total of 205 patients were included in this study.

12.3 Data Collection

For data collection we used the electronic communication and information network for the Styrian federal state hospitals and the Medical University of Graz, called “MEDOCS”.

Demographic, histopathological parameters and clinical data, such as gender, age, proteinuria, gross hematuria, eGFR, systolic and diastolic blood pressure, and serum creatinine levels were collected at the time of renal biopsy and after a minimum follow-up period of 12 months. Use of antihypertensive and/or immunosuppressive therapies was documented for each patient. Presence of proteinuria was measured as either the amount of protein within a 24-hour urine collection (g/24hrs) or as protein to gram creatinine ratio (mg/g Crea) and defined as present or absent. Gross hematuria was measured by urine analysis and defined as present or absent. Using the CKD-EPI equation the eGFR was calculated (91) and defined as ml/min/1,73m^2. Serum creatinine was measured using blood samples and defined as (mg/dl). After a minimum follow-up period of 12 months clinical data were recollected and documented.

12.4 Renal Biopsy Evaluation

Each kidney biopsy specimen was fixed in formalin and routinely processed for light microscopy and immunohistochemical analyses. Light microscopic examination was performed on three micron serial sections of each biopsy after performing hematoxylin eosin, periodic acid-Schiff, aldehyde fuchsin orange G, and periodic acid-silver methenamine stains. For immunohistochemical analyses, each section was stained with antibodies against the immunoglobulins, IgG, IgA and IgM as well as with antibodies against factors of the complement cascade, including c1q, c3c, c4d and c5b-9 (1:20, DAKOCytomation, Glostrup, Denmark).

All renal biopsy specimens were re-assessed by a single pathologist according to the modified Oxford Classification. Mesangial cellularity was scored 0 (0-3 mesangial cells/mesangial area), 1 (4–5 cells), 2 (6–7 cells), and 3 (more than 8 cells) for each glomerulus (1). Segmental glomerulosclerosis (S1) is characterized by a segmental increase in the glomerular matrix with obliteration of capillary lumen with or without hyalinosis or presence of foam cells (1). Endocapillary hypercellularity (E1) is defined by cell proliferation within glomerular capillary lumina, causing narrowing of the lumina (1). Tubular atrophy is defined by thick irregular tubular basement membranes with decreased diameter of tubules. It is scored according to the percentage of cortical area involvement as T0 (0–25% of cortical

area), T1 (26–50% of cortical area), or T2 (>50% of cortical area) (1). Interstitial fibrosis is defined as increased extracellular matrix separating tubules in the cortical area. As tubular atrophy, it is scored as percentage involvement (1). Crescentic lesions are defined as extracapillary cell proliferation of more than two cell layers with >50% of the lesion occupied by cells as C0 (absence of crescents), C1 (crescents in 0-25% of glomeruli), or C2 (crescents in ≥25% of glomeruli). Immunohistochemical analyses were re-evaluated by a single pathologist. In addition, each biopsy specimen was scored for the distinct presence of c3c deposits in semiquantitative fashion according to staining intensity.

12.5 Study Outcomes

The primary study endpoints are defined as the onset of end stage kidney disease (ESKD) and/or 50% decline in eGFR. ESKD is defined as the necessity to perform kidney replacement therapy, which is defined as the onset of permanent hemodialysis, peritoneal dialysis or kidney transplantation.

12.6 Statistical Analysis

We performed statistical analysis using the IBM software SPSS (version 25 and 26). To test normal distribution of continuous variables we performed Kolmogorov-Smirnov test. Quantitative variables and continuous variables are not normally distributed and are expressed as median and interquartile range. Categorical variables are given as numbers (percentages). For inductive statistical analyses, we performed chi-squared test, McNemar test, Mann-Whitney-U test, and Wilcoxon rank-sum test. To determine an independent association between histopathological parameters and a 50% decline in eGFR, univariate and multivariate linear regression analyses were performed.

We generated renal survival curves with the Kaplan–Meier method, and between-group survival was compared by using the log-rank test. Moreover, we performed binary logistic regression analysis to assess the onset of our endpoints according to

metric, and categorical variables. All probabilities are two-tailed, and the level of significance was set at 0.05.

13 Results

13.1 Baseline Characteristics: Clinical and Histopathological Data at Time of Biopsy

All demographic, clinical, and histopathological characteristics of the IgAN study cohort at time of biopsy are presented in Table 1.

	All (n=205)	**M (n=205)**	**E1 (n=49)**	**S1 (n=154)**	**T1 (n=34)**	**T2 (n=24)**	**C1 (n=76)**	**C2 (n=34)**
Age (years)	42 (30-57)	42 (30-57)	47 (30-57)	45 (31-56)	54 (26-63)	47 (26-57)	46 (29-56)	36 (26-54)
Representative biopsies (%)	161 (79)	161 (79)	41 (84)	118 (77)	20 (59)	18 (75)	60 (79)	29 (85)
Follow-up (months)	84 (48-144)	84 (48-144)	60 (24-108)	72 (36-144)	72 (36-96)	72 (48-105)	84 (48-168)	54 (36-111)
Male (%)	136 (66)	136 (66)	33 (67)	100 (65)	24 (71)	19 (79)	50 (66)	19 (56)
Female (%)	69 (34)	69 (34)	16 (33)	54 (35)	10 (29)	5 (21)	26 (34)	15 (44)
Systolic blood pressure (mmHg) n=187	138 (125-150)	138 (125-150)	140 (125-160) n=43	140 (127-150) n=138	140 (130-166) n=32	145 (135-160) n=23	140 (125-160) n=67	140 (125-156) n=30)
Diastolic blood pressure (mmHg) n=185	80 (75-90)	80 (75-90)	85 (79-95) n=42	80 (75-90) n=136	84 (78-91) n=30	85 (80-90) n=23	84 (75-94) n=66	85 (80-93) n=29
Gross hematuria (%)	195 (95)	195 (95)	46 (94)	144 (94)	33 (97)	22 (92)	72 (95)	31 (91)
Proteinuria (%)	180 (88)	180 (88)	43 (88)	133 (86)	29 (85)	20 (83)	69 (91)	31 (91)
Estimated glomerular filtration rate (ml/min per 1.73m^2)	48.9 (22-70.5)	48.9 (22-70.5)	48 (31-70)	44 (26.4-63.2)	31.4 (18.6-46.1)	18,7 (14.4-26.6)	44.8 (23.7-67)	34.4 (18.7-60)
Creatinine (mg/dl)	1.53 (1.08-2.74)	1.53 (1.08-2.74)	1.61 (1.10-2.40)	1.61 (1.24-2.43)	2.02 (1.49-3.48)	3.50 (2.78-4.39)	1.60 (1.18-2.73)	1.87 (1.23-3.42)

>50% reduction of eGFR	36 (18)	36 (18)	9 (18)	30 (20)	10 (29)	3 (13)	16 (21)	6 (18)
Renal survival (combined event)	88 (43)	88 (43)	21 (43)	71 (46)	20 (59)	18 (75)	34 (45)	15 (44)

Table 1: Baseline characteristics of the subjects according to the Oxford Classification at the time of biopsy. Abbreviations: E1: presence of endocapillary hypercellularity; M1: mesangial hypercellularity >0.5; S1: presence of segmental glomerulosclerosis; T1: tubular atrophy/interstitial fibrosis 26–50% of cortical area; T2: tubular atrophy/interstitial fibrosis >50% of cortical area; C1: crescentic lesions in <25% of glomeruli; C2: crescentic lesions in >25% of glomeruli.
Note: Values are expressed as median (interquartile range) or numbers (percentage).

Median age of our IgAN patients was 42 years (18– 85 years, SD ±16 years). 120 (58.5%) patients were younger and 85 (41.5%) patients older than 50 years. The youngest patient was 18, the oldest 85 years old. Two peaks in age distribution were observed: the first between 25 and 30 years and another between 50 and 55 years, respectively (Figure 5).

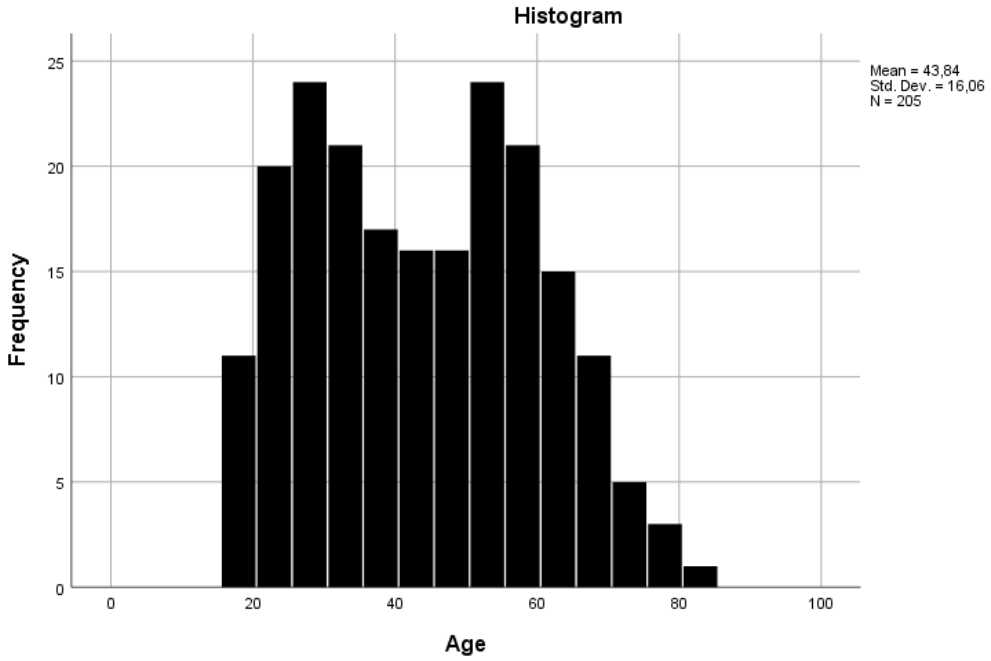


Figure 5: Age distribution of the IgAN cohort

Among all patients younger than 50 years (n=120), 30 patients (25.0%) showed endocapillary hypercellularity (E1), 89 patients (74.2%) segmental sclerosis (S1), 12 patients (10.0%) tubular atrophy/interstitial fibrosis in 26-50% of cortical area (T1), and 14 patients (11.7%) showed tubular atrophy/interstitial fibrosis in >50% of cortical area (T2). In 44 patients (36.7%) crescents in 0-25% of glomeruli (C1), and in 22 patients (18.3%) crescents in >25% of glomeruli (C2) were detected. In IgAN

patients older than 50 years(n=85), 19 patients (22.4%) showed endocapillary hypercellularity (E1), 65 patients (76.5%) segmental sclerosis (S1), 22 patients (25.9%) tubular atrophy/interstitial fibrosis in 26-50% of cortical area (T1) and 10 patients (11.8%) showed tubular atrophy/interstitial fibrosis in >50% of cortical area (T2) (Table 2). In 32 patients (37.6%) crescents in 0-25% of glomeruli (C1), and in 12 patients (14.1%) crescents in >25% of glomeruli (C2) were noted. Patient age did not correlate with the amount of tubular atrophy/interstitial fibrosis (*p-value=0.210*).

	T0, 0-25% tubular atrophy/interstitial fibrosis	**T1, 25-50% tubular atropy/interstitial fibrosis**	**T2, >50% tubular atropy/interstitial fibrosis**
<50 years	94	12	14
>50years	53	22	10

Table 2: Degree of tubular atrophy/interstitial fibrosis of the cortical area according to the age

Our study cohort includes 69 (33.7%) female and 136 (66.3%) male IgAN patients (Figure 6). Gender distribution shows a male to female ratio of 2:1. Gender specific age distribution shows two peaks among male patients, the first peak between 20 to 25 years and another peak between 50 to 60 years, respectively. However, among female patients, age distribution showed only one peak at the age between 25 to 35 years (Figure 7).

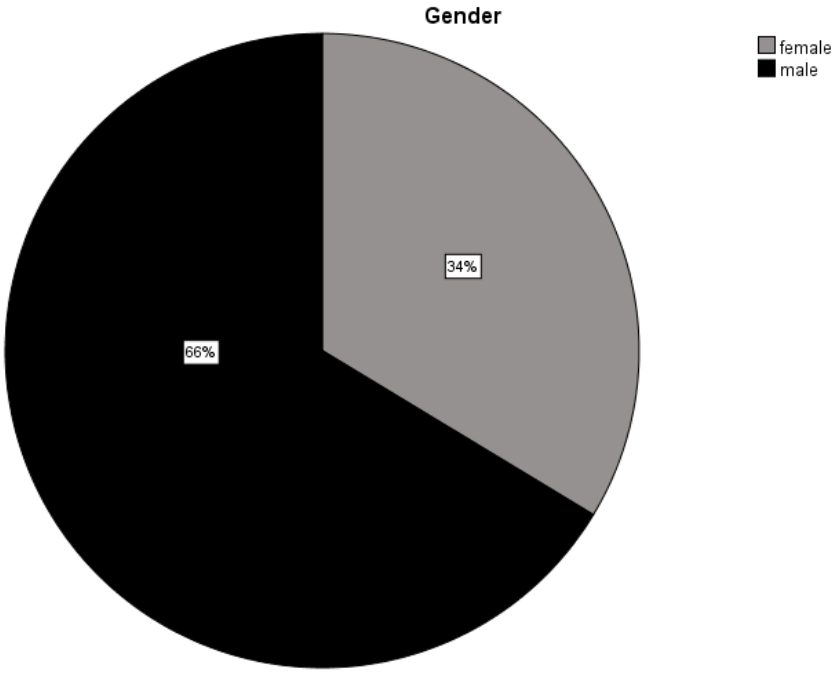


Figure 6: Gender distribution

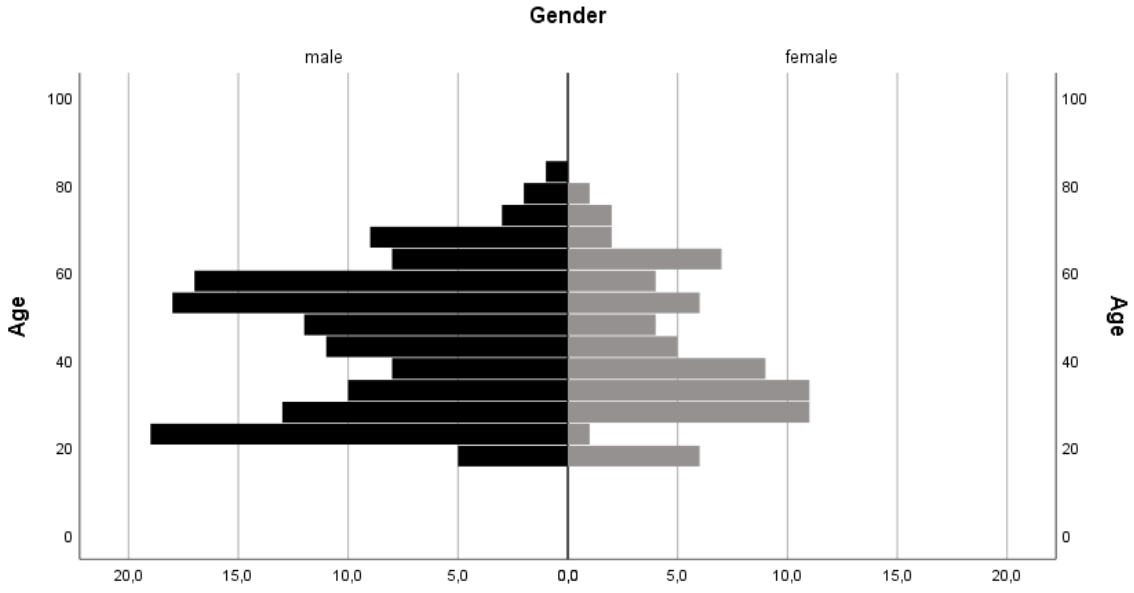


Figure 7: Gender specific age distribution

When comparing female to male IgAN patients, similar data for the presence of endocapillary (E1) and crescentic lesions (C1) as well as for the presence of segmental glomerulosclerosis (S1) and tubular atrophy/interstitial fibrosis (T1, T2) were seen (Table 3).

	E0	E1	S0	S1	T0	T1	T2	C0	C1	C2
Female n=69	53	16	15	54	54	10	5	28	26	15
Male n=136	103	33	36	100	93	24	19	67	50	19

Table 3: Gender-specific histopathological parameters (according to the modified Oxford Classification)

Kidney biopsies with at least 8 glomeruli were available in 161 cases (78.5%), respectively. Median follow-up period was 84 months (18 – 204 months).

In 49 IgAN cases (23.9%), endocapillary hypercellularity (E1) was seen. 154 (75.1%) cases showed segmental glomerulosclerosis (S1). Tubular atrophy and interstitial fibrosis in up to 50% (T1) and more than 50% (T2) of the cortical area was noted in 34 (16.6%) and 24 (11.7%) cases, respectively. Crescentic lesions in up to 25% (C1) of the glomeruli were found in 76 (37.1%) cases, and crescents in over 25% of the glomeruli (C2) were found in 34 (16.6%) patients, respectively.

Cellular crescents were present in 31 (15.1%) and fibro-cellular crescents present in 46 (22.4%) biopsies. In 16 (7.8%) biopsies, fibrous crescentic lesions were found.

Immunohistochemical analysis with the antibody against c3c showed a granular mesangial expression pattern in 147 patients (71.7%).

A decline in eGFR over 50% was noted in 36 patients (17.6%) (Figure 8). Among these, 9 patients (25%) showed endocapillary hypercellularity (E1), 30 patients (83.3%) showed segmental glomerulosclerosis (S1), respectively. In 13 patients (36.1%), tubular atrophy/interstitial fibrosis in more than 25% of cortical area (T1 and T2), and in 22 patients (61.1%) crescents in at least 25% of glomeruli (C1 and C2) was detected.

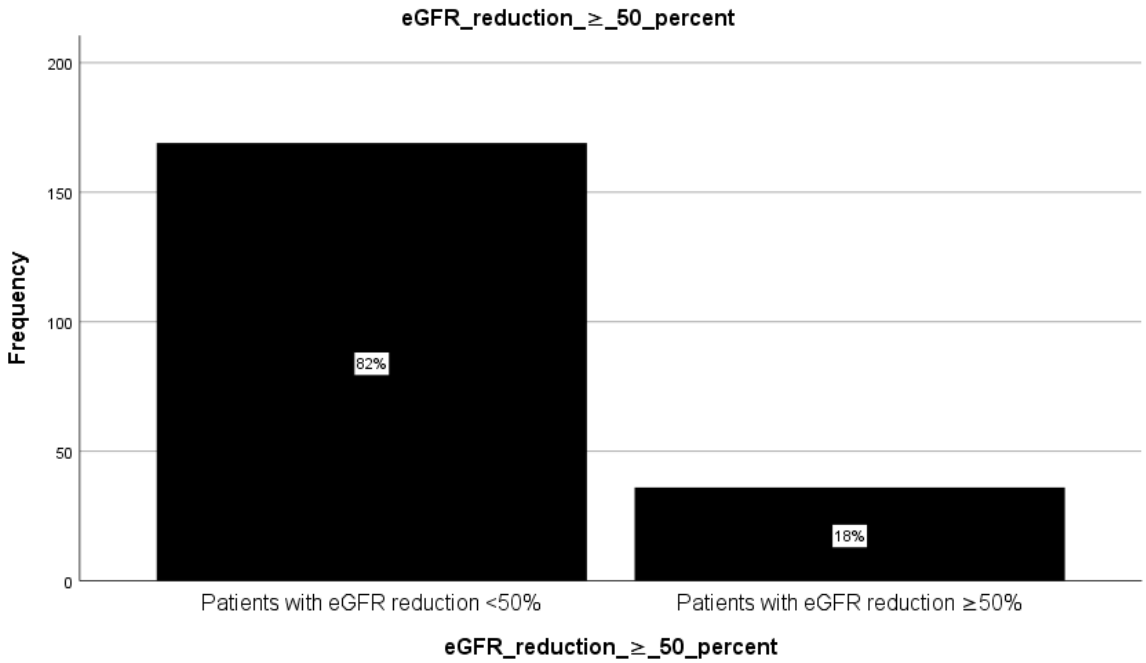


Figure 8: Number of patients with >50% reduction of eGFR after follow-up

88 (43%) IgAN patients experienced a combined event, defined as a reduction of eGFR over 50% and/or the onset of ESKD (Figure 9). We recorded 62 (70.4%) male and 26 (29.6%) female patients who reached said combined event. Among these, 21 patients (23.9%) showed endocapillary hypercellularity (E1) and 71 patients (80.7%) showed segmental glomerulosclerosis (S1), respectively. In 38 patients (43.2%) tubular atrophy/interstitial fibrosis in 26-50% of cortical area (T1), in 18 patients (20.5%) tubular atrophy/interstitial fibrosis in >50% of cortical area (T2), in 34 patients (38.6%) crescents in 0-25% of glomeruli (C1), and in 15 patients (17%) crescents in >25% of glomeruli was detected, respectively.

55 (62.5%) of our IgAN patients underwent kidney transplantation.

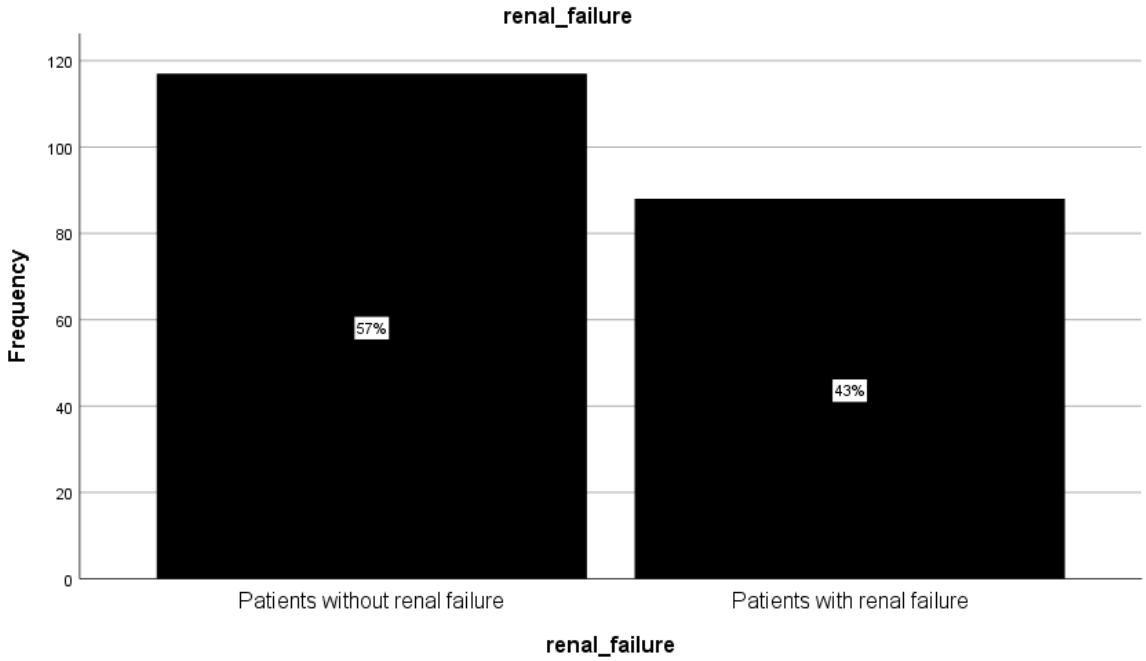


Figure 9: Number of patients experiencing a combined event (onset of ESKD and/or ≥50% reduction of eGFR)

Median systolic blood pressure of our IgAN patients at time of biopsy was 138 mmHg (125-150 mmHg). Patients with endocapillary hypercellularity (E1, n=43) showed a median systolic blood pressure of 140 mmHg (125-160 mmHg). In patients with segmental glomerulosclerosis (S1, n=138) median systolic blood pressure was 140 mmHg (127-150 mmHg). Patients with tubular atrophy/interstitial fibrosis in ≥25% of cortical area (T1/T2, n=32/n=23) showed a median systolic blood pressure of 140 mmHg (130-166 mmHg) and 145 mmHg (135-160 mmHg), respectively. Patients with crescentic lesions (C1/C2, n=67/n=30) showed a median systolic blood pressure of 140 mmHg (125-160 mmHg) and 140 mmHg (125-156 mmHg), respectively. Median diastolic blood pressure of our IgAN study cohort was 80 mmHg (75-90 mmHg). Patients with endocapillary hypercellularity (E1, n=42) showed a median diastolic blood pressure of 85 mmHg (79-95 mmHg). Patients with segmental glomerulosclerosis (S1, n=136) showed a median diastolic blood pressure of 80 mmHg (75-90 mmHg). Patients with tubular atrophy in ≥25% of cortical area (T1/T2, n=30/n=23) showed a median diastolic blood pressure of 84 mmHg (78-91 mmHg) and 85 mmHg (80-90 mmHg), respectively. Patients with crescentic lesions (C1/C2, n=66/n=29) showed a median diastolic blood pressure of 84 mmHg (75-94 mmHg) and 85 mmHg (80-93 mmHg), respectively.

Gross hematuria was noted in 195 patients (95%) at time of biopsy. Among these, in 46 patients (23.6%) endocapillary hypercellularity (E1), in 144 patients (73.8%) glomerulosclerosis (S1), in 55 patients (28.2%) tubular atrophy/interstitial fibrosis in at least 26% of cortical area (T1 and T2), and in 103 patients (52.8%) crescentic lesions (C1 and C2) was detected.

Proteinuria was noted in 180 patients (88%) at time of biopsy. Among these, in 43 patients (23.9%) endocapillary hypercellularity (E1), in 133 patients (73.9%) glomerulosclerosis (S1), in 49 patients (27.2%) tubular atrophy/interstitial fibrosis in at least 26% of cortical area (T1 and T2), and in 100 patients (55.6%) crescentic lesions (C1 and C2) was detected.

Median eGFR was 48.9 ml/min/1.73m^2 (22 – 70.5 ml/min/1.73m^2). In patients with endocapillary hypercellularity (E1), segmental glomerulosclerosis (S1), tubular atrophy/interstitial fibrosis in at least 26% of cortical area (T1 and T2), and crescentic lesions (C1 and C2), median eGFR was 48 ml/min/1.73m^2 (31-70 ml/min/1.73m^2), 44 ml/min/1.73m^2 (26.4-63.2 ml/min/1.73m^2), 23 ml/min/1.73m^2 (16.8-36.5 ml/min/1.73m^2), 44.2 ml/min/1.73m^2 (22.4-63.9 ml/min/1.73m^2, respectively.

Median serum creatinine level was 1.53 mg/dl (1,08 - 2,74 mg/dl) at time of biopsy. In patients with endocapillary hypercellularity (E1), segmental glomerulosclerosis (S1), tubular atrophy/interstitial fibrosis in at least 26% of cortical area (T1 and T2), and crescentic lesions (C1 and C2), median serum creatine was 1.61 mg/dl (1.10-2.40 mg/dl), 1.61 mg/dl (1.24-2.43 mg/dl), 2.87 mg/dl (1.87-3.79 mg/dl), 1.61 mg/dl (1.21-2.88 mg/dl), respectively.

13.2 Comparison of Histological Findings among Groups According to the Modified Oxford Classification at Time of Biopsy

For further analyses, IgAN patients were summarized in histopathological subgroups according to the histopathological categories following the modified Oxford Classification. The comparison of histopathological findings among the groups is given in Table 4.

Pathological variables according to the modified Oxford Classification	All	M1	E1	S1	T1	T2	C1	C2
M1	205 (100)	205 (100)	49 (100)	154 (100)	34 (100)	24 (100)	76 (100)	34 (100)
E1	49 (24)	49 (24)	49 (100)	42 (27)	12 (35)	6 (25)	22 (29)	18 (53)
S1	154 (75)	154 (75)	42 (86)	154 (100)	30 (88)	22 (92)	67 (88)	29 (85)
T1	34 (17)	34 (17)	12 (25)	30 (20)	34 (100)		15 (20)	6 (18)
T2	24 (12)	24 (12)	6 (12)	22 (14)		24 (100)	8 (11)	8 (24)
C1	76 (37)	76 (37)	22 (45)	67 (44)	15 (44)	8 (33)	76 (100)	
C2	34 (17)	34 (17)	18 (37)	29 (19)	6 (18)	8 (33)		34 (100)
Immunohistochemical C3c-positive deposits	147 (72)	147 (72)	38 (78)	115 (75)	28 (77)	16 (67)	62 (82)	24 (71)

Table 4: Comparison of histopathological findings among the groups according to the modified Oxford Classification

In 42 out of 49 IgAN cases (85.7%) with endocapillary hypercellularity (E1), additional segmental glomerulosclerosis (S1) was seen. In 18 cases (36.7%) additional tubular atrophy/interstitial fibrosis of more than 25% of the cortical area and in 40 cases (81.6%) additional crescentic lesions (C1, C2) were detected.

In 42 out of 154 IgAN cases (27.3%) with segmental glomerulosclerosis (S1), additional endocapillary hypercellularity (E1) was seen. In 52 cases (33.8%) additional tubular atrophy/interstitial fibrosis of more than 25% of the cortical area and in 96 cases (62.3%) additional crescentic lesions (C1, C2) were detected.

In 18 out of 58 IgAN cases (31%) with tubular atrophy/interstitial fibrosis of more than 25% of the cortical area (T1, T2), additional endocapillary hypercellularity

(E1) was seen. In 52 cases (89.7%) additional segmental glomerulosclerosis and in 37 cases (63.8%) additional crescentic lesions (C1, C2) were detected.

In 40 out of 110 IgAN cases (36.4%) with crescentic lesions (C1, C2), additional endocapillary hypercellularity (E1) was seen. In 96 cases (87.3%), additional segmental glomerulosclerosis (S1) and in 37 cases (33.6%), additional tubular atrophy/interstitial fibrosis in more than 25% of the cortical area (T1, T2) was detected.

Among the 147 c3c-positive renal biopsies, 38 cases (25.9%) showed endocapillary hypercellularity (E1), 115 cases (78%) showed segmental glomerulosclerosis (S1), 42 cases (28.6%) showed parenchymal atrophy of more than 25% (T1, T2) and in 86 cases (58.5%) crescentic lesions (C1, C2) were present, respectively

13.3 Development of Clinical Parameters after Follow-Up

The development of clinical parameters in relation to the different histological findings according to the modified Oxford Classification after a minimum follow-up period of 12 months is shown in Table 5.

	All (n=150)	**M (n=150)**	**E1 (n=35)**	**S1 (n=108)**	**T1 (n=22)**	**T2 (n=11)**	**C1 (n=53)**	**C2 (n=26)**
Systolic blood pressure (mmHg) n=139	130 (120-147)	130 (120-147)	134 (122-148) n=31	130 (120-145) n=104	131 (117-149) n=20	144 (134-156) n=10	130 (120-146) n=50	134 (120-145) n=24
Diastolic blood pressure (mmHg) n=137	80 (75-90)	80 (75-90)	80 (75-90) n=31	80 (74-87) n=102	80 (70-80) n=20	75 (67-85) n=9	80 (75-86) n=49	80 (70-90) n=23
Gross hematuria (%)	97 (65)	97 (65)	24 (69)	69 (64)	13 (59)	6 (55)	37 (70)	17 (65)
Proteinuria (%)	98 (65)	98 (65)	21 (60)	77 (71)	13 (59)	6 (55)	39 (74)	21 (81)
Estimated glomerular filtration rate (ml/min per 1.73m^2)	51.3 (24-79.1)	51.3 (24-79.1)	62.6 (25.3-82)	48 (22.7-67.7)	25.3 (18.5-38.6)	21.4 (10.3-24)	51 (23.1-68.7)	56.8 (21.4-80)

Creatinine (mg/dl)	1.43 (1.02-2.52)	1.43 (1.02-2.52)	1.28 (0.97-2.57)	1.54 (1.09-2.58)	2.45 (1.85-3.32)	3.03 (2.50-5.12)	1.52 (1.08-2.63)	1.43 (0.95-2.66)
Treatment (%)								
Antihypertensive therapy	132 (88)	132 (88)	34 (97)	97 (90)	19 (86)	11 (100)	49 (93)	25 (96)
Immunosuppressive therapy	70 (47)	70 (47)	20 (57)	50 (46)	14 (64)	3 (27)	31 (59)	18 (69)

Table 5: Baseline characteristics of the patients after a minimum follow-up period of 12 months.
Abbreviations: E1: presence of endocapillary hypercellularity; M1: mesangial hypercellularity >0.5; S1: presence of segmental glomerulosclerosis; T1: tubular atrophy/interstitial fibrosis 26–50% of cortical area; T2: tubular atrophy/interstitial fibrosis >50% of cortical area; C1: crescentic lesions in <25% of glomeruli; C2: crescentic lesions in >25% of glomeruli.
Note: Values are expressed as median (interquartile range) or numbers (percentage).

Median follow-up of the study cohort was 84 months (12– 204 months). Median systolic blood pressure after follow-up was 130 mmHg (120 – 147mmHg). Wilcoxon rank-sum test showed that median systolic blood pressure of IgAN patients significantly decreased in the study cohort over time (*p-value=0.044*). Median eGFR also showed a significant decrease over the course of follow-up (*p-value=0.025*). Median diastolic blood pressure, as well as median serum creatinine did not change significantly during follow-up. There were no significant changes in median systolic and diastolic blood pressure, median eGFR, as well as median serum creatinine for patients with or without endocapillary hypercellularity (E1). Whereas patients with segmental glomerulosclerosis (S1) showed a significant decrease in systolic blood pressure (*p-value=0.006*), in diastolic blood pressure *(p-value=0.*032), and in median eGFR *(p-value=0.*010). In patients lacking segmental glomerulosclerosis, no statistically significant changes in blood pressure, eGFR, and serum creatinine was seen. In patients showing tubular atrophy/interstitial fibrosis in up to 50% (T1) of cortical area, a significant decrease in systolic blood pressure (p-value=0.0.30) and eGFR (p-value=0.0.33) after follow-up was found, respectively. In patients showing tubular atrophy/interstitial fibrosis in over 50% of cortical area no statistically significant changes in blood pressure, eGFR, and serum creatinine was seen. In cases lacking crescentic lesions (C0), no statistically significant changes in blood pressure, eGFR or serum creatinine were seen. However, in patients showing crescents in <25% of the glomeruli (C1), a significant decrease of systolic blood pressure (p-value=0.027) and eGFR (p-value=0.0249) was noted after follow-up. In patients showing crescents in >25% of the glomeruli (C2), blood pressure, eGFR, and serum creatinine did not change significantly over the course of follow-up.

In 98/150 patients (65%), proteinuria was detectable after a follow-up of at least 12 months. McNemar test showed a significant decrease of proteinuria for IgAN patients after follow-up (*p-value<0.001*). In patients with (E1) (*p-value=0.*049) and without endocapillary hypercellularity (E0) (*p-value<0.001*) a significant decrease of proteinuria was seen after follow-up. In patients lacking (S0) and showing segmental glomerulosclerosis (S1), a significant reduction of proteinuria was noted after follow-up (*p-value<0.001* for S0 and *p-value=0.024* for *S1*), respectively.

Patients lacking tubular atrophy/interstitial fibrosis showed a significant decrease in proteinuria after follow-up (*p-value<0.001*). Among IgAN patients showing tubular atrophy/interstitial fibrosis in at least 25% of cortical area (T1 and T2) no significant change in proteinuria over the course of follow-up was seen. Biopsies lacking crescentic lesions (C0) recorded a significant reduction of proteinuria after follow-up (*p-value<0.001*). Patients showing crescents in <25% of the glomeruli (C1) recorded a statistically significant decrease of proteinuria as well (*p-value=0.022*). Patients showing crescents in >25% of the glomeruli showed no significant change in proteinuria.

In 97/150 patients (65%), gross hematuria was detectable after follow-up. McNemar test showed a significant decrease of hematuria in patients with IgAN (*p-value<0.001*). In patients with E lesions (E1) (*p-value=0.039*) and without E lesions (*p-value<0.001*) a significant reduction of hematuria over the course of follow-up was seen. Among IgAN patients lacking (S0) and patients showing segmental glomerulosclerosis (S1), a significant reduction of visible hematuria was noted (*p-value<0.001)* and (*p-value<0.001*), respectively. Patients without significant tubular atrophy/interstitial fibrosis showed a significant reduction in hematuria after follow-up (*p-value<0.001*). In patients showing tubular atrophy/interstitial fibrosis in up to 50% of the cortical area (T1), a significant decrease of hematuria was noted (*p-value0.008*). In patients showing tubular atrophy/interstitial fibrosis in over 50% of the cortical area (T2) no statistically significant change in hematuria was found. In patients lacking crescentic lesions (C0) as well as in patients showing crescents in <25% (C1) and >25% (C2) of the glomeruli, hematuria decreased significantly after follow-up (*p-value<0.001* for C0), (*p-value=0.001* for C1), and (*p-value=0.039* for C2), respectively.

13.4 Clinical and Histological Parameters According to the Type of Treatment

185/205 IgAN patients (90%) received antihypertensive therapy. Among these, in 47 patients (25.4%) endocapillary hypercellularity (E1), in 141 patients (76.2%) segmental glomerulosclerosis (S1), in 31 patients (16.7%) tubular atrophy/interstitial fibrosis in 26-50% of cortical area (T1), in 23 patients (12.4%) tubular atrophy/interstitial fibrosis in over 50% of cortical area (T2), in 72 patients (38.9%) crescents in <25% of the glomeruli (C1), and in 32 patients (17.2%) crescents in >25% of glomeruli (C2) was noted.

125/205 IgAN patients (61%) received immunosuppressive treatment. Among these, in 34 patients (27.2%) endocapillary hypercellularity (E1), in 96 patients (76.8%) segmental glomerulosclerosis (S1), in 26 patients (20.8%) tubular atrophy/interstitial fibrosis in 26-50% of cortical area (T1), in 16 patients (12.8%) tubular atrophy/interstitial fibrosis in over 50% of cortical area (T2), in 54 patients (43.2%) crescents in <25% of the glomeruli (C1), and in 26 patients (20.8%) crescents in >25% of glomeruli (C2) was noted.

Univariate analyses revealed that IgAN patients with lower eGFR and higher creatinine values at time of biopsy, received immunosuppressive therapy significantly more often (*p-value<0.001*). The use of antihypertensive therapy did not correlate with eGFR or serum creatinine at time of biopsy.

In a next step, chi-squared test was performed to test whether any histopathological category of the modified Oxford Classification correlated with the use of antihypertensive or immunosuppressive therapy. IgAN patients with crescentic lesions (C1/C2) were significantly more likely to receive antihypertensive (*p-value=0.039*) and immunosuppressive therapy (*p-value<0.001*), respectively.

13.5 Clinical Parameters in Relation to the Modified Oxford Classification

	At time of biopsy			Rate of renal function decline (linear regression)
	RRsys (mmHg)	**Proteinuria (%)**	**eGFR (ml/min/1.73m2)**	**univariate (ml/min/1.73m2 per year)**
E0	135 (125-48)	137 (88)	45.48 (28.25-65.46)	20.10 (6.75-31.70)
E1	140 (125-160)	43 (88)	48 (31-70.06)	18.25 (7.69-29.09)
p-value	*0.139*	*0.99*	*0.746*	*0.636*
S0	135 (120-143)	47 (92)	55.38 (34.10-87)	22.11 (2.64-38.01)
S1	140 (127-150)	133 (86)	44.07 (26.37-63.22)	18.99 (7.11-29.10)
p-value	*0.062*	*0.273*	***0.019***	*0.436*
T0	130 (121-145)	131 (89)	55.15 (39.76-81.40)	21.53 (6.95-34.45)
T1	140 (130-166)	29 (85)	31.41 (18.60-46.12)	15.49 (6.76-24.00)
T2	145 (135-160)	20 (83)	18.73 (14.36-26.61)	11.80 (4.00-15.10)
p-value	***<0.001***	*0.643*	***0.003***	*0.055*
C0	130 (125-145)	80 (84)	48 (32.86-79.78)	20.51 (6.68-31.89)
C1	140 (125-160)	69 (91)	44.82 (23.66-67.03)	19.86 (7.91-31.70)
C2	140 (125-156)	31 (91)	34.41 (18.71-60)	16.10 (5.60-28.09)
p-value	*0.099*	*0.343*	*0.112*	*0.447*

Table 6: Comparison of clinical parameters at the time of kidney biopsy and decline rate of renal function according to the modified Oxford Classification

Mann-Whitney-U test was performed to test the association of the histopathological categories of the modified Oxford Classification with the clinical parameters at time of biopsy (Table 6). In IgAN patients with endocapillary hypercellularity (E1), only diastolic blood pressure at time of biopsy was significantly higher compared to patients lacking endocapillary hypercellularity (E0, *p-value=0.041*). In cases with segmental glomerulosclerosis (S1), patients showed significantly higher diastolic blood pressure at time of biopsy (*p-value=0.038*), significantly lower eGFR at time

of biopsy (*p-value=0.019*), significantly higher eGFR after follow-up (*p-value=0.002*), significantly higher creatinine at time of biopsy (*p-value=0.026*) and after follow-up (*p-value=0.006*), respectively. Tubular atrophy/interstitial fibrosis (T1/T2) significantly correlated with higher systolic blood pressure (*p-value<0.001*), lower eGFR (*p-value=0.003*) and higher serum creatinine (*p-value=0.001*) at time of biopsy. The presence of crescentic lesions (C1/2) showed a statistically significant association with diastolic blood pressure at time of biopsy. Diastolic blood pressure at time of biopsy was significantly higher (*p-value=0.007*) in patients with crescentic lesions (C1/C2). Furthermore, the presence of crescentic lesions (C1/C2) did not show a significant correlation with hematuria or proteinuria at time of biopsy and after follow-up.

13.6 Prognostic Value of Clinical Parameters, Histological Lesions, and Therapeutic Regimen for Renal Outcome

After a median follow-up of 84 months (12- 204 months), 88/205 (42.9%) IgAN patients reached the primary study endpoint, 36/205 patients (18%) developed a 50% decline in eGFR, 55/205 (27%) patients underwent kidney transplantation, and 77/205 (38%) patients required permanent hemodialysis or peritoneal dialysis, respectively.

In univariate analysis, neither systolic nor diastolic blood pressure at time of biopsy and after follow-up showed significant impact on renal survival. A significant effect on renal failure could be seen in univariate analysis for low eGFR at time of biopsy and high levels of serum creatinine at time of biopsy (*p-value<0.001*), respectively. In multivariate analyses, only diastolic blood pressure after follow-up (*p-value=0.025*) and serum creatinine after follow-up (*p-value=0.021*) remained statistically significant. In patients with a 50% decline in renal function, systolic blood pressure, diastolic blood pressure, eGFR, and serum creatinine at time of biopsy, as well as systolic and diastolic blood pressure after follow-up did not show a statistically significant impact. However, low eGFR and high levels of serum creatinine after follow-up showed a statistically significant effect on adverse renal function (*p-value<0.001*), respectively. Proteinuria and visible hematuria at time of biopsy had no significant effect on renal survival and renal function decline, respectively.

To test the prognostic value of the histopathological categories of the modified Oxford Classification on renal survival, we performed chi-squared tests and a multivariate binary logistic regression analysis. Among patients with endocapillary hypercellularity (E1, n=49), 9 patients (18.4%) experienced a 50% reduction of renal function (*p-value<0.05*) and 21 patients (42.9%) reached renal failure (*p-value<0.05*). However, endocapillary hypercellularity did not prove to be a prognostic factor for renal failure and for a 50% decline in renal function.

Among patients with segmental glomerulosclerosis (S1, n=154), 30 patients (19.5%) showed a reduction of renal function over 50% (*p-value<0.05*) and 71 patients (46%) developed renal failure (*p-value<0.05*). Segmental

glomerulosclerosis did not prove to have a significant prognostic impact on renal failure and on 50% decline of renal function.

Among patients with tubular atrophy/interstitial fibrosis in up to 50% of the cortical area (T1, n=34), 10 patients (29.4%) showed a 50% reduction of renal function (*p-value<0.05*) and 20 patients (58.8%) reached renal failure (*p-value<0.05*). Among patients with tubular atrophy/interstitial fibrosis in more than 50% of the cortical area (T2, n=24), 3 patients (12.5%) showed a 50% decline in renal function (*p-value<0.05*) and 18 patients (75.0%) reached renal failure (*p-value<0.05*). Tubular atrophy/interstitial fibrosis proved to have a significant impact on renal failure. Univariate analysis revealed a significant adverse renal outcome concerning the combined event, development of ESKD and 50% reduction of eGFR in IgAN patients with T1/T2 lesions (*p-value<0.001*). In multivariate analysis, endocapillary hypercellularity (E1), segmental glomerulosclerosis (S1), and the presence of crescentic lesions (C1/C2) did not prove to be statistically significant. For tubular atrophy >25% (T1/T2) however, a tend towards adverse outcome was noted without reaching statistical significance (*p-value=0.070*). In patients with a 50% decline in renal function, T1/T2 lesions did not prove to be a prognostic factor for renal outcome (*p-value=0.129*).

Among patients with crescentic lesions in <25% of glomeruli (C1, n=76), 16 patients (21.1%) showed a 50% reduction of renal function (*p-value<0.05*) and 34 patients (44.7%) reached renal failure (*p-value<0.05*). Among patients with crescentic lesions in >25% of glomeruli (C2, n=34), 6 patients (17.6%) showed a 50% decline in renal function (*p-value<0.05*) and 15 patients (44.1%) reached renal failure (*p-value<0.05*). Crescentic lesions did not prove to be a significant prognostic factor for renal failure and for 50% decline of renal function.

Statistical analyses showed divergent findings for the prognostic value of crescentic lesions in patients receiving immunosuppressive therapy, depending on the number of glomeruli being involved. Patients under immunosuppressive therapy lacking crescentic lesions (C0) reached renal failure significantly more often (*p-value<0.001*) (Table 7). Patients receiving immunosuppressive therapy with crescentic lesions in up to 25% of glomeruli (C1) showed significant worse renal survival with a significantly higher number of patients reaching renal failure (*p-*

value=0.001) compared to IgAN patients not receiving immunosuppressive treatment. (Table 8).

	Patients without renal failure	**Patients with renal failure**
No immunosuppressive therapy	42	8
Any immunosuppressive therapy	14	31
p-value	**<0.001**	

Table 7: Onset of renal failure according to the use of immunosuppressive therapy in patients lacking crescentic lesion (C0)

	Patients without renal failure	**Patients with renal failure**
No immunosuppressive therapy	19	3
Any immunosuppressive therapy	23	31
p-value	**0.001**	

Table 8: Onset of renal failure according to the use of immunosuppressive therapy in patients showing crescentic lesions in up to 25% of the glomeruli (C1)

However, in patients with more than 25% crescentic lesions (C2), no significant impact of immunosuppressive therapy on renal survival was seen compared to IgAN patients not receiving immunosuppressive therapy (*p-value=0.21*).

Patients receiving antihypertensive therapy lacking crescentic lesions (C0) showed a significantly improved renal survival (*p-value=0.005*; Table 9).

	Patients without renal failure	Patients with renal failure
No antihypertensive therapy	13	1
Any antihypertensive therapy	43	38
p-value	**0.005**	

Table 9: Onset of renal failure according to the use of antihypertensive therapy in patients showing no crescentic lesion (C0)

In patients on antihypertensive therapy with up to 25% crescentic lesions (C1), a tend towards improved renal failure not reaching statistical significance was found (*p-value=0.064*). In patients showing more than 25% crescentic lesions (C2), no significant impact of antihypertensive therapy on renal survival was seen.

No significant effect of immunosuppressive and antihypertensive treatment on 50% reduction of renal function in IgAN patients lacking crescents (C0) or in IgAN patients with <25% crescentic lesions (C1) and >25% crescentic lesions (C2) was found.

The role of the “age” of crescentic lesions on the study outcomes was investigated using chi-squared test. Statistical analysis showed that the presence of crescentic lesions, irrespective of the “age” of the crescents, consisting of fibrocellular (mixed) and fibrous (old) extracapillary proliferates, was significantly associated with a 50% decline of renal function and therefore, showed a significantly adverse effect on renal function (*p-value=0.003*). When comparing mainly cellular (fresh) to fibrocellular (mixed) and fibrous (old) crescents, fibrocellular and fibrous crescentic lesions proved to have a significantly adverse impact on renal failure than cellular crescents (*p-value=0.002*).

Table 10 shows the prognostic value of the histopathological categories of the modified Oxford Classification on renal failure and >50% reduction of eGFR over time.

	Patients without renal failure	Patients with renal failure	Patients with eGFR reduction <50%	Patients with eGFR reduction ≥50%
E0	89	67	129	27
E1	28	21	40	9
p-value	*0.991*		*0.865*	
S0	34	17	45	6
S1	83	71	124	30
p-value	*0.110*		*0.209*	
T0	97	50	124	23
T1	14	20	24	10
T2	6	18	21	3
p-value	***<0.001***		*0.129*	
C0	56	39	81	14
C1	42	34	60	16
C2	19	15	28	6
p-value	*0.879*		*0.559*	

Table 10: Prognostic value of the histopathological categories of the modified Oxford Classification on the endpoints

Kaplan–Meier analysis revealed significantly adverse renal survival for patients with tubular atrophy and interstitial fibrosis of more than 25% of cortical area (T1/T2, *p-value<0.001*) (Figure 10).

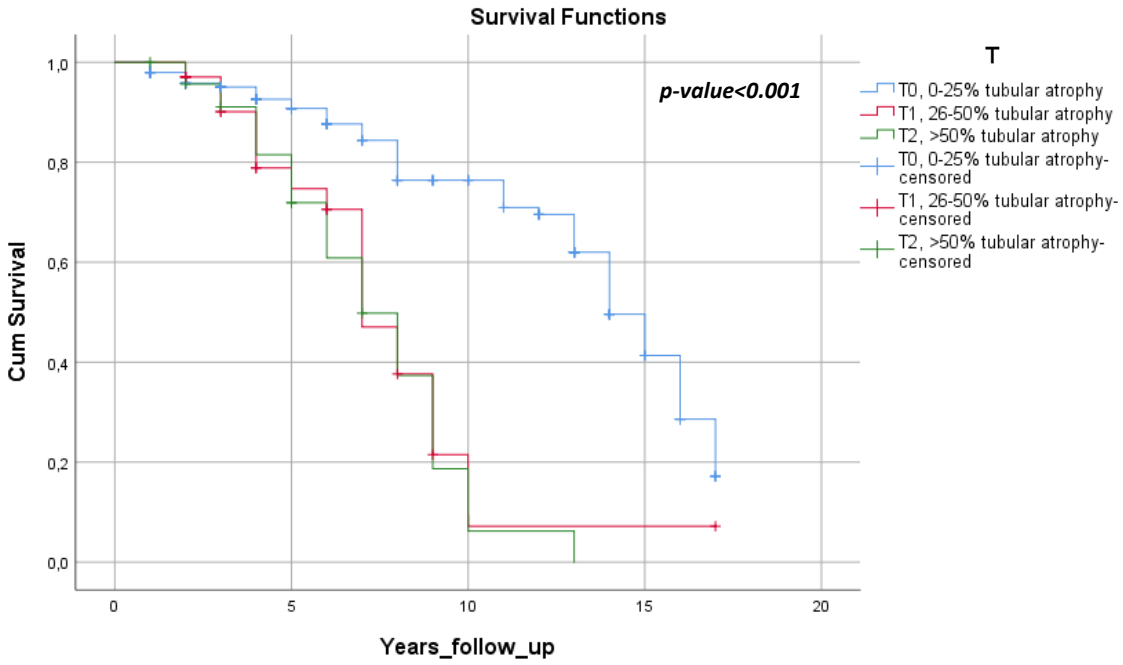


Figure 10: Renal survival according to the extent of tubular atrophy/interstitial fibrosis (T)

No prognostic impact on renal survival was seen for the presence of endocapillary hypercellularity (E1), presence of segmental glomerulosclerosis (S1), or the presence of crescentic lesions (C1/C2) (Figure 11, 12, 13).

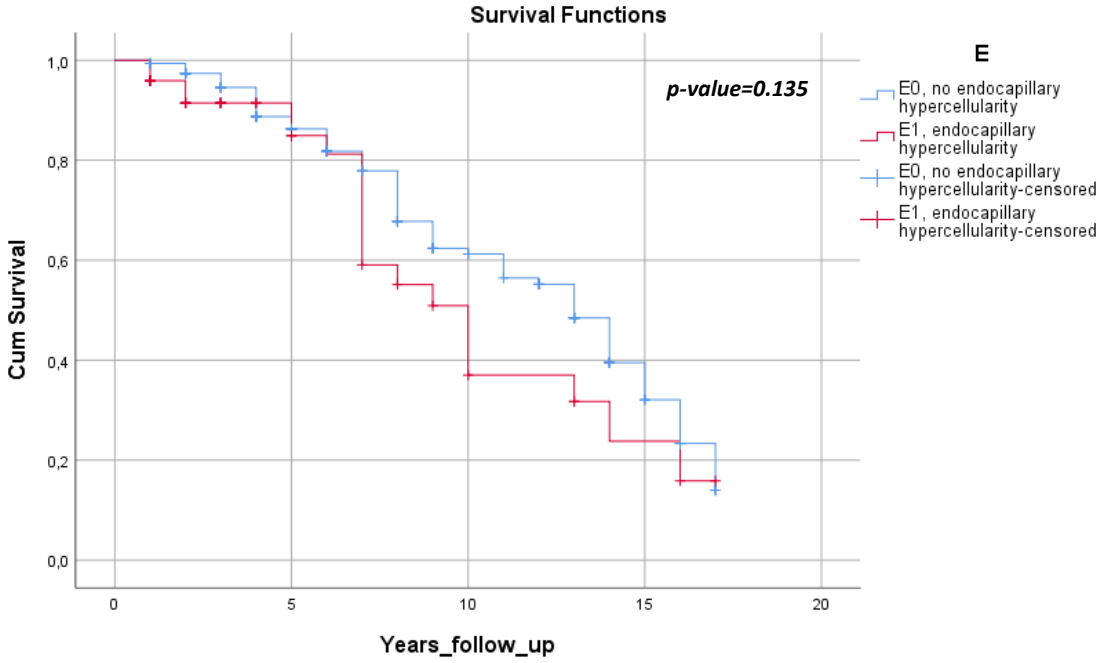


Figure 11: Renal survival according to the presence of endocapillary hypercellularity (E)

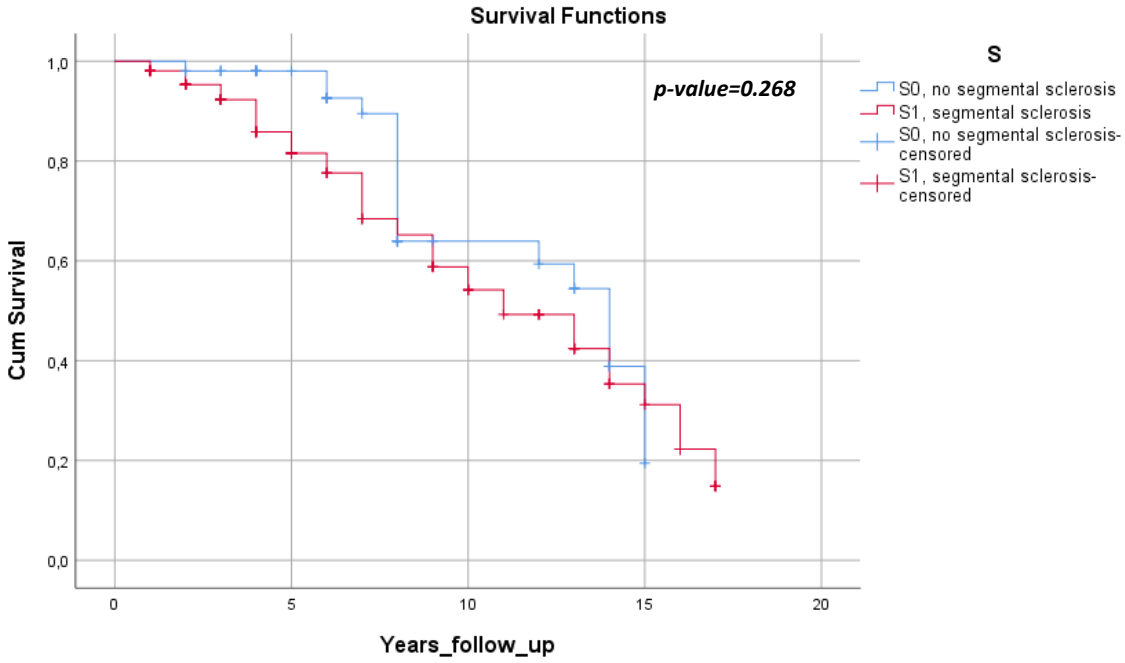


Figure 12: Renal survival according to the presence of segmental glomerulosclerosis (S)

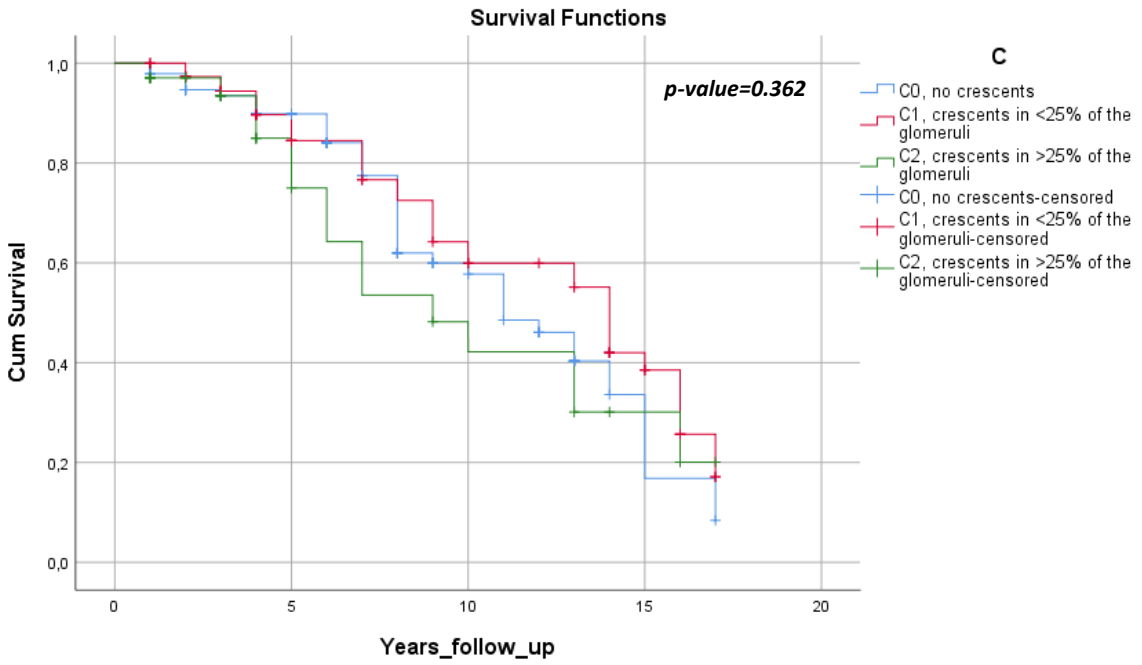


Figure 13: Renal survival according to the extent of glomerular crescent formation (C)

The presence of tubular atrophy and interstitial fibrosis of more than 25% of cortical area (T1/T2) has a significantly worse effect on renal function over time (*p-value=0.002*) (Figure 14).

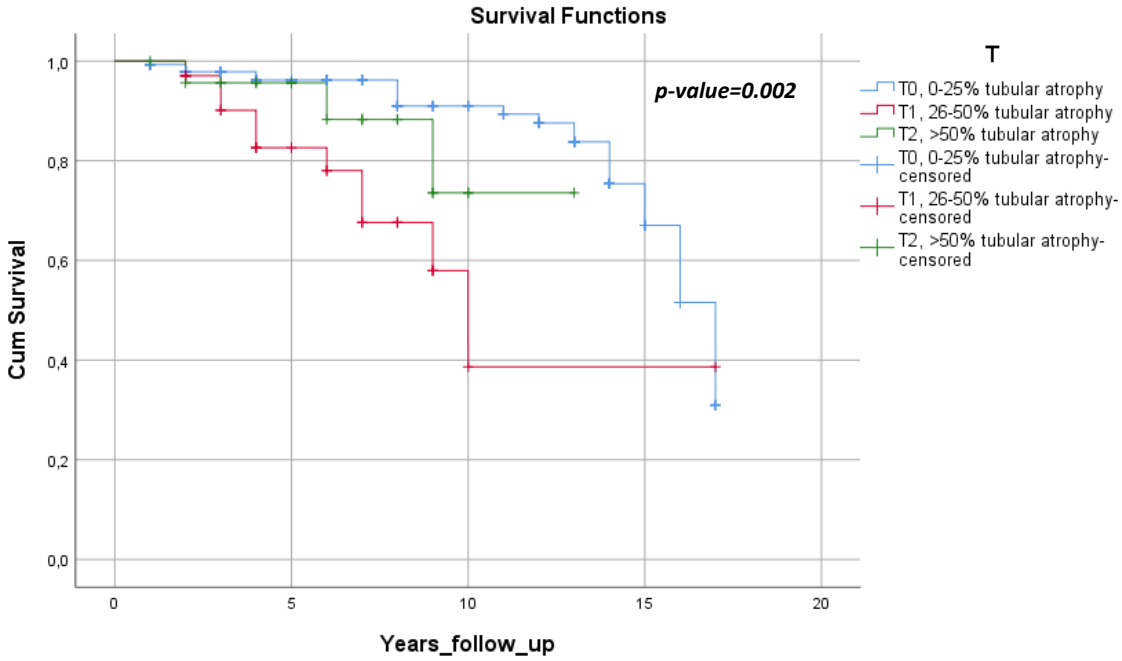


Figure 14: Renal function (eGFR decline >50%) according to the extent of tubular atrophy/interstitial fibrosis (T)

Endocapillary hypercellularity (E1), segmental glomerulosclerosis (S1), and crescentic lesions (C1/C2) showed no significant adverse effects on renal function (Figure 15, 16, 17).

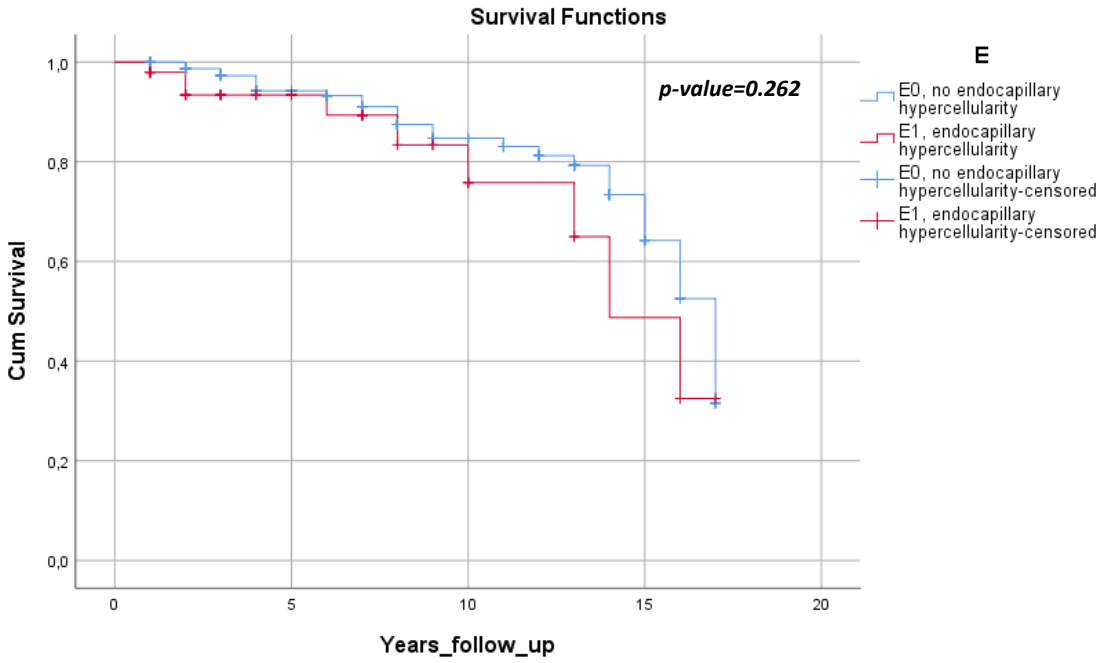


Figure 15: Renal function (eGFR decline >50%) according to the presence of endocapillary hypercellularity (E)

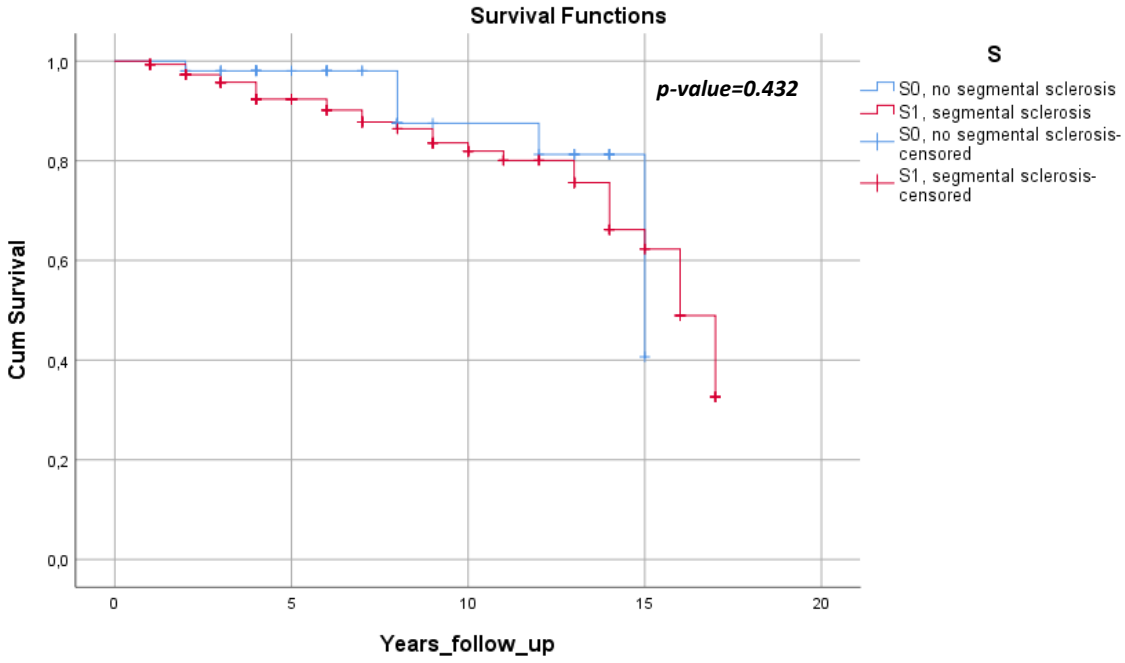


Figure 16: Renal function (eGFR decline >50%) according to the presence of segmental glomerulosclerosis (S)

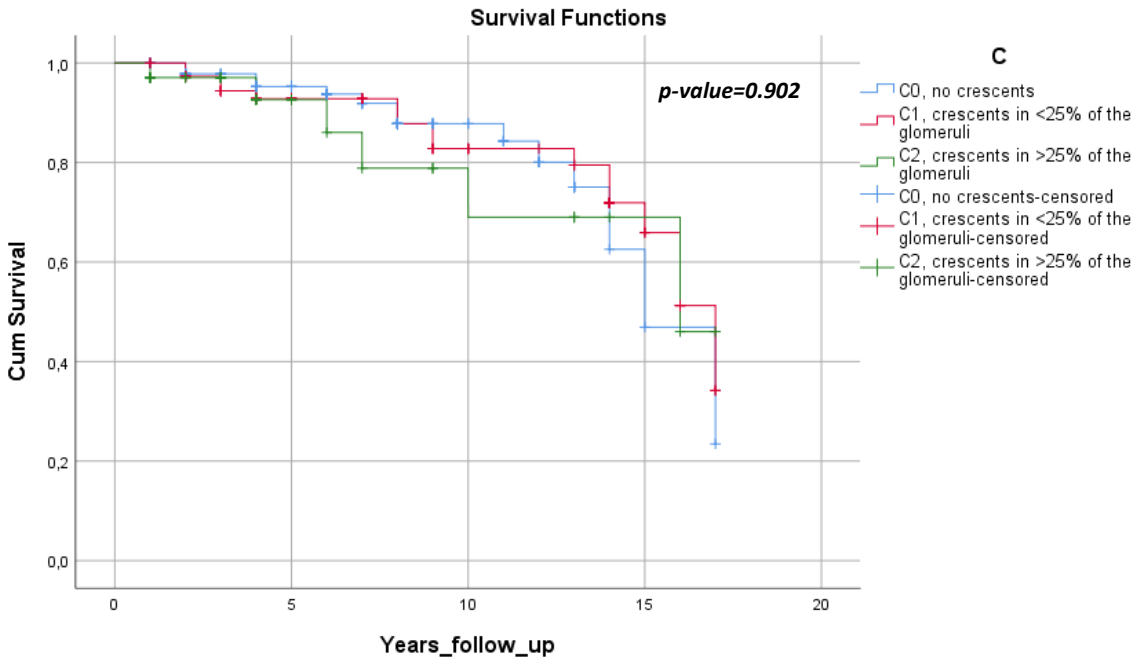


Figure 17: Renal function (eGFR decline >50%) according to the extent of glomerular crescents formation (C)

Finally, we performed chi-squared tests to test the prognostic effect of immunosuppressive and antihypertensive treatment regimens on renal outcome. Univariate analysis showed that IgAN patients under immunosuppressive therapy significantly more often reached renal failure than patients not treated with immunosuppressive medication (*p-value<0.001*) (Table 11). Patients treated with immunosuppressive therapy showed tendencies to adverse effects on 50% decline of eGFR but did not prove to be statistically significant (*p-value=0.057*).

	Patients without renal failure	**Patients with renal failure**
No immunosuppressive therapy	67	13
Any immunosuppressive therapy	50	75
p-value	**<0.001**	

Table 11: Prognostic effect of immunosuppressive therapy on renal survival in all IgAN patients

Patients under antihypertensive treatment showed significantly beneficial effects on eGFR reduction of over 50% (*p-value=0.030*) (Table 12) and statistically significant improved renal survival (*p-value=0.002*) (Table 13).

	Patients with eGFR reduction <50%	**Patients with eGFR reduction ≥50%**
No antihypertensive therapy	20	0
Any antihypertensive therapy	149	36
p-value	**0.030**	

Table 12: Prognostic effect of antihypertensive therapy on eGFR reduction >50% in all IgAN patients

	Patients without renal failure	Patients with renal failure
No antihypertensive therapy	18	2
Any antihypertensive therapy	99	86
p-value	**0.002**	

Table 13: Prognostic effect of antihypertensive therapy on renal survival in all IgAN patients

14 Discussion

The original Oxford Classification proposed in 2009 has been widely adopted in clinical practice as an evidence-based classification system for IgAN (1). In that study three pathologic findings were reported to be independent prognostic markers in IgAN, such as mesangial hypercellularity (M), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). Among patients with endocapillary hypercellularity (E), the rate of renal functional decline was significantly lower in those receiving immunosuppressive therapy. Finally, the original Oxford Classification proposed four parameters, including mesangial (M) and endocapillary (E) hypercellularity, segmental glomerulosclerosis (S), and interstitial fibrosis and tubular atrophy (T), summarized as the so-called MEST score (1,59,66). These findings have been validated by a variety of subsequent studies (10,12,59,68–72,92–94). The original Oxford Classification did not account for the presence of glomerular crescents, since in the original Oxford study (1) and several validation studies with similar restrictive entry criteria (69–72) crescents were not found to be an independent predictor of renal outcomes (9). In the updated Oxford study, the presence of at least 25% of crescents (C1) was significantly predictive of poor renal outcome in patients not receiving immunosuppressive therapy, but not in patients under immunosuppression (59). The C2 category identified patients at risk of poor renal outcome regardless of immunosuppressive therapy (59). Hence, an additional C category in the original MEST score for the presence of glomerular crescents is recommended since 2017: C0 (no crescents), C1 (crescents in less than one fourth of glomeruli), and C2 (crescents in over one fourth of glomeruli), summarized as the modified MEST-C score (9).

We aimed to validate the prognostic value of clinical and histopathological parameters according to the modified Oxford Classification with special emphasize on crescentic lesions.

Our IgAN study cohort includes patients from Styria, Carinthia and Burgenland, representing a Caucasian cohort from the Southeast Austrian regions. Most studies on IgA Nephropathy are retrospective and multi-centered with patients

of different ethnicities (15). A number of single-center studies have analyzed the mortality, and prognostic value of pathological and clinical parameters in IgAN and validated the original Oxford Classification system (12,70,72,93,95–100). Most of these have been conducted in Asian countries, such as Japan, China, Korea, and India with exception of one Polish and one Greek study.

Median age of our IgAN patients was 42 years with nearly 60% of patients younger than and 40% older than 50 years. We found two peaks in age distribution, one between 25 and 30 years and another between 50 and 55 years. Our IgAN patients are at least ten years older than those published in literature, mainly form Asian countries. In a South Korean (99) and Japanese study (100), for instance, median age of IgAN patients was 33 years (25-45 years). In one of the few European studies from Poland median age of IgAN patients was 33 years (98) and in a Greek study (97), median age was with 41 years similar to ours. In the original Oxford study, the median age was 30 years (1). In a multi-center study by Haas et al, mean age of IgAN patients was 35 years (SD±14 years) (9). Most of the above mentioned single-center studies have been conducted in Asian countries showing a median age of IgAN patients of 36 years or younger. One possible explanation might be the implementation of urine screening in routine health check-ups in most Asian countries. The early recognition of urine abnormalities leads to a higher number of renal biopsies and consequently higher numbers of IgAN diagnoses and general, resulting in a higher awareness of clinicians of IgAN in Asian countries compared to European countries. Considering the low age of Asian IgAN patients, who normally constitute a great proportion of the multicenter study cohorts, may probably decrease the median age of the whole cohort and therefore might be an influencing factor of age distribution in a multicenter approach.

In our study, 66% of IgAN patients were male and 34% female with a male to female ratio of 2:1. Comparable data are published in literature. Male to female ratio in a Polish study cohort of 52 IgAN patients was 1.4:1, and a Greek study showed a male to female ratio of 2.6:1 in 50 patients (97,98). However, in Japanese and Chinese studies male to female IgAN ratios of 1:1.4, 1:1.2, 1:1, and 0.92:1 are reported (12,70,96,100). As mentioned earlier, the implementation of urine screening in routine health check-ups with early recognition of urine abnormalities in most Asian countries might explain not only the higher numbers of IgAN

diagnoses in general but also the higher number of female patients getting examined and biopsied. Most multi-center studies show a gender ratio similar to ours. In the original Oxford study, a gender ratio of 2.6:1, in the VALIGA study a ratio of 2.7:1, and in the modified Oxford study a ratio of 1.3:1 is described (1,9,68).

IgAN may cause a wide range of histopathological glomerular changes. We found 49 (23.9%) patients with endocapillary hypercellularity (E1). Similar results were described by Kaneko et al with 20% and by Stangou et al with 26% of IgAN patients showing endocapillary hypercellularity (96,97). In the modified Oxford study, Haas et al reports E1 lesions in 20% of renal biopsies (9). Endocapillary hypercellularity in only 14% of IgAN patients was found in a single-center study conducted by Lee et al (93). Other single- and multi-center studies reported higher percentages of patients with endocapillary hypercellularity with 42% reported by Katafuchi et al (12) and 44% reported by Moriyama et al (100). Shi et al and Kataoka et al described 57% and 53%, respectively (70,95). In the original Oxford study E1 lesions were found in 42% of IgAN patients (1).

We found segmental glomerulosclerosis (S1) in 154 (75.1%) patients. Similar results were described by Katafuchi et al, Shi et al, Moriyama et al, Kataoka et al, and Kaneko et al showing segmental glomerulosclerosis in 79%, 75%, 75%, 81%, and 67% of IgAN patients, respectively (12,70,95,96,100). Lee et al and Stangou et al reported S1 lesions in 58% and 24% (93,97).

We found tubular atrophy/interstitial fibrosis in 26-50% of the cortical area (T1) and tubular atrophy/interstitial fibrosis in >50% of cortical area (T2) in 34 (16.6%) and 24 (11.7%) IgAN patients. Similar data are described in literature. Katafuchi et al, Shi et al, and Stangou et al reported T1 and T2 lesions in 18% and 12%, 14% and 8%, and in 20% and 16%, respectively (12,70,97). Only slight differences were described by other authors showing T1 and T2 lesions in 27% and 10%, 20% and 5%, and in 23% and 6% of IgAN patients (9,93,100). Interestingly, a Japanese single-center study reported T1/T2 lesions in 5% and 2% of 314 IgAN patients (96).

We found crescentic lesions in 110/205 biopsies (53.7%) with 76 cases (37.1%) showing <25% (C1) and 34 (16.6%) cases showing >25% (C2) involved glomeruli, respectively. Comparable results were only found by Kataoka et al showing

crescentic lesions in 53% (95). Higher numbers of crescents have been described by Katafuchi et al and Shi et al. Both report crescentic lesions in at least 60% (12,70). Lower numbers compared to our results have been described by Rafalska et al, Lee et al, and Stangou et al with 17%, 19%, and 18% (93,97,98).

125/205 (60.9%) IgAN patients received immunosuppressive treatment. In our study cohort, patients under immunosuppressive therapy showed a significantly adverse renal survival compared to patients not receiving immunosuppression. Katafuchi et al reported comparable results (12). In contrast to this study, in which only patients receiving steroids were taken into account, we included any class of immunosuppressive treatment, such as glucocorticoids, nucleic acid synthesis inhibitors, cytostatic drugs, calcineurin inhibitors, purine synthesis inhibitors, antimetabolites, and monoclonal antibodies against CD20 into the analysis. In a large single-center study, Moriyama et al found that worse renal survival was significantly associated with the combination of steroid treatment and the administration of other immunosuppressive agents (100). Similar results have been described in the large multi-center study conducted by Haas et al in 2017. In that study, patients not receiving immunosuppressive therapy had higher eGFR, lower proteinuria, fewer crescents, less endocapillary proliferative lesions, and less parenchymal atrophy. Significantly worse renal function was seen in patients treated with immunosuppressive therapy (9). This observation was attributable to the fact that patients who received immunosuppressive therapy most likely represented already advanced and severe cases of IgAN in which such treatment was necessary. No significant association between the use of immunosuppressive therapy and a worse renal outcome was described by Rafalska et al (98). Lv et al could prove that the use of immunosuppressive therapy had beneficial effects on the onset of ESKD, the doubling of serum creatinine, as well as halving of eGFR (81).

185/205 (90.2%) IgAN patients received antihypertensive treatment. Patients under antihypertensive treatment showed, irrespective of histopathological findings on renal biopsy, beneficial effects on renal outcome as well as on renal function. In our study, any antihypertensive agent has been taken into the analyses, whereas in most studies only the use of RAS blockage was investigated. In a prospective study by Praga et al the beneficial effect of antihypertensive treatment in IgAN has been

proven. They could show that a group of IgAN patients treated with Enalapril had a significant improved renal survival in comparison to a control group (101). A more recent study showed an adverse effect for the use of RAS-blockage or calcium-channel-blockage on renal function. While untreated individuals maintained their normal level of eGFR, patients treated with RAS-antagonists or calcium-channel blockers showed a significant decline in renal function (102). However, all treated patients in this study were selected because of severe renal function impairment at the start of the study. Treated IgAN patients initially had lower eGFR, higher proteinuria, and more severe histopathological lesions (102). The effect of immunosuppressive and antihypertensive therapy on renal survival as well as on renal function decline varies substantially in literature. One main explanation for the effect of immunosuppressive therapy in our study was that IgAN patients who received such treatment showed a variety of severe histopathological changes. Active lesions, such as endocapillary hypercellularity (E1) and crescentic lesions (C1/C2) were found in 27% and 64% in kidney biopsies of immunosuppressed patients. Chronic lesions, including segmental glomerulosclerosis (S1) and parenchymal atrophy of more than 25% of the renal cortex, were found in 77% and 64%, respectively. The advanced chronic histopathological changes may explain the adverse clinical outcome in immunosuppressed patients. While T1 and T2 are indicative of severe chronic renal injury and reflect an advanced disease stage, C1 and C2 are considered good targets for immunosuppressive treatment as proliferative/active lesions. This may lead to a form of treatment-bias. The selection of different treatment groups is not standardized among the literature, resulting in substantial heterogeneity regarding the treatment setting among patients at the beginning of the study and consequently among groups that are being examined. In our study cohort, 90% of all patients received antihypertensive treatment which is a rather high number compared with other studies. Moreover, most retrospective studies, including ours, do not have the exact knowledge over the precise dosage of the medication that was administered to the patients. Furthermore, there is no evidence of how compliant the patients were. The use of different antihypertensive agents goes along with different pharmacodynamics and should be examined separately. In order to provide more valid data on the prognostic effects of antihypertensive and immunosuppressive agents in IgAN, standardized, prospective, randomized-controlled-trials are warranted.

Numerous prognostic factors for IgAN have been described in literature, such as blood pressure, eGFR, serum creatinine levels, proteinuria, and hematuria. Most of these clinical parameters have been confirmed decades ago (1,8,66). In our study we could prove that eGFR and serum creatinine at time of biopsy were significantly associated with an adverse renal survival. Approximately 43% of our IgAN patients reached renal failure and nearly 18% developed a >50% decline in eGFR. In the original Oxford study, the authors state that the extend of proteinuria, hypertension, and the excretory renal function (eGFR) are well established clinical parameters predicting risk of progressive chronic kidney disease (1). Proteinuria has been proven to be a valuable marker for disease progression in IgAN, as described by Cattran et al (1). In multivariate analysis only proteinuria was significantly predictive of renal outcome in the recent study by Haas et al (9).

In the original Oxford Classification, three reproducible histopathological variables were identified to be independently predictive of poor renal outcome: mesangial hypercellularity (M), segmental glomerulosclerosis (S), and interstitial fibrosis and tubular atrophy (T) (1,59,66). In patients with endocapillary hypercellularity (E), renal dysfunction was significantly lower in those receiving immunosuppressive therapy. The original Oxford Classification proposed four parameters, including mesangial (M) and endocapillary (E) hypercellularity, segmental glomerulosclerosis (S), and interstitial fibrosis and tubular atrophy (T), summarized as the so-called MEST score (1,59,66). In our study we could show that the extent of tubular atrophy and/or interstitial fibrosis significantly correlated with worse renal survival (ESKD and >50% eGFR decline). Patients with tubular atrophy/interstitial fibrosis in at least 26% of the cortical area showed an adverse renal survival but did not show significant reduction of renal function alone. The presence of endocapillary hypercellularity and segmental glomerulosclerosis did not correlate with renal survival in our study. A variety of studies have been performed to validate the prognostic value of the histopathological parameters proposed in the 2009 Oxford Classification. 16 studies have been re-analyzed in a systematic review and meta-analysis by Lv et al in 2013. The presence of endocapillary lesions (E1) did not prove to be significant regarding kidney failure (94). However, they found S1 and T1/T2 lesions being significantly associated with kidney failure (94). In a 2016

update of the original Oxford Classification, Trimarchi et al found endocapillary hypercellularity not predictive of renal outcome (59). They showed that E1 lesions were only independently associated with worse renal outcome in IgAN patients not receiving immunosuppression (59), suggesting treatment bias, since patients with E1 lesions received immunosuppressive therapy more often leading to improved renal outcome. The same working group reported a significant prognostic value for segmental glomerulosclerosis on adverse renal outcome. They even suggested to add comments to the S lesion of the Classification (podocyte hypertrophy/tip lesions) to account for patients at a higher risk of renal function decline (59). T1/T2 lesions were also found to be predictive of renal survival.

The original Oxford Classification system does not account for the presence of crescentic lesions. In the following years, a number of retrospective studies have been conducted in order to show a prognostic significance of crescentic lesions on renal survival. In our study, we found that crescentic lesions present in <25% of glomeruli (C1) were predictive of renal failure only when adjusted for immunosuppressive therapy. In addition, IgAN patients with C1 lesions are more likely to receiving immunosuppression. Moreover, we showed that among patients under antihypertensive treatment, the absence of crescentic lesions is significantly associated with improved renal survival. As glomerular crescent formation represents a dynamic process, we sub-divided crescentic lesions according to their "age" in mainly cellular ("fresh"), fibro-cellular ("mixed") and fibrous ("old") crescents and tested each for their prognostic value on renal outcome. We found that the presence of crescentic lesions, irrespective of the "age" of the crescents, consisting of fibrocellular (mixed) and fibrous (old) extracapillary proliferates, was significantly associated with a 50% decline of renal function. When comparing mainly cellular (fresh) to fibrocellular (mixed) and fibrous (old) crescents, fibrocellular and fibrous crescentic lesions proved to have a significantly adverse impact on renal failure than cellular crescents. Moreover, mixed (fibrocellular) and old (fibrous) crescents proved to be significantly predictive of adverse renal survival.

Only few studies differentiate between cellular, fibro-cellular or fibrous crescentic lesions in their data collection, but none have described the prognostic value of crescents according to their "age". Trimarchi et al reported an independently predictive value of crescents for a higher risk of ESKD or 50% reduction in initial

eGFR (59). However, these results remained statistically significant only in patients who did not receive immunosuppressive therapy (59). Furthermore, the authors show that in IgAN patients with higher numbers of crescents (>25% of glomeruli), the risk of ESKD or 50% reduction of initial eGFR remained significant even in patients receiving immunosuppression (59). Lv et al report a significant association between the presence of crescents and progression to kidney failure (94). In a systematic review and meta-analysis conducted by Shao et al in 2017, the evaluation of crescents as a predictive marker in IgAN was summarized (103). They performed multivariate analysis models for diverse studies and for different study results. Except of one study every study showed an increased risk of worse renal outcome for patients with crescentic lesions (10–12,70,93,95,96,98,103–105). Furthermore, they could show overall decreased eGFR levels in patients with crescents (1,70,71,92,93,96,103,104). Moreover, patients with crescentic lesions showed overall increased levels of proteinuria (96,103,106,107). They also evaluated the use of immunosuppressive and antihypertensive (RAS-I) therapy. According to Shao et al, patients with crescentic lesions are more likely to receive immunosuppressive treatment (1,70,71,103,108). However, there was no significant difference in the use of RAS-I between patients with or without crescentic lesions (1,70,71,103).

There is a broad consensus on prognostic clinical factors in IgAN patients. However, as discussed above, there are varying results concerning the prognostic value of histopathological parameters. This is most likely attributable to differences in the execution of studies as well as cohort sizes. Additional influencing factors are the inclusion and exclusion criteria for a study cohort. For instance, the original Oxford study cohort excluded all patients with an initial eGFR <30ml/min/1.73m^2, thus excluding all advanced cases (1). Excluding the most severe cases of IgAN leads to selected study results and to lower prevalence of histological findings that might be prognostic of renal outcome. Some studies evaluated the prognostic value of clinical and pathological parameters only in children with alleged IgAN (10,71,104). Possible comorbidities with higher incidences in childhood, such as Schoenlein-Henoch purpura, can influence the real prognostic value of such parameters (10,71,104). Others included children and adults into the same analysis (1).

The most consistent predictor for renal outcome in IgAN published in literature and validated in our study is parenchymal atrophy. One explanation is that it mostly parallels advanced stages of the disease. Crescentic lesions are more frequently seen in advanced IgAN cases. We could not prove the independent prognostic value of crescentic lesions on renal outcomes in our study. This might be explained by the low number of patients with crescentic lesions in our study cohort, limiting the statistical power of the results. In addition, we included cases with less than 8 present glomeruli if the diagnosis could be made straight-forward, running the risk of missing crescentic lesions. Lastly, we had a high number of patients under immunosuppressive therapy. On the one hand, the protective effect of immunosuppression in IgAN is well known and described in many studies. On the other hand, the use of immunosuppression may mask the predictive value of crescentic lesions.

There are several limitations to our study. First and foremost are the limitations inherent to retrospective analyses. By performing review pathology, we aimed to reduce interobserver variability with respect to histopathological diagnosis. The relatively small cohort size of 205 IgAN patients has questionable statistical power. By excluding patients younger than 18 years, we tried to control the homogeneity of the study population. Our IgAN patients come from Styria, Carinthia and Burgenland, thus representing a Caucasian cohort from the southeast part of Austria. Most studies published on IgA Nephropathy are retrospective and multi-centered. On the one hand this leads to a larger number of analyzed patients and a greater statistical power. On the other hand, this also leads to a great heterogeneity of data within the study cohorts. Patients of different ethnicities are analyzed equally although, differences in incidences between ethnicities are described and can cause confounding results (15).

In our study, we show that eGFR and serum creatinine at time of biopsy are significantly associated with worse renal outcome. Furthermore, we validate the predictive value of tubular atrophy/interstitial fibrosis, as the most consistent and reliable histopathological prognostic parameter, on renal survival. We did not find a prognostic effect for endocapillary hypercellularity or segmental glomerulosclerosis on renal survival and renal function in our IgAN cohort. Overall crescentic lesions

did not show significant association with adverse renal outcome. However, when adjusted for patients under immunosuppressive therapy, crescentic lesions were predictive of renal failure. Moreover, mixed (fibrocellular) and old (fibrous) crescents proved to be predictive of adverse renal outcome. Additional prospective studies, preferably in more uniformly treated patient cohorts with higher patient numbers, are needed to validate these conclusions.

15 References

1. Cattran DC, Cook HT, Feehally J, Roberts ISD, Troyanov S, Alpers CE, et al. The Oxford Classification of IgA nephropathy: rationale, clinicopathological correlations, and Classification. Kidney Int. 2009 Sep 1;76(5):534–45.
2. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin a nephropathy in Japan. Am J Kidney Dis. 1997 Apr 1;29(4):526–32.
3. D'Amico G. Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis. 2000 Aug;36(2):227–37.
4. Floege J. The Pathogenesis of IgA Nephropathy: What Is New and How Does It Change Therapeutic Approaches? Am J Kidney Dis. 2011 Dec 1;58(6):992–1004.
5. Colvin RB, Chang A. Diagnostic Pathology: Kidney Diseases. Elsevier Health Sciences; 2019. 1172 p.
6. Zhang Y-M, Zhang H. Update on treatment of immunoglobulin A nephropathy. Nephrology. 2018 Oct 8;23:62–7.
7. Karoui KE, Hill GS, Karras A, Jacquot C, Moulonguet L, Kourilsky O, et al. A Clinicopathologic Study of Thrombotic Microangiopathy in IgA Nephropathy. J Am Soc Nephrol JASN. 2012 Jan;23(1):137.
8. 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 Sep 1;76(5):546–56.
9. Haas M, Verhave JC, Liu Z-H, Alpers CE, Barratt J, Becker JU, et al. A Multicenter Study of the Predictive Value of Crescents in IgA Nephropathy. J Am Soc Nephrol. 2017 Feb 1;28(2):691–701.
10. Shima Y, Nakanishi K, Hama T, Mukaiyama H, Togawa H, Hashimura Y, et al. Validity of the Oxford Classification of IgA nephropathy in children. Pediatr Nephrol. 2012 May 1;27(5):783–92.
11. Walsh M, Sar A, Lee D, Yilmaz S, Benediktsson H, Manns B, et al. Histopathologic Features Aid in Predicting Risk for Progression of IgA Nephropathy. Clin J Am Soc Nephrol CJASN. 2010 Mar;5(3):425.
12. Katafuchi R, Ninomiya T, Nagata M, Mitsuiki K, Hirakata H. Validation Study of Oxford Classification of IgA Nephropathy: The Significance of Extracapillary Proliferation. Clin J Am Soc Nephrol CJASN. 2011 Dec;6(12):2806.
13. McGrogan A, Franssen CFM, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011 Feb 1;26(2):414–30.
14. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. Clin J Am Soc Nephrol. 2017 Apr 3;12(4):677–86.
15. Schena FP, Nistor I. Epidemiology of IgA Nephropathy: A Global Perspective. Semin Nephrol. 2018 Sep;38(5):435–42.

16. 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 Jun;8(6).
17. Zhou F, Zhao M, Zou W, Liu G, Wang H. The changing spectrum of primary glomerular diseases within 15 years: A survey of 3331 patients in a single Chinese centre. Nephrol Dial Transplant. 2009 Mar 1;24(3):870–6.
18. Pan X, Xu J, Ren H, Zhang W, Xu Y, Shen P, et al. Changing Spectrum of Biopsy-Proven Primary Glomerular Diseases over the Past 15 Years: A Single-Center Study in China. New Insights Glomerulonephritis. 2013;181:22–30.
19. Woo K-T, Chan C-M, Chin YM, Choong H-L, Tan H-K, Foo M, et al. Global Evolutionary Trend of the Prevalence of Primary Glomerulonephritis over the Past Three Decades. Nephron Clin Pract. 2010;116(4):c337–46.
20. Habib MA, Badruddoza SM. Pattern of glomerular diseases among adults in Rajshahi, the Northern Region of Bangladesh. Saudi J Kidney Dis Transplant. 2012 Jan 7;23(4):876.
21. Das U, Dakshinamurty KV, Prayaga A. Pattern of biopsy-proven renal disease in a single center of south India: 19 years experience. Indian J Nephrol. 2011 Jan 10;21(4):250.
22. Yahya T, Pingle A, Boobes Y, Pingle S. Analysis of 490 kidney biopsies: data from the United Arab Emirates Renal Diseases Registry. J Nephrol. 1998 Jun;
23. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry and Japan Kidney Disease Registry: Committee Report for 2009 and 2010. Clin Exp Nephrol. 2013 Apr 1;17(2):155–73.
24. Utsunomiya Y, Koda T, Kado T, Okada S, Hayashi A, Kanzaki S, et al. Incidence of pediatric IgA nephropathy. Pediatr Nephrol. 2003 Jun 1;18(6):511–5.
25. Ko KW, Ha S, Jin DK, Cheong H, Choi Y, Kim Y, et al. Childhood renal diseases in Korea. Pediatr Nephrol. 1987 Dec 1;1(4):664–9.
26. Moranne O, Watier L, Rossert J, Stengel B. Primary glomerulonephritis: an update on renal survival and determinants of progression. QJM Int J Med. 2008 Mar 1;101(3):215–24.
27. Braun N, Schweisfurth A, Lohöfener C, Lange C, Gründemann C, Kundt G, et al. Epidemiology of glomerulonephritis in Northern Germany. Int Urol Nephrol. 2011 Dec 1;43(4):1117–26.
28. Peters B, Stegmayr B, Andersson Y, Hadimeri H, Mölne J. Increased risk of renal biopsy complications in patients with IgA-nephritis. Clin Exp Nephrol. 2015 Dec 1;19(6):1135–41.
29. 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 Jan 1;85(1):198–203.
30. Sissons JG, Woodrow DF, Curtis JR, Evans DJ, Gower PE, Sloper JC, et al. Isolated glomerulonephritis with mesangial IgA deposits. Br Med J. 1975 Sep 13;3(5984):611.

31. Power DA, Muirhead N, Simpson JG, Nicholls AJ, Home CHW, Catto GRD, et al. IgA Nephropathy Is Not a Rare Disease in the United Kingdom. Nephron. 1985;40(2):180–4.
32. Batinić D, Sćukanec-Spoljar M, Milosević D, Subat-Dezulović M, Saraga M, Delmis J, et al. Clinical and histopathological characteristics of biopsy-proven renal diseases in Croatia. Acta Medica Croat Cas Hravatske Akad Med Znan. 2007 Sep;61(4):361–4.
33. Polenakovic MH, Grcevska L, Dzikova S. The incidence of biopsy-proven primary glomerulonephritis in the Republic of Macedonia—long-term follow-up. Nephrol Dial Transplant. 2003 Jul 1;18(suppl_5):v26–7.
34. Naumovic R, Pavlovic S, Stojkovic D, Basta-Jovanovic G, Nesic V. Renal biopsy registry from a single centre in Serbia: 20 years of experience. Nephrol Dial Transplant. 2009 Mar 1;24(3):877–85.
35. Donadio JV, Grande JP. IgA Nephropathy. N Engl J Med. 2002 Sep 5;347(10):738–48.
36. Jennette JC, Wall SD, Wilkman AS. Low incidence of IgA nephropathy in Blacks. Kidney Int. 1985 Dec 1;28(6):944–50.
37. 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 Jul 1;16(7):1364–7.
38. Disney A. Australia and New Zealand Dialysis and Transplant Registry Report 1998. ANZ DATA; 1998.
39. Hoy WE, Samuel T, Mott SA, Kincaid-Smith PS, Fogo AB, Dowling JP, et al. Renal biopsy findings among Indigenous Australians: a nationwide review. Kidney Int. 2012 Dec 2;82(12):1321–31.
40. Seedat YK, Nathoo BC, Parag KB, Naiker IP, Ramsaroop R. IgA Nephropathy in Blacks and Indians of Natal. Nephron. 1988;50(2):137–41.
41. Okpechi I, Swanepoel C, Duffield M, Mahala B, Wearne N, Alagbe S, et al. Patterns of renal disease in Cape Town South Africa: a 10-year review of a single-centre renal biopsy database. Nephrol Dial Transplant. 2011 Jun 1;26(6):1853–61.
42. Yeo SC, Cheung CK, Barratt J. New insights into the pathogenesis of IgA nephropathy. Pediatr Nephrol. 2018 May 1;33(5):763–77.
43. Floege J, Feehally J. The mucosa–kidney axis in IgA nephropathy. Nat Rev Nephrol. 2016 Mar;12(3):147–56.
44. Allen AC, Bailey EM, Barratt J, Buck KS, Feehally J. Analysis of IgA1 O-Glycans in IgA Nephropathy by Fluorophore-Assisted Carbohydrate Electrophoresis. J Am Soc Nephrol. 1999 Aug 1;10(8):1763–71.
45. Hiki Y, Odani H, Takahashi M, Yasuda Y, Nishimoto A, Iwase H, et al. Mass spectrometry proves under-O-glycosylation of glomerular IgA1 in IgA nephropathy. Kidney Int. 2001 Mar;59(3):1077–85.
46. Coppo R, Amore A. Aberrant glycosylation in IgA nephropathy (IgAN). Kidney Int. 2004 May;65(5):1544–7.

47. Xu L-X, Zhao M-H. Aberrantly glycosylated serum IgA1 are closely associated with pathologic phenotypes of IgA nephropathy. Kidney Int. 2005 Jul;68(1):167–72.

48. Moldoveanu Z, Wyatt RJ, Lee JY, Tomana M, Julian BA, Mestecky J, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney Int. 2007 Jun;71(11):1148–54.

49. Allen AC, Bailey EM, Brenchley PEC, Buck KS, Barratt J, Feehally J. Mesangial IgA1 in IgA nephropathy exhibits aberrant O-glycosylation: Observations in three patients. Kidney Int. 2001 Sep;60(3):969–73.

50. Gale DP, Molyneux K, Wimbury D, Higgins P, Levine AP, Caplin B, et al. Galactosylation of IgA1 Is Associated with Common Variation in C1GALT1. J Am Soc Nephrol. 2017 Jul 1;28(7):2158–66.

51. Serino G, Sallustio F, Cox SN, Pesce F, Schena FP. Abnormal miR-148b Expression Promotes Aberrant Glycosylation of IgA1 in IgA Nephropathy. J Am Soc Nephrol JASN. 2012 May;23(5):814.

52. Gharavi AG, Kiryluk K, Choi M, Li Y, Hou P, Xie J, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. Nat Genet. 2011 Apr;43(4):321–7.

53. Yanagihara T, Brown R, Hall S, Moldoveanu Z, Goepfert A, Tomana M, et al. In vitro-generated immune complexes containing galactose-deficient IgA1 stimulate proliferation of mesangial cells. Results Immunol. 2012;2:166.

54. Soares MF. An update on pathology of IgA nephropathy. Braz J Nephrol. 2016 Dec;38(4):435–40.

55. Barratt J, Feehally J. Primary IgA Nephropathy: New Insights Into Pathogenesis. Semin Nephrol. 2011 Jul;31(4):349–60.

56. Lai KN. Pathogenesis of IgA nephropathy. Nat Rev Nephrol. 2012 May;8(5):275–83.

57. Coppo R, Amove A, Gianoglio B, Reyna A, Peruzzi L, Roccatello D, et al. Serum IgA and Macromolecular IgA Reacting with Mesangial Matrix Components. IgA Nephrop 25th Year. 1993;104:162–71.

58. Kokubo T, Hiki Y, Iwase H, Tanaka A, Toma K, Hotta K, et al. Protective role of IgA1 glycans against IgA1 self-aggregation and adhesion to extracellular matrix proteins. J Am Soc Nephrol. 1998 Nov 1;9(11):2048–54.

59. Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, et al. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int. 2017 May 1;91(5):1014–21.

60. Lai KN, Leung JCK, Chan LYY, Saleem MA, Mathieson PW, Tam KY, et al. Podocyte injury induced by mesangial-derived cytokines in IgA nephropathy. Nephrol Dial Transplant. 2009 Jan 1;24(1):62–72.

61. Hara M, Yanagihara T, Kihara I. Cumulative Excretion of Urinary Podocytes Reflects Disease Progression in IgA Nephropathy and Schönlein-Henoch Purpura Nephritis. Clin J Am Soc Nephrol. 2007 Mar 1;2(2):231–8.

62. Wang C, Ye Z, Peng H, Tang H, Liu X, Chen Z, et al. Effect of aggregated immunoglobulin A1 from immunoglobulin A nephropathy patients on nephrin

expression in podocytes. Nephrology. 2009 Mar 1;14(2):213–8.

63. Lai KN, Leung JCK, Chan LYY, Saleem MA, Mathieson PW, Lai FM, et al. Activation of podocytes by mesangial-derived TNF-α: glomerulo-podocytic communication in IgA nephropathy. Am J Physiol-Ren Physiol. 2008 Apr 1;294(4):F945–55.
64. Chan LYY, Leung JCK, Tsang AWL, Tang SCW, Neng Lai KAR. Activation of tubular epithelial cells by mesangial-derived TNF-α: Glomerulotubular communication in IgA nephropathy. Kidney Int. 2005 Feb;67(2):602–12.
65. Maillard N, Wyatt RJ, Julian BA, Kiryluk K, Gharavi A, Fremeaux-Bacchi V, et al. Current Understanding of the Role of Complement in IgA Nephropathy. J Am Soc Nephrol. 2015 Jul 1;26(7):1503–12.
66. Coppo R, Troyanov S, Camilla R, Hogg RJ, Cattran DC, Terence Cook H, et al. The Oxford IgA nephropathy clinicopathological Classification is valid for children as well as adults. Kidney Int. 2010 May;77(10):921–7.
67. Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, et al. Mayo Clinic/Renal Pathology Society Consensus Report on Pathologic Classification, Diagnosis, and Reporting of GN. J Am Soc Nephrol JASN. 2016 May;27(5):1278.
68. 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 1;86(4):828–36.
69. Herzenberg AM, Fogo AB, Reich HN. Validation of the Oxford Classification of IgA nephropathy. Kidney Int. 2011 Aug 1;80(3):310–7.
70. Shi S-F, Wang S-X, Jiang L, Lv J-C, Liu L-J, Chen Y-Q, et al. Pathologic Predictors of Renal Outcome and Therapeutic Efficacy in IgA Nephropathy: Validation of the Oxford Classification. Clin J Am Soc Nephrol CJASN. 2011 Sep;6(9):2175.
71. Le W, Zeng C-H, Liu Z, Liu D, Yang Q, Lin R-X, et al. Validation of the Oxford Classification of IgA nephropathy for pediatric patients from China. BMC Nephrol. 2012;13:158.
72. Lee H, Yi SH, Seo MS, Hyun JN, Jeon JS, Noh H, et al. Validation of the Oxford Classification of IgA Nephropathy: A Single-Center Study in Korean Adults. Korean J Intern Med. 2012 Sep;27(3):293.
73. Barratt J, Feehally J. Treatment of IgA nephropathy. Kidney Int. 2006 Jun;69(11):1934–8.
74. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. Kidney Int. 2006 Jun;69(11):1939–44.
75. 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.
76. 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 3;373(23):2225–36.
77. Berthoux F, Mariat C, Maillard N. Overweight/obesity revisited as a predictive

risk factor in primary IgA nephropathy. Nephrol Dial Transplant. 2013 Nov 1;28(suppl_4):iv160–6.

78. Kittiskulnam P, Kanjanabuch T, Tangmanjitjaroen K, Chancharoenthana W, Praditpornsilpa K, Eiam-Ong S. The Beneficial Effects of Weight Reduction in Overweight Patients With Chronic Proteinuric Immunoglobulin A Nephropathy: A Randomized Controlled Trial. J Ren Nutr. 2014 May;24(3):200–7.
79. Pozzi C, Andrulli S, Vecchio LD, 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 1;15(1):157–63.
80. Lv J, Zhang H, Chen Y, Li G, Jiang L, Singh AK, et al. Combination Therapy of Prednisone and ACE Inhibitor Versus ACE-Inhibitor Therapy Alone in Patients With IgA Nephropathy: A Randomized Controlled Trial. Am J Kidney Dis. 2009 Jan;53(1):26–32.
81. Lv J, Xu D, Perkovic V, Ma X, Johnson DW, Woodward M, et al. Corticosteroid Therapy in IgA Nephropathy. J Am Soc Nephrol JASN. 2012 Jun;23(6):1108.
82. 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. The Lancet. 2017 May;389(10084):2117–27.
83. Kyburz D, Brentano F, Gay S. Mode of action of hydroxychloroquine in RA—evidence of an inhibitory effect on toll-like receptor signaling. Nat Clin Pract Rheumatol. 2006 Sep;2(9):458–9.
84. Ziegler HK, Unanue ER. Decrease in macrophage antigen catabolism caused by ammonia and chloroquine is associated with inhibition of antigen presentation to T cells. Proc Natl Acad Sci U S A. 1982 Jan;79(1):175.
85. Gao R, Wu W, Wen Y, Li X. Hydroxychloroquine alleviates persistent proteinuria in IgA nephropathy. Int Urol Nephrol. 2017 Jul 1;49(7):1233–41.
86. Smith J, McDaid JP, Bhangal G, Chawanasuntorapoj R, Masuda ES, Cook HT, et al. A Spleen Tyrosine Kinase Inhibitor Reduces the Severity of Established Glomerulonephritis. J Am Soc Nephrol JASN. 2010 Feb;21(2):231.
87. McAdoo SP, Reynolds J, Bhangal G, Smith J, McDaid JP, Tanna A, et al. Spleen Tyrosine Kinase Inhibition Attenuates Autoantibody Production and Reverses Experimental Autoimmune GN. J Am Soc Nephrol JASN. 2014 Oct;25(10):2291.
88. McAdoo SP, Bhangal G, Page T, Cook TH, Pusey CD, Tam FWK. Correlation of disease activity in proliferative glomerulonephritis with glomerular spleen tyrosine kinase expression. Kidney Int. 2015 Jul;88(1):52.
89. Ring T, Pedersen BB, Salkus G, Goodship THJ. Use of eculizumab in crescentic IgA nephropathy: proof of principle and conundrum? Clin Kidney J. 2015 Oct;8(5):489.
90. Rosenblad T, Rebetz J, Johansson M, Békássy Z, Sartz L, Karpman D. Eculizumab treatment for rescue of renal function in IgA nephropathy. Pediatr Nephrol. 2014 Nov 1;29(11):2225–8.

91. Levey AS, Stevens LA, Schmid CH, Zhang Y (Lucy), Castro AF, III, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009 May 5;150(9):604.

92. Zeng C-H, Le W, Ni Z. A Multicenter Application and Evaluation of the Oxford Classification of IgA Nephropathy in Adult Chinese Patients. Am J Kidney Dis. 2012 Nov 1;60(5):812–20.

93. Lee MJ, Kim SJ, Oh HJ, Ko KI, Koo HM, Kim CH, et al. Clinical implication of crescentic lesions in immunoglobulin A nephropathy. Nephrol Dial Transplant. 2014 Feb 1;29(2):356–64.

94. 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. 2013 Nov;62(5):891–9.

95. Kataoka H, Ohara M, Shibui K, Sato M, Suzuki T, Amemiya N, et al. Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. Clin Exp Nephrol. 2012 Oct 1;16(5):706–12.

96. Kaneko Y, Yoshita K, Kono E, Ito Y, Imai N, Yamamoto S, et al. Extracapillary proliferation and arteriolar hyalinosis are associated with long-term kidney survival in IgA nephropathy. Clin Exp Nephrol. 2016 Aug 1;20(4):569–77.

97. Stangou M, Bantis C, Skoularopoulou M, Korelidou L, Kouloukouriotou D, Scina M, et al. Th1, Th2 and Treg/T17 cytokines in two types of proliferative glomerulonephritis. Indian J Nephrol. 2016 Jun;26(3):159.

98. Rafalska A, Franczuk J, Franczuk P. Stratifying risk for progression in IgA nephropathy: how to predict the future? Pol Arch Med Wewn. 2014;124:365–72.

99. Lee H, Kim DK, Oh K-H, Joo KW, Kim YS, Chae D-W, et al. Mortality of IgA Nephropathy Patients: A Single Center Experience over 30 Years. PLoS ONE. 2012;7(12).

100. Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, et al. Prognosis in IgA Nephropathy: 30-Year Analysis of 1,012 Patients at a Single Center in Japan. PLoS ONE. 2014;9(3).

101. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA Nephropathy with ACE Inhibitors: A Randomized and Controlled Trial. J Am Soc Nephrol. 2003 Jun 1;14(6):1578–83.

102. Riispere Ž, Kuudeberg A, Seppet E, Sepp K, Ilmoja M, Luman M, et al. Significance of clinical and morphological prognostic risk factors in IgA nephropathy: follow-up study of comparison patient groups with and without renoprotection. BMC Nephrol. 2017 Mar 14;18(1):89.

103. Shao X, Li B, Cao L, Liang L, Yang J, Wang Y, et al. Evaluation of crescent formation as a predictive marker in immunoglobulin A nephropathy: a systematic review and meta-analysis. Oncotarget. 2017 Jul 11;8(28):46436.

104. Edström Halling S, Söderberg MP, Berg UB. Predictors of outcome in paediatric IgA nephropathy with regard to clinical and histopathological variables (Oxford Classification). Nephrol Dial Transplant. 2012 Feb 1;27(2):715–22.

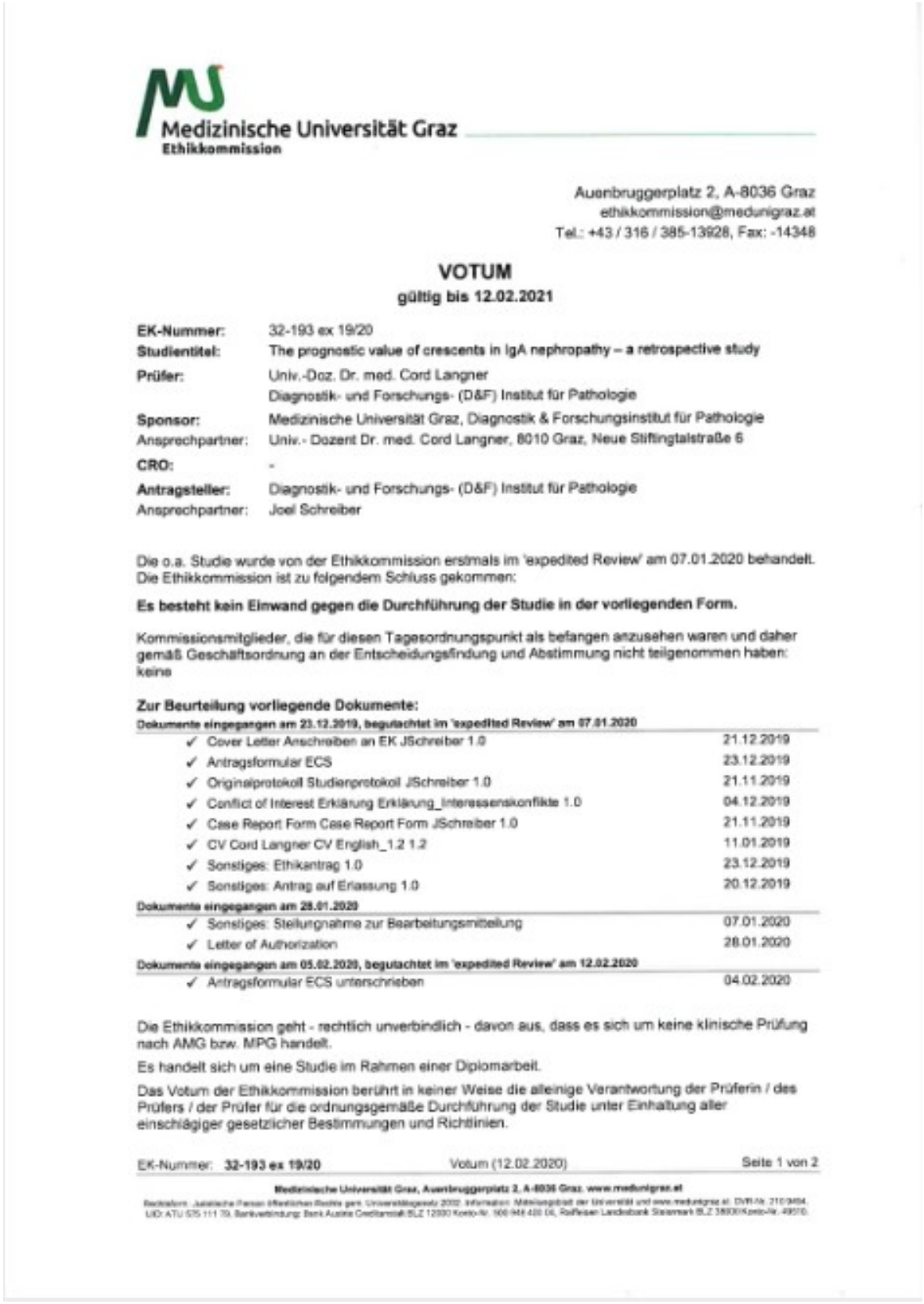
105. Lv J, Yang Y, Zhang H, Chen W, Pan X, Guo Z, et al. Prediction of Outcomes in Crescentic IgA Nephropathy in a Multicenter Cohort Study. J Am Soc Nephrol JASN. 2013 Dec;24(12):2118.

106. Bazzi C, Rizza V, Raimondi S, Casellato D, Napodano P, D'Amico G. In Crescentic IgA Nephropathy, Fractional Excretion of IgG in Combination with Nephron Loss Is the Best Predictor of Progression and Responsiveness to Immunosuppression. Clin J Am Soc Nephrol CJASN. 2009 May;4(5):929.

107. Li J, Liu C-H, Gao B, Xu D-L. Clinical-pathologic significance of CD163 positive macrophage in IgA nephropathy patients with crescents. Int J Clin Exp Med. 2015;8(6):9299.

108. Chan SK, Lo HL, Ho YW, Tam CH, Tang WCA, Lam CKD, et al. Outcome of IgAN With or Without Crescent Formation—A Restrospective Kidney Survival Analysis. Hong Kong J Nephrol. 2015;2 Supplement(17):S40–1.

16 Attachment



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VOTUM
gültig bis 12.02.2021

EK-Nummer:	32-193 ex 19/20
Studientitel:	**The prognostic value of crescents in IgA nephropathy – a retrospective study**
Prüfer:	Univ.-Doz. Dr. med. Cord Langner Diagnostik- und Forschungs- (D&F) Institut für Pathologie
Sponsor:	Medizinische Universität Graz, Diagnostik & Forschungsinstitut für Pathologie
Ansprechpartner:	Univ.- Dozent Dr. med. Cord Langner, 8010 Graz, Neue Stiftingtalstraße 6
CRO:	-
Antragsteller:	Diagnostik- und Forschungs- (D&F) Institut für Pathologie
Ansprechpartner:	Joel Schreiber

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 07.01.2020 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 23.12.2019, begutachtet im 'expedited Review' am 07.01.2020	
✓ Cover Letter Anschreiben an EK JSchreiber 1.0	21.12.2019
✓ Antragsformular ECS	23.12.2019
✓ Originalprotokoll Studienprotokoll JSchreiber 1.0	21.11.2019
✓ Conflict of Interest Erklärung Erklärung_Interessenskonflikte 1.0	04.12.2019
✓ Case Report Form Case Report Form JSchreiber 1.0	21.11.2019
✓ CV Cord Langner CV English_1.2 1.2	11.01.2019
✓ Sonstiges: Ethikantrag 1.0	23.12.2019
✓ Sonstiges: Antrag auf Erlassung 1.0	20.12.2019
Dokumente eingegangen am 28.01.2020	
✓ Sonstiges: Stellungnahme zur Bearbeitungsmitteilung	07.01.2020
✓ Letter of Authorization	28.01.2020
Dokumente eingegangen am 05.02.2020, begutachtet im 'expedited Review' am 12.02.2020	
✓ Antragsformular ECS unterschrieben	04.02.2020

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 12. Februar 2020

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Dimai
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

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