Diploma Thesis

The acute/rapidly - progressive nephritic syndrome in Europe - a retrospective study

written by

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Zusammenfassung

Einleitung: Nierenbiopsieregister können Inzidenz, Prävalenz und demografische Unterschiede von Nierenerkrankungen ermitteln und bei Diagnose, Prognose und letztendlich Therapie unterstützen. In Europa existieren in mehreren Ländern solche Register. Nicht nur genetische und umweltliche Faktoren beeinflussen Prävalenz und Inzidenz, sondern auch unterschiedliche Biopsie-Indikationsstellungen in verschiedenen Ländern, Regionen und Institutionen. In dieser Studie beschreiben wir die Einrichtung eines Nierenbiopsieregisters an der Medizinischen Universität Graz und versuchen die regionale Prävalenz, Alters- und Geschlechtsverteilung sowie klinischen Verlauf von PatientInnen mit proliferativen Glomerulopathien zu ermitteln.

Methoden: Die zwischen 2007 und 2017 durchgeführten Nierenbiopsien sowie klinische und epidemiologische Patientendaten als auch immunologische und nicht-immunologische Labordaten zum Zeitpunkt der Biopsie, wurden in ein neu entwickeltes Register zusammengeführt. Darüber hinaus wurde die Nierenfunktion, anhand der Kreatininwerte, über einen Zeitraum von 5 Jahren nachverfolgt. Weiters wurden Komplikationsraten nach Nierenbiopsien erhoben.

Ergebnisse: Aus den insgesamt 973 durchgeführten Nierenbiopsien erfolgten 419 an Nierentransplantaten. Von den 554 Eigennierenbiopsien wurden nach Ausschluss von Wiederholungsbiopsien, nicht repräsentativen Biopsien und Biopsien mit unzureichender Patienteninformation 506 Biopsien in unsere Kohorte aufgenommen, wobei in 238 nativen Nierenbiopsien proliferative Glomerulopathien diagnostiziert wurden. Die häufigsten proliferativen Glomerulopathien waren IgA-Nephropathie (12,3%), Lupusnephritis (12,1%), PR3-ANCA-assoziierte Glomerulonephritis (6,3%) und MPO-ANCA-assoziierte Glomerulonephritis (5,9%).

PatientInnen mit IgA-Nephropathie mit einem MEST score von T1 und T2 wiesen ein höheres Serumkreatinin auf (T1: 2,8 mg/dl; T2: 4,4 mg/dl), als PatientInnen mit T0 (1,9mg/dl). Ein T1 oder T2 score wurde bei Männern häufiger als bei Frauen beobachtet (51,6% vs. 13,4%). Ein höherer T-score war mit schlechterer Prognose (ESKD oder Tod) im Follow-up assoziiert (T1: 50,0%; T2: 100,0%; T0: 8,7%).

Interessanterweise waren Frauen mit MPO-ANCA assoziierter Glomerulonephritis um 15 Jahre älter als Frauen mit PR3-ANCA assoziierter Glomerulonephritis (68±10 Jahre vs. 53±15 Jahre, p=0,002). Bei Männern konnte sich kein Altersunterschied feststellen lassen. Insgesamt benötigten mehr PatientInnen mit PR3-ANCA assoziierter Glomerulonephritis Plasmapherese und Nierenersatztherapie als PatientInnen mit MPO-ANCA assoziierter Glomerulonephritis (Plasmapherese: 46,9% vs. 36,7% und Nierenersatztherapie: 40,6% vs. 20,0%). Bei PatientInnen mit ANCA-negativer pauci-immuner Glomerulonephritis war keine Plasmapherese oder Nierenersatztherapie notwendig.

Conclusio: Neben einer auffälligen Altersdifferenz bei Patientinnen mit ANCA-assoziierter Glomerulonephritis, zeigte sich im Europavergleich, wie in den meisten anderen Europäischen Ländern das die IgA-Nephropathie die häufigste primäre Glomerulopathie ist. Eine universelle Terminologie der verschiedenen Glomerulopathien kann nicht nur zum Verständnis des Krankheitsprozesses beitragen, sondern ist auch für die Durchführung epidemiologischer Studien von entscheidender Bedeutung.

Abstract

Introduction: Renal biopsy registries can establish incidence, prevalence and demographic differences of renal diseases and assist in diagnosis, prognosis and ultimately therapy. In Europe various renal biopsy registries exist. Incidence and prevalence are not only influenced by genetic and environmental differences, but also alter depending on biopsy indication in each country, region and center. In this study we describe the establishment of a renal biopsy registry at the Medical University of Graz, and evaluate regional prevalence, demographic differences and clinical data in patients with proliferative glomerulopathies.

Methods: Between 2007 and 2017 patients who underwent renal biopsy were evaluated and transferred in a newly developed registry. In addition, epidemiological and clinical data as well as various immunological and non-immunological laboratory data, at the time the patient underwent biopsy, were gathered. Creatinine values were followed over a period of 5 years. At last we evaluated complications following renal biopsies.

Results: A total of 973 renal biopsies were performed. Thereof 419 biopsies were performed in patients with a renal allograft. Of the 554 native biopsies, repeated biopsies, not representative biopsies, and biopsies with missing patient information were excluded. A total 506 native renal biopsies were evaluated with 238 biopsies being categorized as proliferative glomerulopathies. The most common proliferative glomerulopathy were IgA nephropathy (12,3 %), lupus nephritis (12,1%), PR3-ANCA associated glomerulonephritis (6,3%) and MPO-ANCA associated glomerulonephritis (5,9%).

In IgA nephropathy, when T-score (MEST-classification) was T1 or T2, which was more often seen in men (51,6% vs. 13,4%), serum-creatinine was higher (T1: 2,8mg/dl; T2: 4,4mg/dl) compared to T0 (1,9mg/dl) and was associated with worse outcomes (ESKD or death) in the follow up (T1: 50,0%; T2: 100,0%; T0:8,7%).

Interestingly, female patients with MPO-ANCA associated glomerulonephritis were 15 years older than female patients with PR3-ANCA associated glomerulonephritis (68a±10a vs. 53a±15a, p=0,002). No significant age difference in ANCA associated glomerulonephritis was found in men.

More patients PR3-ANCA associated glomerulonephritis required plasmapheresis and renal replacement therapy (RRT) than patients with MPO-ANCA associated glomerulonephritis

(Plasmapheresis: 46,9% vs. 36,7% and RRT: 40,6% vs. 20%). No patient with ANCA negative glomerulonephritis required either plasmapheresis or renal replacement therapy.

Conclusion: In addition to a noticeable age difference in female patients with ANCA-associated glomerulonephritis, a comparison across Europe showed that, IgA nephropathy was the most common primary glomerulopathy in our cohort. This is true for most other European countries.
Universal terminology can not only help understanding disease process but is essential when conducting epidemiological studies.

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1. Glossary and Abbreviations

SLE = Systemic lupus erythematosus

LN = Lupus nephritis

MCD = Mixed connective tissue disease

IgAN = IgA nephropathy

ANCA = Anti neutrophil cytoplasmic antibodies

ANCA associated GN = Anti neutrophil cytoplasmic antibodies glomerulonephritis

MPO = Myeloperoxidase

GPA = Granulomatosis with polyangiitis

MPA = Microscopic polyangiitis

PR3 = Proteinase 3

Anti-GBM antibodies = Anti glomerular basement membrane antibodies

HSP = Henoch-Schonlein Purpura

MCD = Minimal change disease

MN = Membranous nephropathy

FSGS = Focal segmental glomerulosclerosis

AGD = Anti-GBM disease = Goodpasture's disease

C3GN = C3 glomerulonephritis

IAGN = Infection associated GN = Infection associated glomerulonephritis

FGN = Fibrillary glomerulonephritis

IM-MPGN = Immune complex mediated glomerulonephritis

MPGN = Immune complex mediated glomerulonephritis

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4. Introduction

Glomerular diseases can present in different clinical pictures. Today, we differentiate between patients with asymptomatic findings of hematuria and/or proteinuria, with nephritic or nephrotic syndrome, those with rapidly progressive glomerulonephritis (GN) and those with recurrent episodes of inflammation(1). Most diseases can manifest both with nephrotic and nephritic features, but there is usually a tendency for one to predominate(2) *(see figure 1).* There is a correlation between clinical presentation and histopathology. Proliferative glomerulopathies (glomerulonephritis) classically cause nephritic features and non-proliferative glomerulopathies cause nephrotic features. Medical history, clinical examination, imaging and serologic testing can guide the diagnosis, but the definitive diagnosis is based on the histological findings of a renal biopsy. The incidence of glomerular disease varies around the globe, not only correlating with race, age, gender but also based on the diagnostic yield for performing renal biopsies in different countries and centers. Renal biopsy registries can establish incidence, prevalence demographic differences of renal diseases and assist the clinician in diagnosis, prognosis and ultimately therapy. In Europe national renal biopsy registries exist in Spain(3), Scotland(4), the Czech Republic(5), Italy(6), Denmark(7), Lithuania(8), Norway(9) and Sweden(10). Regional and single center registries exist in Germany(11), Poland(12), Estonia(13), Serbia(14), France(15), Romania(16), Finland(17), the Netherlands(18) and Northern Ireland(19). The aim of this thesis is to establish a renal biopsy registry at the Medical University of Graz and collect data to show distribution of age, gender, and seasonal differences on renal biopsy proven

Figure 1 *Typical presentation of glomerular disease. Direction of triangle indicates strength of tendency. Modified from Brenner and Rectors, The kidney 10th edition*

glomerular diseases, in which nephritic features dominate. We have chosen a time frame between 2007 and 2017, clinical characteristics and laboratory data were thoroughly collected at the time of biopsy and creatinine levels were evaluated for the following 5 years.

4.1 Historical Perspective

Today's literature nomenclature of glomerular diseases is often unclear and confusing, among students and physicians alike. To understand why this diversity exists, we must go back to 1827 when English-physician Richard Bright published his observations of diseased dropsical patients in his "Reports of Medical Cases" demonstrating a clear correlation between patients with edema, proteinuria and kidney disease(20). Bright illustrated a variety of different macroscopic pathologic alterations in diseased dropsical patients and correlated proteinuria, edema and renal disease. Bright established three different macroscopic changes in diseased kidneys, "generally attended by decidedly albuminous character of the urine"(20). The term Bright's disease (Morbus Brightii) became synonymous with kidney disease accompanied by edema and albuminuria(21)
With the advance in microscopic examination of post-mortem kidneys in patients who succumbed to Bright´s disease it became evident that Richard Bright described a variety of different pathologic entities. Those of degenerative (non-inflammatory) changes and those of inflammatory changes. In 1914 Theodor Fahr and Franz Volhard published their immensely influential book "Die Brightsche Nierenkrankheit". They addressed that Morbus Brightii turned into an umbrella term for both kidney diseases with inflammatory (nephritis) as well those with non-inflammatory (nephrosis) changes(21). Volhard and Fahr systemized Morbus Brightii in three groups: Nephritis, nephrosis and nephrosclerosis. Nephrosis was used as an anthesis to nephritis, describing renal pathologies without an inflammatory process. The term nephrosis made many transformations over the next decades, subsequently turning into the nephrotic syndrome(22). Today the nephrotic syndrome is a clearly defined syndrome as presence of heavy proteinuria (protein excretion greater than 3.5 g/24 hours) with hypoalbuminemia and commonly associated with edema, hyperlipidemia and lipiduria(23). In clear contrast to the nephritic syndrome, while often used as antagonist to the nephrotic syndrome, the definition remains elusive. This might be due the fact that nephrotic features were seen in different disease entities and the need for clarity was immense. In contrast to what was thought to cause nephritis.
In "Die Brightsche Nierenkrankeit" Theodor Fahr and Franz Volhard wrote: "The cause of all nephritis is with almost no exception bacterial infections", and was thought to be exceedingly caused by Streptoccoci(21). Patients most notable presented with acute onset of gross hematuria, hypertension and edema. Today also known as the Volhard triad. Each

is unique by itself, however in conjunction pathognomonic for acute glomerulonephritis. In 1950 Addis simplified it in his book “Glomerular nephritis” with the following equation “Streptococcal infection + X = glomerular nephritis”(24). Today we know that there are various distinct causes resulting in inflammation of the glomeruli. In fact, poststreptococcal glomerulonephritis just accounts for a small minority of biopsy proven renal diseases in western, so-called developed countries. A study in France analyzing biopsy proven kidney disease showed a progressive decrease in the incidence of poststreptococcal glomerulonephritis between 1976 and 1990 from 12% to 2%(15). This is in stark contrast to less developed countries with more than 95% of all poststreptococcal glomerulonephritis cases confined to its borders(25).

Pathognomonic microscopic alterations in the glomeruli of patients in poststreptococcal glomerulonephritis are diffuse endocapillary hypercellularity including polymorphonuclear leukocytes and monocytes(26).

Today IgA nephritis, first described by Berger in 1968(27) is the most prevalent pattern of primary glomerulonephritis in most Western and Asian countries, where renal biopsy is widely used as an investigative tool(1). If endocapillary hypercellularity is the classic pathological correlative to poststreptococcal glomerulonephritis, mesangial hypercellularity is that to IgA nephritis(28). However, there is a wide degree of pathologic variations in the glomerular tuft, ranging from focal mesangial proliferation to full blown crescentic glomerulonephritis with rapidly progressive renal failure. The most common presentation is the incidental finding of microscopic hematuria with or without proteinuria or macroscopic hematuria(29). The latter is more common in children or young adults’ than in the elderly(26). Acute renal failure is seen in less than 5% of cases(30).

In 1942 Ellis, whilst approaching the topic of glomerular disease from a clinical standpoint, wrote about some patients’ rapidly progressive course of nephritis with death in a matter of weeks or months. This subsequently became rapidly progressive glomerulonephritis. Back then, it was thought to be an extremely severe form of poststreptococcal glomerulonephritis(31) and can cause renal failure and death in severe cases(32). Most patients described by Ellis probably had a different underlying etiology than poststreptococcal glomerulonephritis. It was not up until 1968 when Bacani reported on eight patients who had rapidly progressive glomerulonephritis without evidence of streptococcal infection, clearly differentiating between poststreptococcal glomerulonephritis and rapidly progressive glomerulonephritis. He showed distinct histological patterns between patients who had poststreptococcal glomerulonephritis and

those with rapidly progressive glomerulonephritis(33). His patients' "course of illness until admission to the hospital was insidious and remarkable only for the lack of history suggesting severe acute glomerulonephritis"(33). All patients died within 13 and 19 weeks. Today, rapidly progressive glomerulonephritis it is generally known as clinical syndrome manifested by features of glomerular disease in the urinalysis and by progressive loss of renal function over a comparatively short period of time (days, weeks or months)(34). This definition has its own limitations. Firstly, the disease onset might be insidious and delayed diagnosis is not uncommon. Secondly, if the correct therapy is initiated, renal function deterioration can be halted promptly. Thirdly, different diseases can mimic glomerulonephritis. For example, malignant hypertension, thrombotic microangiopathy and atheroembolic kidney disease can all cause rapid deterioration in renal function and show evidence of glomerulonephritis in the urinalysis. The pathologic hallmark of rapidly progressive glomerulonephritis is diffuse (in ≥50% of representative glomeruli) crescent formation, therefore also known as crescentic glomerulonephritis. These terms are often used synonymously. Crescentic glomerulonephritis can be classified in four groups (I) with linear staining of anti-GBM antibodies (II) with granular staining of immune deposits on the capillary wall (III) with absent or scanty staining of immunoglobulins on immunofluorescence (IF), and (IV) with dominant complement factor C3 deposition without significant immunoglobulin staining on IF.

Any glomerulonephritis can have recurrent episodes of inflammation ergo a more "chronic course". On microscopy extensive tubular atrophy accompanied by tubulointerstitial fibrosis and sclerosis of the glomerular tuft is the hallmark of chronic glomerulonephritis. Clinical studies illustrate that tubulointerstitial fibrosis appears to inversely correlate better with current and future renal function than glomerular scarring. There is often a disconnect between clinicians and pathologists, because glomerulonephritis may appear clinically acute and show chronic parenchymal damage and vice versa(35). Today, the diagnosis of chronic glomerulonephritis is often made presumptive in patients with shrunken kidneys, proteinuria and renal impairment without biopsy, leading to overestimation in end-stage-kidney-disease registry data(1).

There is a strong correlation between histologic and clinical presentation *(see figure. 2 and 3)* and survival rate(36). Yet, clinical presentation can be evasive e.g. patients with minimal change disease may present with nephritic features such as microscopic hematuria, hypertension and acute kidney injury(37). Crescentic glomerulonephritis can in comparison manifest itself as nephrotic syndrome. Physical examination, history taking,

serologic testing and imaging can guide the clinician in diagnosis. At last definitive diagnosis, severity, activity, and chronicity of the renal lesion is made based on the histological findings by the pathologist.

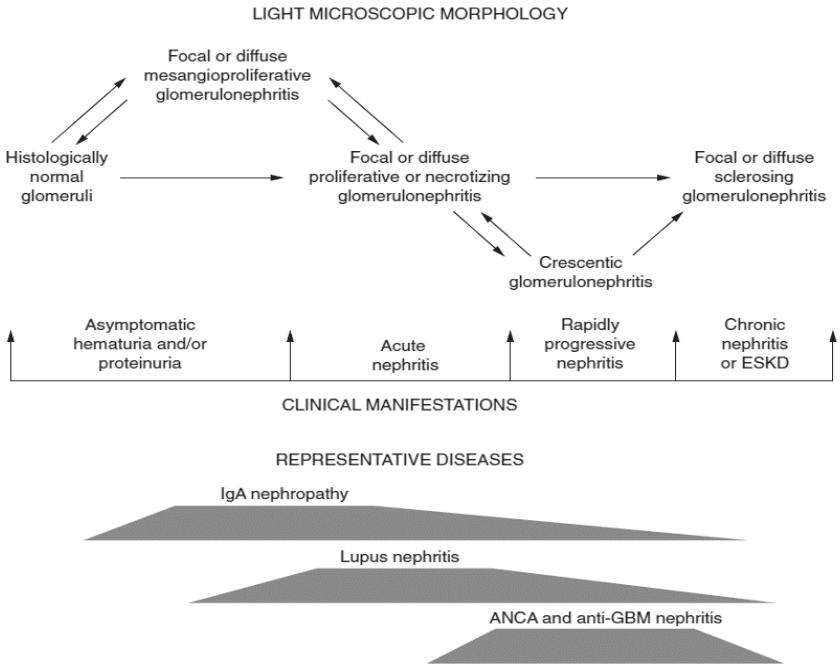

Figure 2 *Diagram depicting the continuum of histological changes that can be caused by glomerular inflammation and usual clinical presentation, from Heptinstall's Pathology of the kidney 7th edition.*

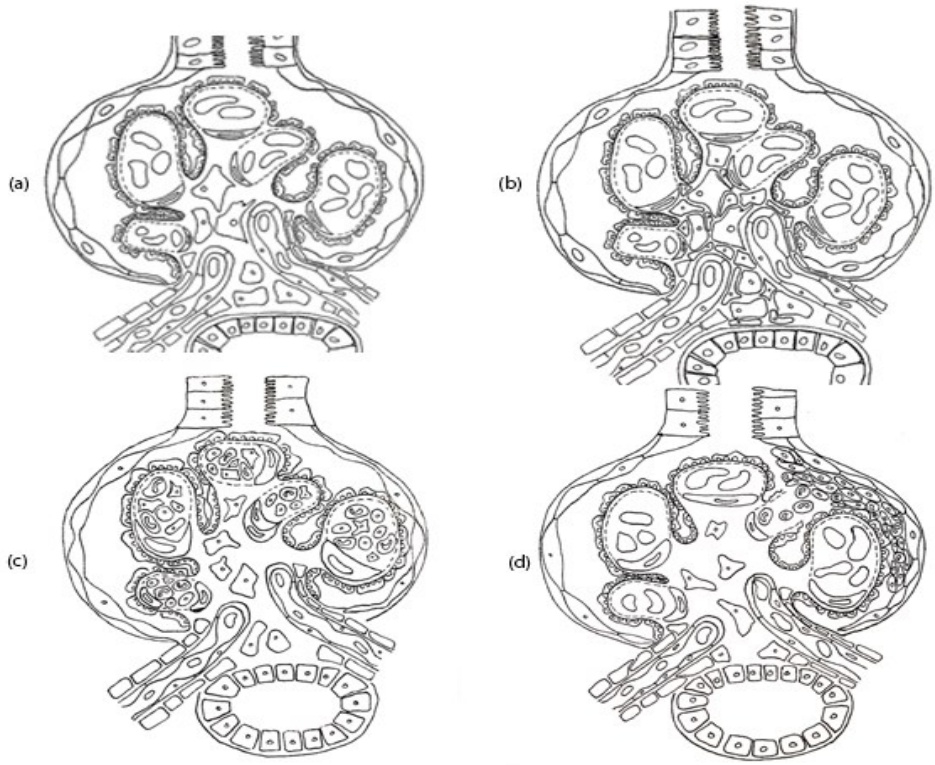

Figure 3 *Pattern of injury (a) normal glomerulus (b) mesangial hypercellularity: often associated with asymptomatic hematuria (c) endocapillary hypercellularity, often associated with acute glomerulonephritis (d) extra-capillary hypercellularity, often associated with rapidly progressive glomerulonephritis, self-illustrated*

Figure 2 illustrates the continuum of histologic changes affecting the kidney and figure 3 shows how each glomerulus may look in proliferative glomerulonephritis. Note there can be an overlap seen on histology between 3b, 3c and 3d.

4.2 Terminology

4.2.1 Systemic lupus erythematosus, lupus like nephritis and mixed connective tissue disease

Since systemic lupus erythematosus can affect any organ system and clinical presentation can vary in each patient, a classification system was first developed in 1972 by the American College of Rheumatology. It was intended to classify patients in population surveys, evaluating the natural history of disease, and to homogenize patient groups for therapeutic trials of the disease(38). The criteria were revised in 1982 to include immunological studies(39). In 2012 the classification was improved on by the Systemic Lupus Collaborating Clinics Criteria (SLICC) with some notable modifications to increase sensitivity(40). One noteworthy revision was the fact that lupus nephritis and presence of autoantibodies to nuclear antigens **(**ANA) now was sufficient for the classification of systemic lupus erythematosus. A subset of patients with biopsy proven 'lupus nephritis' never develop other (extrarenal) symptoms of systemic lupus erythematosus or a positive ANA, therefore do not meet the criteria of systemic lupus erythematosus. These disease entities have been described as 'ANA-negative lupus nephritis' 'lupus-like nephritis' and 'seronegative lupus nephritis'(29). The newest classification system was published by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in 2019(41). They argue that systemic lupus erythematosus is an autoantibody driven disease. An ANA of at least 1:80 should be used as entry criteria to be classified as systemic lupus erythematosus. Simplified no ANA - no systemic lupus erythematosus. While previous classifications used a binary system, the newest classification system is a point-based system *(see figure 4)*. Using the 1982 ACR criteria 4 of 11 manifestations were required to be classified as systemic lupus erythematosus. In the classification criteria of 2019, each manifestation has a different value. The cut off to be classified as systemic lupus erythematosus is a score of 10 points *(see figure 4)*.

Mixed connective tissue disease first described by Sharp and colleagues(42) is a distinct disease entity with overlapping features of systemic lupus erythematosus, scleroderma and

polymyositis. Glomerular alterations in mixed connective tissue disease are parallel to those seen in systemic lupus erythematosus(26).

Glomerular pathologic changes in systemic lupus erythematosus, lupus like nephritis and mixed connective tissue disease encompass proliferative glomerular disease as well as a membranous pattern of injury, each pathologic alteration affecting presentation, prognosis and treatment(43). For this reason a classification has been introduced by the WHO as foundation for clinical trials(44). The classification system has been revised several times. In 2004 an updated version has been proposed by the International Society of Nephrology and the Renal Pathology Society *(see figure 4)*(45). Simplified lupus nephritis can be subdivided in six classes. Lupus nephritis class I shows, no pathologic glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence. Lupus nephritis class II displays mesangial proliferation, class III and IV demonstrates focal *(<50%)* and diffuse *(≥ 50%)* intracapillary or extra capillary proliferation. Class V mimics the pattern of membranous nephropathy on light microscopy, and class VI shows advanced *(≥90%)* sclerotic glomeruli. Class V may occur with class III and IV.

SLICC classification criteria for systemic lupus erythematosus (2012)[72]	EULAR/ACR classification criteria for systemic lupus erythematosus (2019)[40]	
To diagnose systemic lupus erythematosus either	**Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)**	
	Do not count a criterion if there is a more likely explanation than SLE	
Biopsy-proven nephritis compatible with SLE	**Occurrence of a criterion on at least one occasion is sufficient**	
ANA or anti-dsDNA antibodies	**SLE classification requires at least one clinical criterion and ≥10 points**	
	Criteria need not occur simultaneously	
OR	**Within each domain, only the highest weighted criterion is counted toward the total score**	
	Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled	
≥1 clinical and immunological criteria each and ≥4 total for positive SLE diagnosis	Fever	2
Clinical criteria	Leukopenia	3
Acute cutaneous lupus	Thrombocytopenia	4
Chronic cutaneous lupus	Autoimmune hemolysis	4
Oral ulcers	Delirium	2
Nonscarring alopecia	Psychosis	3
Synovitis	Seizure	5
Serositis	Non-scarring alopecia	2
Renal involvement	Oral ulcer	2
Neurologic involvement	Subacute cutaneous OR discoid lupus	4
Hemolytic anemia	Acute cutaneous lupus	6
Leukopenia or lymphopenia	Pleural or pericardial effusion	5
Thrombocytopenia	Acute pericarditis	6
	Joint involvement	6
Immunological criteria	Proteinuria >0.5g/24h	4
ANA above laboratory reference range	Renal biopsy Class II or V lupus nephritis	8
Anti-dsDNA above laboratory reference range, except ELISA (2x above laboratory reference range)	Renal biopsy Class III or IV lupus nephritis	10
Anti-Smith (SM) antibodies	Anti-cardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant	2
Antiphospholipid antibody	Low C3 OR low C4	3
Complement factor consumption	Low C3 AND low C4	4
Positive direct Coombs test	Anti-dsDNA antibody OR Anti-Smith antibody	6

Figure 4 *SLICC (2012) and EULAR/ACR 2019 criteria for systemic lupus erythematosus*

Designation	Description	Characteristic Clinical Features
Class I: minimal mesangial lupus nephritis	No LM abnormalities; isolated mesangial IC deposits on IF and/or EM	Normal urine or microscopic hematuria
Class II: mesangial proliferative lupus nephritis	Mesangial hypercellularity or matrix expansion with mesangial IC deposits on IF and/or EM	Microscopic hematuria and/or low-grade proteinuria
Class III: focal lupus nephritis[a]	<50% of glomeruli on LM display segmental (<50% of glomerular tuft) or global (>50% of glomerular tuft) endocapillary and/or extracapillary proliferation or sclerosis; mesangial and focal subendothelial IC deposits on IF and EM	Nephritic urine sediment and subnephrotic proteinuria
Class IV: diffuse lupus nephritis[a]	≥50% of glomeruli on LM display endocapillary and/or extracapillary proliferation or sclerosis; class IV-S denotes ≥50% of affected glomeruli have segmental lesions; class IV-G denotes ≥50% of affected glomeruli have global lesions; mesangial and diffuse subendothelial IC deposits on IF and EM	Nephritic and nephrotic syndromes, hypertension, reduced kidney function
Class V: membranous lupus nephritis[b]	Diffuse thickening of the glomerular capillary walls on LM with subepithelial IC deposits on IF and EM, with or without mesangial IC deposits	Nephrotic syndrome
Class VI: advanced sclerosing lupus nephritis	>90% of glomeruli on LM are globally sclerosed with no residual activity	Markedly reduced kidney function, hypertension

[a]Both class III and class IV may have active (proliferative), chronic, inactive (sclerosing), or combined active and chronic lesions subclassified as A, C, or A/C, respectively.
[b]Class V may coexist with class III or class IV, in which case both classes are diagnosed.
EM, Electron microscopy; *IC*, immune complex; *IF*, immunofluorescence; *LM*, light microscopy.

Figure 5 *Classification system of lupus nephritis from National Kidney Foundation's Primer on Kidney Diseases, 7th Edition*

4.2.2 IgA nephropathy and IgA vasculitis (Henoch–Schonlein purpura)

IgA vasculitis and IgA nephropathy are both driven by IgA deposition. Both are likely on different points of one disease spectrum(46).

Renal histopathological changes can be indistinguishable to another. Both show (co-) dominant staining with IgA and in both histological changes may range from mesangial proliferation to crescent formation. The latter is more frequently seen in IgA vasculitis, particularly in children(26). The decisive difference between IgA nephropathy and IgA vasculitis, is that there is no evidence of systemic vasculitis in IgA nephropathy. Common extrarenal manifestations of IgA vasculitis involve the skin, joints and the gastrointestinal tract. Skin involvement shows palpable purpura and petechiae. Previously assumed to be a disease primarily affecting children and teenagers, this no longer holds true. In fact, the incidence rate of IgA vasculitis might be 3-6 times higher in adults than previously reported(47). The diagnostic criteria of IgA vasculitis have been revised in 2010, which has a higher sensitivity than the previously implemented 1990 American College of Rheumatology (ACR) classification system(48). To diagnose IgA vasculitis the following clinical characteristic are required *(see table 1)*: Purpura or petechiae (not related to

thrombocytopenia) AND at least one of the following: abdominal pain, arthritis or arthralgia, renal involvement, leucocytoclastic vasculitis with predominant IgA deposition or proliferative glomerulonephritis with predominant IgA deposits(49). IgA vasculitis should not be confounded with secondary causes of IgA nephropathy, in most cases caused by impaired clearance of IgA immune complexes due to liver cirrhosis(50).

Table 1 *ACR and EULAR/PRINTO/PRES for IgA vasculitis (Henoch-Schonlein purpura)*

ACR classification criteria (1990)[47]	EULAR/PRINTO/PRES classification criteria (2010)[48]
Two of the following criteria	**Purpura or petechiae**
	AND one of the following four criteria:
1) age≤20 years	1) abdominal pain
2) palpable purpura	2) arthritis or arthralgia
3) acute abdominal pain	3) renal involvement
4) biopsy showing granulocytes in the walls of the small arterioles or venules	4) leucocytoclastic vasculitis with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits

EULAR/PRINTO/PRES = European League Against Rheumatism/ Paediatric Rheumatology International Trials Organisation/ Paediatric Rheumatology, ACR = American College of Rheumatology, IgA = Immunoglobulin A

4.2.2.1 MEST score

Since the biopsy in IgA nephropathy can show various alterations, a classification system was proposed in 2009 to better predict outcome of patients with IgA nephropathy(28). This classification system has been verified by further retrospective studies(51). The M E S T score *(see figure 6)* consists of four distinct pathological changes. M = mesangial hypercellularity, E = endocapillary hypercellularity, S = segmental sclerosis and T = tubular atrophy / interstitial fibrosis. Each category is divided into 0 or 1 (M0, M1, E0, E1, S0, S1) but the T score which consists of T0, T1, T2. The M and T - score depend on the percentage of affected glomeruli and the degree of tubular atrophy and interstitial fibrosis, respectively. The S and E - score depend on the presence or absence of segmental sclerosis or endocapillary hypercellularity. A metanalysis conducted in 2013 concluded that that M, S and T lesions as well as crescent formation are a predictor for poor prognosis. No association between E score and kidney failure was shown(52). In 2016 the MEST score was expanded to include C = crescent formation(51).

Histologic Variable	Definition	Score
Mesangial hypercellularity	Mesangial hypercellularity score defined by the proportion of glomeruli with mesangial hypercellularity	M0 ≤0.5 M1 >0.5
Endocapillary hypercellularity	Hypercellularity because of increased number of cells within glomerular capillary lumina, causing narrowing of the lumina	E0 absent E1 present
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis but not involving the whole tuft or the presence of an adhesion	S0 absent S1 present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	T00%–25% T126%–50% T2 >50%

Note: Scoring should be assessed on period acid-Schiff-stained sections.

Figure 6 *MEST score, from National Kidney Foundation's Primer on Kidney Diseases, 7th Edition*

4.2.3 Pauci immune glomerulonephritis and ANCA associated GN

In 1979, Stillmant and colleagues recognized that in patients with crescentic glomerulonephritis biopsies displaying a lack (paucity) of immune complexes (pauci immune glomerulonephritis) outnumbered patients who had anti-GBM antibodies or immune complex induced renal disease(32). Today we know that most of these patients have elevated antineutrophil cytoplasmic antibodies (ANCAs) directed either against myeloperoxidase (MPO) or proteinase 3 (PR3). Approximately 85% to 95% of active pauci-immune crescentic glomerulonephritis are found to be either MPO ANCA or PR3 ANCA positive(26). Patients without elevated ANCAs and pauci immune glomerulonephritis are therefore called ANCA negative 'pauci' immune glomerulonephritis. The term ANCA associated glomerulonephritis is generally used to include MPO, PR3 and ANCA negative 'pauci' immune glomerulonephritis. Most patients with elevated ANCAs and pauci immune glomerulonephritis suffer either from granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). In most cases antibodies are directed against PR3 *(70%)* in granulomatosis with polyangiitis. In microscopic polyangiitis 50% of cases have antibodies directed against MPO and 40 % against PR3(1). Prognosis and therapy correlates better with antigen specificity than clinical syndrome, it has been proposed to classify the disease by ANCA specificity rather than clinical syndrome(52, 53). Diagnosis of ANCA specificity makes a more homogeneous patient cohort, for studies. This is due the fact that differentiating between MPA and GPA can be challenging especially in the absence of biopsy results. Antibody levels alone are not sufficient, for the diagnosis of GPA or MPA.

4.2.4 Membranoproliferative glomerulonephritis and C3 glomerulopathy

The term membranoproliferative glomerulonephritis describes a pattern of injury, displaying thickening of the capillary wall with a double contour, so-called “tram-track” appearance and hypercellularity in the glomerular tuft. Historically it was and still is classified depending on the location of deposits on electron microscopy in MPGN type I, MPGN type II and MPGN type III. Various etiologies can cause a membranoproliferative pattern on light microscopy. Therapy and prognosis differ based on the underlying disease. A newer classification has moved onto categorizing MPGN based on the pathogenesis rather than the pattern of injury. There are two general pathways which can cause membranoproliferative glomerulonephritis: (I) immunocomplex mediated disease, and (II) disease caused by derailments of the complement system *(see figure 7).* Immune complex mediated disease has various etiologies. Hepatitis C is the most common cause of infection associated with MPGN(29). Other infections associated with membranoproliferative glomerulonephritis are hepatis B, endocarditis, shunt infections, visceral abscesses, leprosy, malaria, schistosomiasis and mycoplasma(55). Additional causes for immune complex associated MPGN are diseases associated with plasma cell dyscrasias, fibrillary glomerulonephritis and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren’s syndrome and mixed connective tissue disease(55). In immune complex mediated membranoproliferative glomerulonephritis the double contours form as a result of immune complex deposition. In contrast to complement mediated glomerulonephritis damage to the glomerular basement membrane is driven by dysregulation of the alternative pathway, a rare disease process affecting 0.2 to 1 cases per million in Europe(56). On immunofluorescence this activation can be seen by strong staining for C3 and no (or no significant) staining for immune complexes. To diagnose C3 glomerulopathy C3 staining needs to be at least two orders of magnitude higher than other immuncomplexes(57). Other patterns of injury include mesangial proliferative pattern, endocapillary proliferation and crescent formation(26). Chronic thrombotic microangiopathy can drive duplication of the basement membrane, mimicking membranoproliferative glomerulonephritis on light microscopy. Immunofluorescence would not detect any immune complexes in these cases(29). This further shows the importance of differentiating between different etiologies of membranoproliferative glomerulonephritis.

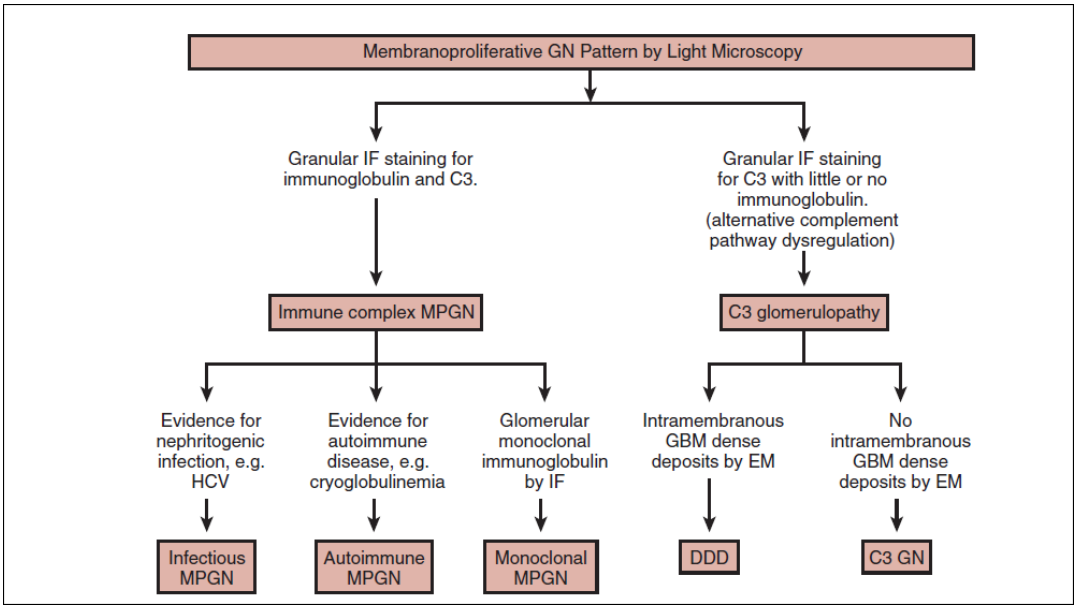

Figure 7 *Overview of membranoproliferative glomerulonephritis, from Brenner and Rectors, The kidney 10th edition*

4.2.5 Goodpasture disease and Goodpasture syndrome

In 1919 the American physician and pathologist Ernest Goodpasture described patients with pulmonary hemorrhage and crescentic glomerulonephritis(58). The name was attached to anti-GBM disease by Stanton and Tange in 1958(59). In retrospect the pathologic findings of Goodpasture's patients are more consistent with systemic vasculitis rather than anti-GBM disease(60). Goodpasture's disease is an anti-GBM mediated disease which can cause crescentic glomerulonephritis with or without lung hemorrhage. Classically in older individuals pulmonary hemorrhage may be absent(61). Goodpasture's syndrome in its original sense describes the concurrent appearance of (I) crescentic glomerulonephritis and (II) pulmonary haemorrhage, sometimes called "pulmonary-renal syndrome"(29).

A clinical syndrome also seen in ANCA associated vasculitis. Some patients may in fact have ANCA and anti-GBM autoantibodies in their serum. This so called dual positivity occurs in 1/3 to 1/2 of all patients with elevated anti-GBM autoantibodies and is more frequently associated with MPO ANCA than PR3 ANCA(61, 62). Clinical prodrome and relapse rate of these patients seems to be similar to ANCA associated disease, while early presentation is similar to anti-GBM disease(63).

The histological hallmark in Goodpasture's disease on renal biopsy is fibrinoid necrosis and crescentic glomerulonephritis. Compared to pauci-immune glomerulonephritis the crescents

are in general all active (cellular), whilst in the latter there is more heterogeneity in crescents ranging from cellular over fibro-cellular to fibrous crescents. On immunohistochemistry linear immunoglobulin G (IgG) staining along the glomerular basement membrane accompanied with lesser staining of C3 is observed, linear staining of immunoglobulin A (IgA) and immunoglobulin M (IgM) have also been detected in a few cases(64).

4.2.6 Infection associated glomerulonephritis and endocapillary proliferative GN

As mentioned historically glomerulonephritis was mostly seen in children who had a previous diagnosis of streptococcal infection. This disease entity is known as poststreptococcal or postinfectious glomerulonephritis. Diffuse endocapillary glomerulonephritis with monocytes and neutrophils is the classic pathological correlative to poststreptococcal glomerulonephritis and often used synonymously. A variety of diseases can cause a diffuse endocapillary hypercellularity, including IgA nephropathy and lupus nephritis. Furthermore, many causative pathogens other than Streptococci have been associated with glomerulonephritis, including other bacteria, viruses and parasites(29). In today's literature the term postinfectious glomerulonephritis is used to describe both patients in which infection is still ongoing and infection has already resolved(26). Treatment may vary between those two groups and therefore a more correct terminus for glomerulonephritis with ongoing infections is infection associated glomerulonephritis. The term infection associated glomerulonephritis alludes to its own set of issues. Infection may trigger other glomerulopathies like IgA nephropathy(65), ANCA associated glomerulonephritis(66), podocytopathies e.g. HIV-associated nephropathy(67) and others. These diseases are not referred to in a broader sense when talking about infection associated glomerulonephritis, postinfectious glomerulonephritis or 'acute' endocapillary proliferative glomerulonephritis. In industrialized countries, much of the weight of infection associated glomerulonephritis has shifted to adults with staphylococcal infection rather than streptococcal infection(68). Affected adults are usually immune compromised, in association with alcoholism, diabetes, and or drug addiction(69). Pathologic alteration seen on light microscopy typically mimics changes in post streptococcal glomerulonephritis. The immunohistology may differ depending on the causative pathogen. In infections due to Staphylococcus there is generally

a dominant or predominant staining for IgA(26). Intriguingly, patients with ongoing staphylococcal infection may show purpuric skin changes. Terms like ‘post-staphylococcal infection Henoch-Schonlein purpura (PSI-HSP)’ or ‘Henoch-Schonlein purpura like nephritis’ have been introduced to describe this entity (69, 70, 71, 26).

4.2.7 Fibrillary glomerulonephritis

Fibrillary glomerulonephritis is a rare disease affecting approximately 1% of native biopsies in industrialized countries(73). Fibrillary glomerulonephritis is defined by glomerular accretion of fibrils, which differ from those seen in amyloidosis by their larger size and the absent of apple green birefringence when stained with Congo red(29). Newer evidence suggests that it is an immune complex mediated disease directed against DNAJB9(74). The histopathologic alterations are vast showing proliferative changes like mesangial proliferation, membranoproliferative pattern of injury, to crescentic glomerulonephritis. In addition, membranous pattern of injury has been observed(26).

5. Methods

We examined biopsy proven glomerulopathies at the Medical University of Graz between January 1st of 2007 and December 31st of 2017. Patient identification in whom a renal biopsy was performed have been collected since 2007 at the Clinical Division of Nephrology. This thesis is organized in 3 parts. In **Part I - renal biopsies** - patients were identified in the hospital information system 'MEDOCS', an excel chart connecting each patient to a histological diagnosis was created. Patients with a renal allograft were excluded. Per patient just the first representative biopsy was used, to eliminate overrepresentation of certain renal diseases, notably lupus nephritis, in which repeated biopsies are not infrequent. In **Part II - renal diseases** - the incidence and distribution of sex, age and pathology were analyzed. Unclear diagnoses were discussed with the attending nephrologists of the Division of Nephrology. In addition, our renal biopsy register was compared to various European registries. In **Part III - proliferative glomerulonephritis** – all glomerular diseases which primarily show proliferative changes on light microscopy including lupus nephritis, IgA nephropathy, pauci-immune glomerulonephritis, anti-GBM disease, membranoproliferative glomerulonephritis, infection associated glomerulonephritis, fibrillary glomerulonephritis, C3 glomerulopathy and other immune complex mediated glomerulonephritides were evaluated more intensively. Established scores/classes/grading of disease entities were used to subclassify lupus nephritis and IgA nephritis as given by the pathologist report. In Part III we collected data from the electronic record system at the Medical University of Graz including renal biopsy diagnosis pattern of injury, date of biopsy, age at biopsy, sex, weight, height, BMI, Diabetes mellitus, active hepatitis B, hepatitis C, and/or Human Immunodeficiency Virus (HIV) infection. Lab values such as creatinine in mg/dl, albumin in g/dl, C-reactive protein in mg/l, parathormone level in pg/ml, the complete blood count (hemoglobin in g/dL, leukocytes in 10^9/l and platelets 10^9/l) and quantitative measurements of urine analysis including albuminuria in mg/g creatinine or mg/day, proteinuria in urine mg/g creatinine or mg/24h and hematuria in erythrocytes/µl were assessed. Creatinine maximum was evaluated with a ~ 2 week cut off before and after biopsy. In addition, we gathered data from the electronic health record system MEDOCS to assess for creatine levels after 1 month, 1 year, 2 years, and 5 years after biopsy. Further serologic studies included complement pathway activation by measuring for serum C3, C4

and evidence of autoimmune mediated disease by assessing levels of ANAs, ANCAs (U/ml), anti-dns antibody (U/ml), anti-GBM antibodies (U/ml) and evidence of elevated IgA levels. A cut off time frame for laboratory parameters of 3 months before and after the biopsy was used. Furthermore, the need for acute renal replacement therapy and plasmapheresis was evaluated. In addition, we evaluated if the patient required long term renal replacement therapy and recorded the date of death, if available. For the last two objectives data was evaluated until December 2019. Clinical characteristics were evaluated to further classify disease types.

In Part III (proliferative glomerulonephritis) seven different topics were addressed. Firstly, various clinical parameters of all diseases are compared with each other. Secondly, renal diseases with more than 50 confirmed cases were evaluated. Thirdly, MPO, PR3 and ANCA negative glomerulonephritis were compared. Fourthly, IgA nephropathy with IgA vasculitis were compared. In addition, we took a closer look on the MEST score and its impact on creatinine level and prognosis. Next systemic lupus erythematosus lupus like nephritis and mixed connective tissue diseases were compared with each other. All other glomerulopathies (rare glomerulopathies) were argued independently. Furthermore, patients with crescentic glomerulonephritis were evaluated.
At last we evaluated complication associated with renal biopsies, focusing on post puncture hematoma, bleeding requiring radiological intervention or surgery and bleeding leading to death.

Part I	Part II	Part III
Excel chart connecting each patient to a histological diagnosis and excluding patients with renal organ transplants.	Distribution of sex, age and biopsy proven renal diseases. Comparison of European registries	Data collection of glomerulopathies which primarily present with nephritic features.

	Histopathology	Evaluated diseases in Part III
Non proliferative	Minimal change disease	
	Membranous pattern of injury[a]	
	Focal segmental glomerulosclerosis	
Proliferative	**Mesangioproliferative glomerulonephritis**	**IgAN, lupus nephritis, C3GN**
	Membranoproliferative glomerulonephritis	**IC mediated MPGN[b] and complement mediated MPGN**
	Proliferative glomerulonephritis	**IgA nephropathy and lupus nephritis**
	Acute diffuse proliferative GN	**Infection associated glomerulonephritis**
	Crescentic glomerulonephritis	**ANCA assoc. GN, IC-mediated glomerulonephritis**

a) In addition to membranous nephropathy lupus nephritis and fibrillary glomerulonephritis can have a membranous pattern of injury
b) Immune complex mediated MPGN include auto immune disease associated glomerulonephritis, infection associated glomerulonephritis and fibrillary glomerulonephritis

Figure 8 *Timeline and evaluated diseases in Part III*

The statistical analysis was conducted with Microsoft Excel 365 and IBM SPSS Statistics Version 26. The null hypothesis was rejected when the p-value was lower than or equal 0,05. A Shapiro-Wilk-Test determined if the data was normally distributed. If any of the analyzed dataset showed non-normally distribution a nonparametric test was applied, either Mann-Whitney-U-Test for 2 independent variables or Kruskal-Wallis-Test for more than 2 independent variables. If the Kruskal-Wallis-Test showed a significance value of p lower than or equal 0,05, a post hoc analysis was run, and p-values were adjusted using the Bonferroni correction for multiple tests. If the assumption of normality was maintained, an independent t-test was applied. The Student's t-test in data with normal distributions and equal variances. The Welch's t-test in data with normal distributions and unequal variances. Homogeneity of variances was determined by a Levene's test for equality of variances.

6. Results

6.1 Part I - Renal biopsies

6.1.1 Total renal biopsies

Overall, 973 renal biopsies were performed between the 1st January of 2007 and the 31st December of 2017 *(see table 2)*. The frequency of renal biopsies increased almost every year until reaching its peak in 2014 with 116 biopsies. Then it levelled of around 100 biopsies per year. The first four years accounted for just 22.5 percent half of the biopsies *(44,4 %)* performed between 2014 and 2017.

Table 2 *Total biopsies in numbers and percentage per year*

	Total biopsies in numbers	**Total biopsies in *%***
2007	36	*3,7*
2008	41	*4,2*
2009	65	*6,7*
2010	77	*7,9*
2011	106	*10,9*
2012	103	*10,6*
2013	113	*11,6*
2014	116	*11,9*
2015	102	*10,5*
2016	114	*11,7*
2017	100	*10,3*
Total	973	*100*

In total 554 native kidney tissues were examined compared to 419 allograft organs *(see table 3).* The most native biopsies conducted were in 2013 and 2014 with 70 and 71, respectively. Only in 2017 more allografts biopsies *(n=53)* were performed than native biopsies *(n=47)*.

Table 3 *Total native and allograft biopsies in numbers per year*

	Total biopsies	*%*	Native biopsies	*%*	Allografts	*%*
2007	36	*3,7*	25	*2,6*	11	*1,1*
2008	41	*4,2*	30	*3,0*	11	*1,1*
2009	65	*6,7*	40	*4,1*	25	*2,5*
2010	78	*8,0*	47	*4,9*	29	*3,0*
2011	106	*10,9*	55	*5,6*	51	*5,2*
2012	103	*10,6*	53	*5,4*	50	*5,1*
2013	113	*11,6*	70	*7,2*	43	*4,4*
2014	116	*11,9*	71	*7,3*	45	*4,6*
2015	102	*10,5*	51	*5,2*	51	*5,2*
2016	114	*11,7*	65	*6,7*	49	*5,0*
2017	100	*10,3*	47	*4,8*	53	*5,4*
Total	973	*100*	554	*57*	419	*43*

6.2 Part II - Renal diseases

6.2.1 Native renal biopsies of the Medical University of Graz

Most biopsies (excluding repeated biopsies) were performed in male patients (*n=290*) compared to female patients *(n=227) (see table 4 and figure 9)*. Of the total native biopsies *(n=517)* (excluding repeated biopsies), in one patient it was impossible to ascertain the sex of the patient, resulting in a total of 516 patients.

Table 4 *Age composition of patients who underwent renal biopsies per year (excluding repeat biopsies)*

	Female		Male		Total	
Age	n	*%*	n	*%*	n	*%*
18-30	50	*22,1*	46	*15,9*	96	*18,6*
30-40	34	*15,0*	35	*12,1*	69	*13,4*
40-50	45	*19,9*	43	*14,8*	88	*17,0*
50-60	33	*14,6*	69	*23,8*	102	*19,8*
60-70	42	*18,6*	62	*21,4*	104	*20,2*
70-80	17	*7,5*	33	*11,4*	50	*9,7*
80-90	5	*2,2*	2	*0,7*	7	*1,4*
Total	226	*100*	290	*100*	516	*100*

Note: *One person's sex could not be ascertained. (n= 516), n = number of cases*

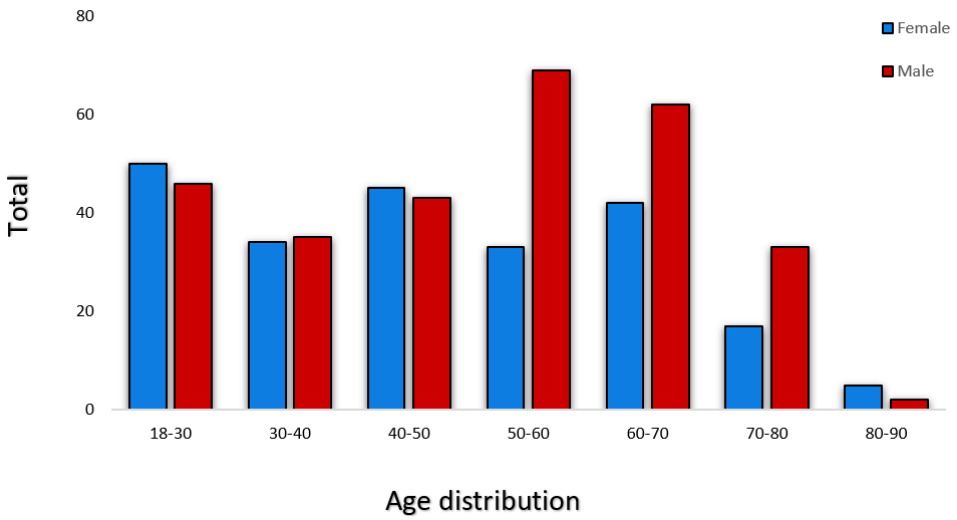

Figure 9 *Bar graph depicting age composition and sex of native renal biopsies (excluding repeated biopsies) female = blue, male = red*

Of the total (excluding repeated biopsies) of 517 native biopsies, four people were unable to be ascertained in the hospital information system. They were therefore excluded from the cohort. A further 7 patients' specimens were not representative, making a total of 506 biopsies being further evaluated *(see figure 10).* The diseases were divided into two groups those which normally show proliferative (group II) changes on light microscopy and those which do not (group I). Note that lupus nephritis or fibrillary glomerulonephritis may show a non-proliferative pattern. For the sake of completion, they were not excluded from group II. One patient was assigned one diagnosis. The number of patients with multiple pathologies is described under each table.

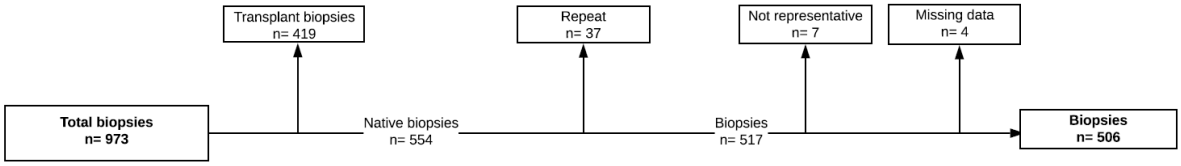

Figure 10 *Overview of the cohort formation of native renal biopsies*

Table 5 *Non proliferative glomerulopathies, vascular disease, interstitial disease and others*

	n	%
Vascular disease	73	*14,4*
Membranous nephropathy	54	*10,7*
Diffuse podocytopathies	56	*11,0*
Minimal change disease	31	*6,1*
Focal segmental glomerulosclerosis	22	*4,3*
IgM nephropathy	3	*0,6*
Tubulointerstitial disease	36	*7,1*
Tubulointerstitial nephritis without other pathology	12	*2,4*
Acute kidney injury without other pathology	19	*3,7*
Cast nephropathy	5	*1,0*
Amyloidosis	14	*2,7*
Amyloidosis associated to plasma cell dyscrasia	10	*1,9*
Secondary Amyloidosis	3	*0,6*
Amyloidosis NOS	1	*0,2*
Normal glomeruli	8	*1,6*
Heriditary glomerulopathy	6	*1,2*
Neoplasia	2	*0,4*
Others	19	*3,7*
Total	268	*53*

n = number of cases (% were calculated from n=506)

In group I *(see table 5)* vascular diseases *(n=73)* containing diabetic nephropathy, thrombotic microangiopathies, malignant and benign nephrosclerosis as well as adaptive focal segmental glomerulosclerosis tops the list. Patients with vascular disease only showed vascular changes without an additional pathology. Vascular disease is followed by membranous nephropathy *(n=54)* and diffuse podocytopathies *(n=56)* containing minimal change disease *(n=31)* focal segmental glomerulosclerosis *(n=22)* and IgM nephropathy

(n=3). In two patients diagnosed with minimal change disease no electron microscopy result was attainable. Both presented with nephrotic syndrome and showed 'minimal changes' on light microscopy. Tubulointerstitial nephropathy (TIN) accounts for 36 patients. Subdivided into cast nephropathy *(n=5),* tubulointerstitial nephritis without any other pathology *(n=12)* and acute kidney injury without any other pathology *(n=19).* Two patients with IgA nephropathy had concurrent diffuse effacement of the foot processes *(56 plus 2),* making a total of 58 patients with podocytopathies *(if more than one diagnosis were to be counted)*. One patient had IgA nephropathy membranous nephropathy *(54 plus 1)* and thin basement membrane disease *(6 plus 1).* One patient with fibrillary glomerulonephritis had simultaneous occurring membranous nephropathy *(54 plus 2),* making a total of 56 patients with membranous nephropathy *(if more than one diagnosis were to be counted)*. Due to the high prevalence of vascular disease there is significant overlap with other diseases. In total 58 biopsies additional displayed concomitant vascular alterations. Tubulointerstitial nephritis and acute kidney injury, was seen in 17 patients and 84 patients, respectively. Amyloidosis accounts for 14 cases. One patient with membranous nephropathy showed lambda light chain restricted amyloidosis as well *(14 plus 1)*. One patient with amyloidosis could not be classified as either AL or AA amyloidosis given here as "Amyloidosis NOS" = not other specified. "Others" include 10 patients were no definitive diagnosis could be made. In total 268 patients are in this group *(53%)* compared to 238 in group II *(47%)(see table 6).*

Table 6 *Total proliferative glomerulonephritis*

	n	*%*
IgA (co-) dominant staining	75	*14,8*
IgA nephropathy	*62*	*12,3*
IgA vasculitis (HSP)	*13*	*2,5*
Lupus nephritis pattern of injury	73	*14,4*
Systemic lupus erythematosus	61	*12,1*
Mixed connective tissue disease	*6*	*1,0*
Lupus-like nephritis	*6*	*1,3*
Lupus classification	73	
Class I	*2*	
Class II	*4*	
Class III	*16*	
Class IV	*16*	
Class V	*11*	
Class III+V	*13*	
Class IV + V	*9*	
Class VI	*0*	
Not classified	*2*	
ANCA associated glomerulonephritis	67	*13,2*
PR3-ANCA associated glomerulonephritis	*32*	*6,3*
MPO-ANCA associated glomerulonephritis	*30*	*5,9*
ANCA negative glomerulonephritis	*5*	*1*
Immune complex mediated MPGN	8	*1,6*
Infection associated MPGN	*4*	*0,8*
Autoimmune disease associated MPGN	*1*	*0,2*
Other	*3*	*0,6*
Fibrillary glomerulonephritis	5	*1,0*
Goodpasture's disease	4	*0,8*
with lung hemorrhages	*3*	*0,6*
without lung hemorrhages (Goodpasture's syndrome)	*1*	*0,2*
C3 glomerulonephritis	3	*0,6*
Infection associated glomerulonephritis	3	*0,6*
Total	238	*47*

percentage were calculated from 506 biopsies, n = number of cases

In group II *(see table 6)* 75 patients displayed IgA (co)-dominant staining on immunofluorescence. The vast majority had no evidence of systemic involvement *(n=62).* Two of the 62 patients had underlying liver cirrhosis. Thirteen patients showed evidence of systemic vasculitis and therefore are classified under IgA vasculitis (Henoch-Schonlein purpura). Two of the patients with skin involvement had endocapillary proliferation and

intracapillary neutrophils. Both patients had ongoing infection. One or both cases might be cases of 'Staphylococcal associated Henoch-Schonlein-purpura'. IgA 'deposition' glomerulonephritis is followed by a lupus nephritis pattern of injury *(n=73).* Six patients with lupus nephritis carry a diagnosis of mixed connective tissue disease. One of these patients had a probable diagnosis of mixed connective tissue disease. Six patients did not meet the "2019 European League Against Rheumatism/American College of Rheumatology Criteria for Systemic Lupus Erythematosus", and therefore were categorized under "lupus-like" nephritis. Four of the patients never had an elevated ANA titer and two patients had positive ANA titer but did not meet the threshold of 10 points to be classified as systemic lupus erythematosus. The most prevalent class in all patients with mixed connective tissue disease, lupus nephritis and lupus like nephritis is class V *(n=33),* in most cases combined with class III *(n=13)* and class IV *(n=9).* The most common single occurring classes are III and IV with 16 cases each. Lupus nephritis class I and II only accounted for six cases.

Sixty-seven patients displayed a lack of immune staining on immunofluorescence. Of these 67 patients with pauci-immune glomerulonephritis, 32 had anti–neutrophil cytoplasmic antibodies (ANCAs) targeting proteinase 3 (PR3), 30 had ANCAs targeting myeloperoxidase (MPO) *(n=23)* and five were ANCA negative *(n=5)*. One patient with pauci immune glomerulonephritis had concomitant IgA nephropathy *(62 plus 1).*

Eight patients had immune complex mediated membranoproliferative glomerulonephritis. Note that two patients with C3 glomerulopathy and one patient with fibrillary glomerulonephritis, also displayed a membranoproliferative pattern of injury. Fibrillary glomerulonephritis *(n=5),* Goodpasture's disease *(n=4),* C3 glomerulonephritis *(n=3)* and infection associated glomerulonephritis *(n=3)* are rare in our cohort each with less than ten confirmed cases.

Table 7 *Mean and median age in proliferative glomerulonephritis*

	Total				Female				Male			
	n	Age (Mean)	*SD*	Age (Median)	**n**	Age (Mean)	*SD*	Age (Median)	**n**	Age (Mean)	*SD*	Age (Median)
IgA (co) dominant staining	**75**	47	*16*	49	**24**	47	*17*	49	**51**	48	*15*	47
IgA nephropathy	**62**	46	*15*	44	**19**	47	*16*	42	**43**	46	*15*	44
IgA-vasculitis (HSP)	**13**	54	*18*	57	**5**	48	*25*	52	**8**	57	*13*	57
Lupus nephritis pattern of injury	**73**	36	*13*	36	**58**	36	*13*	36	**15**	37	*13*	36
SLE nephritis	**61**	36	*13*	37	**49**	36	*13*	38	**12**	37	*13*	35
Lupus like nephritis	**6**	27	*14*	24	**4**	23	*3*	23	**2**	34	*13*	34
Mixed connective tissue disease	**6**	43	*8*	45	**5**	42	*16*	44	**1**	48		48
ANCA associated GN	**67**	58	*15*	60	**36**	60	*15*	60	**31**	56	*13*	58
MPO-ANCA associated GN	**32**	63	*15*	64	**17**	68	*10*	68	**13**	57	*19*	64
PR3-ANCA associated GN	**30**	54	*14*	54	**17**	53	*15*	55	**15**	55	*14*	53
ANCA negative GN	**5**	51	*11*	49	**2**	45	*6*	45	**3**	56	*12*	54
Goodpasture's disease	**4**	39	*25*	32	**2**	30	*16*	30	**2**	48	*36*	48
Immune-complex mediated MPGN	**8**	63	*8*	61	**1**	61		61	**7**	63	*8*	61
Fibrillary glomerulonephritis	**5**	64	*8*	60	**2**	58	*4*	58	**3**	69	*8*	73
C3-dominant glomerulonephritis	**3**	34	*27*	19	**0**				**3**	34	*27*	19
Infection associated GN	**3**	54	*21*	53	**1**	34		34	**2**	65	*16*	65
Total	**238**				**124**				**114**			

SD = standard deviation, n= number of cases; Age was given as mean and standard deviation in years.

Table 7 illustrates the age and gender distribution of proliferative glomerulonephritis. There is a male dominance in IgA nephropathy and IgA vasculitis with a male to female ratio *(2,3:1)* and *(2,2:1)* respectively. In systemic lupus erythematosus, mixed connective tissue disease and lupus like nephritis, there is female dominance with a male to female ratio *(1:4), (1:5)* and *(1:2).* In patients with pauci immune glomerulonephritis there is a slightly larger number of female individuals compared to male patients with a male to female sex ratio of *(1:1,2).* This ratio is similar in MPO and PR3 ANCA associated glomerulonephritis. Three men and two women had no elevated ANCAs and had a lack of immune complex staining. C3 glomerulonephritis and immune complex mediated membranoproliferative glomerulonephritis (MPGN) is more frequent in men than in women with no female patient with C3 glomerulonephritis and just one with immune complex mediated membranoproliferative glomerulonephritis. In total more women *(n=124)* than men *(n=114)* with proliferative glomerulonephritis had undergone a renal biopsy.

The mean age of individuals with ANCA associated glomerulonephritis is 60 for females and 56 for males. The average age of patients suffering from systemic lupus erythematosus is 36 in women and 37 in men. IgA nephropathy has an average age of 47 and 48 for men and women, respectively. Women with MPO ANCA associated glomerulonephritis are on average 15 years older than women with PR3 ANCA associated glomerulonephritis. Women with elevated MPO ANCAs are on average 11 and 13 years older than men with MPO ANCA and PR3 ANCA associated glomerulonephritis, respectively.

A Shapiro-Wilk test and visual interpretation was performed to test the age distribution for normality: Valid cases *(n = 238*), Mean age = 48 years, *(95%-CI: 45 – 50 years)*. The age distribution is not normally distributed *(p<0,01; Shapiro - Wilk - Test)*. A nonparametric test for more than 2 independent samples was run to determine a statistically significant difference in age between 13 different disease groups. Age distribution between disease groups was dissimilar, which was assessed visually by comparing boxplots. The mean ranks were statistically significantly different between assessed groups $[\chi^{2(12)} = 79{,}52,\ p < 0{,}001;$ *Kruskal-Wallis Test]*.

In addition, a Kruskal Wallis test was run to compare age in ANCA associated glomerulonephritis, 'IgA nephropathy and IgA vasculitis' and lupus nephritis pattern of injury, which showed a statistically significant age distribution between all groups *(p< 0,001)*. A post hoc pairwise comparison displayed a statistically significant difference: ANCA associated glomerulonephritis vs. lupus nephritis pattern of injury *(p<0,001)* lupus

nephritis pattern of injury vs. 'IgA nephropathy and IgA vasculitis' *(p<0,001)*, 'IgA nephropathy and IgA vasculitis' vs. ANCA associated glomerulonephritis *(p=0,001).*

Table 8 *Mean age distribution in non-proliferative glomerulopathies, vascular disease, interstitial disease and others*

	Female			**Male**		
	n	Age	*SD*	**n**	Age	*SD*
Vascular disease	**16**	48	*15*	**57**	52	*14*
Membranous nephropathy	**18**	55	*16*	**36**	53	*14*
Minimal change disease	**12**	51	*15*	**19**	53	*20*
FSGS	**10**	43	*14*	**12**	48	*15*
IgM	**2**	35	*16*	**1**	43	
Amyloidosis	**6**	53	*18*	**8**	63	*6*
TIN	**16**	49	*22*	**20**	42	*20*
Normal	**5**	39	*20*	**3**	31	*6*
Hereditary nephropathy	**3**	36	*19*	**3**	47	*5*
Neoplasia	**0**			**2**	43	*13*
Other	**9**	43	*16*	**10**	50	*17*
Total	**97**			**171**		

SD = standard deviation, n = number of cases Age is given as median

The gender distribution of non-proliferative glomerulopathies displayed male-biased sex ratio in membranous nephropathy *(1:2)* minimal change disease *(1:1,6)* and focal segmental glomerulosclerosis (FSGS) *(1:1,2)*, vascular disease and tubulointerstitial nephropathy displayed a male-biased sex ratio of *(1:5,1)* and *(1:1,25).* Less common pathologies in this group are IgM nephropathy *(f:m, 2:1)*, amyloidosis *(f:m, 1:1,3)* hereditary nephropathy *(f:m, 1:1)* and neoplastic changes with no female and two male patients. Five women and three men had no pathologic alterations. In total 97 females and 171 males are in group I, making a female to male ratio of *(1:1,8).*

The average age of female individuals with vascular disease is on average 48 years old, in contrast to male patients with 52 years. Women and men are comparatively the same age who suffer from membranous nephropathy and minimal change disease (*55 to 53 and 51 to 53)*. Men with focal segmental glomerulosclerosis are on average five years older than women. One more notable difference is the fact, that men with amyloidosis are on average 10 years older than female individuals suffering from the same disease.

6.2.2 European renal registries in comparison

Our results *(see figure 11)* corresponded with results from other European countries. For instance, IgA nephropathy is the most common primary glomerulopathy of our cohort. This is true for every other evaluated European country in which IgAN was reported. One exception is Serbia where IgA nephropathy *(7,7%)* as well as mesangioproliferative glomerulonephritis *(15,5%)* was reported. In countries where IgA nephropathy was not reported mesangioproliferative glomerulonephritis is the most common primary glomerulonephritis. These include Denmark *(26,1%),* Poland *(41,7%)* and Romania *(19,1%).* The most common primary glomerulonephritis in Europe can be seen on a Map of Europe in figure 13. There seems to be a higher prevalence of lupus nephritis in our cohort *(12,1%)* than most European countries except Serbia *(17,7%).* The prevalence of lupus nephritis is shown as heat map in figure 15. Clearly illustrating a higher prevalence of lupus nephritis in Serbia and Austria compared to other European countries. The highest prevalence of proliferative glomerulonephritis in our cohort is ANCA associated glomerulonephritis *(13,2%)* followed by IgA nephropathy *(12,3%)* and lupus nephritis in systemic lupus erythematosus *(12,1%).* ANCA associated glomerulonephritis had the highest incidence in our cohort of any other European country, in which ANCA associated glomerulonephritis was evaluated as a separate entity. Austria is followed by Norway with 9,9% *(8,6% MPO and PR3 +1,3% ANCA negative disease)* and by the Netherlands *(9,12%).* Anti-GBM disease or Goodpasture's disease is extremely rare in each country where it was evaluated, accounting for less than 1% in each country except the Netherlands *(1,19%).* The highest prevalence of non-proliferative glomerulopathy in our cohort is membranous nephropathy with 10,7%. Membranous nephropathy is the most common non-proliferative glomerulopathy in most evaluated European countries. Exceptions are Spain, Romania, Estonia, Lithuania and Denmark, in all of which, but Denmark, FSGS is the most common non proliferative glomerulopathy. In Denmark minimal change disease has the highest prevalence of all non-proliferative glomerulopathies with 17,5% *(see figure 14).*

Figure 12 illustrates if the evaluated registry was from a single, regional or national center. Information about population, total evaluated biopsies and commentary to each country is given. Most registries were either national or regional registries, with single center registries only in in Estonia, France, Germany and Serbia. Poland's and Northern

Ireland’s registry is a single center registry, but they are serving a central region in Poland´s case and all six counties in Northern Ireland`s instance. Evaluated national registries of Europe are in the Czech Republic, Denmark, Italy, Lithuania, Northern Ireland, Norway and Scotland. In several centers just adult kidneys were evaluated, including Austria, France, Netherlands, Northern Ireland, Poland, Romania, and Scotland. Adult and children renal biopsies were evaluated in the Czech Republic, Denmark, Estonia, Finland and Germany. The evaluated time frame ranged from one year in Norway to 24 years in Germany. Evaluated biopsies range from 578 in Estonia to 23262 in Italy. Of course, strongly varying between participating centers and time frame. As well as evaluated cohorts.

			Nephrotic			Nephrotic and Nephritic		Asymptomatic hematuria		Nephritic									
		Biopsies	MCD	MN	FSGS	MPGN	LN	MsPGN	IgAN	HSP	EPGN(PSGN)	cGN	VN	ANCA	Anti-GBM	Vascular disease	TIN	DN	AM
Austria	**2007- 2017**	**506**	**6,1%**	**10,7%**	**4,3%**	**1,6%**	**12,1%**		**12,3%**	**2,5%**	**0,6%**			**13,2 %**	**0,8%**	**14,4%**	**7,1%**		**2,7%**
Czech-Republic[5]	1994- 2011	10472	639	743	723	334	745	345	2150	179	87	126	595	/	/	390	348	425	321
			6,1%	7,1%	6,9%	3,2%	7,1%	3,3%	20,5%	1,7%	0,8%	1,2%	5,7%	/	/	3,7%	3,3%	4,1%	3,1%
Denmark[7]	1985- 1997	2380	417	276	325	122	/	622	/	/	98	286	/	/	/	84	/	/	/
			17,5%	11,6%	13,6%	5,1%	/	26,1%	/	/	4,1%	12%	/	/	/	3,5%	/	/	/
Estonia[13]	2001- 2010	547	35	11	40	19	41	14	88	3	28	8	18	(2+1)	(2)	42	45	8	26
			6,4%	2,0%	7,3%	3,50%	7,50%	2,60%	16,10%	0,50%	5,10%	1,5%	3,2%	/	/	7,30%	8,2%	1,50%	4,80%
Finland[17]	1980- 2000	3310	102	240	81	78	/	239	718	/	21/57	117	/	/	/	60	487	/	130
			3%	7,3%	2,5%	2,40%	/	7,20%	21,70%	/	0,6% / 1,7%	3,50%	/	/	/	1,80%	14,70%	/	3,90%
France[15]	1976- 1990	480	*	85	*	32	/	28	161,0	/	33	25,0	/	/	/	/	/	/	/
			*	17,7%	*	6,6%	/	5,8%	33%	/	6,8%	5,2%	/	/	/	/	/	/	/
Germany[11]	1990- 2013	1208	74	105	74	/	58	/	245	/	/	132	/	/	/	124	43	/	/
			6%	9%	6%	/	5%	/	20%	/	/	11%	/	/	/	10%	4%	/	/
Italy[6]	1987- 1995	20074	957	2456	1370	827	1322	985	4318	449	370	536	677	/	36	684	767	501	548
			4,8%	12,2%	6,8%	4,1%	6,6%	4,9%	21,5%	2,2%	1,8%	2,7%	3,4%	/	0,20%	3,4%	3,8%	2,5%	2,7%
Lithuania[8]	1994- 2012	3640	178	171	285	270	79	89	737	/	87	248	/	/	/	174	204	41	221
			4,9%	4,7%	7,8%	7,40%	2,20%	2,50%	20,30%	/	2,4	6,8	/	/	/	4,8%	5,6%	1,1%	6,1%
Netherlands[18]	1978- 2003	1348	63	131	55	29	55	14	170	21	29	/	/	123	16	53	75	/	33
			4,67%	9,72%	4,08%	2,15%	4,08%	1,04%	12,61%	1,56%	2,2%	/	/	9,12%	1,19%	3,93%	5,56%	/	2,45%
Northern Ireland (UK)[19]	1976- 2005	1844	89	267	52	96	/	/	352	/	/	/	/	/	/	65	110	/	/
			4,8%	14,5%	2,8%	5,2%	/	/	19,1%	/	/	/	/	/	/	3,5%	6%	/	/
Norway[9]	2018	603	23	34	24	16	26	5	110	5	5	/	/	69	4	51	50	44	14
			3,8%	5,6%	4%	2,7%	4,3%	0,8%	18,2%	0,8%	0,8%	/	/	9,9%	0,7%	8,5%	8,3%	7,3%	2,3%
Poland[12]	1990- 2010	746	45	68	58	117	48	311	/	6	2	6	30	/	1	/	/	13	34
			6,0%	9,1%	7,8%	15,7%	6,4%	41,70%	/	0,8%	0,30	0,8%	4,0%	/	0,13%	/	/	1,74%	4,6%
Romania[16]	1995- 2004	606	34	45	46	118	47	116	/	/	/	32	33	/	/	14	9	/	/
			5,6%	7,4%	7,6%	19,50%	7,8%	19,10%	/	/	/	5,2%	5,4%	/	/	2,3%	1,5%	/	/
Scotland (UK)[4]	*2002- 2006*	*2480*																	
Serbia[14]	1987- 2006	1626	78	205	197	110	287	252	125	/	21	55	60	/	4	73	51	25	33
			4,8%	12,6%	12,1%	6,8%	17,7%	15,5%	7,7%	/	1,3%	3,4%	3,7%	/	0,02%	4,5%	3,1%	1,5%	2,0%
Spain[3]	1994- 1999	7016	547	681	702	302	617	/	1066	/	/	/	512	/	/	379	/	/	281
			7,8%	9,7%	10%	4,3%	8,8%	/	15,2%	/	/	/	7,30%	/	/	5,40%	/	/	4%

Figure 11 *European renal registries; Abbreviations: MCD = Minimal change disease, MN = Membranous nephropathy, FSGS = Focal segmental glomerulosclerosis, MPGN = Membranoproliferative glomerulonephritis, LN = Lupus nephritis, MsPGN = Mesangioproliferative glomerulonephritis, IgAN = IgA nephropathy, HSP = Henoch-Schonlein purpura, EPGN = Endocapillary proliferative glomerulonephritis, PSGN = Post streptococcal glomerulonephritis or Post infectious glomerulonephritis, cGN = crescentic glomerulonephritis or rapidly progressive glomerulonephritis or extra-capillary glomerulonephritis VN = Vasculitis, ANCA = ANCA associated glomerulonephritis, Anti-GBM = Goodpasture's disease, TIN = Tubulointerstitial nephritis, DN = Diabetic nephropathy, AM = Amyloidosis. Data does NOT include all biopsy results but just selected disease entities. Vascular nephropathy and Tubulointerstitial disease do NOT always contain all diseases. Which diseases were used can be seen in figure 12. Percentage is calculated from total enrolled biopsies*

	Years	Center	Population	Evaluated biopsies	Enrolled biopsies	Disease breakdown and commentary
Austria	**11**	**National**	**Adults**	**973**	**506**	**MPGN = immune complex mediated membranoproliferative glomerulonephritides , Vascular disease = Diabetic nephropathy, malignant and benign nephrosclerosis and TMA ANCA= includes ANCA negative pauci immune glomerulonephritis, LN = Lupus nephritis in systemic lupus erythematosus**
Czech-Republic[5]	18	National	Adults and children	10472	10472	TIN = Tubulointerstitial nephritis; Vascular disease= benign nephrosclerosis (*n=312*) and malignant nephrosclerosis (*n=78*).
Denmark[7]	11.7	National	Adults and children	2380 (*including 2,0 % re-biopsies and 3,4 % of patients twice)*	2380	Vascular disease = [Hypertensive nephropathy (*n=60*) and HUS/TTP (*n=24*) Hypertensive nephropathy= malignant nephrosclerosis (*n=11*) and benign nephrosclerosis (*n=49*)]
Estonia[13]	10	Single center	Adults and children	578	547	Vasculitides = [Systemic vasculitis (*n=9*) and Wegener granulomatosis (*n=9*)]; cGN = [ANCA pos. glomerulonephritis (*n= 2*); ANCA neg. glomerulonephritis (*n=1*), anti-glomerular basement membrane nephritis (*n=2*), non-classified crescentic glomerulonephritis (*n=3*)]; TIN = [Interstitial nephritis(*n=38*), acute tubular necrosis (*n=3*), cast nephropathy (*n=1*) and nephrocalcinosis (*n=1*) Vascular disease = [Changes in hypertension (*n=37*) and nephrosclerosis (*n=49*) and TMA (*n=1*)]
Finland[63]	21	Regional	Adults and children	3648	3310	Proliferative endocapillary glomerulonephritis = [Glomerulonephritis, endocapillary proliferative (*n=57*) and glomerulonephritis acute exsudative (*n=21*)]; Crescentic glomerulonephritis = Glomerulonephritis, extra-capillary
France[15]	15	Single center	Adults	942	480 (*Primary glomerulonephritis*)	Minimal change disease and Focal segmental glomerulosclerosis were given as Nephrosis *(n=55, 11,4%)* and there was an extra column for Focal segmental glomerulosclerosis (FSG) without nephrotic syndrome *(n=51, 10,6%);* EPGN = Post streptococcal glomerulonephritis
Germany[11]	24	Single center	Adults and children	2243	1208	cGN = Rapidly progressive glomerulonephritis; TIN = Acute Tubulointerstitial nephritis. Vascular disease = Nephrosclerosis
Italy[6]	9	National	-	23262	20074	Vascular disease = [Benign nephrosclerosis (*n=463*), thrombotic microangiopathy (*n =113*) malignant nephrosclerosis (*n=90*), cortical necrosis (*n=18*)]. Data used from the online IRRB (Italian Registry of Renal Biopsies) database; EPGN = Poststreptococcal glomerulonephritis
Lithuania[8]	18	National	-	5368	3640	In total 16,3 % vascular nephropathies. Vascular disease (selected diseases) = [HUS/TTP active (*n =2*), Arteriosclerosis NOS (*n=63*), TMA (*n = 83*), Nephrosclerosis (*n =26*)]. Tubulointerstitial disease = [Interstitial nephritis, diffuse (*n=97*), Interstitial nephritis, focal (*n=107*)]
Netherlands[18]	25	Regional	Adults	1348	1348	ANCA associated glomerulonephritis = [(PR3 ANCA *(n=55*) MPO ANCA (*n=63*) MPO and PR3 combined (*n=4*)]; IgA nephropathy = [Primary (*n=148*) and secondary (*n=22*)]; Vascular disease = Hypertension/arteriosclerosis (*n=53*)]
Northern Ireland (UK)[19]	30	National (Belfast hospital) *	Adults	1844	1844	TIN = Tubulointerstitial disease (not further specified); Vascular disease = Vascular disease (not further specified).
Norway[9]	1	National	-	603	603	DPGN = Endocapillary glomerulonephritis Vascular disease = [Benign nephrosclerosis (n=26) malignant nephrosclerosis (n=3) and TMA (n=4) TIN = [Acute tubular necrosis (n=10) and Tubulointerstitial nephritis (n=27) Granulomatosis TIN/ Sarcoidosis (n=2) TIN drug associated (n=7) TIN with uveitis (n=2) TIN autoimmune disease associated (n=1). Calcineurin inhibitor toxicity (n=3) FSGS= [Primary FSGS (n=10) and secondary FSGS (n=14)] Amyloidosis = [Amyloidosis not classified (n=2) and Amyloidosis AA (n=6) and Amyloidosis AL (n=6)
Poland[12]	20	Regional *(Single tertiary nephrology center)*	*Adults*	746	746	Disease breakdown: MsPGN = Mesangioproliferative glomerulonephritis including IgA nephropathy. Amyloidosis = Secondary Amyloidosis; EPGN = Post streptococcal glomerulonephritis
Romania[16]	10	Regional (2 centers in separate regions)	Adults	635	606	MsPGN = Mesangioproliferative glomerulonephritis including IgA nephropathy, TIN = Tubulointerstitial disease (not further specified); Vascular disease = Vascular disease (not further specified).
Scotland (UK)[4]	5	National	Adults	2480	2480	Results were only given in biopsies per million per year. Not all centers biopsy results were included. IgA nephropathy was the most frequent diagnosed primary glomerulonephritis
Serbia[14]	20	Single center	Adults	2362	1626	Vascular disease = [Nephrosclerosis (*n = 59*), HUS (*n = 7*), renal infarction (*n = 5*), eclampsia (*n = 4*); TIN = [Chronic tubulointerstitial nephritis (*n = 28*), acute tubulointerstitial nephritis (*n= 16*) multiple myeloma associated tubulointerstitial nephropathy (*n=7*)]; EPGN = Post streptococcal glomerulonephritis
Spain[3]	6	National	Adults and children	7016	7016	Vascular disease = Nephrosclerosis

Figure 12 *European renal registry commentary; Renal services in Northern Ireland are delivered by a Regional Nephrology Unit in Belfast City Hospital and five sub-regional units. All renal biopsy specimens are analysed at a central pathology laboratory in the Department of Pathology, Belfast City Hospital*(19)*. Abbreviations: HUS = hemolytic uremic syndrome, TTP = thrombotic thrombocytopenic purpura*

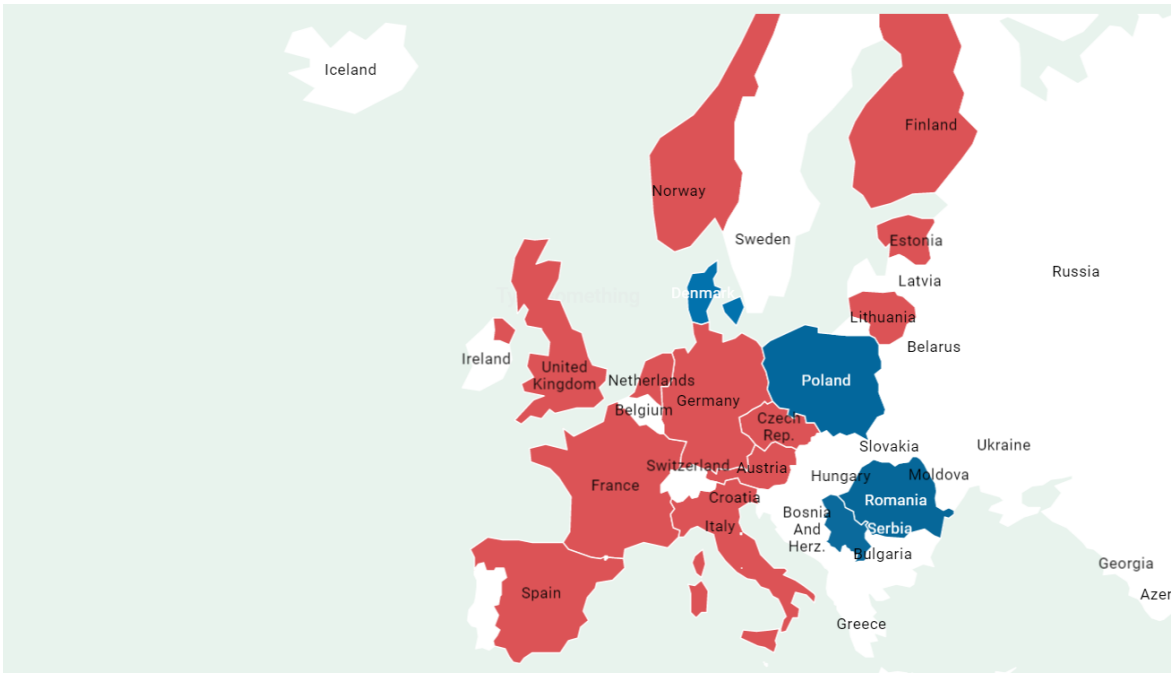

Figure 13 *Most common primary glomerulonephritis IgA nephropathy (red) mesangioproliferative glomerulonephritis (blue), illustrated with Infogram.com*

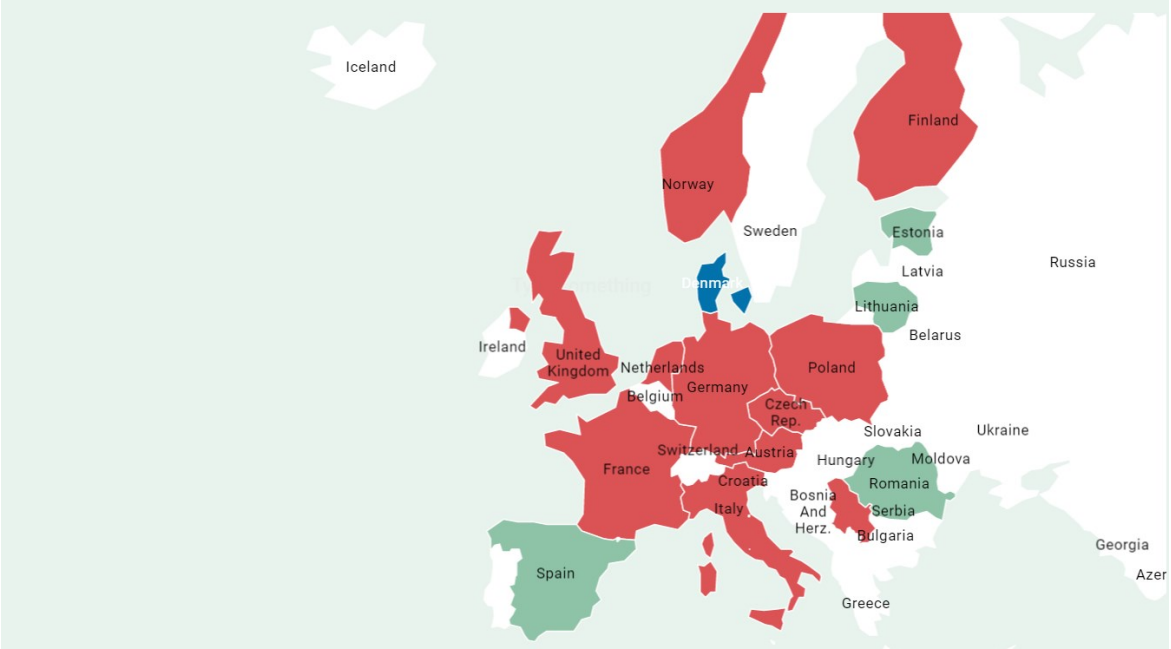

Figure 14 *Most common non proliferative glomerulopathy membranous nephropathy (red), minimal change disease(blue), focal segmental glomerulosclerosis (green), illustrated with Infogram.com*

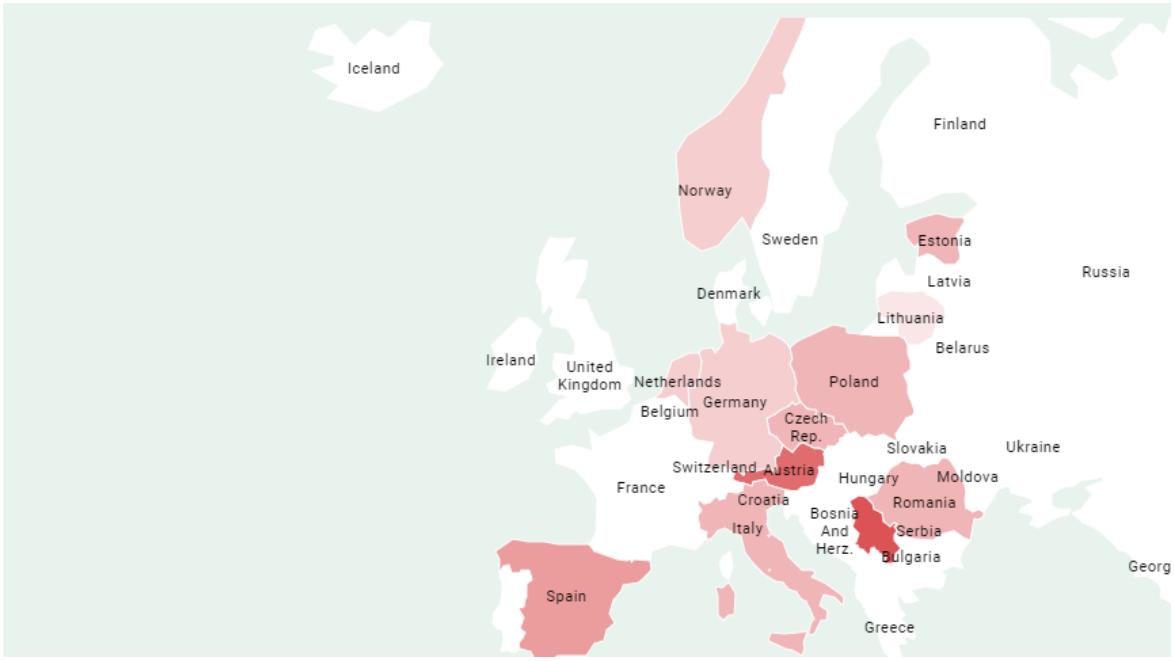

Figure 15 *Heat map depicting prevalence of lupus nephritis, data used from figure 11 illustrated with Infogram.com*

6.3 Part III - Proliferative glomerulonephritis

6.3.1 Overview proliferative glomerulonephritis

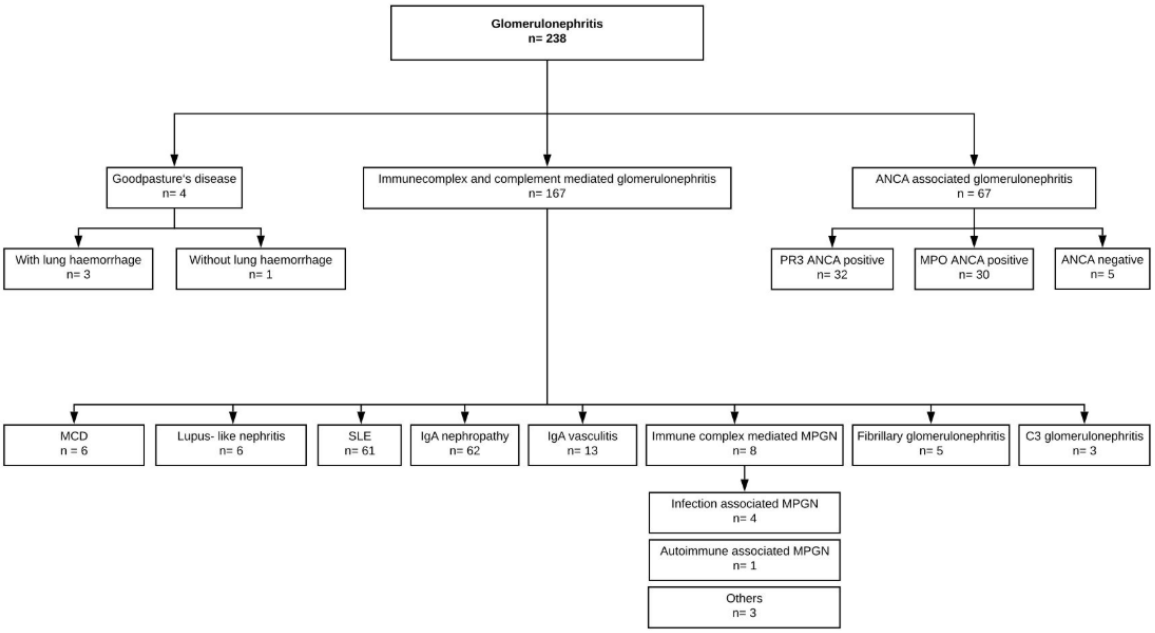

Figure 16 *Illustration of proliferative glomerulonephritis at the Medical University of Graz between 2007 and 2017*

Figure 16 illustrates that three proliferative diseases had more than 50 cases. These include IgA nephropathy *(n = 62),* lupus nephritis *(n = 61)* and ANCA associated glomerulonephritis *(n = 67)*.

Table 9 Mean of weight, height BMI, active antihypertensive drugs and comorbidities shown by cases of active hepatitis B and C and Diabetes mellitus *in proliferative glomerulonephritis*

	Female				**Male**				**Comorbidities in n**			
	kg	cm	BMI	AAD	kg	Height	BMI	AAD	Hep B	Hep C	DM	DM in %
IgA nephropathy and IgA vasculitis	64,4	162	24,9	1,7	89,4	180	27,4	1,9	1	0	8	*10,7*
IgA nephropathy	*62,5*	*163,1*	*23,7*	*1,8*	*89,4*	*180,5*	*27,4*	*1,8*	*1*	*0*	7	*11,3*
IgA-vasculitis (HSP)	*71,4*	*158*	*28,6*	*1,4*	*89,4*	*177,5*	*27,7*	*2,5*	*0*	*0*	1	*7,7*
Lupus nephritis pattern on biopsy	66	167,6	23,4	1,6	87,4	181,9	26,4	1,8	0	0	3	*4,1*
SLE nephritis	*67,3*	*168,04*	*23,72*	*1,43*	*85,21*	*181,33*	*25,82*	*1,75*	*0*	*0*	3	*4,9*
Lupus like nephritis	*58,5*	*166,5*	*21,03*	*1,5*	*92,5*	*186*	*26,95*	*2*	*0*	*0*	0	*0*
Mixed connective tissue disease	*60,3*	*164,8*	*22,3*	*3*	*104*	*180*	*32,1*	*2*	*0*	*0*	0	*0*
ANCA associated GN	73,8	164,9	27	1,8	78,9	176,9	25,2	1,7	0	0	13	*19,4*
MPO-ANCA associated vasculitis	*78,8*	*164,6*	*29*	*2,2*	*76,3*	*173,3*	*25,3*	*1,5*	*0*	*0*	8	*26,7*
PR3-ANCA associated vasculitis	*68,5*	*165,3*	*25,1*	*1,3*	*79*	*178,9*	*24,7*	*1,7*	*0*	*0*	3	*9,4*
Non-ANCA associated vasculitis	*75,6*	*165*	*27*	*2*	*89,8*	*183*	*26,9*	*2,3*	*0*	*0*	2	*40*
Goodpasture's disease	68,3	164	25,4	2,5	85	171,5	29,2	1	0	0	0	*0*
Immune-complex mediated MPGN	66	170	22,8	1	83	174,9	27,1	3,6	0	2	3	*37,5*
Fibrillary glomerulonephritis	86,5	165,5	31,9	3	87	176	28,3	1,3	0	0	1	*20*
C3-glomerulonephritis					75,3	172,7	24,9	1,7	0	0	0	*0*
Infection associated GN	50	164	18,6	1	91,5	179	28,6	2,5	0	0	2	*66,7*

kg= weight, cm =height, BMI = body mass index, AAD = antihypertensive agencies and number of cases with active hepatitis B active hepatitis C or Diabetes mellitus = DM, DM % calculated from all cases in the given disease type.

Table 10 *Mean creatinine(mg/dl) at different moments after biopsy in proliferative glomerulonephritis*

	At Biopsy	Max	1m	1y	2y	5y
IgA nephropathy and IgA vasculitis	2,13	2,53	2,12	2,16	2,13	2,54
IgA nephropathy	*2,21*	*2,62*	*2,27*	*2,4*	*2,21*	*2,64*
IgA-vasculitis (HSP)	*1,79*	*2,11*	*1,53*	*1,24*	*1,11*	*0,73*
Lupus nephritis pattern on biopsy	1,25	1,46	1,23	1,03	1,1	1,38
SLE nephritis	*1,09*	*1,21*	*1,12*	*0,96*	*1,06*	*1,31*
Lupus like nephritis	*2,6*	*3,46*	*2,57*	*1,51*	*1,38*	*1,21*
Mixed connective tissue disease	*1,74*	*1,97*	*1,29*	*1,51*	*1,71*	*2,44*
ANCA associated glomerulonephritis	3,29	3,98	2,61	2,42	2,16	1,88
MPO-ANCA associated vasculitis	*3,44*	*4,05*	*2,75*	*2,42*	*2,31*	*2,04*
PR3-ANCA associated vasculitis	*3,3*	*4,13*	*2,55*	*2,36*	*2,06*	*1,75*
Non-ANCA associated vasculitis	*2,37*	*2,68*	*2,2*	*2,93*	*2,21*	*2,08*
Goodpasture's disease	5,92	7,58	5,96	4,41	1,18	7,84
Immune-complex mediated MPGN	3,82	4,61	2,69	3,5	3,63	3,02
Fibrillary glomerulonephritis	4,82	5,08	3,46	5,06	8,19	
C3-dominant glomerulonephritis	1,25	1,3	1,22	1,22	1,16	1,67
Infection associated GN	2,65	4,31	1,29	1,16		

Table 9 illustrates height weight and BMI of patients with a proliferative glomerulonephritis and the average number of active antihypertensive drugs as well as clinical data on active hepatitis B and C infection and if the patient carried a diagnosis of diabetes mellitus. Female patients with fibrillary glomerulonephritis have the highest BMI (Body-mass-index) with 31,9 kg/m^2 followed by ANCA associated glomerulonephritis with 27kg/m^2. Only female patients with a lupus nephritis pattern of injury, IgA nephropathy, immune complex mediated MPGN and infection associated glomerulonephritis had an BMI less than 25 kg/m^2. Note, that the last two only had one case each. The average BMI of male patients was over 25 kg/m^2 in every proliferative glomerulonephritis. Interestingly, the average BMI of female patients with ANCA associated glomerulonephritis is higher than of male patients with the same disease, compared to IgA nephropathy in which male patients have a higher BMI than women. Active hepatitis B and C is extremely rare in our cohort with only 1 and 2 confirmed cases, respectively. Unsurprisingly, Diabetes mellitus is more common in

diseases which generally affect older individuals. Thirteen patients with ANCA associated glomerulonephritis had diabetes mellitus compared to 8 and 3 patients with IgA nephropathy and systemic lupus erythematosus.

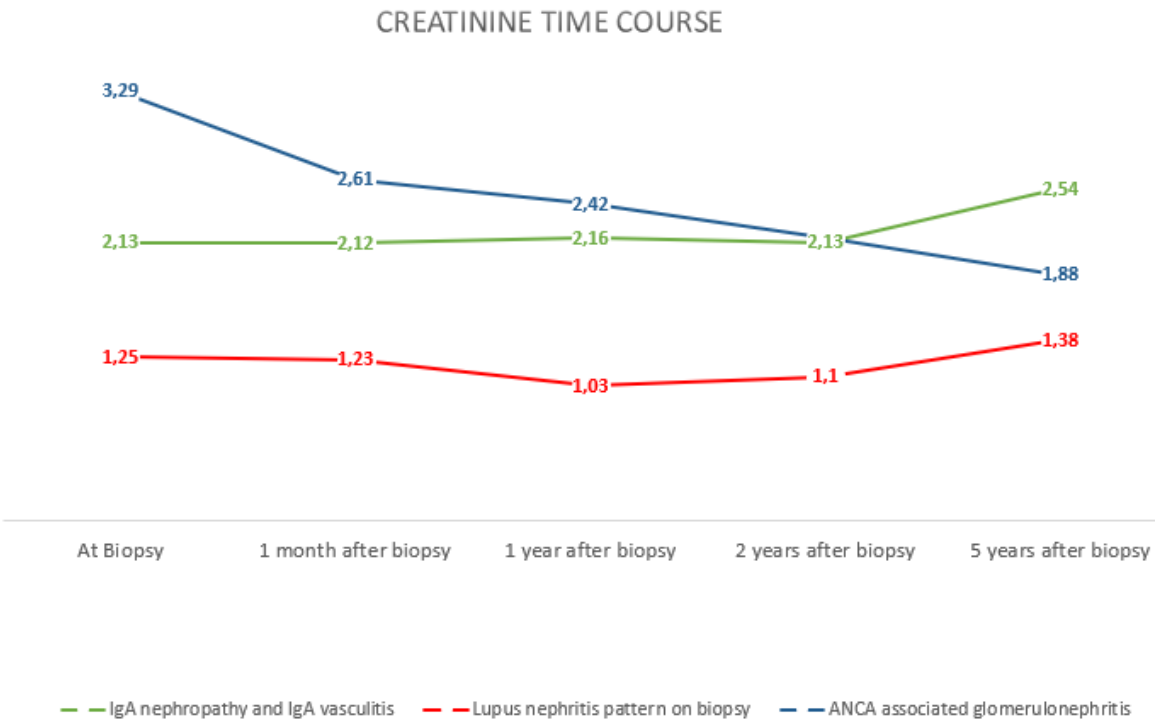

Figure 17 *Serum-Creatinine-values difference in 'IgA nephropathy and IgA vasculitis' (green), lupus nephritis pattern on biopsy (red) and ANCA associated glomerulonephritis (blue) at the time of biopsy and time course illustrating creatinine change over the next 5 years. Creatinine level given in mg/dl.*

Table 10 illustrates the creatinine values at various dates after biopsy in 'IgA nephropathy and IgA vasculitis', lupus nephritis pattern of injury and ANCA associated glomerulonephritis. The most notable difference is that ANCA associated glomerulonephritis has the highest initial creatinine value *(3,29mg/dl)*. After 2 years the average creatinine in IgA nephropathy *(2,13mg/dl)* is the same as in ANCA associated glomerulonephritis and after 5 years creatinine has surpassed the average creatinine level of ANCA associated glomerulonephritis by ~0,6mg/dl. Figure 17 illustrates creatinine change over 5 years of 'IgA nephropathy and IgA vasculitis', lupus nephritis pattern of injury and ANCA associated glomerulonephritis. At biopsy ANCA associated glomerulonephritis displays the highest creatinine value. Creatinine of ANCA associated glomerulonephritis shows a negative trend over 5 years. Average creatinine in 'IgA nephropathy and IgA vasculitis' and lupus nephritis pattern of injury is on average higher after 5 years than at biopsy.

Table 11 illustrates various lab values and quantitative urine measurements around the time patients underwent renal biopsy. Average PTH level is higher in infection associated glomerulonephritis *(PTH = 265),* Goodpasture's disease *(PTH = 177)*, ANCA associated glomerulonephritis *(PTH = 138)*, immune complex mediated glomerulonephritis *(PTH =135)* and fibrillary glomerulonephritis *(PTH = 116)* than in 'IgA nephropathy and IgA vasculitis' *(PTH = 100),* patients with a lupus nephritis pattern of injury *(PTH = 43)* and patients with C3 glomerulonephritis *(PTH = 40*). Platelet level seem to follow the same pattern with higher levels in Goodpasture's disease *(Platelets =325),* ANCA associated glomerulonephritis *(Platelets = 357)*, immune complex mediated glomerulonephritis *(Platelets = 269)* and fibrillary glomerulonephritis *(Platelets = 361)* than in 'IgA nephropathy and IgA vasculitis' *(Platelets = 244),* patients with a lupus nephritis pattern of injury *(Platelets = 227)* and patients with C3 glomerulonephritis *(Platelets = 253*). Infection associated glomerulonephritis does not follow this trend with an average platelet number of 210. Patients with a PTH over 100 have a higher average creatinine *(see table 11)* than patients with a PTH less than 100. The average creatinine after 5 years in IgA nephropathy is higher in ANCA associated glomerulonephritis. Even though, PTH is higher in ANCA associated glomerulonephritis than in IgA nephropathy around biopsy.

Table 11 *Mean of various laboratory values parameters in proliferative glomerulonephritis*

	Albumin	CRP	Leukocytes	Hb	Platelets	PTH	Proteinuria	Albuminuria	Hematuria
IgA nephropathy and IgA vasculitis	3,59	9,94	8,07	12,61	243,96	99,52	2363,71	1882,13	511,13
IgA nephropathy	*3,65*	*9,04*	*7,62*	*12,72*	*238,77*	*102,72*	*2452,84*	*1982,93*	*502,39*
IgA-vasculitis (HSP)	*3,33*	*14,18*	*10,21*	*12,08*	*268,31*	*85,14*	*1945,46*	*1432,38*	*552,82*
Lupus nephritis pattern on biopsy	3,57	8,01	6,62	11,71	227,9	43,1	4207,59	2252,34	448,19
SLE nephritis	*3,59*	*7,71*	*6,34*	*11,54*	*230,98*	*37,37*	*2725,76*	*2065,49*	*503,3*
Lupus like nephritis	*3,83*	*9,87*	*9,04*	*13,57*	*190,17*	*40,55*	*2933,67*	*1753,2*	*53,48*
Mixed connective tissue disease	*3,15*	*9,2*	*7*	*11,58*	*234,33*	*78,8*	*20299,83*	*4318,83*	*249,42*
ANCA associated glomerulonephritis	3,38	57,36	12,97	9,64	357,46	138,37	1800,68	1352,16	559,25
MPO-ANCA associated glomerulonephritis	*3,55*	*45,73*	*12,09*	*9,43*	*318,03*	*166,89*	*1205,58*	*886,52*	*542,76*
PR3-ANCA associated glomerulonephritis	*3,23*	*75,97*	*14,2*	*9,53*	*400,56*	*118,07*	*1753,54*	*1339,74*	*561,57*
Non-ANCA associated glomerulonephritis	*3,46*	*8,06*	*10,45*	*11,58*	*318,2*	*94,17*	*5654,2*	*3943,6*	*643,36*
Goodpasture's disease	3,43	33,48	9	9,1	324,75	177,4	5180	2857	1166,1
Immune-complex mediated MPGN	3,13	20,66	7,18	10,83	269,38	135,26	5942	4442,63	6807,33
Fibrillary glomerulonephritis	2,74	21,2	8,21	9,38	361,6	116,5	8345,6	5988,2	1090,34
C3-dominant glomerulonephritis	3,13	1,4	5,86	13,67	253,67	40,15	4264,67	3636,67	704,73
Infection associated Glomerulonephritis	3,47	26,87	10,02	10,5	210	265,3	4965	3621	916,9

Leukocytes in in 10^9/l, Hb = hemoglobin in g/dl, platelets = 10^9/l, CRP = C-reactive protein in mg/l, PTH = parathormone level in pg/ml, albumin in g/dl, hematuria in erythrocytes/µl, , proteinuria and albuminuria in (mg/g creatinine) ***Note:*** *Proteinuria and albuminuria were in most cases given in mg/g creatinine and in some patients in mg/day. (due to the correlation between mg/g and mg/day*(75) (76)*, these data were used interchangeably for this analysis)*

6.3.2 IgA nephropathy, systemic lupus erythematosus, ANCA associated glomerulonephritis

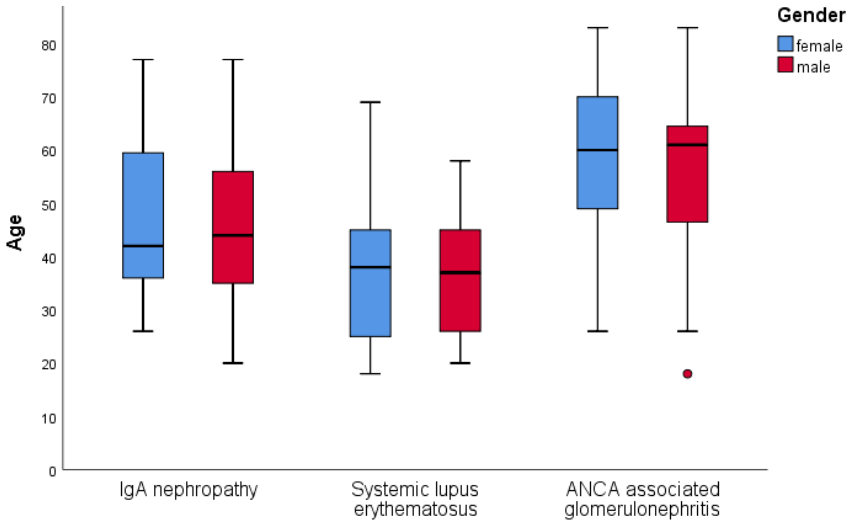

Figure 18 *Boxplot comparison of age distribution in IgA nephropathy, systemic lupus erythematosus and ANCA associated glomerulonephritis, female = blue, male = red*

The median age of male and female patients with IgA nephropathy is above the age of 40 years, with 44 years in male patients and 42 years in female patients. The median age of male and female patients with systemic lupus erythematosus is under 40 years, with 38 years in female individuals and 35 years in male individuals. The median age of people with ANCA associated glomerulonephritis is just around the age of 60 years, with 60 years in female patients and 61 in male patients.

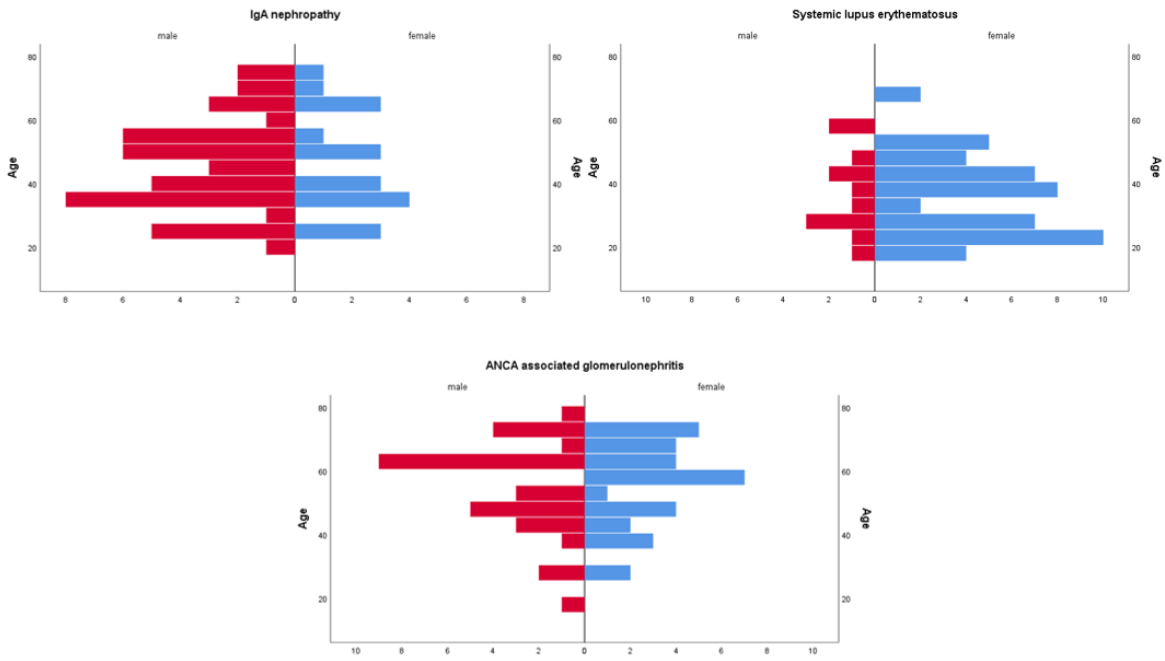

Figure 19 *Population pyramid in IgA nephropathy, systemic lupus erythematosus and ANCA associated glomerulonephritis, x-axis = number of cases, female = blue, male = red*

Figure 19 shows the age distribution of patients with systemic lupus erythematosus, IgA nephropathy and ANCA associated glomerulonephritis. The age pyramid in patients with systemic lupus erythematosus shows a clear difference in occurrence of each disease. In female patient the highest frequency of cases is just around the age of 20. In contrast, patients with IgA nephropathy show the highest rate of cases around the age 40 and in ANCA associated glomerulonephritis the highest amount of cases is just around 60 for both males and females. Illustrating a 20-year gap between each disease.

Table 12 *Creatinine levels at various moments*

	IgAN			SLE			ANCA			p- value[a]	p-value[b]		
	M	*SD*	Median	M	*SD*	Median	M	*SD*	Median	SLE vs. IgAN vs. ANCA	SLE vs. IgAN	SLE vs. ANCA	ANCA vs. IgAN
At biopsy	2,2	*1,6*	1,61	1,1	*0,71*	0,92	3,3	*2*	2,92	p<0,001	p<0,001	p<0,001	p=0,006
Maximum	2,6	*2,1*	1,86	1,2	*0,8*	0,96	4	*2,3*	3,41	p<0,001	p<0,001	p<0,001	p=0,003
1 month	2,3	*1,5*	1,65	1,1	*0,61*	0,98	2,6	*1,6*	2,22	p<0,001	p<0,001	p<0,001	p>0,05
1 year	2,4	*2,4*	1,49	1	*0,43*	0,86	2,4	*2*	1,69	p<0,001	p<0,001	p<0,001	p>0,05

Creatinine in mg/dl, SD = standard deviation, M = mean, ***a)*** *p-value calculated with Kruskal -Wallis Test, asymptotic significances are displayed* ***b)*** *A post hoc pairwise comparisons were adjusted by the Bonferroni correction for multiple tests. Adjusted p-values are presented. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed.*

Table 13 *Laboratory values, evaluated at biopsy in IgAN, SLE, and ANCA associated GN*

	IgAN			SLE			ANCA			p-value[a]	p-value[b]		
	M	*SD*	Median	M	*SD*	Median	M	*SD*	Median	SLE vs. IgAN vs. ANCA	SLE vs. IgAN	SLE vs. ANCA	ANCA vs. IgAN
Leukocytes	7,6	*2,4*	7,37	6,3	*3,3*	5,06	13	*5,4*	5,06	p<0,001	p=0,037	p<0,001	p<0,001
Hb	12,7	*2,4*	12,9	11,5	*2*	11,3	9,6	*1,5*	11,3	p<0,001	p>0,05	p<0,001	p<0,001
Platelets	239	*83*	230	231	*97*	210	359	*171*	210	p<0,001	p>0,05	p<0,001	p<0,001
CRP	9	*14*	2,9	8	*12*	2,8	57	*66*	2,8	p<0,001	p>0,05	p<0,001	p<0,001
PTH	103	*147*	49,7	37	*14*	35,95	138	*126*	35,95	p<0,001	p=0,031	p<0,001	p=0,007

Leukocytes in in 10^9/l, Hb = hemoglobin in g/dl, platelets = 10^9/l, CRP = C-reactive protein in mg/l, PTH = parathormone level in pg/ml, M = mean, SD= standard deviation, ***a)*** *p-value calculated with Kruskal -Wallis Test, asymptotic significances are displayed* ***b)*** *A post hoc pairwise comparisons were adjusted by the Bonferroni correction for multiple tests. Adjusted p-values are presented. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed*

Table 12 displays mean and median creatinine values at various moments. The mean creatinine value is higher in ANCA associated glomerulonephritis at biopsy, maximum around biopsy, one month and one year after biopsy than in IgA nephropathy and systemic lupus erythematosus. The mean creatinine value of IgA nephropathy and ANCA associated glomerulonephritis level out after one year at 2,40 and 2,42 respectively. Creatinine in systemic lupus erythematosus is lower than IgA nephropathy and ANCA associated glomerulonephritis at every measured date. A Kruskal - Wallis Test was run to determine a significant difference in creatinine levels between IgA nephropathy, systemic lupus erythematosus and ANCA associated glomerulonephritis. Visual boxplot analyzation *(see figure 20)* displayed dissimilar distribution between groups. Distribution of creatinine levels is significantly different between all groups at every measured instance. A subsequent pairwise comparison showed significantly different distribution between all paired groups, but creatinine levels after 1 – month and 1 – year between IgA nephropathy and ANCA associated glomerulonephritis.

Table 13 illustrates CBC (complete blood count) PTH and CRP level differences between IgA nephropathy, systemic lupus erythematosus and ANCA associated glomerulonephritis. Demonstrating that especially ANCA associated diseases have higher leucocytes, platelets and CRP level, but lower hemoglobin levels when patients underwent biopsy. Visual boxplot analyzation *(see figure 21)* displayed dissimilar distribution between groups.

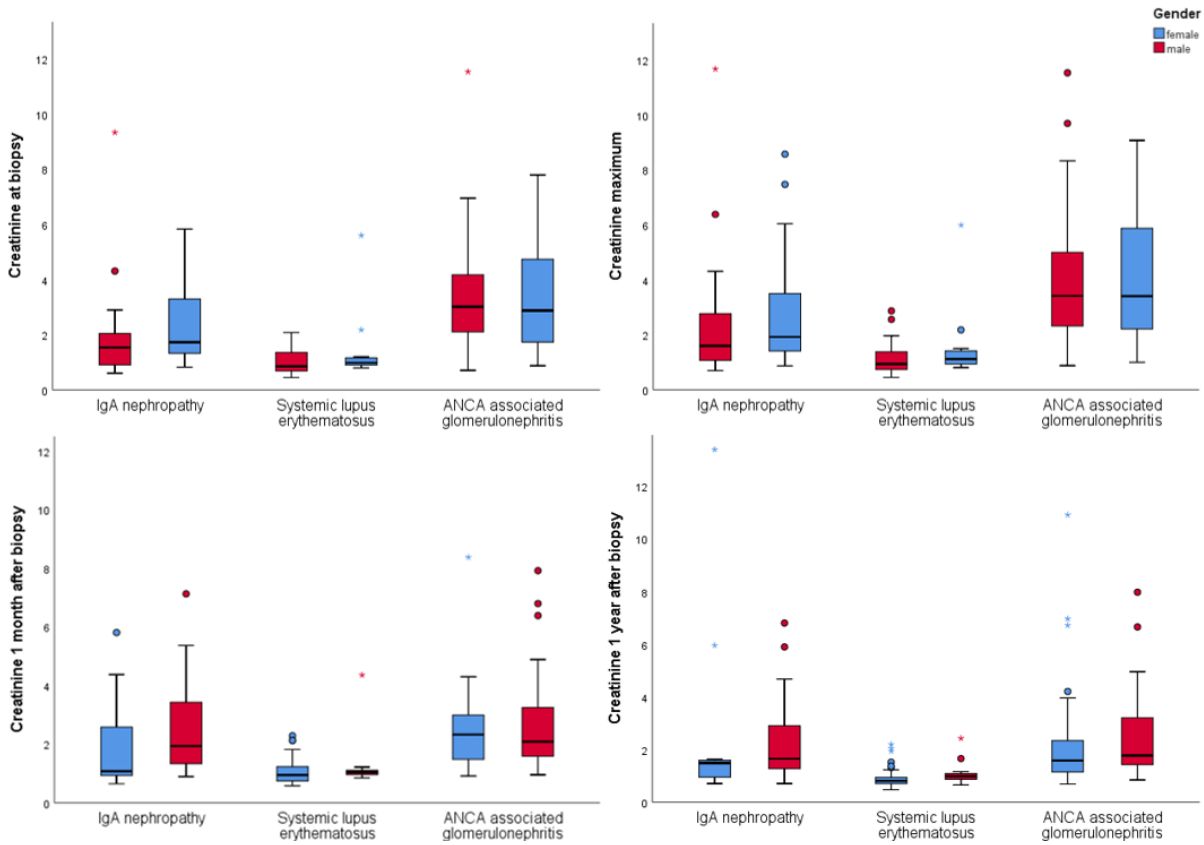

Figure 20 *Boxplot comparison of creatinine at different moments in IgA nephropathy, systemic lupus erythematosus, and ANCA associated glomerulonephritis, female = blue, male = red*

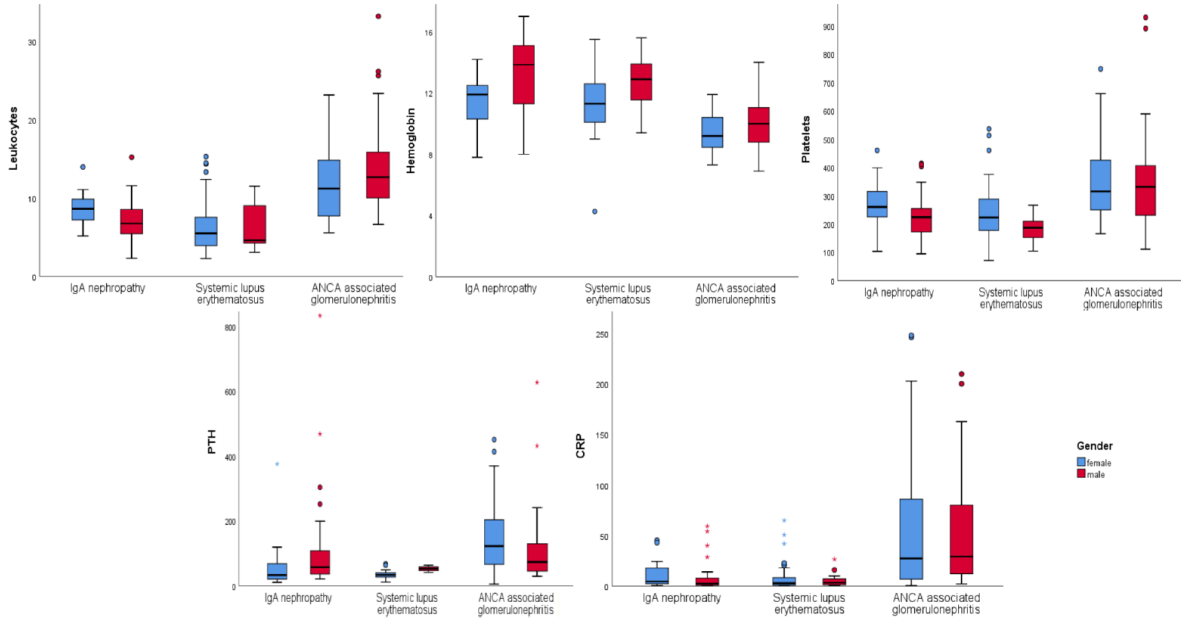

Figure 21 *Boxplot comparison of leukocytes, hemoglobin and platelets, PTH and CRP at biopsy between IgA nephropathy, systemic lupus erythematosus, and ANCA associated glomerulonephritis, Leukocytes in in 10^9/l, Hb = hemoglobin in g/dl, platelets = 10^9/l, CRP = C-reactive protein in mg/l, PTH = parathormone level in pg/ml, female = blue, male = red*

Table 14 *Intervention and prognosis in IgA nephropathy, SLE and ANCA associated glomerulonephritis*

		IgAN		**SLE**		**ANCA**	
		n	*%*	n	*%*	n	*%*
RRT	No	58	*93,5*	61	*100*	48	*71,6*
	Yes	4	*6,5*	0	*0,0*	19	*28,4*
				60	*98,4*		
Plasmapheresis	No	62	*100*	60	*98,4*	41	*61,2*
	Yes	0	*0,0*	1	*1,6*	26	*28,8*
Death and or ESKD	No	32	*51,6*	50	*82*	44	*65,7*
	Yes	20	*32,3*	6	*9,8*	18	*26,9*
	Unknown	10	*16,1*	5	*8,2*	5	*7,5*

RRT = Renal replacement therapy, ESKD = end stage kidney disease, n = number of cases

Table 14 displays how many patients required acute renal replacement therapy or plasmapheresis when they underwent renal biopsy. In addition, it compares how many patients either died or required long term renal replacement therapy up until December of 2019.

Four patients with IgA nephropathy required renal replacement therapy at the time of their diagnosis, unsurprisingly none required plasmapheresis. No patient with systemic lupus required renal replacement therapy. One needed plasmapheresis, this was done because the patient was primarily in therapy because of a catastrophic antiphospholipid syndrome. Compared to IgA nephropathy and systemic lupus erythematosus, ANCA associated glomerulonephritis presented extremely fulminant, with 19 patients requiring renal replacement therapy and 26 requiring plasmapheresis.

The long-term prognosis is vastly different between each disease group 32,30% of all patients with IgA nephropathy required long term renal replacement or have passed away. Compared to 26% of patients with ANCA associated disease and 9,8% of patients with systemic lupus erythematosus.

Table 15 *Various immunological markers evaluated at time of biopsy in IgAN, SLE and ANCA associated GN*

		IgAN		**SLE**		**ANCA a. GN**	
		n	*%*	n	*%*	n	*%*
Comp. consumption	no	38	*92,7*	9	*17*	43	*86*
	yes	3	*7,3*	44	*83*	7	*14*
ANA	negative	39	*86,7*	5	*8,8*	54	*85,7*
	positive	6	*13,3*	52	*91,2*	9	*14,3*
dsDNA	negative	40	*93*	17	*29,8*	53	*98,1*
	positive	3	*7*	40	*70,2*	1	*1,9*
ANCA ELISA	negative	41	*93,2*	29	*93,5*	5	*7,5*
	PR3	1	*2,3*	0	*0,0*	32	*47,8*
	MPO	2	*4,5*	2	*6,5*	30	*44,8*
ANCA IFA	negative	40	*90,9*	30	*96,8*	6	*9*
	c-ANCA	2	*4,5*	0	*0,0*	31	*46,3*
	p-ANCA	2	*4,5*	1	*3,2*	30	*44,8*

Comp. consumption = Complement consumption of complement protein C3 and/or C4, ANA = Antinuclear antibodies, dsDNA = Anti-double stranded DNA antibody, ELISA = Enzyme-linked Immunosorbent Assay, IFA=Immunofluorescence assay, n = number of cases

Table 15 illustrates different immunological markers around the time the patient underwent renal biopsy. In systemic lupus erythematosus the rate of complement consumption was 83%, compared to only 14% in ANCA associated disease and 7,3% in patients with IgA nephropathy. ANA was elevated in 91,2 %. It must be stated that all patients with systemic lupus erythematosus were at one-point ANA positive, otherwise they would not have been categorized as systemic lupus erythematosus. The reason they are negative in our cohort is because the cut off of three months before and after biopsy was applied, when evaluating this data. Elevated anti-double stranded DNA antibodies (dsDNA) were seen in 70,2% of patients with lupus nephritis. Two patients had elevated MPO ANCA and one of them had an elevated p-ANCA. Interestingly three patients with IgA nephropathy had elevated ANCA levels. One with elevated MPO ANCA was just above the upper limit of normal. One had cystic fibrosis. One patient with IgA nephropathy and elevated MPO levels presented as a sclerotic end stage kidney. The pathologist noted that the changes are most indictive of a longstanding IgA nephropathy. Figure 22 and 23 illustrate pie chart comparison of complement consumption and positive ANA levels between IgA nephropathy, systemic lupus erythematosus and ANCA associated glomerulonephritis.

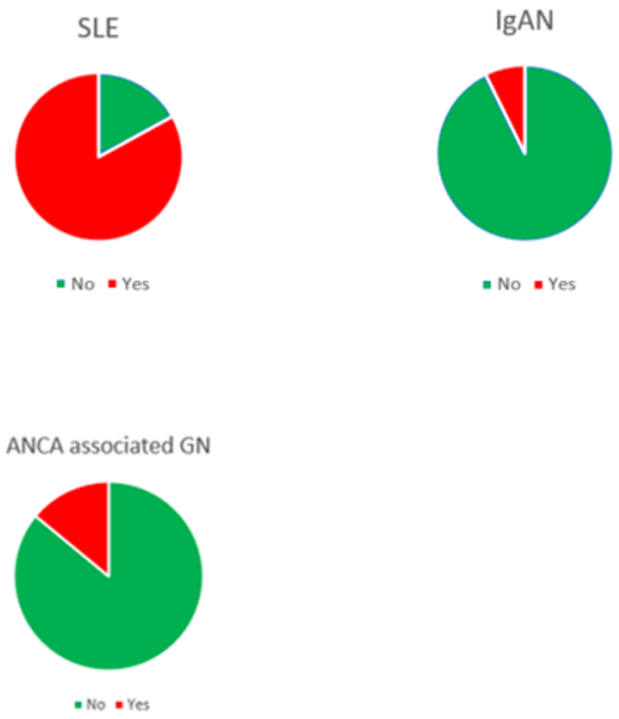

Figure 22 *Complement consumption in IgA nephropathy, systemic lupus erythematosus, and ANCA associated glomerulonephritis*

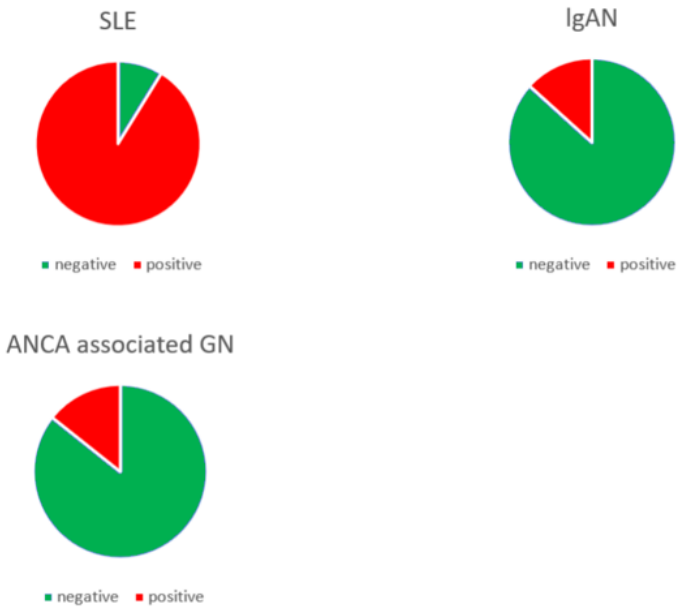

Figure 23 *Pie chart comparison of ANA levels in IgA nephropathy, systemic lupus erythematosus, and ANCA associated glomerulonephritis*

6.3.3 ANCA associated glomerulonephritis

In total 67 patients were diagnosed with ANCA associated 'pauci immune' glomerulonephritis. Thirty patients *(44,85%)* had elevated MPO levels and 32 patients *(47,8%)* had increased PR3 levels and five people *(7,5%)* had neither elevated MPO or PR3 levels.

Table 16 *Need for intervention, prognosis and ANCA type in ANCA associated glomerulonephritis*

		MPO-ANCA		**PR3-ANCA**		**ANCA-neg.**	
		n	*%*	n	*%*	n	*%*
Plasmapheresis	no	19	*63,3*	17	*53,1*	5	*100*
	yes	11	*36,7*	15	*46,9*	0	*0,0*
RRT	no	24	*80,0*	19	*59,4*	5	*100*
	yes	6	*20,0*	13	*40,6*	0	*0,0*
Death and or ESKD	No	18	*60,0*	24	*75,0*	2	*40,0*
	Yes	9	*30,0*	7	*21,9*	2	*40,0*
	Unknown	3	*10,0*	1	*3,1*	1	*20,0*
ANCA ELISA	negative	0	*0,0*	0	*0,0*	5	*100*
	PR3	0	*0,0*	32	*100*	0	*0,0*
	MPO	30	*100*	0	*0,0*	0	*0,0*
ANCA IFA	negative	0	*0,0*	1	*3,1*	5	*100*
	c-ANCA	0	*0,0*	31	*96,9*	0	*0,0*
	p-ANCA	30	*100*	0	*0,0*	0	*0,0*

RRT= Renal replacement therapy, ESKD = end stage kidney disease, ELISA = Enzyme-linked Immunosorbent Assay, IFA=Immunofluorescence assay, n = number of cases

Table 16 illustrates differences between all three subgroups of ANCA associated glomerulonephritis including ANCA negative glomerulonephritis. In total eleven patients *(36,7%)* with positive MPO ANCA levels were treated with plasmapheresis and six patients needed *(20%)* renal replacement therapy. In contrast to 15 patients *(46,9%)* with elevated

PR3 level requiring renal replacement therapy and 13 patients *(40,6%)* plasmapheresis. No patient with ANCA negative glomerulonephritis required either plasmapheresis or renal replacement therapy.

The long-term prognosis differs between each disease group. Nine patients *(30%)* with elevated MPO levels have succumbed to their disease or progressed to end stage kidney disease, compared to seven *(21,9%)* with PR3 ANCA and two patients *(40%)* who were ANCA negative. One person with PR3 ANCA did not have elevated c-ANCA levels, this is due to the fact that the patient was c-ANCA positive but because of immune suppressive therapy her levels decreased, and they were not detectable around the time of renal biopsy. PR3 level was only weakly positive at that time.

Table 17 *Age comparison in ANCA associated glomerulonephritis*

MPO				**PR3**				**ANCA-neg.**				**p-value[a]**	**p-value[b]**		
n	Age	*SD*	Median	**n**	Age	*SD*	Median	**n**	Age	*SD*	Median	MPO vs. PR3 vs. ANCA neg.	MPO vs. PR3	MPO vs. ANCA neg.	PR3 vs. ANCA neg.
30	63	15	64	**32**	54	14	54	**5**	51	11	49	p=0,014	p= 0,023	p>0,05	p>0,05

SD = standard deviation n = number of cases ***a)*** *p-value calculated with Kruskal -Wallis Test, Asymptotic significances are displayed.* ***b)*** *A post hoc pairwise comparisons were adjusted by the Bonferroni correction for multiple tests. Adjusted p-values are presented. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed*

Table 18 *Age and sex comparison between MPO and PR3 ANCA associated glomerulonephritis*

	MPO						**PR3**						**p-value[a,b]**
	n	Age	*SD*	Median	*Max*	*Min*	**n**	Age	*SD*	Median	*Max*	*Min*	
Female	**17**	68	*10*	68	*83*	*49*	**13**	53	*15*	55	*74*	*26*	p=0,002
Male	**17**	57	*19*	64	*80*	*18*	**15**	55	*14*	53	*83*	*30*	p>0,05

SD = standard deviation, n = number of cases Max = Maximum, Min = Minimum ***a)*** *p-value calculated with Welch-Test for female patients (2-tailed significance) is displayed* ***b)*** *p-value calculated with independent t-test for male patients*

Table 17 illustrates the age difference between ANCA associated glomerulonephritis. Individuals with MPO ANCA are on average about 10 years older than their counterparts with elevated PR3 ANCA and patients with ANCA negative disease.

Table 18 clearly shows that this age difference is only apparent in female patients and not male patients. The age distribution in female and male patients in MPO, PR3 and ANCA negative glomerulonephritis is also illustrated as boxplot in figure 24.
In summary women with MPO-ANCA associated GN were significantly older at time of biopsy compared to other pauci-immune GN patients.

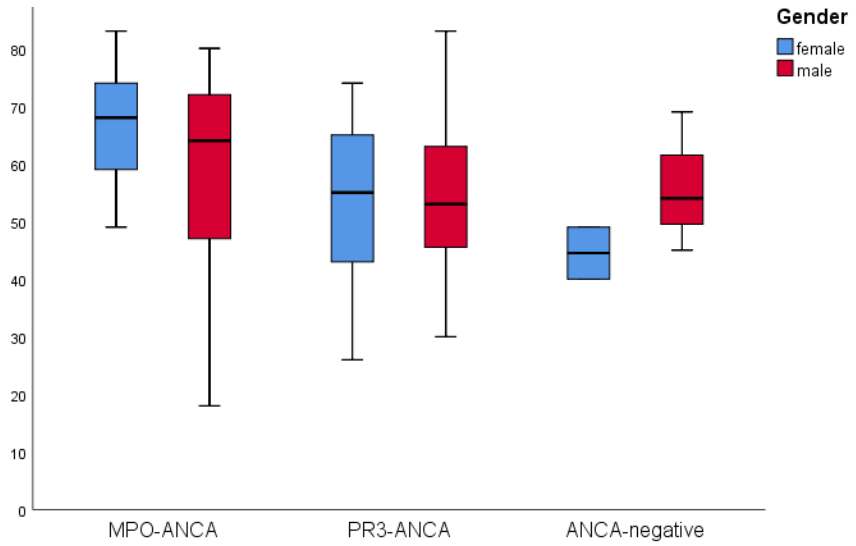

Figure 24 *Boxplot comparison of age distribution in ANCA associated glomerulonephritis female = blue, male = red*

6.3.4 IgA nephropathy and IgA vasculitis

Table 19 *IgA level comparison between IgA nephropathy and IgA vasculitis*

	IgA nephropathy		**IgA vasculitis**	
IgA level	n	*%*	n	*%*
Normal	35	*79,5*	4	*44,4*
Elevated	9	*20,5*	5	*55,6*

n = number of cases

Table 19 and figure 25 illustrate that 55,6 % of patients with IgA vasculitis had an elevated IgA level compared to only 20,5 % of patients with IgA nephropathy.

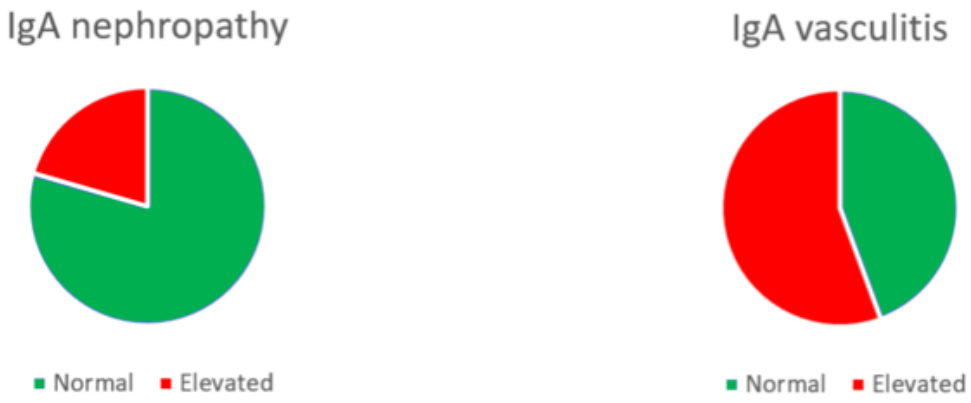

Figure 25 *Pie chart of IgA levels in IgA nephropathy and IgA vasculitis*

6.3.4.1 MEST score

Table 20 *Frequency of each group in M E S T score in IgAN*

MEST	female	%	male	%	Total	%
M0	1	*6,7*	3	*9,7*	4	*8,7*
M1	14	*93,3*	28	*90,3*	42	*91,3*
E0	10	*66,7*	24	*77,4*	34	*73,9*
E1	5	*33,3*	7	*33,6*	12	*26,1*
S0	5	*33,3*	9	*29*	14	*30,4*
S1	10	*66,7*	22	*71*	32	*69,6*
T0	13	*86,6*	15	*48,4*	28	*60,9*
T1	1	*6,7*	9	*29*	10	*21,7*
T2	1	*6,7*	7	*22,6*	8	*17,4*

M = mesangial hypercellularity, E = endocapillary cellularity, S = segmental sclerosis and T = tubular atrophy / interstitial fibrosis, n = number of cases.

Of 62 patients with IgA nephropathy in 46 Patients the MEST score was evaluated by the pathologist. The most prevalent score of each group was M1 *(n=42),* E0 *(n=34),* S1 *(n=32)* and T0 *(n=28).* Notably, only 2 female patients had an T score higher than T0. Compared to 16 male patients with a score higher than T0.

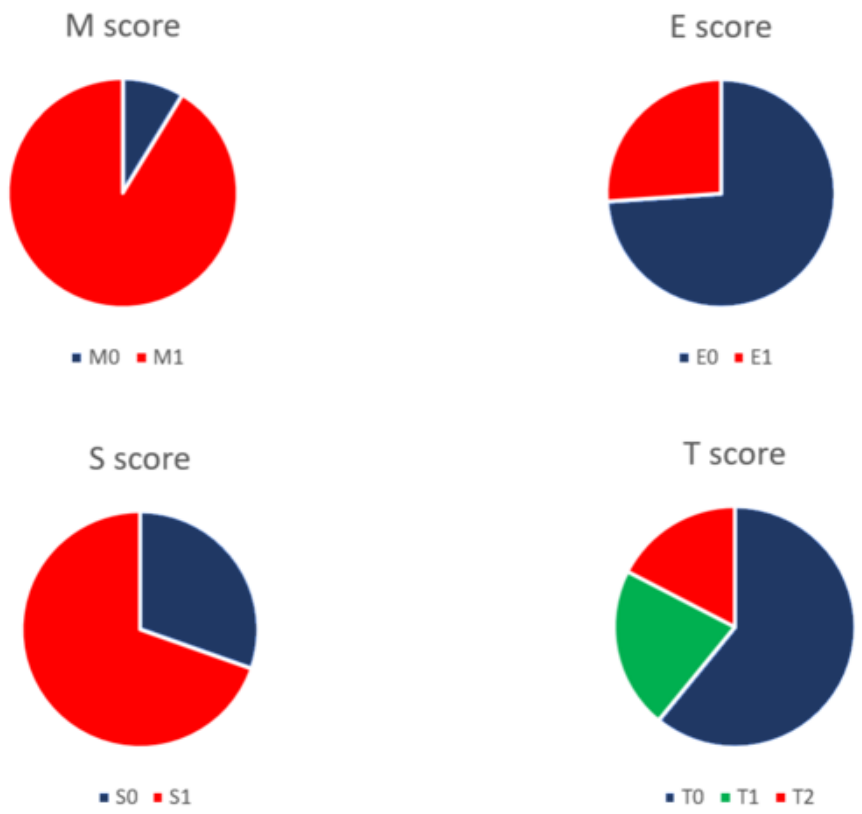

Figure 26 *Frequency of each group in M E S T score*

Table 21 *MEST score (T0, T1, T2) and its effect on creatinine maximum*

MEST	*n*	%	creatinine	*SD*	Median	p–value[a]	p-value[b]	
T0	28	*60,9*	1,91	*2,01*	1,51		T0 vs T1	p =0,03
T1	10	*21,7*	2,8	*1,13*	2,81	p<0,001	T1 vs T2	p>0,05
T2	8	*17,4*	4,42	*1,29*	3,74		T0 vs T2	p<0,001

SD = standard deviation T = tubular atrophy / interstitial fibrosis, n = number of cases, SD = standard deviation, creatinine in mg/dl
a) *p-value calculated with Kruskal -Wallis Test, Asymptotic significances are displayed.*
b) *A post hoc pairwise comparisons were adjusted by the Bonferroni correction for multiple tests. Adjusted p-values are presented. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed*

Table 21 shows a statistically significant difference *(p<0,001)* in creatinine maximum between T0, T1 and T2. The mean creatinine value increases by ~1 mg/dl between T0 and T1 and by ~1,5 mg/dl between T1 and T2. The median creatinine value increases by ~1,3 mg/dl between T0 and T1 and by ~1 mg/dl between T1 and T2 *(see table 21 and figure 27)*. Most patients *(60,9%)* had a score of T0 and just 17,4% had a T-score of T2 *(see table 20 and figure 26)*. Data showed a statistically significant difference between T0 compared to

T1 and T2 *(p =0,03) (p<0,001).* There was no statistically significant difference between T1 and T2 *(p>0,05).* In T1 and T2 there are combined only 18 cases, compared to 28 in T0.

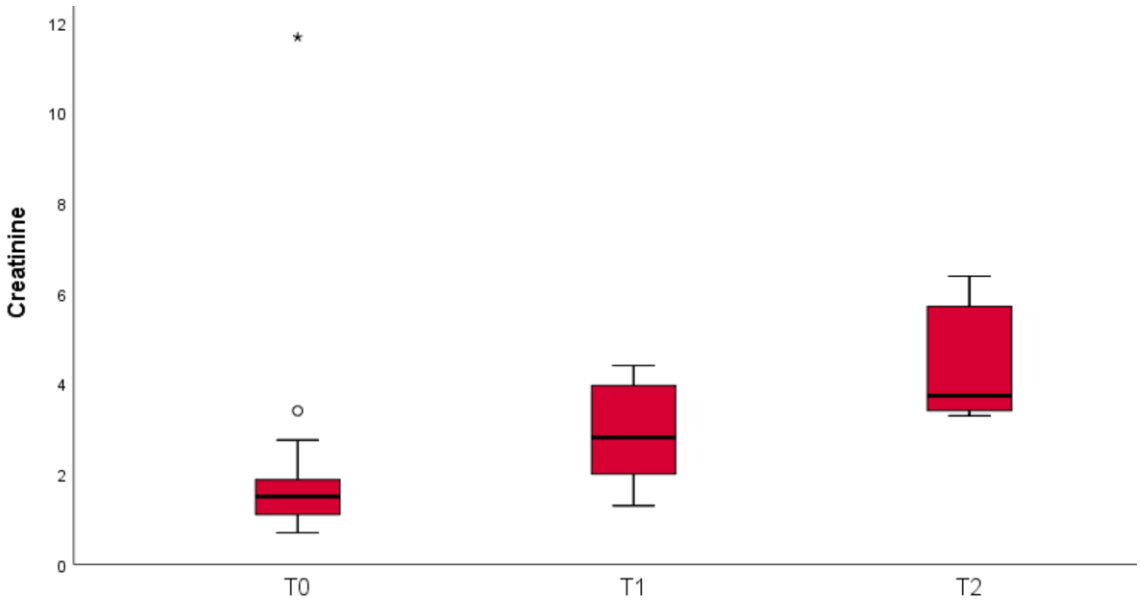

Figure 27 *Boxplot comparison of creatinine maximum (mg/dl) in IgA nephropathy with T0, T1, and T2 score*

Table 22 *T score and prognosis in IgA nephropathy*

	T0		**T1**		**T2**	
	n	%	n	%	n	%
Total	23	*100*	10	*100*	6	*100*
Death and or ESKD	2	*8,7*	5	*50*	6	*100*

ESKD = end stage kidney disease, n = number of cases

Using an endpoint of 2019, 7 patients were lost to follow up. 39 Patients were evaluated if they required renal replacement therapy or have passed away depending on their T-score. In 8,7% of patients with a score of T0 are either dead or require renal replacement therapy compared to 50% of patients with T1 and 100% of patients with T2. In total 7 patients were lost to follow up 5 in T0 and 2 in T2.

6.3.5 Systemic lupus erythematosus lupus like nephritis and mixed connective tissue disease

Table 23 *Creatinine levels at various moments in SLE, lupus like nephritis and MCD*

	SLE			**Lupus like**			**MCD**			**p-value[a]**
	M	*SD*	Median	M	*SD*	Median	M	SD	Median	SLE vs. MCD vs. Lupus like
biopsy	1,1	*0,7*	0,92	2,6	*1,9*	2,99	1,7	*1,2*	1,33	
maximum	1,2	*0,8*	0,96	3,4	*2,9*	2,63	2	*1,3*	1,78	p >0,05
1 month	1,1	*0,6*	0,98	2,57	*2,1*	2,22	1,3	*0,7*	0,82	

M = mean, SD = standard deviation, Creatinine in mg/dl,
a) *p-value calculated with Kruskal -Wallis Test.*

Table 23 illustrates that mean and median creatinine values in lupus like nephritis are higher at biopsy, creatinine maximum around biopsy and 1-month after biopsy compared to MCD and SLE. Values between the groups show no statistically significant difference *(p >0,05).* Creatinine maximum is also displayed as boxplot in figure 28.

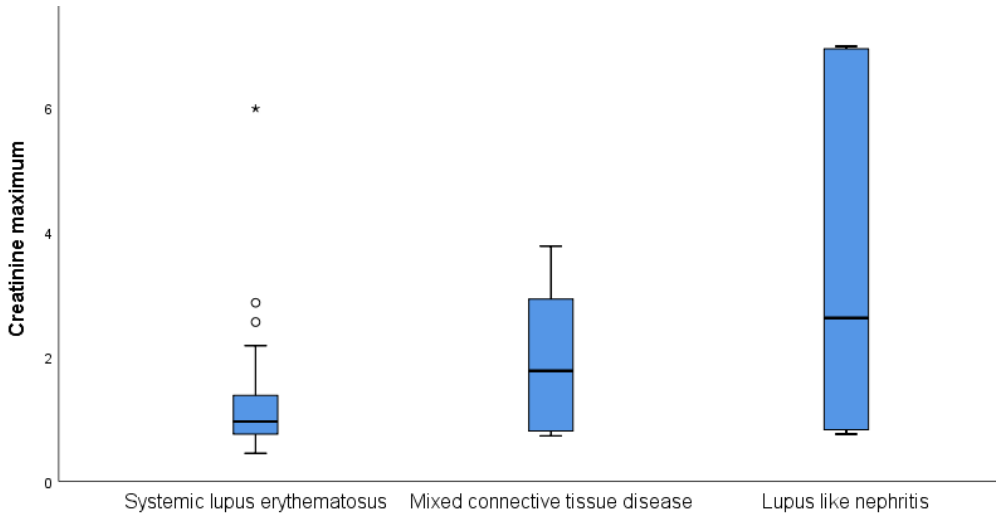

Figure 28 *Boxplot comparison of creatinine maximum(mg/dl) in SLE, MCD and Lupus like nephritis*

Table 24 *Class comparison between SLE, MCD and lupus like nephritis*

	SLE	MCD	Lupus like
Class I	0	0	2
Class II	2	1	1
Class III	15 (16)	0	1
Class III + V	*12*	*0*	*1 (2)*
Class IV	13	3	0
Class IV + V	*9*	*0*	*0*
Class V	9	2	0
Class VI	0	0	0
Not classified	(1)[a]	0	(1)[b]
Total	61	6	6

[a] *displayed focal segmental proliferation = class III*
[b] *displayed membranous pattern and focal segmental scars = class III + V*

Table 24 shows class distribution between systemic lupus erythematosus, mixed connective tissue disease and lupus like nephritis. Four of the 6 patients with lupus like nephritis never had a positive ANA in our institution. Two patients with class I had an incidental finding of lupus nephritis on biopsy. The primary kidney diagnoses were acute kidney injury and thrombotic microangiopathy, respectively. One patient with class II tested positive for ANAs, but no other evidence of systemic lupus erythematosus was detectable. Therefore, the patient did not reach the threshold of 10 points to be classified as such. One patient who was not classified had no evidence of systemic lupus erythematosus at the time of biopsy. The pathologist report noted only a mesangioproliferative and focal segmental proliferation. Strictly speaking this is a class III, making a total of 16. The second patients (who was not classified) report stated, “a membranous pattern and focal segmental scars, suspicious for lupus nephritis”. This would represent a class III (c) + V, making a total of 2 in this group.

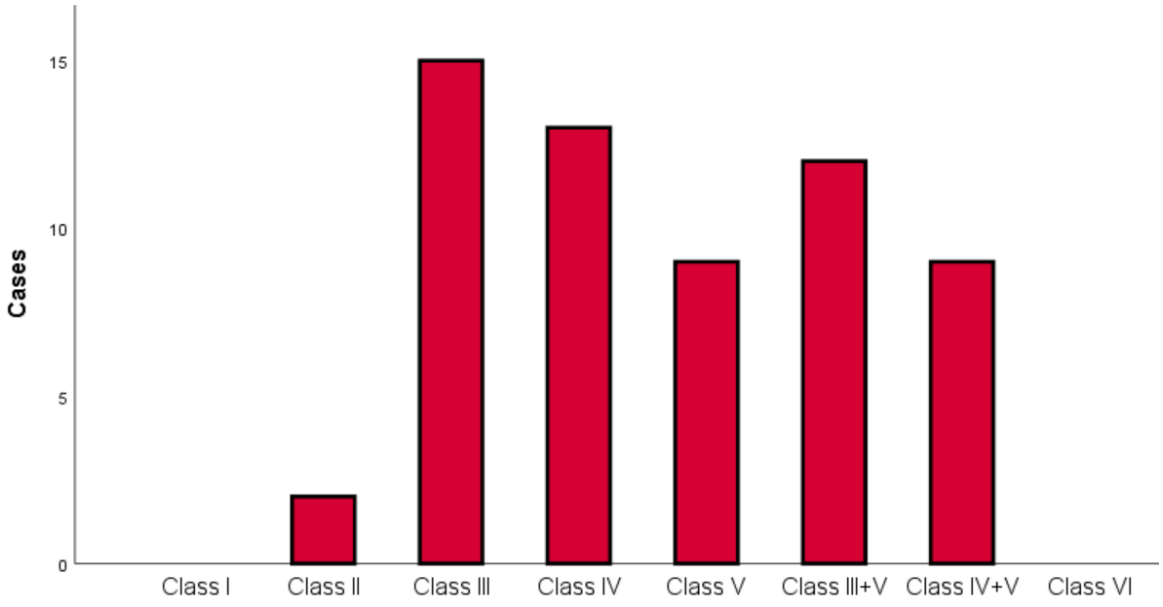

Figure 29 *Class distribution in systemic lupus erythematosus*

Figure 29 illustrates the class distribution of lupus nephritis in systemic lupus erythematosus. The most frequent diagnosed class was class III *(n=15)* followed by class IV *(n=13)* and, class III+V *(n=12)*. Class V and IV+V had 9 cases each. There were no cases of class I and VI. Class II had less than 5 cases.

6.3.6 Rare Glomerulopathies

6.3.6.1 Goodpasture`s disease and Goodpasture's syndrome

Table 25 *Goodpasture`s disease and Goodpasture's syndrome*

	Sex	Age	Pulmonal bleeding	ANCA	MPO	GBM
Patient 1	male	22	Yes	Neg.		>100
Patient 2	female	41	Yes	MPO	13,9	53,2
Patient 3	female	18	Yes	Neg.		>100
Patient 4	male	73	No	MPO	7,2	>100

In our cohort 4 patients were diagnosed with Goodpasture's disease. Three patients not only had renal involvement but also presented with hemoptysis. These three patients suffer therefore from Goodpasture's syndrome. Only patient number 4 did not develop pulmonal bleeding. He suffered from Goodpasture's disease but not from Goodpasture`s syndrome. Patient number 2 has to be addressed separately, because the biopsy (limited representative) displayed a pauci immune type of pattern. Presumably, because of the highly elevated anti-GBM titer and only slightly elevated MPO titer she carried a diagnosis of Goodpasture's disease.

6.3.6.2 Membranoproliferative glomerulonephritis and C3 glomerulopathy

Table 26 *Associations in membranoproliferative glomerulopathies*

	Sex	Age	Pathogenesis	Type	Association
Patient 1	Male	76	Immune complex	Type III	Infection
Patient 2	Male	66	Immune complex	Type I	RA
Patient 3	Male	61	Immune complex		Hep C
Patient 4	Female	55	Immune complex	Type I	Fibrillary GN
Patient 5	Male	60	Immune complex	Type I	No association
Patient 6	Female	61	Immune complex		No association
Patient 7	Male	65	Complement mediated	Type I	C3GN.
Patient 8	Male	18	Complement mediated	Type I	C3GN.
Patient 9	Male	59	Immune complex		Hep C
Patient 10	Male	68	Immune complex	*Type* I	Infection
Patient 11	Male	50	Immune complex	Atypical	*'Adenocarcinoma'*

RA = rheumatoid arthritis, Hep C = chronic hepatitis C infection, C

In total 11 biopsies were signed out as membranoproliferative glomerulonephritis. Patient number 11 was treated with Gemcitabine to treat an underlying carcinoma of the pancreas when he developed an atypical hemolytic uremic syndrome. The biopsy showed double contours, which can be seen in thrombotic microangiopathies but had additional subendothelial immune complexes, which would be absent in a membranoproliferative pattern caused by thrombotic microangiopathy(29). The pathologist reported both the thrombotic microangiopathy and an "atypical membranoproliferative glomerulonephritis" The remaining patients had either complement mediated (complement-m. MPGN) (*n=2*) or immune complex mediated membranoproliferative glomerulonephritis (Immune-c. MPGN) (*n=8*) *(see table 26).* Of the immune complex mediated two patients had active hepatitis C infection, one patient had a repeated biopsy after one month which showed randomly aligned fibrils with a diameter of 12-13 nm triggering the diagnosis of fibrillary glomerulonephritis. One patient had rheumatoid arthritis. One was treated for an abscess when his creatinine levels started to rise, and the subsequent biopsy displayed a MPGN type III. Only in two patients no apparent cause was linked to the membranoproliferative glomerulonephritis. There is a clear male predominance in our cohort (*n=9*) with only two females (*n=2*).

Most patients were signed out as MPGN Type I *(n=6)* only one had an MPGN Type III (*n=1*) pattern.

Table 27 *Patients with C3 glomerulonephritis*

	Age	Sex	Histopathology
Patient 1	19	Male	MPGN pattern
Patient 2	65	Male	MPGN pattern
Patient 3	18	Male	Mesangioproliferative pattern

In total 3 patients were diagnosed with C3 glomerulopathy *(0,6%)*. Two had a membranoproliferative pattern. One patient had a mesangioproliferative pattern on renal biopsy.

6.3.6.4 Infection associated glomerulonephritis

Table 28 *Associations in infection associated glomerulonephritis*

	Age	Sex	Histo.	Associated Infection	DM
Patient 1	53	Male	EPGN	Erysipelas	Yes
Patient 2	34	Female	EPGN	Myocarditis	No
Patient 3	76	Male	EPGN	UTI	Yes

Histo = Histopathology, EPGN = endocapillary proliferative glomerulonephritis DM = Diabetes mellitus UTI = Urinary tract infection

Two male patients one female patient were signed out as endocapillary glomerulonephritis. Each showed evidence of an infection. Patient one was treated for a skin tissue infection, patient two had biopsy proven myocarditis and patient three was treated for an urinary tract infection. Two of the patiens had diabetes mellitus.

Table 29 *Various parameters evaluated at biopsy in rare glomerulopathies*

		AGD	C3GN	IAGN	FGN	IM-MPGN	
Death and or ESKD	No	1	3	1	1	4	
	Yes	3	0	0	4	3	
	Unknown	0	0	2	0	1	
Renal replacement therapy	no	0	3	1	4	4	
	yes	4	0	2	1	4	
Plasmapheresis	no	1	3	3	4	7	
	yes	3	0	0	1	1	
Complement consumption	no	3	1	1	3	5	
	yes	1	2	1	0	1	
ANCA ELISA	negative	2	3	1	4	5	
	PR3	0	0	1	0	1	
	MPO	2	0	0	1	1	
ANCA_IFA	negative	3	3	3	4	6	
	c-ANCA	0	0	0	1	0	
	p-ANCA	1	0	0	0	1	
ANTI GBM antibodies	normal	0	3	3	5	7	
	elevated	4	0	0	0		0

ESKD = end stage kidney disease, n = number of cases, AGD = Goodpasture's disease, C3GN = C3 glomerulonephritis, IAGN = infection associated glomerulonephritis, FGN = fibrillary glomerulonephritis, IM-MPGN = immune complex mediated membranoproliferative glomerulonephritis

Table 29 illustrates clinical interventions, complement consumption and various immunological data, from rare glomerulopathies. Because of the sparsity only some notable data will be mentioned here. Firstly, 50% of patients with Goodpasture's disease had elevated MPO ANCA, tough only slightly elevated. Four of five patients with fibrillary glomerulonephritis have either passed away or require long term renal replacement therapy. One patient with fibrillary glomerulonephritis suffered from granulomatosis with polyangiitis and had highly elevated MPO ANCA. The renal biopsy did not show a pauci immune pattern of injury but displayed non-branching randomly aligned fibrils.

6.3.7 Crescentic glomerulonephritis

Table 30 *Crescentic glomerulonephritis at the Medical University of Graz.*

	n	*%*
ANCA associated glomerulonephritis	53	*75,7*
MPO-ANCA associated glomerulonephritis	*25*	*35,7*
PR3-ANCA associated glomerulonephritis	*25*	*35,7*
Non-ANCA associated glomerulonephritis	*3*	*4,3*
Lupus nephritis pattern of injury	6	*8,5*
SLE nephritis	*5*	*7,1*
Mixed connective tissue disease	*1*	*1,4*
Goodpasture's disease	4	*5,7*
IgA nephropathy	3	*4,3*
Fibrillary glomerulonephritis	2	*2,9*
Immune-complex mediated MPGN	2	*2,9*
Total	70	*100*

Crescentic glomerulonephritis = Biopsy with ≥ 50% crescents of representative glomeruli, n = number of cases, % calculated from total of 70 biopsies.

The most prevailing biopsy result displaying equal or more than 50% crescents are ANCA associated glomerulonephritis *(n=53)* followed by 'lupus' nephritis *(n=6)*, Goodpasture's disease *(n=4)* and IgA nephropathy *(n=3) (see table 30 and figure 30)*.

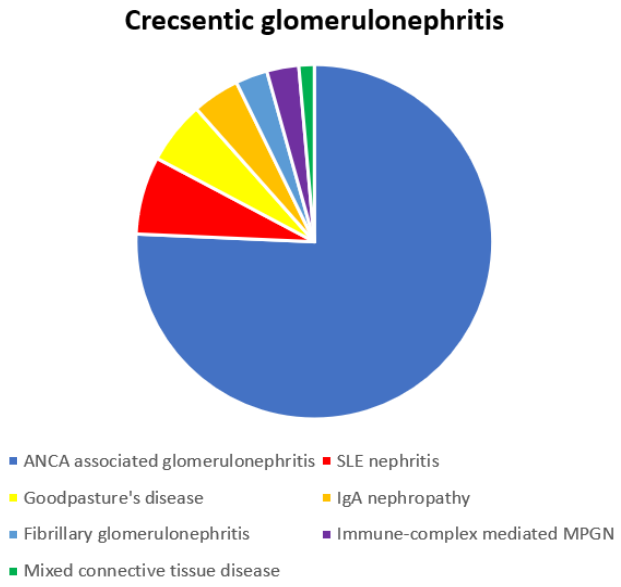

Figure 30 *Pie chart of crescentic glomerulonephritis at the Medical University of Graz between 2007 and 2017*

6.4 Complication rate of native renal biopsy

Table 31 *Complication rate of 238 evaluated biopsies. % calculated from 238*

Evaluated biopsies	n	*%*
No complication	170	*71,4*
Not attainable	41	*17,2*
(Perirenal) Hematoma	18 (19)	*7,6 (8)*
Macrohematuria	7	*2,9*
Bleeding requiring radiological intervention	1	*0,4*
Bleeding requiring surgery	0	*0*
Bleeding leading to death	0	*0*
Other	0	*0*
Total	238	*100*

n = number of cases

Table 31 illustrates complication rate of 238 evaluated biopsies. The majority of patients had no complications *(n = 170)*. In 41 patients there were missing information in the hospital information system. Therefore, the patient's history could not be fully evaluated. 18 patients showed a perirenal hematoma in a control sonography. One patient had a 4 x 2 cm local subcutaneous hematoma. Seven patients had macrohematuria and one patient had bleeding requiring radiological intervention

7. Discussion

It is difficult to compare the rate of biopsies with registries from different countries because some of the evaluated countries have national, regional or single center registries. In addition, some only evaluated biopsies of adults and some of adults and children. Furthermore, in certain registries only a subset of biopsies was evaluated. Countries with single center institution and only biopsies from adult patients include Serbia and France. Serbia presented 2362 biopsies in two decades averaging 118 biopsies per year. France had only 942 biopsies in 15 years, averaging 63 biopsies per year. At the Division of Nephrology of the Medical University of Graz, there were 973 biopsies in 11 years, making a total of 88 biopsies each year. It is crucial to mention that up to the year of 2010 there was never a biopsy rate exceeding 80 biopsies per year. Only considering, the last 7 years the average biopsy rate is 108 per year. This seems to reflect the average biopsy rate of today.

Before discussing the primary focus of this thesis, I want to comment on non-glomerular diseases in figure 11. Vascular and tubulo- interstitial nephropathy (TIN) consist of various subgroups, as they were not always given as its own entity. They had to be added up in some papers. Tubulointerstitial disease and vascular disease might therefore consist of different diseases in each country. For example, one country might report TIN as 13% and another country might report cast nephropathy 1%, acute tubulointerstitial nephritis 4% and acute kidney injury 2%. Making a total of 7%. The exact subgroups are given in figure 12. This needs to be taken into consideration when evaluating these disease entities.

The fact that renal biopsies are not performed in every patient, we must assume that the true prevalence of glomerulopathies is higher than assumed. This is particularly true for diseases which often remain subclinical. For instance, in a country or institution with a stricter biopsy policy renal disease like IgA nephropathy is artificially lowered and consequently more severe glomerulonephritides occur comparatively more frequent. This is in contrast to a country with liberal biopsy policy. Asymptomatic renal diseases only presenting with microhematuria and/or proteinuria will consequently increase in frequency. This explains partly why countries, where renal biopsy is widely used as investigative tool, have high rates of IgA nephropathy(1). There are several limiting factors, which can make comparison of glomerular diseases problematic between different countries and time periods. This is in some cases even misleading. I will try to clarify what I mean with problematic and misleading in the next couple of pages.

With progress in medicine and better understanding of pathophysiology nomenclature changes over time. 'Old' nomenclature refers in many cases to pathological alterations. With increasing knowledge on the underlying disease, pathogenesis and understanding that pathologic changes can be the end product of various disease processes. Terminology needs to adapt to better reflect pathogenesis. Yet, change often takes time and may happen at different speeds between various countries, counties and even institutions, making it extremely tedious, difficult and in some cases even misleading when comparing different renal registries from different time periods.

The first and maybe most noticeable difference evaluating renal biopsy registries reflects the fact that immunofixation (IF) was not frequently used in some countries especially in the late 1980's to mid-90's therefore underestimating IgA nephropathy. In Poland immunofluorescence was not frequently used before 1995. When IF was routinely performed, the frequency of IgAN among MesGN increased and reached 100% in the end of the second decade(12). In figure 13 both are depicted in different colors red and blue, respectively. It is not unreasonable to assume IgA nephropathy is the most abundant primary glomerulopathy in all these countries. Of course, this is only an assumption and cannot be proven retrospectively.

The next issue I encountered concerned 'diffuse endocapillary glomerulonephritis'. As with mesangioproliferative glomerulonephritis this just describes a pathohistological picture and can be seen in various disease entities, including but not limited to IgA nephropathy, lupus nephritis and other infection related glomerulonephritides. It was, and still is commonly used to describe histological changes in poststreptococcal glomerulonephritis, which typically include polymorphonuclear leukocytes and monocytes(26). From reviewing the papers of various countries, I was unable to clearly differentiate endocapillary proliferative, post streptococcal glomerulonephritis and other infection associated glomerulonephritides. These typically represent one and the same disease, they all are listed in figure 11 in the column under EPGN (endocapillary proliferative glomerulonephritis).

The next two challenges I encountered deal with vasculitis and crescentic glomerulonephritis. The latter describes a diffuse extracapillary glomerulonephritis affecting ≥ 50% of the representative glomeruli. It represents the most extreme presentation of any proliferative glomerulonephritis including but not limited to lupus nephritis and IgA nephropathy. An overview of glomerulonephritides, which displayed ≥ 50% crescents of the representative glomeruli at the Medical University of Graz can be seen in table 30. This table illustrates why it can be misleading to classify glomerular disease as crescentic

glomerulonephritis. Twenty-four percent of all cases with crescentic glomerulonephritis in our cohort where in fact not ANCA associated glomerulonephritis. Unclear for decades, today we know most cases are the result of small vessel vasculitis, mostly driven by anti-neutrophil cytoplasmic antibodies (ANCAs) directed against proteinase-3 (PR3) and myeloperoxidase (MPO). Most cases of ANCA associated glomerulonephritis reflect two disease phenotypes, microscopic polyangiitis or granulomatosis with polyangiitis. Both are small vessel vasculitides. When evaluating figure 11 some countries did use vasculitis and crescentic glomerulonephritis as two separate entities, making it impractical to extract valuable information.

Membranoproliferative glomerulonephritis still frequently used today may be last bastion of outdated nomenclature. Our cohort is a great example on why it is essential to investigate for an underlying disease if the biopsy specimen shows a membranoproliferative pattern of injury. In total, eleven patients were signed out as membranoproliferative glomerulonephritis. Nine were immune complex mediated and two complement mediated. One patient was treated with Gemcitabine due to an adenocarcinoma of the pancreas before. MPGN has been associated with solid tumors (76, 77, 78, 79).Two patients had an active hepatitis C infection, one had fibrillary glomerulonephritis, one had ongoing infection and one had rheumatoid arthritis. In two patients no association was found retrospectively. Unsurprisingly, treatment and prognosis vary largely depending on the underlying etiology.

A new standardized classification and reporting of glomerulonephritis published in 2019(81), suggests a pathologist's report should include, amongst other information, pattern of injury as well as primary diagnosis. Trying to compare renal registries from different periods gets even more complicated, when taking in consideration that classification systems change over the years. This fact can be illustrated when looking back at classification systems for systemic lupus erythematosus. In the first published criteria in 1972 4 of 11 manifestations were needed to be classified a systemic lupus erythematosus. But, since renal involvement with systemic lupus erythematosus is associated with morbidity and mortality most clinicians agreed that this in fact is systemic lupus erythematosus. In 2012 a revised classifications system was introduced, arguing that a biopsy proven lupus nephritis and a positive ANA is sufficient to classify a patient as systemic lupus erythematosus. This has shown to increase sensitivity in the diagnosis of systemic lupus erythematosus(40). Consequently, more patients were diagnosed with systemic lupus erythematosus. Interestingly, a patient with positive ANA and lupus nephritis class II or class V without any

other evidence of systemic involvement and positive immunological markers, would meet the criteria of systemic lupus erythematosus using the SLICC criteria, but not applying the EULAR/ACR classification system of 2019, since lupus nephritis class II or V have each a value of 8 and thus not meeting the threshold of 10. These nuances must be considered, when assessing different epidemiological studies.

In contrast to nomenclature and classification of proliferative glomerulonephritis the terminology in non-proliferative glomerulopathies has been rather stagnant. Maybe with the exception of focal segmental sclerosis, which can occur as primary disease but may also result from adaptive changes. Conditions like morbid obesity, reflux nephropathy, unilateral renal agenesis and sickle cell anemia can cause focal segmental scarring(82). In light microscopy these two can be indistinguishable from each other, only when evaluating electron microscopy the latter typically shows intact or only focally effaced foot processes(83). This fact has to be takin into consideration when evaluating renal registries from countries and periods where electron microscopy is or was not used frequently. At last it is pivotal to mention that some studies only evaluated biopsy results but not clinical characteristics. This inevitable obscures data. A patient can have IgA nephropathy on biopsy and carry a diagnosis of IgA vasculitis. The pathologist might not be aware at the time of looking at his slides that the patient developed purpuric changes on his skin.

All that being said, IgA nephropathy *(12,3%)* is the most common primary glomerulonephritis in our cohort. I have to mention that two patients had underlying liver cirrhosis, so these two are technically speaking not primary diseases. Since I did not evaluate non proliferative glomerulopathies for secondary causes, it is fair to assume that some of these cases are also due to an underlying disease. With that in mind subtracting two patients makes a total of 60 which is still higher than the next most common primary glomerulopathy (membranous nephropathy) with 54 cases. IgA nephropathy is the most common primary glomerulonephritis not only in Europe, but also in Asian countries like China(84), Japan(85) and Singapore(86). This is in stark contrast to African countries in which minimal change disease and focal segmental glomerulosclerosis are the most frequent primary glomerulopathies(87). Yet, even in Europe there seems to be a high fluctuation of IgA nephropathy ranging between 12% and 21% between different countries. This may be explained because of different biopsy policies in different countries. Additional 13 patients showed an IgA (co-) dominant staining in our cohort but had purpuric skin changes when they underwent biopsy.

Depending if you were to classify ANCA associated glomerulonephritis as one, or three distinct diseases, the most prevalent secondary glomerulopathy is either systemic lupus erythematosus *(12,1%)* or ANCA associated glomerulonephritis *(13,2%)* subdivided into PR3-ANCA associated glomerulonephritis *(6,3%),* MPO-ANCA associated glomerulonephritis *(5,9%)* and ANCA negative glomerulonephritis *(1%).* Norway and the Netherlands reported the prevalence of ANCA associated glomerulonephritis to be ~10% in their countries. ANCA negative glomerulonephritis made up to 7,5% of patients with pauci immune pattern of injury in our cohort, compared to Norway with 8 out of 60 cases *(13,3%).* The rate of ANCA negativity in pauci immune glomerulonephritis is estimated to range between 85% and 95%(26). A paper published in Japan reported an annual incidence of MPO ANCA positive nephritis at around ~ 4% and PR3 ANCA positive patients at less than 0,5%(85). A publication from China reported elevated MPO ANCA in 92% of their patients with ANCA associated glomerulonephritis, compared to 8% of individuals with an increased PR3 ANCA level(88). In a cohort of 502 patients in North Carolina (USA) 283 patients were MPO ANCA positive *(56%)* and 219 had elevated PR3 ANCA *(43%)*(89). In Europe PR3 ANCA associated vasculitis has a higher frequency in northern Europe and MPO ANCA associated vasculitis is more common in southern Europe(90). The low frequency of PR3 ANCA positivity in Asia compared to our cohort and other cohorts in Europe and America suggests that either environmental factors or genetic factors play a role in the pathogenesis of ANCA associated disease.

One notable difference is that the prevalence of lupus nephritis is significantly higher in our cohort *(12,1%)* than in Germanys *(5%),* a country with similar ethnic make-up as Austria. The only country surpassing Austria is Serbia *(17,7%)* a country situated in the Balkans. In our cohort 73 people *(14,4%)* showed a lupus nephritis type of injury on renal biopsy. Six carried a diagnosis of mixed connective tissue disease and six did not meet the criteria for systemic lupus erythematosus. Four of them never had a positive ANA *(5,4%).* May Y Choi, Ann E Clarke et al.(91) showed that incidence of ANA negative ”SLE” in a cohort of 1137 patients was 6,2%. Some of the patients in our cohort were only a short time in our care, so they might test positive for ANA in the future.

IgA vasculitis (Henoch-Schonlein Purpura) has a slightly higher frequency rate in our patient population compared to other European countries. Newer evidence suggests that the incidence rate in IgA vasculitis is higher than previously reported(49). This might be due to

the fact that the revised classification criteria from EULAR/PRINTO/PRES (EPP) is not commonly applied. The EPP classification system has a higher sensitivity than the ACR classification system published in 1990(47) *(see table 1).* Fibrillary glomerulonephritis *(0,98%),* C3 glomerulopathy *(0,59%),* infection associated glomerulonephritis *(0,59%),* and Goodpasture's diseases *(0,79%),* each had less than 1,0% of total native biopsies. Added up they still contribute to 3,6%, a non-negligible amount. The only patient with Goodpasture's disease who did not present with pulmonal bleeding also happened to be the oldest patient, this is consistent with the literature on this topic(61). Two patients had in addition to highly elevated anti-GBM antibodies elevated (if only moderately) MPO ANCA. Dual positivity is reported in the literature to be 1/3-1/2 of cases with elevated anti-GBM autoantibodies(61, 62). All patients with C3 glomerulonephritis were male in our patient population. In contrast to a 10 year observation at Mayo clinic with 114 diagnosed patients showed a male to female ratio of 1,2:1(92).When comparing epidemiological and laboratory data between proliferative glomerulonephritis some differences clearly stand out. Notable sex ratios can be seen in systemic lupus erythematosus with 4-times more female patients than male patients. The female-based sex ratio in systemic lupus erythematosus has been shown in various studies to be around 9:1(92, 93). A systemic review of prevalence of biopsy-proven lupus nephritis reported the ratio as low as 1:1 in Pakistan compared to 8,4:1 in northern England(95). Ratios of 5:1 have been reported in the UK and China(95, 96), suggesting a higher rate of renal involvement in systemic lupus erythematosus in men than women. The most common classes in our cohort were class III and IV. Followed by class III +V, IV+V and V. I must mention that three of the ten patients classified with lupus nephritis class V had an additional classification of class I *(n=1)* and II *(n=2).* Using the International Society of Nephrology/Renal Pathology Society 2004 Classification of Lupus Nephritis, class V can only be combined with class III and IV(45) and mesangial hypercellularity may in fact be a part of class V, all three biopsies are grouped in class V. When correlating the average creatinine between lupus nephritis and lupus like nephritis the values were on average higher than those in patients with systemic lupus erythematosus. This can be explained, because in some cases renal biopsy was not performed for evaluating renal involvement in systemic lupus erythematosus. The 'lupus like nephritis' was an 'incidental' finding in addition to the primary cause driving the creatinine elevation. This also explains why some patients did not meet the classification criteria.

Patients with ANCA associated disease were on average older than patients with systemic lupus erythematosus and IgA nephropathy. Patients with MPO ANCA associated disease

were on average nine years older than patients with elevated PR3 ANCA. This observation was also made in other studies(89). In our patient cohort the age difference was only apparent in female patients. Females were on average 68 years of age in MPO associated glomerulonephritis compared to 53 years in PR3 associated GN. This is in contrast to male patients with an average age of 57 in MPO positive patients to 55 in PR3 positive patients.

In conclusion, the most common proliferative glomerulonephritis in our cohort are IgA nephropathy *(12,3%)* followed by lupus nephritis *(12,1%),* PR3 ANCA associated glomerulonephritis *(6,3%)* and MPO ANCA associated glomerulonephritis *(5,9%)*. I want to acknowledge the fact that my thesis is primarily laid out to be an epidemiological study and should be seen as such. Further studies are essential to confirm laboratory trends ascertained in this thesis. Patients with just incidental finding of glomerular disease were still counted as such, even though there was a 'more severe' pathological finding. This element has to be taken in consideration when evaluating laboratory data. Yet, our data clearly shows a trend in severity of different proliferative glomerulonpathies and how tubular atrophy (T-score) influences creatinine and clinical outcome.

I want to mention one notable finding. PTH, often used as a marker of chronicity, in ANCA associated glomerulonephritis *(PTH = 138)* is higher than in IgA nephropathy *(PTH = 103)* at renal biopsy. Yet, when comparing long term prognosis *(see table 14)* and creatinine change in both diseases. IgA nephropathy seem to have a worse prognosis. The average creatinine in IgA nephropathy at biopsy is 2,21 mg/dl compared to 3,29 mg/dl in ANCA associated glomerulonephritis. After 5 years the average creatinine in IgA nephropathy is 2,64 mg/dl and 1,88 mg/dl in ANCA associated glomerulonephritis *(see table 10),* suggesting that PTH elevation is not only a marker for chronicity but also elevated in acute renal failure.

It is astonishing how our knowledge of glomerular disease has transformed, since the first renal biopsies performed in humans, and with improvement of technique, it has become a safe procedure with a death rate of 0,02%(29). At the Medical University of Graz out of 239 evaluated biopsies severe complications requiring radiological intervention was seen in one patient *(0,4%)* compared to a meta-analysis which showed a 0,6% rate of angiographic interventions(29). No deaths have been reported in 238 biopsies. In 41 cases there was missing information in the hospital information system. Therefore, the patient's history could not be fully evaluated. This issue mainly affects post-biopsy ultrasonography information. Complications like macrohematuria were usually noted separately. It is fair to

assume that all these biopsies had no complications, at least no severe complications. There might be an artificial low number of ‘small’ hematomas.

7.1 Strengths and Weaknesses

One weakness of this study is that the retrospective data collection was extremely tedious and often difficult to acquire and had to be transferred by hand into a newly developed renal registry. Even though I worked meticulously, due to the large amount of data and far reaching topics human error cannot be ruled out. Patient information was collected in a handwritten notebook, and while we compared the results to a separate list from the pathology division and added missing patients, some biopsies may be missing in both lists.

One of the biggest strengths of this thesis is that it tries to unravel the bewildering terminology and gives a perspective on why universal nomenclature is essential for studying diseases. In addition to histopathology this thesis takes clinical context into consideration, further subclassifying glomerulopathies depending on clinical features, separating this thesis from many other epidemiological studies on biopsy proven glomerular disease. This thesis was primarily laid out to be an epidemiological study. Yet, there are several interesting findings besides epidemiological data. These can be interpreted as foundation for further scientific studies.

8. References

1. Johnson Richard J, Feehally J, Floege J, Marco T. Comprehensive Clinical Nephrology 6th Edition. Edinburgh, London, New York, Oxford, Philadelphia, St Louis, Sydney: Elsevier; 2019.
2. Gilbert Scott J, Weiner D. National Kidney Foundation Primer on Kidney Diseases. Philadelphia: Elsevier; 2014.
3. Rivera F. Frequency of renal pathology in Spain 1994-1999. Nephrol Dial Transplant. 2002;
4. McQuarrie EP, MacKinnon B, Young B, Yeoman L, Stewart G, Fleming S, et al. Centre variation in incidence, indication and diagnosis of adult native renal biopsy in Scotland. Nephrol Dial Transplant. 2009;
5. Maixnerova D, Jancova E, Skibova J, Rysava R, Rychlik I, Viklicky O, et al. Nationwide biopsy survey of renal diseases in the Czech Republic during the years 1994–2011. J Nephrol. 2014;
6. ITALIAN REGISTRY OF RENAL BIOPSIES [Internet]. [cited 2020 Apr 14]. Available from: http://www.irrb.net/images/M_images/MAC/table4.htm
7. Heaf J, Løkkegaard H, Larsen S. The epidemiology and prognosis of glomerulonephritis in Denmark 1985-1997. Nephrol Dial Transplant. 1999;
8. Brazdziute E, Miglinas M, Gruodyte E, Priluckiene J, Tamosaitis A, Bumblyte IA, et al. Nationwide renal biopsy data in Lithuania 1994–2012. Int Urol Nephrol. 2015;
9. ANNUAL REPORT 2018 The Norwegian Renal Registry [Internet]. [cited 2020 Apr 14]. Available from: https://www.nephro.no/nnr/AARSRAPPORT_NNR_2018_ToC.pdf
10. Jarrick S, Lundberg S, Welander A, Fored CM, Ludvigsson JF. Clinical validation of immunoglobulin A nephropathy diagnosis in Swedish biopsy registers. Clin Epidemiol. 2017;
11. Zink CM, Ernst S, Riehl J, Helmchen U, Gröne HJ, Floege J, et al. Trends of renal diseases in Germany: Review of a regional renal biopsy database from 1990 to

2013. Clin Kidney J. 2019;

12. Kurnatowska I, Jędrzejka D, Małyska A, Wągrowska-Danilewicz M, Danilewicz M, Nowicki M. Trends in the incidence of biopsy-proven glomerular diseases in the adult population in central poland in the years 1990-2010. Kidney Blood Press Res. 2012 May;35(4):254–8.

13. Riispere Ž, Ots-Rosenberg M. Occurrence of kidney diseases and patterns of glomerular disease based on a 10-year kidney biopsy material: A retrospective single-centre analysis in Estonia. Scand J Urol Nephrol. 2012 Oct;46(5):389–94.

14. 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;

15. Simon P, Ramée MP, Autuly V, Laruelle E, Charasse C, Cam G, et al. Epidemiology of primary glomerular diseases in a French region. Variations according to period and age. Kidney Int. 1994;

16. Covic A, Schiller A, Volovat C, Gluhovschi G, Gusbeth-Tatomir P, Petrica L, et al. Epidemiology of renal disease in Romania: A 10 year review of two regional renal biopsy databases. Nephrology Dialysis Transplantation. 2006.

17. Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. [cited 2020 Apr 14]; Available from: https://academic.oup.com/ndt/article-abstract/23/1/193/1924779

18. Van Paassen P, Van Breda Vriesman PJC, Van Rie H, Tervaert JWC. Signs and symptoms of thin basement membrane nephropathy: A prospective regional study on primary glomerular disease - The Limburg Renal Registry. In: Kidney International. 2004.

19. Hanko JB, Mullan RN, O'Rourke DM, McNamee PT, Maxwell AP, Courtney AE. The changing pattern of adult primary glomerular disease. Nephrol Dial Transplant. 2009;

20. Bright R. 1. Reports of Medical Cases, selected with a view of illustrating the symptoms and cure of Diseases, by a reference to Morbid Anatomy. Am J Med Sci. 1828;

21. Volhard F, Fahr T. Die Bright'sche Nierenkrankheit: Klinik, Pathologie und Atlas. (Bright's Kidney Disease: Clinic, Pathology and Atlas). Springer. Berlin, Heidelberg; 1914. 247–280 p.

22. Cameron JS, Hicks J. The origins and development of the concept of a "nephrotic syndrome." In: American Journal of Nephrology. 2002.

23. Glassock RJ, Fervenza FC, Hebert L, Cameron JS. Nephrotic syndrome redux. Nephrol Dial Transplant. 2015;

24. Addis T. Glomerular Nephritis. New York: The Macmillan Company; 1950.

25. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infectious Diseases. 2005.

26. Charles JJ, Olson JL, Silva FG, D'Agati VD. Heptinstall's pathology of the kidney. Heptinstall's Pathology of the Kidney. 2014.

27. Berger J, Hinglais N. Les ddpôts intercapillaires d'IgA-IgG. J d"urologie Nephrol. 1968;

28. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts ISD, Troyanov S, et al. The Oxford classification of IgA nephropathy: Rationale, clinicopathological correlations, and classification. Kidney Int. 2009;

29. Trachtman H, Herlitz LC, Lerma E V., Hogan JJ. Glomerulonephritis. Glomerulonephritis. Cham, Switzerland; 2019.

30. Packham DK HTYHECNKBGA renal failure in I nephropathy. Acute Renal Failure in IgA Nephropathy . Clin Nephrol [Internet]. 1994 [cited 2020 Jun 11];349–53. Available from: https://pubmed.ncbi.nlm.nih.gov/7882597/

31. Ellis A. NATURAL HISTORY OF BRIGHT'S DISEASE. CLINICAL, HISTOLOGICAL AND EXPERIMENTAL OBSERVATIONS. Lancet. 1942;

32. Stilmant MM, Bolton WK, Sturgill BC, Schmitt GW, Couser WG. Crescentic glomerulonephritis without immune deposits: Clinicopathologic features. Kidney Int. 1979;

33. Bacani RA, Velasquez F, Kanter A, Pirani CL, Pollak VE. Rapidly progressive (nonstreptococcal) glomerulonephritis. Ann Intern Med. 1968;69(3):463–85.

34. Gerald Appel, Andre A Kaplan. Overview of the classification and treatment of rapidly progressive (crescentic) glomerulonephritis - UpToDate [Internet]. [cited 2020 Feb 2]. Available from: https://www.uptodate.com/contents/overview-of-the-classification-and-treatment-of-rapidly-progressive-crescentic-glomerulonephritis?search=Rapidly progressive glomerulonephritis&source=search_result&selectedTitle=1~77&usage_type=default&display_rank=1

35. Mihatsch MJ. A Modern Classification of Glomerulonephritis. A Step Forward for the Pathologist. Pathol Res Pract. 1979;

36. Kincaid-Smith P, D'Apice AJF, Atkins RC. Progress in glomerulonephritis. New York, Chichester, Brisbane, Toronto: A Wiley Medical Publication; 1979.

37. Hoyer J, Kuhlmann U. Nephrologie : Pathophysiologie, Klinik, Nierenersatzverfahren. Stuttgart, New York: Thieme; 2015.

38. Cohen AS, Canoso JJ. Criteria for the classification of systemic lupus erythematosus—status 1972. Arthritis Rheum [Internet]. 1972 Sep 1 [cited 2020 Apr 30];15(5):540–3. Available from: http://doi.wiley.com/10.1002/art.1780150512

39. Tan EM, Cohen AS, Fries JF, Masi AT, Mcshane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum [Internet]. 1982 Nov 1 [cited 2020 Apr 30];25(11):1271–7. Available from: http://doi.wiley.com/10.1002/art.1780251101

40. Petri M, Orbai AM, Alarcõn GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the systemic lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012 Aug 1;64(8):2677–86.

41. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol [Internet]. 2019 [cited 2020 Apr 15];71(9):1400–12. Available from: https://drive.google.com/

42. Mixed Connective Tissue Disease. Br Med J. 1972 Nov 11;4(5836):315.

43. KDIGO GN Guideline update-Evidence summary Lupus nephritis [Internet]. [cited 2020 May 6]. Available from: https://kdigo.org/wp-content/uploads/2018/08/Chap-12-Lupus-nephritis-evidence-summary_final_profiles.pdf

44. Agnes B. Fogo MK. Diagnostic Atlas of Renal Pathology. Third Edition. Agnes B. Fogo MK, editor. Diagnostic Atlas of Renal Pathology. Elsevier; 2017. 19–294 p.

45. Weening JJ, D'agati VD, Schwartz MM, Seshan S V, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Vol. 65, Kidney International. 2004.

46. Monteiro RC. New insights in the pathogenesis of IgA nephropathy. Nefrologia. 2005;25(SUPPL.2):82–6.

47. Hočevar A, Rotar Z, Jurčić V, Pižem J, Čučnik S, Vizjak A, et al. IgA vasculitis in adults: The performance of the EULAR/PRINTO/PRES classification criteria in adults. Arthritis Res Ther. 2016 Mar 2;18(1).

48. Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of henoch-schönlein purpura. Arthritis Rheum. 1990;33(8):1114–21.

49. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010 May;69(5):798–806.

50. Newell GC. Cirrhotic Glomerulonephritis: Incidence, Morphology, Clinical Features, and Pathogenesis. Am J Kidney Dis. 1987 Mar 1;9(3):183–90.

51. 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.

52. 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;

53. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al.

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Vol. 75, Annals of the Rheumatic Diseases. BMJ Publishing Group; 2016. p. 1583–94.

54. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: The role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum. 2012 Oct;64(10):3452–62.

55. Masani N, Jhaveri KD, Fishbane S. Update on membranoproliferative GN. Clin J Am Soc Nephrol. 2014;

56. Smith RJH, Appel GB, Blom AM, Cook HT, D'Agati VD, Fakhouri F, et al. C3 glomerulopathy — understanding a rare complement-driven renal disease. Vol. 15, Nature Reviews Nephrology. Nature Research; 2019. p. 129–43.

57. D'Agati VD, Bomback AS. C3 glomerulopathy: What's in a name. Vol. 82, Kidney International. Nature Publishing Group; 2012. p. 379–81.

58. Goodpasture WE. The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci. 1919;158:863.

59. STANTON MC, TANGE JD. Goodpasture's syndrome (pulmonary haemorrhage associated with glomerulonephritis). Australas Ann Med. 1958 May 1;7(2):132–44.

60. Jones DA, Jennette JC, Falk RJ. Goodpasture's syndrome revisited. A new perspective on glomerulonephritis and alveolar hemorrhage. N C Med J. 1990 Aug 1;51(8):411–5.

61. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med. 2001 Jun 5;134(11):1033–42.

62. Bosch X, Mirapeix E, Font J, Borrellas X, Rodriguez R, Lopez-Soto A, et al. Prognostic implication of anti-neutrophil cytoplasmic autoantibodies with myeloperoxidase specificity in anti-glomerular basement membrane disease. Clin Nephrol. 1991;

63. McAdoo SP, Tanna A, Hrušková Z, Holm L, Weiner M, Arulkumaran N, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal

survival, frequency of relapse, and outcomes compared to single-seropositive patients. Kidney Int. 2017 Sep 1;92(3):693–702.

64. Churg J, Bernstein J, Glassock RJ. Renal disease : classification and atlas of glomerular diseases. Igaku-Shoin, New York, Tokyo: Igaku-Shoin; 1995. 541 p.

65. Wyatt RJ, Julian BA. MEdical progress: IgA nephropathy. Vol. 368, New England Journal of Medicine. Massachussetts Medical Society; 2013. p. 2402–14.

66. Konstantinov K, Emil S, Barry M, Kellie S TA. Glomerular disease in patients with infectious processes developing antineutrophil cytoplasmic antibodies. Hindawi Publ Corp. 2013;18.

67. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. Vol. 377, New England Journal of Medicine. Massachussetts Medical Society; 2017. p. 2363–74.

68. Nasr SH, Fidler ME, Valeri AM, Cornell LD, Sethi S, Zoller A, et al. Postinfectious glomerulonephritis in the elderly. J Am Soc Nephrol. 2011 Jan 1;22(1):187–95.

69. KDIGO Clinical Practice Guideline for Glomerulonephritis KDIGO [Internet]. 2012 [cited 2020 Feb 11]. Available from: http://www.kidney-international.org

70. Mandai S, Aoyagi M, Nagahama K, Arai Y, Hirasawa S, Aki S, et al. Renal Failure Post-Staphylococcal infection Henoch-Schönlein purpura nephritis: a case report and review of the literature) Post-Staphylococcal infection Henoch-Schönlein purpura nephritis: a case report and review of the. Ren Fail [Internet]. 2013 [cited 2020 May 6]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=irnf20

71. Mandai S, Aoyagi M, Nagahama K, Arai Y, Hirasawa S, Aki S, et al. Post-Staphylococcal infection Henoch-Schönlein purpura nephritis: A case report and review of the literature. Vol. 35, Renal Failure. 2013. p. 869–74.

72. Satoskar AA, Molenda M, Shim R, Zirwas M, Variath RS, Brodsky S V., et al. Henoch-Schönlein purpura-like presentation in IgA-dominant staphylococcus infectionassociated glomerulonephritis - A diagnostic pitfall. Clin Nephrol. 2013 Apr;79(4):302–12.

73. Alpers CE, Kowalewska J. Fibrillary glomerulonephritis and immunotactoid

glomerulopathy. J Am Soc Nephrol. 2008 Jan 1;19(1):34–7.

74. Nasr SH, Vrana JA, Dasari S, Bridoux F, Fidler ME, Kaaki S, et al. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis. Kidney Int Reports. 2018;3(1):56–64.

75. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of Single Voided Urine Samples to Estimate Quantitative Proteinuria. N Engl J Med. 1983 Dec 22;309(25):1543–6.

76. Schwab SJ, Christensen RL, Dougherty K, Klahr S. Quantitation of Proteinuria by the Use of Protein-to-Creatinine Ratios in Single Urine Samples. Arch Intern Med. 1987 May 1;147(5):943–4.

77. Chan S, Oliver KA, Gray NA. An association between membranoproliferative glomerulonephritis and metastatic colorectal carcinoma: a case report. J Med Case Rep [Internet]. 2016 Dec 20 [cited 2020 May 6];10(1):199. Available from: http://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-016-0979-3

78. Pai P, Bone J.M, McDicken I, Bell G.M. Solid tumour and glomerulopathy. QJM. 1996;89:361–7.

79. Usalan C, Emri S. Membranoproliferative glomerulonephritis associated with small cell lung carcinoma. Int Urol Nephrol. 1998;30(2):209–13.

80. Ryu JH, Chung SS, Ryu DR, Kim SJ, Kang DH, Sung SH, et al. A case of membranoproliferative glomerulonephritis associated with metastatic colon cancer. Vol. 28, Korean Journal of Internal Medicine. Korean Association of Internal Medicine; 2013. p. 254–7.

81. Sethi S, Fervenza F. Standardized Classification and reporting of glomerulonephritis. Nephrol Dial Transplant. 2019;34:193–9.

82. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011 Dec 22;365(25):2398–411.

83. D'Agati V. The many masks of focal segmental glomerulosclerosis. Kidney Int. 1994;46(4):1223–41.

84. Yang Y, Zhang Z, Zhuo L, Chen DP, Li WG. The Spectrum of Biopsy-Proven

Glomerular Disease in China: A Systematic Review. Vol. 131, Chinese Medical Journal. Wolters Kluwer Medknow Publications; 2018. p. 731–5.

85. 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;17(2):155–73.

86. Woo KT, Chan CM, Lim C, Choo J, Chin YM, Teng WL, et al. Changes in primary glosmerulonephritis in Singapore over four decades. Clin Nephrol. 2019 Mar 1;91(3):155–61.

87. Okpechi IG, Ameh OI, Bello AK, Ronco P, Swanepoel CR, Kengne AP. Epidemiology of histologically proven Glomerulonephritis in Africa: A systematic review and meta-analysis. PLoS One. 2016 Mar 1;11(3).

88. Hong Y, Shi P, Liu X, Yang L, Li K, Xu F, et al. Distinction between MPO-ANCA and PR3-ANCA-associated glomerulonephritis in Chinese patients: a retrospective single-center study. Clin Rheumatol [Internet]. 2019 Jun 8 [cited 2020 May 7];38(6):1665–73. Available from: http://link.springer.com/10.1007/s10067-019-04458-9

89. Jennette JC, Nachman PH. ANCA glomerulonephritis and vasculitis. Clin J Am Soc Nephrol. 2017 Oct 1;12(10):1680–91.

90. Scott DGI, Watts RA. Epidemiology and clinical features of systemic vasculitis. Vol. 17, Clinical and Experimental Nephrology. 2013. p. 607–10.

91. Choi MY, Clarke AE, St. Pierre Y, Hanly JG, Urowitz MB, Romero-Diaz J, et al. Antinuclear Antibody–Negative Systemic Lupus Erythematosus in an International Inception Cohort. Arthritis Care Res. 2019 Jul 1;71(7):893–902.

92. Ravindran A, Fervenza FC, Smith RJH, De Vriese AS, Sethi S. C3 Glomerulopathy: Ten Years' Experience at Mayo Clinic. Mayo Clin Proc. 2018 Aug 1;93(8):991–1008.

93. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: An update. Vol. 30, Current Opinion in Rheumatology. Lippincott Williams and Wilkins; 2018. p. 144–50.

94. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult

systemic lupus erythematosus in California and Pennsylvania in 2000: Estimates obtained using hospitalization data. Arthritis Rheum. 2007 Jun;56(6):2092–4.

95. Wang H, Ren Y Le, Chang J, Gu L, Sun LY. A systematic review and meta-analysis of prevalence of biopsy-proven lupus nephritis. Arch Rheumatol. 2018 Mar 1;33(1):17–25.

96. Patel M, Clarke AM, Bruce IN, Symmons DPM. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: Evidence of an ethnic gradient. Arthritis Rheum [Internet]. 2006 Sep 1 [cited 2020 May 7];54(9):2963–9. Available from: http://doi.wiley.com/10.1002/art.22079

97. Pan Q, Li Y, Ye L, Deng Z, Li L, Feng Y, et al. Geographical distribution, a risk factor for the incidence of lupus nephritis in China. BMC Nephrol [Internet]. 2014 May 1 [cited 2020 May 7];15(1):67. Available from: http://bmcnephrol.biomedcentral.com/articles/10.1186/1471-2369-15-67