ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΠΜΣ

«ΕΠΙΔΗΜΙΟΛΟΓΙΑ - ΜΕΘΟΔΟΛΟΓΙΑ ΕΡΕΥΝΑΣ ΣΤΙΣ ΒΙΟΪΑΤΡΙΚΕΣ ΕΠΙΣΤΗΜΕΣ, ΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ ΚΑΙ ΤΗ ΔΗΜΟΣΙΑ ΥΓΕΙΑ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Ανάλυση από το Εθνικό Αρχείο Καταγραφής των ασθενών με Εστιακή Τμηματική Σπειραματοσκλήρυνση (Focal Segmental Glomerulosclerosis) στην Ελλάδα.

ΙΩΑΝΝΗΣ ΕΛ. ΜΙΧΕΛΑΚΗΣ

ΑΘΗΝΑ, ΕΤΟΣ 2022

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
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NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

ATHENS MEDICAL SCHOOL

Association of clinical and laboratory characteristics with remission, relapsing disease and kidney function impairment long-term in patients with Primary Focal Segmental Glomerulosclerosis: a retrospective cohort analysis from the Greek Registry.

IOANNIS EL. MICHELAKIS

ATHENS, 2022

Η παρούσα Διπλωματική Εργασία εγκρίθηκε τη 10η Νοεμβρίου 2022.

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I. ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η Εστιακή Τμηματική Σπειραματοσκλήρυνση (ΕΤΣΣ) αποτελεί ένα ιστολογικό πρότυπο σπειραματικής βλάβης, κοινό σε διάφορες νεφρικές παθήσεις, παρά μία ξεχωριστή νοσολογική οντότητα (Shabaka, Tato Ribera and Fernández-Juárez, 2020). Ένας μη τεκμηριωμένος μέχρι σήμερα παράγοντας διαπερατότητας προκαλεί βλάβη των ποδοκυττάρων και ποικίλου βαθμού εξάλειψη των προσεκβολών τους. Μπορεί να διακριθεί σε πρωτοπαθή, δευτεροπαθή και γενετική μορφή, με βάση την αιτιοπαθογένεια της βλάβης. Η πρωτοπαθής μορφή εκδηλώνεται κλινικά ως βαρύ νεφρωσικό σύνδρομο με ή χωρίς επηρεασμένη νεφρική λειτουργία και υπέρταση. Τόσο η παθογένεια, όσο και τα ιστολογικά πρότυπα, αλλά και η κλινική πορεία και εξέλιξη παρουσιάζουν μεγάλη ετερογένεια. Παρουσιάζουμε δεδομένα από το Πανελλήνιο Αρχείο καταγραφής ασθενών με ΕΤΣΣ μη δευτεροπαθούς αιτιολογίας.

Σκοπός: Περιγραφή των κλινικών και εργαστηριακών χαρακτηριστικών μιας μεγάλης κοόρτης ενήλικων ασθενών με πρωτοπαθή FSGS και συσχέτιση με την κλινική πορεία της νόσου.

Υλικό και Μέθοδος: Μελετήθηκαν 580 ασθενείς (35% γυναίκες), μέσης ηλικίας 46 ετών, όλοι με ιστολογική τεκμηρίωση ΕΤΣΣ και απουσία σαφούς δευτεροπαθούς αιτίου, από 21 νεφρολογικά κέντρα στην Ελλάδα. Δεδομένα καταγράφηκαν από το 1986 και ο μέσος χρόνος παρακολούθησης ήταν τα 7 έτη. Για την περιγραφή των κλινικών και εργαστηριακών χαρακτηριστικών ενήλικων ασθενών με πρωτοπαθή ΕΤΣΣ και τη διερεύνηση συσχετίσεων μεταξύ αυτών με την ανταπόκριση στη θεραπεία και την μακροχρόνια έκβαση των ασθενών, εφαρμόστηκαν μοντέλα λογαριθμιστικής παλινδρόμησης και αναλογικών κινδύνων.

Αποτελέσματα: Κατά την έναρξη της παρακολούθησης, το 60% των ασθενών είχαν καλώς διατηρημένη νεφρική λειτουργία (GFR >60 ml/min), ενώ πλέον του 50% εμφάνιζαν νεφρωσικού επιπέδου πρωτεϊνουρία και σοβαρή υποαλβουμιναιμία. Ανοσοκατασταλτική αγωγή έλαβαν οι ασθενείς (42%) με βαρύ νεφρωσικό σύνδρομο, με συνήθεις θεραπευτικές επιλογές τα κορτικοστεροειδή, τους αναστολείς καλσινευρίνης ή συνδυασμούς των ανωτέρω. 29% συνδυασμό κορτικοστεροειδών με κυκλοσπορίνη. Ύφεση (πλήρη ή μερική) εμφάνισε το 78% (385 ασθενείς), με την πλειονότητα αυτών να έχουν λάβει ανοσοκατασταλτική αγωγή (76% των ασθενών με πλήρη ύφεση Vs. 51% των ανθεκτικών περιπτώσεων, p<0.001). Από το πολυπαραγοντικό μοντέλο τακτικής λογαριθμιστικής παλινδρόμησης, η ηλικία (COR:1.02, p=0.01), μικρότερες τιμές του δείκτη μάζας σώματος (COR:0.93, p=0.007), ο υψηλός ρυθμός σπειραματικής διήθησης (COR:1.01, p=0.001) και η χορήγηση ανοσοκατασταλτικών (COR:2.38, p=0.001), αναδείχθηκαν ανεξάρτητοι παράγοντες που σχετίστηκαν με αυξημένες πιθανότητες για πλήρη ανταπόκριση στη θεραπεία, έναντι επίτευξης μερικής ή καθόλου απάντησης. Οι ασθενείς οι οποίοι εμφάνισαν υποτροπή της νόσου μετά από ύφεση είχαν βαρύτερη νόσο κατά τη διάγνωση (υψηλότερες τιμές πρωτεϊνουρίας και σοβαρότερη υποαλβουμιναιμία, p<0.001) και υψηλότερο BMI, ενώ το 19% Vs. 2.5% όσων ήταν ελεύθεροι υποτροπών (p<0.01) εμφάνισαν νεφρική νόσο τελικού σταδίου. Ο ισχυρότερος παράγοντας πρόγνωσης της μακροχρόνιας εξέλιξης της ΕΤΣΣ σε τελικό στάδιο ή θάνατο ήταν η ανταπόκριση, τόσο πλήρης, όσο και μερική (HR: 0.03 και 0.19, αντίστοιχα, p<0.001), ανεξαρτήτως πρωτεϊνουρίας στη διάγνωση. Διατηρημένη νεφρική λειτουργία σχετίστηκε με υψηλότερες πιθανότητες επίτευξης πλήρους, παρά μερικής ή καθόλου ανταπόκρισης. Τα ευρήματα αυτά διατηρήθηκαν και σε υποαναλύσεις μεταξύ μόνο των ασθενών με νεφρωσικό σύνδρομο στη διάγνωση και αυτών που έλαβαν ανοσοκατασταλτικά. Στο τέλος της παρακολούθησης, 92 ασθενείς (16%) είχαν ενταχθεί σε αιμοκάθαρση και 24 (4%) είχαν αποβιώσει.

Συμπέρασμα: Η ΕΤΣΣ είναι μία ιδιοπαθής σπειραματική πάθηση με συχνά δυσμενή έκβαση. Ωστόσο, η ανταπόκριση στη θεραπεία οδηγεί σε καλά μακροπρόθεσμα αποτελέσματα.

Λέξεις-Κλειδιά: ΕΤΤΣ, σπειραματοπάθεια, ύφεση, υποτροπή, ανοσοκατασταλτικά, ΧΝΝ-ΤΣ, θάνατος.

II. ABSTRACT

Introduction: Focal Segmental Glomerulosclerosis (FSGS) is a histologic lesion and one of the most common primary glomerular diseases to terminate in end-stage renal disease (ESRD). FSGS pathogenesis involves a putative circulating factor, not identified to date, which cause damage to the podocytes and foot process effacement. Clinically is presented with nephrotic syndrome, various kidney damage impairment and hypertension. There are variable histopathologic features, each one related with different prognosis and clinical course. The study presents a summary of basic clinical and laboratory characteristics of patients from the Greek Registry of Primary FSGS.

Objective: The description of basic clinical and laboratory characteristics of a large cohort of adults with primary FSGS and the association with the clinical course of the disease.

Materials & Methods: A total of 580 patients (35% females) were analyzed, with a median age of 46 years old, all with biopsy-proven FSGS and without presumable secondary etiology of the disease, from 21 different nephrology departments in the Greek territory. Demographic and laboratory patients' characteristics were recorded since 1986 and the median time of follow-up was 7 years. Ordinal logistic and COX regression analyses were performed to estimate the effect of baseline parameters on remission and progression to ESRD or death.

Results: At the initial assessment, around 60% of the patients had preserved renal function (GFR >60 ml/min). Treatment was administered in 319 patients, based on their clinical features of nephrotic-range proteinuria and hypoalbuminemia. Corticosteroids and calcineurin inhibitors were the main treatment regimens, either as initial therapy or for the relapsing disease. Complete or partial remission were induced in 385 patients (78%), with the vast majority of whom to be under immunosuppressive therapy (76% of complete responders Vs. 51% of non-

responders, p<0.001). Age (COR:1.02, p=0.01), optimal BMI (COR:0.93, p=0.007), greater GFR (COR:1.01, p=0.001) and immunosuppressants (COR:2.38, p=0.001) were strongly related with higher probability of complete over partial or none remission after performing multivariate ordinal logistic regression analysis. Patients who relapsed after either remission were those who presented with heavier proteinuria and severe hypoalbuminemia (p<0.001) and greater BMI than those who never relapsed, while 19% Vs. only 2.5% of the latter (p<0.01) progressed to ESRD. Complete and partial remission were strongly correlated (HR: 0.03 και 0.19, αντίστοιχα, p<0.001) with a better prognosis in terms of renal and patient survival, adjusting for the level of proteinuria at diagnosis. Preserved kidney function was also associated with longer time to ESRD or death in the multivariate analysis, common findings in the subgroups of those with nephrotic syndrome or those who were treated with immunosuppressants. At 7 years of follow-up, 92 patients (16%) were on renal replacement therapy and 24 (4%) died.

Conclusion: Primary FSGS is a glomerular disease with increasing rate of progression to ESRD. The therapeutic goal is to achieve complete or partial remission, as it preserves the renal function and is related with longer renal survival.

Keywords: FSGS, podocytopathies, remission, relapse, immunosuppressants, ESRD, death.

III. INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histologic pattern of glomerular injury, rather than a specific disease entity (Deegens, Steenbergen and Wetzels, 2008). It is caused by diverse clinicopathological etiologies, each one with a different mechanism, with the podocyte injury and depletion to be the main themes of lesion (Haas *et al.*, 1997). It is characterized of sclerosis in parts (*segmental*) of at least one glomerulus (*focal*) in a kidney biopsy specimen. It concerns one of the leading causes of kidney disease worldwide, a common underlying lesion found in adults and children with nephrotic syndrome (40% and 20% respectively) (Sprangers, Meijers and Appel, 2016). Several studies have reported FSGS as one of the most prevalent primary glomerulopathy to terminate in end-stage renal disease (ESRD) and the leading glomerular lesion of ESRD in the US. More specifically, around 50% to 70% of patients with persistent nephrotic proteinuria reach ESRD in less than a decade after diagnosis; one of the worst prognosis among primary glomerular diseases (Braden *et al.*, 2000, Sprangers, Meijers and Appel, 2016). Racial background strongly affects the risk for progression to ESRD, with patients of black race to have a greater risk than white individuals. The diagnosis depends on the integration of medical history, clinical and laboratory findings and renal histopathology.

III.I Epidemiology

The absolute incidence and prevalence are difficult to ascertain, given the variations in accessibility, indications and mainly the pathology support for kidney biopsy globally. A systematic review on 2011 (McGrogan, Franssen and de Vries, 2011), reported an annual incidence rate ranging from 0.2-1.8/100.000 population/year. The prevalence of FSGS and its association with ESRD seem to be increasing worldwide, especially relatively to other glomerular diseases (Rosenberg and Kopp, 2017). The factors responsible for the increasing rates of

FSGS are largely unknown; some of the increase, however, may be likely attributable to the broader list of indications for kidney biopsy and its wider availability across the years. Obesity and chronic inflammation are to be incriminated, as well, but data are lacking to justify it.

As a lesion is one of the most common diagnoses in patients with nephrotic syndrome in the United States, accounting for about 30-35% of all cases (Haas *et al.*, 1997) and is the leading primary glomerulopathy identified in adults with ESRD in the US. Back in 1980, only 0.2% of patients with ESRD was diagnosed with FSGS, with the accountable percent by 2000 to be 2.3%, noting an 11-fold increase (Kitiyakara, Eggers and Kopp, 2004). In other countries, by comparison, the lesion of FSGS is a less common cause of nephrotic syndrome and ESRD, with membranous nephropathy, minimal change disease, diabetic nephropathy and lupus nephritis to be mainly reported (Glassock, 2014). There are several reasons for this discrepancy. The main one is that most data originating from the US considered FSGS a single histopathological entity and did not distinguish primary and secondary FSGS. These two entities are characterized by different etiologies, pathophysiologic mechanisms and prognosis.

FSGS can occur at any age; around 7-10% of cases in children and 20-30% in adults with nephrotic syndrome are to be attributed at FSGS. The black race has a fourfold higher lifetime risk for ESRD than the Whites and Asians, and males seem to be at 1.5 to 2-fold greater risk than females (Korbet *et al.*, 1996)

III.II Classification

Classification of FSGS is multifaceted and includes a variety of considerations; pathophysiologic, histologic and genetic ones. The main factor distinguishing each class from each other is the cause of the histologic pattern (D'Agati *et al.*, 2004).

Primary FSGS

It is a distinct entity and is best defined when other types cannot be clearly substantiated. It is quite likely that patients with the diagnosis of primary FSGS would be reassigned when new genes and environmental factors will be further evaluated. Most often presents with nephrotic-range proteinuria and/or nephrotic syndrome, with low albumin levels in plasma and hyperlipidemia. The *tip*, *collapsing* and *not otherwise specified (NOS)* type are the histological manifestations of primary FSGS. It is the most common form in adolescents and young adults, but it can occur at any age (De Vriese *et al.*, 2018). Biopsy specimens from patients with primary FSGS show complete foot process effacement, a characteristic finding in this form of the disease. The basis of therapy for primary FSGS are immunosuppressive agents, including glucocorticoids and calcineurin inhibitors.

Secondary FSGS

This entity concerns FSGS that develops as an adaptive response to glomerular hypertrophy or hyperfiltration. For that reason, many researchers refer to that type of the lesion as adaptive, or more accurately post-adaptive FSGS (Barisoni, Schnaper and Kopp, 2007). Disorders associated with reduced renal mass and renal vasolidation includes unilateral renal agenesis, prematurity, small gestation age and renal nephropathy. Drugs and toxins (heroin, interferon, pamidronate), as well as viral infections (particularly HIV-1, CMV, EBV), have been described as potential causes of secondary FSGS, by causing damage to the podocytes. It often presents with non-nephrotic range proteinuria and a degree of kidney function impairment, with total glomerular filtration rate (GFR) often at normal or even elevated levels at the time of diagnosis and normal serum albumin. Findings in renal biopsy supportive of secondary FSGS include large glomeruli, perihilar scars among glomeruli and partial foot process effacement (De Vriese *et al.*,

2018).Patients with secondary FSGS are treated with general supportive measures, such as blood pressure control and dietary sodium and protein restriction.

Genetic FSGS

It refers to patients with either susceptibility genes, particularly *APOL1* gene, (Kopp *et al.*, 2011) or patients with high-penetrance mutations, manifested by Mendelian or maternal inheritance. Up to 38 genes have been described to be associated with FSGS, with this number to rise every year due to the dissemination of whole-exome sequencing techniques (Lepori *et al.*, 2018). Many genes have been associated with extra-renal manifestations as well. Patients may present with massive proteinuria and nephrotic syndrome at early childhood and it is supported that every family member with a child who has FSGS should undergo a genetic test. Therapy for genetic FSGS is generally conservative, based on the renin – angiotensin – aldosterone system (RAAS) antagonism.

FSGS of unknown cause

Those type of FSGS lesion refers to cases when clinical and histopathologic findings on renal biopsy are similar to those of secondary FSGS, but a clear etiology cannot be determined, despite extensive evaluation and genetic analysis.

III.III Pathologic Features and Pathogenesis

Damage to the podocyte is the initial event in the pathogenetic process and diffuse foot process effacement is the earliest pathologic manifestation seen in the development of FSGS. A putative circulating factor, toxic to the podocyte, causes generalized podocyte dysfunction, manifested by widespread foot process effacement (Rosenberg and Kopp, 2017). The identity of these factors has not yet

been clearly established (Savin *et al.*, 1996). Specific observations in renal grafts, nevertheless, support the existence of such toxic factors; in patients developing FSGS posttransplant, remission of proteinuria with plasmapheresis (Deegens *et al.*, 2004) and Induction of proteinuria in rats that were administered serum from FSGS patients (Le Berre *et al.*, 2000). The pathogenesis involves almost certainly different circulating factors, but there is no factor conclusively shown to underlay all forms of primary FSGS. Putative circulating permeability factors include the soluble form of the urokinase plasminogen activator receptor (suPAR) (Shankland and Pollak, 2011), cardiotrophin-like cytokine factor 1 (CLCF1) (Sharma *et al.*, 2015) and microRNAs (Gebeshuber *et al.*, 2013). suPAR acts via activation of integrins, which play a role in the regulation of mature foot process and the adhesion to the glomerular basement membrane (Shankland and Pollak, 2011). CLCF1 has been detected in high levels in the plasma of patients with recurrent FSGS and its role continues to be investigated, while the expression of specific microRNAs inhibits the expression of several genes important for the podocyte function.

The histologic findings are indistinguishable on light microscopy (LM) between primary and secondary FSGS, with an exception of the collapsing type, which will be discussed in the next section (De Vriese *et al.*, 2018). Electron microscopy (EM) examination of the kidney biopsy better assesses the extent of podocyte foot process effacement and help in differentiating primary from secondary FSGS. In particular, primary FSGS is associated with diffuse foot process effacement (image 1), while this abnormality is commonly segmental in the secondary forms.

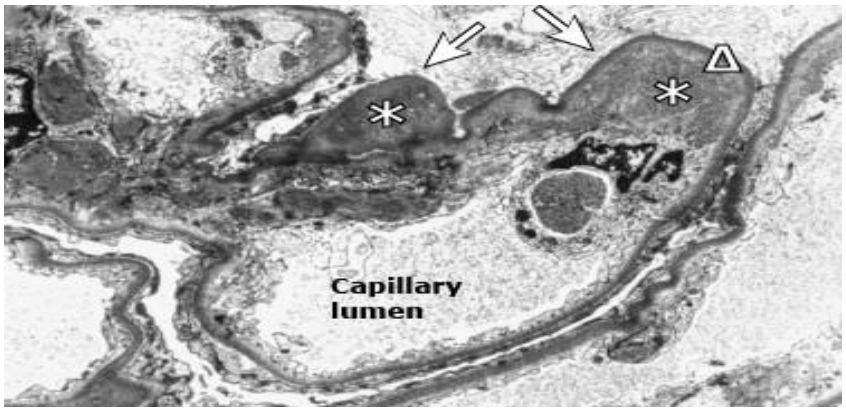


Image 1. Electron micrograph in FSGS shows diffuse epithelial cell foot process fusion (arrows). Deposits of hyaline (*) are found under the glomerular basement membrane (Δ) (Courtesy of Helmut Rennke, MD).

Secondary FSGS denotes the pattern of glomerulosclerosis that develops in the course of a number of renal diseases in which there is reduced number of functioning nephrons or hemodynamic stress on an initial normal nephron population. It is most common in the setting of obesity, hypertensive nephrosclerosis, sickle cell anemia and processes with significant loss of functioning nephrons. Glomerular hypertrophy is a constant finding in light microscopy. Most forms of secondary FSGS have discrete segmental scars, involving the perihilar regions of hypertrophied glomeruli. By contrast, podocyte hypertrophy and hyperplasia are less frequent than in primary type. Moreover, the degree of foot process fusion is mild in general, affecting less than 50% of the total glomerular capillary surface area. Due to the fact that there is a variability in the etiologies and patterns of secondary form, the extent of foot process fusion cannot be used as an absolute criterion to distinguish primary from secondary FSGS.

In the context of pathogenesis, glomerulosclerosis of secondary FSGS results as an adaptive response to hypertrophy and hyperfiltration of the glomerulus. Reduced renal mass, reflux nephropathy, ischemia, congenital renal absence or surgical removal, result in intraglomerular hypertension and hypertrophy in the remaining glomeruli. Increased wall tension causes mechanical stress on the

connection between glomerular basement membrane (GBM) and podocytes, leading to dilatation of capillaries. If the tension on the podocytes is severe and prolonged, they are detached from the GBM, promoting cell auto-injury via the lysosomal system (Nagata and Kriz, 1992). The detachment of podocytes is the first committed lesion to segmental sclerosis.

Because the development of FSGS is an adaptive mechanism, a response to a loss of functioning nephrons, the majority of patients have chronic renal insufficiency, preceding for months or even years the development of nephrotic proteinuria. Exception to the above is the FSGS due to obesity – for many experts it should be studied alone as Obesity-related glomerulopathy (Kambham *et al.*, 2001) – in which patients have supernormal GFR, reflecting a hyperfiltration state by an increased body to renal mass ratio (Darouich *et al.*, 2011). Sleep apnea and hypoxia seem to play a key role in the development of the disease, through the activation of renin-angiotensin system.

Segmental areas of glomerulosclerosis can be induced also in patients with initially normal renal mass, in conditions such as diabetic nephropathy and sickle cell anemia.

Heroin abuse may be associated with FSGS, with the pathogenesis of heroin nephropathy to remain uncertain. Administration of several drugs, such as interferon-alpha (IFN-α), bisphosphonates (particularly pamidronate), anabolic steroids, and anthracyclines has been reported to produce a direct nephrotoxic effect on podocytes. FSGS lesions have also been reported in a number of viral infections, particularly with HIV, causing mainly the collapsing variant of FSGS.

It is remarkable, that in a recent clinicopathological study that distinguished primary from secondary FSGS, it was, as previously reported, observed that the incidence rate of FSGS is increasing; the proportion, however, between these two types has remained stable the last three decades (Hommos *et al.*, 2017).

In general, morphologic characteristics seen on kidney biopsy cannot distinguish between genetic and non-genetic forms.

III.IV Histologic Variants

FSGS comprises a number of morphologic subtypes, with noteworthy differences in therapeutic strategies and prognosis. Five main light microscopy patterns have been defined, based upon Columbia classification (D'Agati, Kaskel and Falk, 2011):

- *not otherwise specified (NOS)*,
- *collapsing*,
- *tip*,
- *perihilar* and
- *cellular* variants.

It is a common belief that these patterns do not reflect different pathogenetic mechanisms of development, but probably they are the consequence of differences in the severity and the extent of podocyte injury.

FSGS NOS

To make the histologic diagnosis of FSGS NOS, the collapsing, tip, perihilar and cellular variants must be excluded (D'Agati, 2003). It constitutes the generic lesion FSGS, with the terms *classic FSGS* or *usual type FSGS* to be common synonyms in the literature. It is the most common morphologic pattern and reviews of repeat biopsies examinations suggest that all the other variants can evolve into this pattern over time, as the diseases progresses and chronic lesions are increasing.

FSGS NOS is characterized on light microscopy by segmental areas of mesangial collapse and sclerosis in some glomeruli, but not in all (image 2). The number of

glomeruli affected by segmental lesions depends on the severity of the disease, but also the number of serial sections examined. Mild mesangial hypercellularity and partial occlusion of the capillary lumens by hyaline deposits are commonly seen.

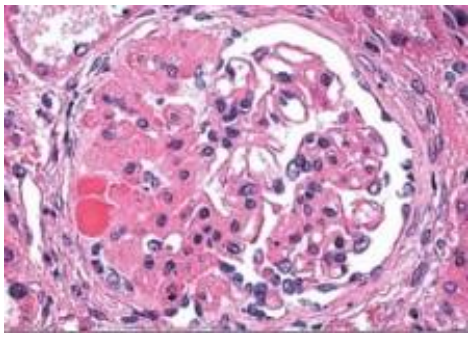


Image 2. FSGS NOS does not meet the criteria for any different variable. Foot-process effacement is the main finding in a biopsy-specimen (D'Agati, 2003).

Immunofluorescence microscopy does not reveal immune deposits, except for what may represent non-specific binding of immunoglobulin M (IgM) and complement (C3 and C1) in sclerotic lesions.
By electron microscopy, the lesions of segmental sclerosis display wrinkling and retraction of GBM and accumulation of inframembranous hyaline, resulting in narrowing or even occlusion of the glomerular capillary lumina.

Directly overlying the lesions of segmental sclerosis there usually is complete foot process effacement, with podocyte hypertrophy. Detachments of the podocytes may be present as well.

Collapsing FSGS

The designation of collapsing – also known as *collapsing glomerulopathy* – is applied to cases in which at least one glomerulus displays segmental or global obliteration of the glomerular capillary lumina by wrinkling and collapse of GBM. The glomerular collapse must be accompanied by striking hypertrophy and hyperplasia of the overlying podocytes, which have enlarged, open vesicular nuclei with nucleoli and rarely mitotic figures (image 3). Podocytes display a dysregulated

phenotype of increased rates in proliferation and apoptosis. They become less cohesive and may actually detach and shed into the urinary space. Unlike FSGS NOS, glomeruli in collapsing variant lack hyalinosis and hypercellularity is uncommon.

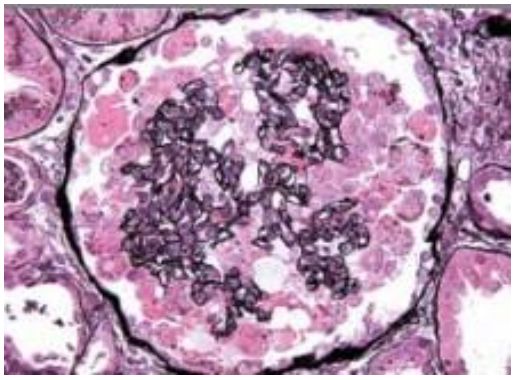


Image 3. In the collapsing variant, hypertrophy and hyperplasia of the epithelial cells, with severe foot-process effacement are common (D'Agati, 2003).

By immunofluorescence, there are segmental deposits of IgM, C3 and rarely C1 in collapsing segments.

It may be confused with forms of crescentic glomerulonephritis, but the presence of necrotizing lesions in the underlying tuft is uncommon and the podocytes have a different morphology.

Given its unique pathology, it has been suggested that this variant should not be considered a variant of FSGS. Often presents with heavy proteinuria and severe kidney function impairment. Patients are often resistant to therapy, have a rapid progression to ESRD and is commonly seen in patients with HIV infection.

Tip FSGS

The tip variant is characterized by epithelial cell injury and foam cell accumulation, occurring at the "tip" (the peripheral 25% of the glomerular tuft, next to the origin of the proximal tubule) of the glomerulus (image 4).

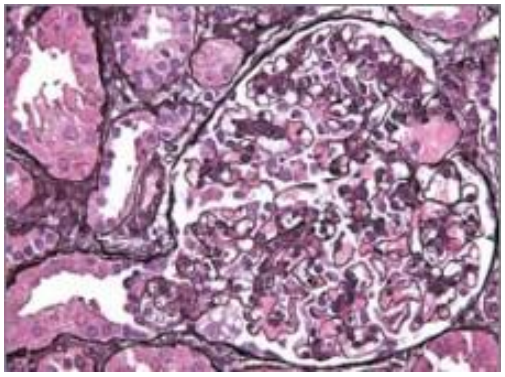


Image 4. The tip lesion, although presented with severe foot-process effacement, it has the least tubular atrophy and segmental fibrosis as a histologic variant (D'Agati, 2003).

The designation of tip lesion requires the exclusion of the collapsing variant. The early lesion is characterized by confluence of swollen, hypertrophied visceral epithelial cells, with parietal or tubular epithelial cells at the tubular pole. The affected lobule will display endocapillary hypercellularity, with foam cells and hyalinosis.

Immunofluorescence microscopy may show positive staining for IgM and C3 in sclerotic lesions in the mesangium.

Tip lesions are not specific and may occur in the setting of a variety of glomerular diseases, including membranous glomerulopathy, IgA nephropathy or diabetic glomerulosclerosis (Huppes, Hené and Kooiker, 1988). Given the above, rather than being a unique pattern, the tip lesion may be a variant or an early form of the above glomerulopathies and they should be carefully excluded to apply the designation of tip FSGS.

The tip lesion identify a subset of patients who are more likely to respond to glucocorticoid therapy than patients with the other variants (Thomas *et al.*, 2006).

Perihilar FSGS

This category requires the tip, collapsing and cellular variant to be excluded. It consists of sclerosis and hyalinosis in the perihilar area in more than 50% of segmentally sclerotic glomeruli (image 5, D'Agati, 2003). Glomerulomegaly and adhesions are common. Foam cells may be present in the sclerotic lesions. Typically, podocyte hypertrophy and hyperplasia are less frequent than in the other types.

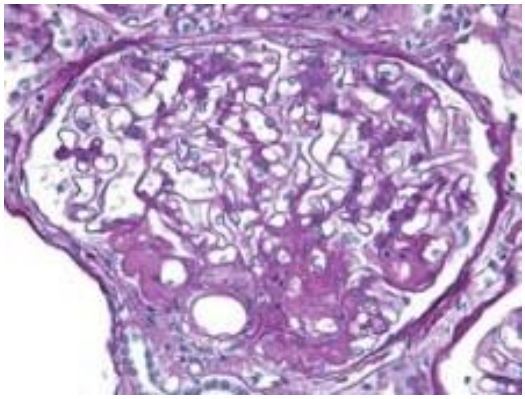


Image 5. Perihilar hyalinosis involves the majority of affected glomeruli. Foot-process effacement is relatively mild (D'Agati, 2003).

Immunofluorescence and electron microscopy findings are similar to those seen in FSGS NOS.

Although the perihilar variant occurs with primary FSGS, it is much more often observed with secondary FSGS, due to processes associated with increased glomerular capillary pressure, as an adaptive response.

Cellular FSGS

The cellular form of FSGS is characterized by the presence of at least one glomerulus with segmental endocapillary hypercellularity, in which capillary lumens are usually occluded (image 6). The endocapillary cells include endothelial cells, foam cells and infiltrating leucocytes. Tip and collapsing variants should be excluded to establish the diagnosis of the cellular type.

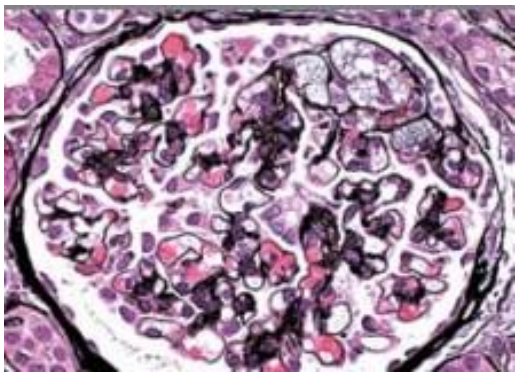


Image 6. Segmental lesion, with hypercellularity. Foam cells and severe foot-process effacement are commonly found in a specimen with cellular FSGS D'Agati, 2003.

By immunofluorescence, there is focal and segmental glomerular positivity for IgM and C3. Diffuse foot process effacement is typically seen on electron microscopy.

Many pathologists suggest that the cellular and collapsing variants, both presenting with heavy proteinuria, are the same lesion. The cellular variant, however, is often responsive to immunosuppressive therapy, compared to the collapsing lesions.

III.V Clinical Features

As mentioned above, patients with primary FSGS often present with acute onset of nephrotic syndrome, with heavy proteinuria, hypoalbuminemia, peripheral edema and hyperlipidemia (Rydel *et al.*, 1995, Cattran and Rao, 1998). Several studies (Chun, 2004) have reported that more than 70% of patients with primary FSGS, with hematuria (50%) and hypertension (20%) to be present at diagnosis as well. Kidney function impairment may be seen at presentation in approximately 20-50% of patients (Sethi *et al.*, 2014).

In secondary FSGS, proteinuria and kidney insufficiency are slowly progressing over time. Proteinuria is usually in the non-nephrotic range, serum albumin levels are within normal and no clinical signs of edema are present (Praga *et al.*, 1999). However, there are several cases of virus and drug-associated FSGS, in which clinical findings of nephrotic syndrome are reported.

While the range of proteinuria and albuminemia can contribute in distinguishing primary from secondary FSGS, only by using techniques of genetic analysis this can be done for primary and genetic FSGS. The resistance to immunosuppressive therapy is suggestive of genetic background, but this is not always the case. The onset of the disease in the early childhood is also an important feature which should raise the suspicion for a genetic case.

Differentiating primary, secondary and genetic FSGS

Differentiating between primary, secondary, and genetic forms of FSGS has important therapeutic and prognostic implications (Rosenberg and Kopp, 2017). During the evaluation of a patient with a biopsy-confirmed FSGS lesion, clinical and histologic features are taken into account to differentiate between the different forms of FSGS. Most patients with primary or secondary FSGS can be distinguished by the presence or absence of the nephrotic syndrome, the presence of identifiable risk factors for secondary FSGS, and the degree of podocyte foot process effacement visualized by EM examination of the kidney biopsy. However, these clinicopathologic features do not always identify patients with genetic causes of FSGS. In patients who cannot be classified by clinicopathologic assessment, genetic testing should be considered. In addition, in patients with an FSGS lesion, the presence of a family history of chronic kidney disease (CKD) or ESRD or physical findings suggestive of a syndromic presentation should prompt genetic testing.

III.VI Prognosis

There is a wide variety of clinical and pathological features predicting the outcome in a patient with FSGS. Black race, heavy proteinuria, increased degree of kidney function impairment and severe interstitial fibrosis and tubular atrophy (IFTA) in

biopsy specimen are all associated with a poor prognosis. Nevertheless, the most important predictor of a good or bad outcome in FSGS is the response to therapy.

III.VI.I. **Definition of Response** (Rovin et al., 2021)

Complete Remission (CR): a complete remission is achieved when there is reduction of proteinuria to <300 mg/day, stable serum creatinine and serum albumin > 3.5 g/dL.

Partial Remission (PR): a partial remission is a reduction in proteinuria to between 300 mg and 3.5 g/day and a decrease of >50% from baseline, with or without a return of serum albumin to normal.

Relapse: a relapse is a return of proteinuria to >3.5 g/day in patients who previously achieved a CR or an increase in proteinuria of >50% in patients with PR.

Patients who have partial or complete remission have better outcomes than those who are resistant or dependent to therapy (Chun, 2004, D'Agati, Kaskel and Falk, 2011, Troyanov *et al.*, 2005).

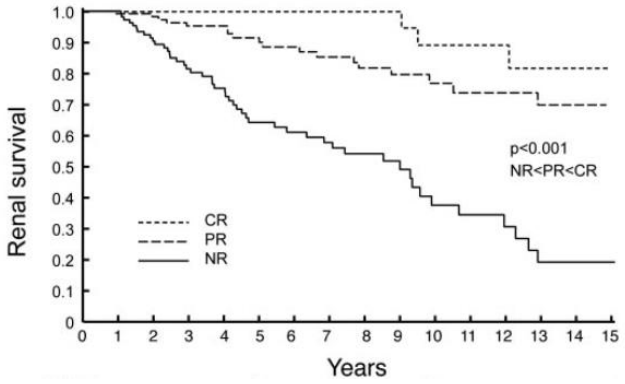


Figure 1. Renal survival estimates for patients with primary FSGS and different response status. The complete responders has significant longer renal survival (Troyanov *et al.*, 2005)

The histologic variant is strongly correlated with the remission status and remission rates are higher for the tip, perihilar and NOS variants (Thomas *et al.*, 2006). Renal

survival is inversely related to remission status; tip has the best and collapsing the worst renal survival rates (Thomas *et al.*, 2006, Stokes *et al.*, 2006).
In general, secondary FSGS has much better prognosis than the primary form, as the remission rates with renin – angiotensin inhibition have increased likelihood in those patients.

III.VII Treatment

III.VII.I. Goals of Therapy

The goal of therapy in FSGS is to induce a complete or partial remission of proteinuria and preserve renal function. This is primarily achieved with the use of agents with immunosuppressive properties and with a direct action on glomerular podocytes, as the glucocorticoids and calcineurin inhibitors (CNIs). There are also supportive measures, such as the renin – angiotensin inhibition. As mentioned above, even partial remission is associated with improved long-term survival (Korbet, 1998, Troyanov *et al.*, 2005).

III.VII.II. Primary FSGS

In patients with primary FSGS who present with *nephrotic syndrome*, the suggested initial treatment consists of glucocorticoids, rather than a calcineurin inhibitor (CNI) (Chun, 2004, Troyanov *et al.*, 2005). Patients left untreated have a poor prognosis. When there is a high risk for glucocorticoid-induced toxicity, in patients who have diabetes, are obese, have high risk for developing osteoporosis or are older than 70 years old, a CNI (cyclosporine or tacrolimus) is a suggested alternative. Low doses of glucocorticoids can be administered with the CNIs. CNIs should be avoided in patients with progressed kidney function impairment (GFR < 30 ml/min/1.73 m ^{2}), as they are nephrotoxic. For the same reason they should not be administered in patients with significant vascular or interstitial disease on kidney

biopsy. In cases when neither glucocorticoids nor CNIs can be given, alternative options include mycophenolate mofetil (MMF), rituximab (RTX), plasmapheresis and adrenocorticotropic hormone (ACTH) gel, but none of these therapies have been shown to be effective.

High-dose glucocorticoid therapy can be given as 1 mg/kg/day (maximum dose 60-80 mg/day) or as 2 mg/kg (maximum dose 120 mg every other day) on alternate days. The full dose should be given once daily in the morning, to minimize suppression of the hypophyseal-adrenal axis. A response to these doses may take up to 16 weeks, which is followed by a slow tapering of the dose for up to 6 months (Banfi *et al.*, 1991). Prednisone induces remission in 40-80% of patients with preserved kidney function, with the responders, as noted before, to have better long-term outcomes (Troyanov *et al.*, 2005).

Cyclosporine can be given in two divided doses of 3 to 5 mg/kg/day, adjusting the dose as necessary to target a trough level between 100-176 ng/ml for 4 to 6 months to induce remission (Rovin *et al.*, 2021). If tacrolimus is used, two divided doses of 0.05-0.1 mg/kg/day are administered for 4-6 months, adjusting the dose as necessary to target a trough level between 5-10 ng/ml. Patients are more likely to remain in remission if CNI therapy is continued for at least 12 months if tolerated, before a slow tapering of the dose. Furthermore, CNIs exert direct effects on the podocytes, that enhances their survival and stabilize the actin cytoskeleton (Schonenberger *et al.*, 2011).

CNIs are the treatment of choice in *glucocorticoid-resistant* (persistence of proteinuria >3.5 g/day with <50% reduction from baseline after 16 weeks of high-dose glucocorticoid therapy) and glucocorticoid-dependent FSGS (when relapse occurs during or within two weeks of completing glucocorticoid therapy) (Cattran *et al.*, 1999), with or without low-dose prednisone, rather than continuing glucocorticoids or no therapy. Existing data, although restricted to glucocorticoid-resistant FSGS *or* glucocorticoid-dependent FSGS, support the use of cyclosporine. However, many experts believe tacrolimus is equal to cyclosporine

and that it should be administered in females, as it is associated with fewer cosmetic side effects. Studies on CNIs are restricted).

All patients receiving glucocorticoids, CNIs or a combination of these should be also treated with general supportive measures (dietary sodium and protein restriction, blood pressure and hyperlipidemia control, RAAS inhibitors to reduce proteinuria). Sodium-glucose co-transporter 2 (SGLT2) inhibitors may be of benefit, but data are limited. This is consistent with the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases (Rovin *et al.*, 2021).

III.VII.III. Relapsing Disease

Relapse is typically defined as a return in proteinuria to >3.5 g/day in patients who had previously undergone a complete remission or an increase in proteinuria of >50% in patients with partial remission. It occurs approximately in 30% of patients after a complete and in >50% of patients after a partial remission (Troyanov *et al.*, 2005). In patients treated with glucocorticoids and had either remission, without significant side effects a course of prednisone is repeated. If significant glucocorticoid-induced toxicity during initial therapy has been developed or multiple relapses are reported, the recommendations suggest treating with a CNI, with or without low-dose glucocorticoids or with mycophenolate mofetil, if GFR is <30 ml/min/1.73 m^2.

There are several therapies for the treatment of primary FSGS under investigation, with clinical trials of an endothelin receptor antagonists (sparsentan) and a different type of CNI (voclosporin) to be the in progress.

There is little evidence to recommend glucocorticoid or CNI therapy in patients presenting with non-nephrotic range proteinuria and normal serum albumin levels.

III.VII.IV. Secondary and Genetic FSGS

Once a diagnosis of FSGS is established on biopsy, secondary etiologies should be ruled out before the initiation of a therapy for primary FSGS. For patients with secondary FSGS, cessation of the offending drug or effective treatment of the underlying condition, combined with supportive measures, is the therapy of choice. These include renin – angiotensin system inhibition, blood pressure control and dietary or protein restriction.

Patients with proven genetic forms usually do not respond to immunosuppressive therapy and should also be treated with supportive measures.

III.VIII The Greek Registry of patients with FSGS

Medical registries provide highly reliable data and have been used in several fields of medicine for many years. They have evolved from calculating basic epidemiological data to diverse applications in prevention, early diagnosis, screening programs and health care planning and decision making for disease control. Hellenic Society of Nephrology in an attempt to record the natural history of glomerulopathies (IgA nephropathy, membranous nephropathy, FSGS) developed a few years ago three different registries for the renal diseases above. The registry of FSGS includes almost 700 patients with primary FSGS in Greece, from 21 different nephrology departments in the Greek territory. Data were collected since 1982 and were updated in mid-2020. The Greek Registry of FSGS is, to the best of our knowledge, the biggest in the literature to date, including all the biopsy-proven cases of primary FSGS the last 40 years in Greece. Clinical and laboratory parameters at diagnosis and at the end of follow-up were recorded. Remission status, treatment regimens and the need for renal replacement therapy with hemodialysis or transplantation were reported for the majority of the patients.

IV. AIM & OBJECTIVES

Focal and segmental glomerulosclerosis is one of the most common causes of primary glomerular disease that terminates in renal failure. The incidence and prevalence of both primary and secondary FSGS have risen the last decades (Hommos *et al.*, 2017). The association of clinical and laboratory parameters with renal prognosis in patients with primary FSGS have been investigated in several cohorts over the last years. Additionally, the impact of immunosuppressive medication on proteinuria and renal survival in patients with primary FSGS has been assessed in several studies. However, the knowledge on primary FSGS is still expanding and it is still important to investigate the association of demographic and laboratory characteristics with renal prognosis and the impact of immunosuppressive therapy on renal survival. The Greek Registry of FSGS includes all the biopsy-proven cases of primary FSGS in Greece since 1986, making it one of the largest cohorts of the disease ever described.

This retrospective cohort study aimed at providing a summary of the basic information for clinical and laboratory characteristics available on medical registry of FSGS, describing the parameters associated with the response to therapy and the achievement of complete or partial remission and the risk factors for relapsing disease and finally estimating the effect of different predisposing factors to an unfavorable outcome and long-term prognosis of these patients.

V. MATERIALS & METHODS

V.I Study Design

A retrospective cohort, multi-center study was conducted to provide information for basic clinical and laboratory parameters and treatment protocols for primary FSGS in Greece. The target population included all the diagnosed cases of primary FSGS in Greece the last 4 decades. In total, 699 patients, all with biopsy-proven FSGS, were recorded from 21 different Nephrology departments in the Greek territory (table 1).

Table 1. Nephrology departments which contributed in the development of the Greek National Registry for patients with Primary Focal Segmental Glomerulosclerosis.

Nephrology Departments	Number of patients
Laiko General Hospital (Athens)	117
Ippokrateio General Hospital (Thessaloniki)	110
General Hospital of Nikaia (Athens)	99
Venizeleio Hospital (Heraklion)	47
Korgialeneio – Benakeio (Athens)	39
Ioannina University Hospital	37
General University Hospital of Larissa	29
Evaggelismos Hospital (Athens)	28
General Hospital of Athens “G. Gennimatas”	25
University General Hospital of Heraklion “PAGNI”	24
General Hospital of Chania	22
General University Hospital of Patras	21
General Hospital of Ioannina “G. Hatzikostas”	20
General University Hospital of Alexandroupolis	15
General Hospital of Athens “Aretaieion”	12
General Hospital of Volos “Achillopouleion”	11
“Papageorgiou” General Hospital of Thessaloniki	11
“AHEPA” General University Hospital of Thessaloniki	10
Attikon University Hospital (Athens)	9
“Hippokration” General Hospital (Athens)	8
General Hospital of Thessaloniki “G. Papanikolaou”	5

V.II Study Population / Inclusion & Exclusion Criteria

Patients with disorders strongly related with the secondary class of FSGS or with family history of FSGS were excluded; only those who did not have any clear etiology for the adaptive FSGS were finally included in the Registry. In the study population, only adult patients and those with follow-up greater than 12 months were included (flowchart).

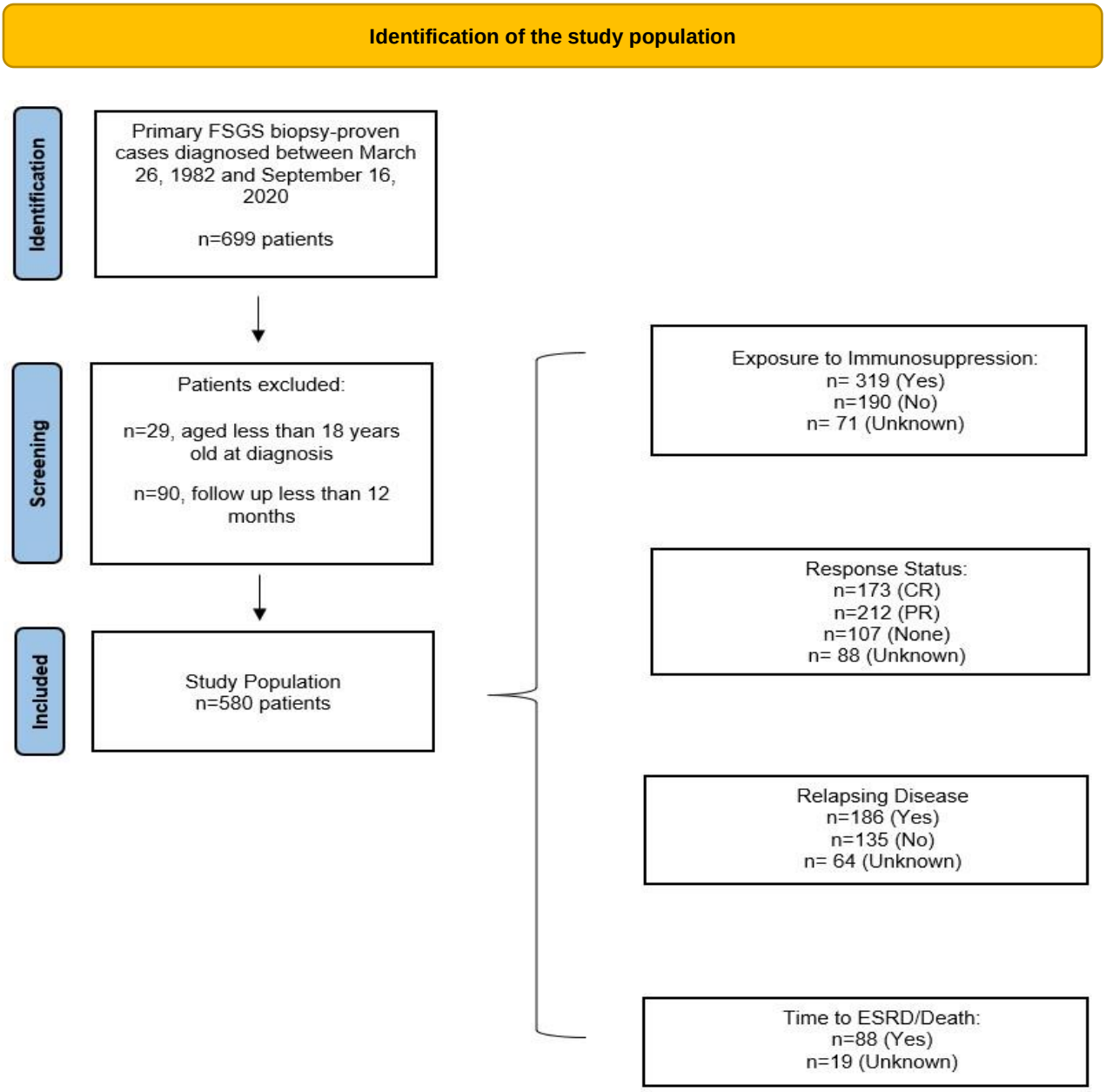
Patients with less than 12 months of follow-up were excluded, since response to therapy, relapsing disease and progression to ESRD or death require long-lasting assessment. Recognizing, moreover, the differences between pediatric patients and adults (Kiffel, Rahimzada and Trachtman, 2011), patients younger than 18 years old were not included in the analysis making a final study population of 580 adult patients, with a median follow-up of 7 years. No difference was observed among demographics, laboratory parameters and exposure to immunosuppressants between the participants and the patients excluded. There were 29 patients who were less than 18 years old and 90 patients who had a follow-up of less than a year.

V.III Data Collection & Variables Measured

Data were collected to record all patients since March 26, 1982 and they were revised and updated in 2020 by all 21 centers. Definitions of response (complete or partial remission), relapsing disease and the treatment doses were a priori determined to be in accordance with the latest edition of Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases (Cattran *et al.*, 2012), when the evaluation of the above was made.

Basic demographic parameters recorded included age, gender and body mass index (BMI), while laboratory characteristics were collected at the time of diagnosis

and at the end of follow-up. These included serum creatinine and albumin levels, GFR, a lipid panel and 24h urine protein excretion. Information about microscopic hematuria, hypertension and exposure to antihypertensive agents were also assessed. Therapy with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) is presented as any exposure to either or both classes of agents. The need and type of immunosuppression regimen administered was recorded, as well.



Flowchart: Identification of the study population and patients included in each different outcome analysis.

V.IV Definitions

Response and relapsing disease were defined according to the KDIGO recommendations (Cattran *et al.*, 2012):

Complete response (CR) was defined as a reduction of proteinuria to <300 mg/day or urine protein to creatinine ratio (UPCR) <300 mg/g, stable serum creatinine and serum albumin > 3.5 g/dL.

Partial Remission (PR) was defined as a reduction in proteinuria to between 300 mg and 3.5 g/day or UPCR 300-3500 mg/g and a decrease of >50% from baseline.

Patients who achieved both CR and PR were included only in the CR group.

Relapse was recorded when there is a return of proteinuria to >3.5 g/day or UPCR >3500 mg/g in patients who previously achieved a CR or an increase in proteinuria of >50% in patients with PR.

End stage renal disease (ESRD) was defined as the initiation of renal replacement therapy or renal transplantation. Time to ESRD or death was defined as the years from the diagnosis of FSGS till the initiation of renal replacement therapy or death.

V.V Statistical Analysis

Continuous variables were expressed as the mean value and standard deviation or median value and interquartile range (IQR), whereas categorical variables as frequencies and percentages. To investigate the differences between baseline demographic, clinical and laboratory variables between patients who received or not immunosuppressants and those who had at least one relapse or never relapsed, the *t* test and Mann−Whitney *U* test for independent samples for continuous variables and the χ^2 and Fisher exact test for categorical variables were

applied. When different response to therapy was investigated (CR, PR, none response), the one-way analysis of variance (ANOVA) for continuous variables and the χ^2 and Fisher exact test for categorical variables were applied. Univariate ordinal logistic regression analyses were performed to estimate the prognostic effect of various variables on the type of response. Predictors for time to ESRD were examined using Cox proportional hazardregression analysis. Variables that were found to be significant in the univariate analyses and those with significant clinical value from the literature (age, sex, GFR) were included in the multivariate models. Significance was set at $\alpha=0.05$. The estimated cumulative odds ratios (CORs) and hazard ratios (HRs) of both the univariate and multivariate models, as well as the related p values, are presented. Data were analyzed using Stata 17.0 software (Stata Corporation, College Station, TX. All tests proceeded as 2 tailed.

VI. RESULTS

The study population consists of 580 patients with primary FSGS, who had a median follow-up of 7 years. More than 30% of the patients had a median follow-up of more than a decade (Table 2). As mentioned before, 90 patients had less than 12 months of follow-up and were excluded from the analysis.

Table 2. Years of follow-up for the patients with primary FSGS in Greece.

Follow-Up	N	%
1-5 years	149	35
5-10 years	141	34
10-15 years	79	19
15-20 years	40	9
>20 years	12	3
Median / IQR	7 / 7.7 years	

* IQR: interquartile range

The basic demographic and laboratory characteristics of the patients are illustrated on table 3. Particularly, the patients had a mean age of 46 years old, males were mainly affected (65%) and they were overweight (mean BMI=27 kg/m^2), in general. Severe kidney function impairment (GFR <30 ml/min/1.73 m^2) was shown at <10% of the cases at diagnosis, while almost 60% had a preserved renal function (GFR >60 ml/min/1.73 m^2), with the mean GFR to be around 70 ml/min/1.73 m^2 and the serum creatinine level to lie around 1.39 mg/dL. Nephrotic-range proteinuria (>3.5 g/day) was detected at 299 patients (54%) (median proteinuria= 3.8 g/day), while hypoalbuminemia (<3.5 g/dL) at 234 patients (44%). Combined, these two clinical features were reported at almost 40% of the cases. Around 70% were hypertensive at the baseline assessment and were treated with ACE inhibitors or ARBs. Microscopic hematuria was found at 335 patients (63%). The lipid profile of the patients was characterized by high levels of serum cholesterol and triglycerides, and optimal levels of serum HDL.

Table 3. Baseline demographic and laboratory characteristics of patients with primary FSGS at the time of diagnosis.

Variables	Mean ± SD, Median/IQR, N/%
Age (years) (Mean ± SD)	46 ± 15
Gender (Female) (N/%)	200 / 35
BMI (kg/m^2) (Mean ± SD)	27 ± 5
Serum Creatinine (mg/dl) (Mean ± SD)	1.39 ± 0.7
eGFR [CKD-EPI (ml/min)] (Mean ± SD)	69.7 ± 31
eGFR [CKD-EPI (ml/min)] >60 (N/%)	258 / 58
30 – 60 (N/%)	148 / 33
< 30 (N/%)	43 / 9
Urine Protein (g/day) (Median/IQR)	3.8 / 4.1
Urine Protein >3.5 (g/day) (N/%)	299 / 54
Serum Protein (g/dl) (Mean ± SD)	6.3 ± 1
Serum Albumin (g/dl) (Mean ± SD)	3.4 ± 0.9
Serum Albumin < 3.5 g/(dL) (N/%)	234 / 44
Arterial Hypertension (N/%)	367 / 69
ACEi / ARB* (N/%)	395 / 87
Microscopic Hematuria (N/%)	335 / 63
Cholesterol (mg/dl) (Mean ± SD)	265 ± 91
Triglycerides (mg/dl) (Mean ± SD)	209 ± 113
HDL (mg/dl) (Mean ± SD)	55 ± 22
Hb (g/dl) (Mean ± SD)	13.5 ± 1.9

***** BMI: body mass index, eGFR : estimated Glomerular Filtration Rate, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, ACEi: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, HDL: high-density lipoprotein, Hb: hemoglobin

Exposure to immunosuppressants was reported for 509 patients, of whom 319 patients (62.6%) received different immunosuppressive regimens. It is important to note that 71 patients (12% of the population) had unknown immunosuppression status. The type of immunosuppression administered is illustrated in figure 2. Steroids were the most common initial treatment, either as monotherapy (135 patients, 42%) or in combination with cyclosporine, cyclophosphamide or MMF (data not shown). In total, 84% of the cases who were treated with immunosuppressants were given corticosteroids, while the second most usual option was cyclosporine (125 patients, 39%). Overall, remission was induced in 385 patients (78%). In detail, 173 patients (35%) and 212 (43%) achieved complete and partial response, respectively. Only 22% of the cases was characterized as non-responders (table 4) and for 88 patients the remission status could not be identified.

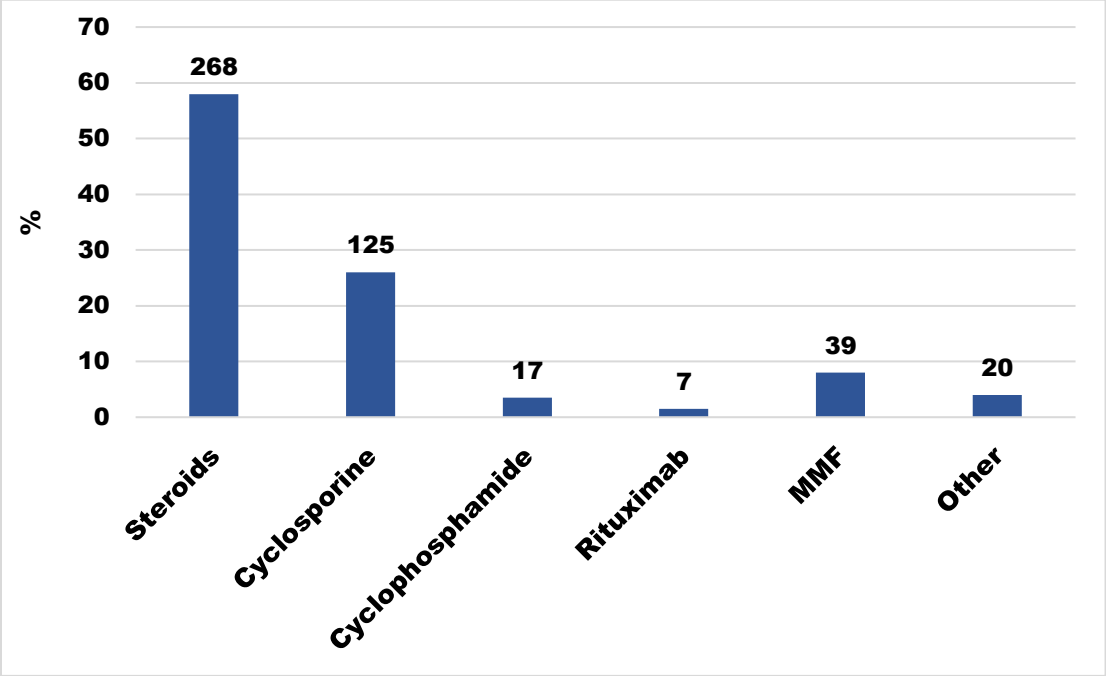


Figure 2. Type of immunosuppressive therapy administered in patients with primary FSGS. Above each bar the number of patients treated with each category is shown.

Table 4. Hard outcomes reported in the patients during the follow-up period.

Variables	N / %
Response (Either Remission)	385 / 78
Complete Remission	173 / 35
Partial Remission	212 / 43
None	107 / 22
Relapsing Disease	185 / 48
1 – 3 episodes	171 / 92
> 3 episodes	14 / 8
ESRD	93 / 16
Death	24 / 4

***** ESRD: end-stage renal disease

Relapsing disease was frequent among responders. Around half of them reported at least one episode of relapse. For 171/185 (92%) of them, 1 to 3 flares were recorded, while the rest had more than 3 episodes during the follow-up. Relapses did not differ among responders with different remission status (Supplementary Table 1). In the total cohort, 93 patients progressed to ESRD and to renal replacement therapy and 24 patients (10 of whom were on dialysis) died, with a median time to each event of 5 and 8.5 years, respectively. Renal transplantation was performed in 4 patients, 3 of whom were on dialysis at the time of the procedure.

Among patients with known immunosuppression (I/S) status (Yes Vs. No) (table 5), BMI was shown to be significantly different.

Table 5. Differences in characteristics and disease progression between patients who were administered or not immunosuppressants (I/S).

Characteristics	I/S N=319	No I/S N=195	p-value
Age (years) (Mean ± SD)	45 ± 25	47 ± 22	0.22
Gender (Female) (N/%)	115 / 36	62 / 32	0.44
BMI (kg/m^2) (Mean ± SD)	26 ± 6.7	28 ± 7.5	**0.04**
Serum Creatinine (mg/dl) (Mean ± SD)	1.2 ± 0.7	1.2 ± 0.7	0.96
eGFR [CKD-EPI (ml/min)] (Mean ± SD)	68 ± 48	65 ± 51	0.88
eGFR [CKD-EPI (ml/min)] >60 (N/%)	158 / 59	94 / 54	
30 – 60 (N/%)	77 / 29	69 / 38	**0.04**
< 30 (N/%)	30 / 12	12 / 8	
Urine Protein (g/day) (Median/IQR)	4.9 / 4	2 / 1.8	**<0.001**
Proteinuria >3.5 (g/day) (N/%)	237 / 76	40 / 21	**<0.001**
Serum Albumin (g/dl) (Mean ± SD)	3 ± 1.4	4 ± 6.5	**<0.001**
Serum Albumin < 3.5 (g/dL) (N/%)	192 / 62	26 / 14	**<0.001**
Hypertension (N/%)	211 / 66	136 / 71	0.23
ACEi / ARB (N/%)	226 / 84	164 / 92	**0.01**
Response (Either Remission) (N/%)	254 / 83	118 / 70	0.08
Complete Remission (N/%)	127 / 41.5	39 / 23	
Partial Remission (N/%)	127 /41.5	79 /47	**<0.001**
None Response (N/%)	52 / 17	50 / 30	
Relapsing Disease (N/%)	148 / 65	27 /34	**<0.001**
ESRD (N/%)	58 / 18	24 / 12	0.09
Death (N/%)	13 / 4	6 / 3	0.59

ACEi: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers

Patients who received immunosuppressants had slightly lower BMI, while no age and gender differenced were observed. While GFR levels did not seem to vary between the two groups, patients who presented with GFR <30 ml/min/1.73 m^2 had a greater chance to belong in the group who was given I/S. Patients who presented with nephrotic-range proteinuria were treated with I/S (76% Vs. 21% who did not receive I/S, $p<0.001$), as well as those with severe hypoalbuminemia (62% I/S Vs. 14% without I/S, $p<0.001$). Hypertensive patients were equally distributed, while ESRD and death incidence did not differ significantly between the groups.

Patients who were treated with different protocols of immunosuppressants were those who presented with severe disease at the initial assessment (heavier proteinuria, lower levels of serum albumin), but as expected, they achieved higher rates of remission, especially complete (41.5% Vs. 23%, $p<0.001$). This finding is verified in the multivariate regression analysis (table 6), in which the immunosuppression status remains statistically significant, even when adjustments for proteinuria and serum albumin levels are made.

Differences in baseline demographic and clinical characteristics, and disease progression among complete, partial and non-responders are shown in Supplementary table 1. No difference in age was reported. Non-responders were mainly males and hypertensive, while GFR levels were remarkably lower at diagnosis. Responders had lower BMI, better preserved kidney function, as depicted by GFR and serum creatinine levels. Complete responders had heavier proteinuria at diagnosis (4.7 g/day Vs. 3/5 g/day for PR Vs. 3 g/day for NR). Immunosuppressive regimens were commonly administered in those who achieved either remission, while serum albumin levels were notably lower in complete responders, than in those who responded partially or not.

In table 6, estimations on the effect of several independent variables on the achievement of response are illustrated. Older age did not seem to have an effect on the response (COR: 0.99, *p-value*=0.56), while female patients had better prognosis, as they had higher chance of achieving a complete, rather than a partial or no response (COR: 1.5, *p-value*=0.02). Nephrotic-range proteinuria and severe hypoalbuminemia were strongly associated with the achievement of remission and higher cumulative probabilities of complete versus partial remission (COR: 1.54, p-value=0.01 and COR: 2.05, p-value<0.01, respectively). Mild kidney function impairment (higher levels of GFR), and treatment with immunosuppressants were found to be strongly related with response, even partial. Patients with greater BMI (COR: 0.93, *p-value*=0.008) and hypertension (COR: 0.47, p-value<0.001) had a statistically significant greater risk of having a resistant disease (none response) or response only partially.

In the multivariate analysis, older patients seemed to be at lower risk of achieving partial remission or none response (COR: 1.02, *p-value=0.01*). The female gender in the multivariate model did not remain a significant predictor of response (COR: 1.24, *p-value*=0.46), because adjustments for hypertension were made. Males were the ones that were at greater risk of having elevated levels of blood pressure (64% of males Vs. 30% of females were hypertensive, *p-value*<0.001). Proteinuria greater than 3.5 g/day (COR: 1.29, p-value=0.44) and serum albumin levels <3.5 g/dL (COR: 1.39, p-value=0.34), although associated in a statistically significant way with complete remission, because of their strong correlation with the administration of immunosuppressive therapy, they both lost their significance as predictors of response (the same occurs even when they are examined as continuous variables) in the multivariate analysis. GFR, BMI levels, and the administration of I/S remained independent predictors of response, when adjustments for age, gender, hypertension, proteinuria of nephrotic-range and severe hypoalbuminemia were made.

Table 6. Predictors of Response (CR Vs. PR Vs. None Response).

	Univariate Models			Multivariate Model		
Variables	**COR**	**95% CIs**	**p-value**	**COR**	**95 CIs**	**p-value**
Age (years)	0.99	0.98, 1.01	0.56	1.02	**1.01, 1.05**	**0.01**
Gender (Male)	Reference Category					
Female	1.51	**1.06, 2.13**	**0.02**	1.24	0.69, 2.24	0.46
BMI (kg/m^2)	0.93	**0.89, 0.98**	**0.008**	0.93	**0.88, 0.98**	**0.007**
Hypertension (No)	Reference Category					
Yes	0.47	**0.32, 0.68**	**<0.001**	0.59	0.31, 1.09	0.09
Serum Creatinine (mg/dl)	0.37	**0.28, 0.49**	**<0.001**			
eGFR (ml/min)	1.01	**1.01, 1.02**	**<0.001**	1.01	**1.01, 1.03**	**0.001**
Urine protein (g/day)	1.05	**1.001, 1.1**	**0.01**			
Proteinuria (<3.5 g/day)	Reference Category					
>3.5 g/day	1.54	**1.1, 2.1**	**0.01**	1.29	0.67, 2.46	0.44
Serum albumin (g/dL)	0.68	**0.56, 0.82**	**<0.001**			
S. Albumin (>3.5 g/day)	Reference Category					
<3.5 g/day	2.05	**1.46, 2.9**	**<0.001**	1.39	0.69, 2.8	0.34
Immunosuppression (No)	Reference Category					
Yes	2.21	**1.55, 3.16**	**<0.001**	2.38	**1.22, 4.63**	**0.01**

*COR: cumulative odds ratio, CIs: confidence intervals

In table 7, a comparison of the different baseline characteristics between individuals who had at least one relapse and those who never relapsed is illustrated. Patients on both groups had similar age and kidney function at the time of the diagnosis. More than 60% of individuals in each group were hypertensive and were almost all treated with ACE inhibitors or ARBs.

Table 7. Comparison of patients that never relapsed versus ever relapsed.

Characteristics	Relapse N=186	Never Relapse N=135	p-value
Age (years) (Mean ± SD)	44.5 ± 15	45.5 ± 21	0.34
Gender (Female) (N/%)	75 / 40	41 / 30	0.06
BMI (kg/m^2) (Mean ± SD)	27 ± 4	24.4 ± 6	**0.01**
Serum Creatinine (mg/dl) (Median/IQR)	1.1 / 0.6	1.2 / 0.7	0.47
eGFR [CKD-EPI (ml/min)] (Median/IQR)	73 / 30	77 / 30	0.26
eGFR [CKD-EPI (ml/min)] >60 (N/%)	87 / 62	78 / 67	
30 – 60 (N/%)	44 / 31	30 / 26	0.62
< 30 (N/%)	9 / 6	7 / 6	
Urine Protein (g/day) (Median/IQR)	5.7 / 4.3	4.8 /4.6	**0.007**
Proteinuria >3.5 (g/day) (N/%)	128 / 70	69 / 51	**0.001**
Serum Albumin (g/dl) (Median/IQR)	3.1 / 0.9	3.4 / 1	**0.02**
Serum Albumin < 3.5 (g/dL) (N/%)	108 / 60	62 / 46	**0.01**
Hypertension (N/%)	107 / 61	82 / 63	0.23
ACEi / ARB (N/%)	129 / 89	103 / 89	0.8
Immunosuppression (Yes) (N/%)	148 / 84	77 / 59	**<0.001**
Corticosteroids (monotherapy)	54 / 51	37 / 59	0.3
Corticosteroids + Cyclosporine	51 / 48	25 / 40	
Complete Response (N/%)	87 / 48	60 / 45	0.54
ESRD (N/%)	29 / 19	3 / 2.5	**<0.001**
Death (N/%)	10 / 5	5 / 3	0.48

Notably, the percentage of patients having achieved complete remission did not differ between those who had no relapse and those who had at least one (45% Vs.

48%, *p-value*=0.54). Individuals who had a flare had heavier proteinuria (5.7 g/day Vs. 4.8 g/day, *p-value*=0.007), more severe hypoalbuminemia (3.1 g/dL Vs. 3.4 g/dL, *p-value*=0.002) and greater BMI levels compared to those who never relapsed (27 kg/m^2 Vs. 24.4 kg/m^2, *p-value*=0.01). There was no significant difference in the two main immunosuppressive regimens administered in the patients of this cohort after the initial assessment (corticosteroids as monotherapy or in combination with cyclosporine) among the two groups. However, between those with at least one relapse, 84% were on immunosuppressants, while in those with no relapse only 59% was I/S administered (*p-value*<0.001).

Relapse was reported in approximately half of the patients after a complete or partial remission (supplementary table 1). The timing of relapse may range from 20-36 months following a complete remission, while a later relapse is developed at least several months after discontinuation of therapy. Treatment of relapsing disease is shown in figure 3.

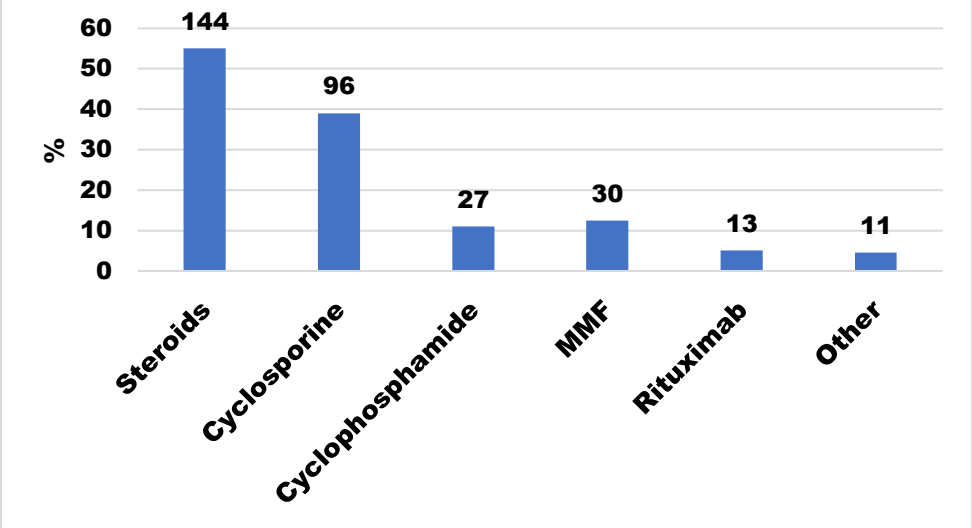


Figure 3. Type of immunosuppressive therapy administered in patients with relapsing disease. Above each bar the number of patients treated with each category is shown.

For most patients who previously had a complete or partial remission with glucocorticoids or CNIs, a repeat course of prednisone or CNIs, respectively - rather than switching therapy - was administered. MMF and rituximab were common alternatives, usually in combination with other categories.

In total, 106 patients progressed to ESRD or died during the follow-up period, with a median time to the composite event of ESRD / Death at 5 years (5 and 8.5 years, respectively). Time to ESRD / Death was reported for 88 patients.

In Cox regression analysis (table 8), the basic demographic characteristics of gender, age and BMI did not show any significant association with the time to ESRD or death. Greater serum creatinine and urine protein levels at the initial assessment were strongly related with shorter time to progression in ESRD or death (HR=2.53 and 1.05, respectively, *p-value*<0.04). Hypertensive patients were at high risk for ESRD and death (HR=2.23, p=0.04), while those with higher GFR levels (HR=0.96, P<0.001) had 4% reduced risk for progressing in an unfavorable outcome, compared to those with more severe kidney function impairment. It is interesting that neither nephrotic-range proteinuria, nor severe hypoalbuminemia show significant - but only a trend towards shorter time - effect on time to the composite outcome. The administration of immunosuppressants was not related with the renal and patient survival (time before ESRD or death), while the induction of response was the stronger independent predictor in the analysis (figure 4).

Table 8. COX regression analysis estimations for time to ESRD and death.

	Univariate Models			Multivariate Model		
Variables	**HR**	**95% CIs**	**p-value**	**HR**	**95 CIs**	**p-value**
Age (years)	1.01	0.99, 1.03	0.12	0.99	0.97, 1.01	0.63
Gender (Male)	Reference Category					
Female	0.77	0.49, 1.22	0.27	0.93	0.51, 1.7	0.82
BMI (kg/m^2)	0.97	0.92, 1.03	0.43			
Hypertension (No)	Reference Category					
Yes	2.23	**1.28, 3.86**	**0.04**	1.19	0.57, 2.45	0.63
Serum Creatinine (mg/dl)	2.53	**2.1, 3.06**	**<0.001**			
eGFR (ml/min)	0.96	**0.95, 0.97**	**<0.001**	0.97	**0.96, 0.99**	**<0.001**
Urine protein (g/day)	1.05	**1.01, 1.1**	**0.04**	1.07	0.99, 1.17	0.06
Proteinuria (<3.5 g/day)	Reference Category					
>3.5 g/day	1.49	0.95, 2.34	0.08			
Serum albumin (g/dL)	0.81	0.64, 1.03	0.09			
S. Albumin (>3.5 g/day)	Reference Category					
<3.5 g/day	1.26	0.81, 1.96	0.30			
Immunosuppression (No)	Reference Category					
Yes	1.33	0.8, 2.21	0.26			
Response (None)	Reference Category					
PR	0.16	**0.09, 0.27**	**<0.001**	0.19	**0.1, 0.35**	**<0.001**
CR	0.03	**0.009, 0.2**	**<0.001**	0.03	**0.009, 0.1**	**<0.001**

*HR: hazard ratio, CIs: confidence intervals

Complete and partial responders had 84% (OR: 0.16, *p-value*<0.001) and 97% (OR: 1.03, *p-value*<0.001), respectively, reduced risk of progressing to ESRD or die during the follow-up compared with the non-responders). When responders were compared to each other in terms of time to ESRD, complete responders had almost 80% reduced risk of progressing to ESRD than partial ones (HR=0.19, p=0.008, data not shown).

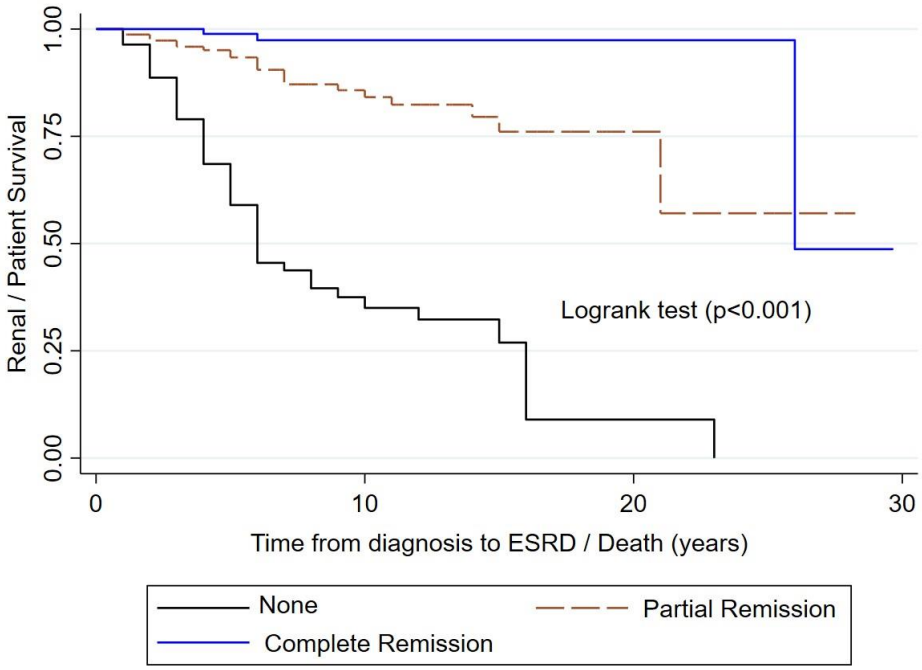


Figure 4. Kaplan-Maier survival estimates of renal and patient survival in patients with different response status.

The response status was identified as the strongest independent predictor for progression to the unfavorable outcome of ESRD and death in the multivariate analysis. GFR remained significant after adjustments for response status, proteinuria, presence of hypertension, age and gender, with a reduced risk of 3% for every unit increase in GFR at the initial assessment. Patients with higher levels of proteinuria presented with a weak trend towards severe kidney impairment and death during follow-up (HR:1.07, p=0.06), while the cut-off of 3.5 g/day (nephrotic-range proteinuria), after adjustments for response, GFR and demographics, was not associated with the time to ESRD or death. Hypertension and demographic parameters did not point out any significant effect on the dependent variable.

We performed a sensitivity analysis in two subgroups of the present cohort; once in patients who were treated with immunosuppressants and next in those who had nephrotic- range proteinuria. As expected, based on the estimations of the analysis

in table 8, the results remained the same, with response and GFR to be independent predictors of time to ESRD and death, even in these subgroups.

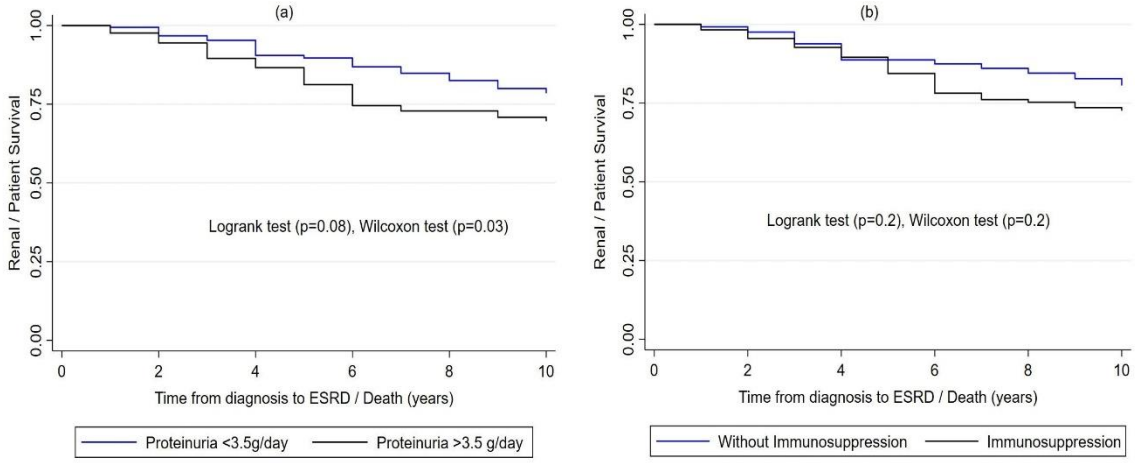


Figure 5. Kaplan-Maier survival estimates of renal and patient survival in patients with different severity of proteinuria at diagnosis (a) and exposure to immunosuppressive regimens (b).

In the following table 9, laboratory parameters at the end of follow-up point out that almost 85% of the cohort had non-nephrotic range proteinuria, with a median urinary excretion of 1 g/day and normal serum albumin levels (3.9 g/dL). Kidney function was slightly impaired during the assessment (median GFR=51 ml/min/1.73m^2). However, closely half of the patients (42%) had a well-preserved renal function, with GFR>60 m/min.

Table 9. Laboratory characteristics of patients with primary FSGS at the end of follow-up.

Variables	Mean ± SD, Median/IQR, N/%
Serum Creatinine (mg/dl) (Median/IQR)	1.4 / 1.6
eGFR [CKD-EPI (ml/min)] (Median/IQR)	51 / 55
eGFR [CKD-EPI (ml/min)] >60 (N/%)	181 / 42
30 – 60 (N/%)	127 / 29
< 30 (N/%)	122 / 29
Urine Protein (g/day) (Median/IQR)	1 / 2.1
Urine Protein >3.5 (g/day) (N/%)	84 / 17
Serum Protein (g/dl) (Mean ± SD)	6.3 ± 1
Serum Albumin (g/dl) (Mean ± SD)	3.9 ± 0.6
Serum Albumin < 3.5 g/(dL) (N/%)	66 / 14

VII. DISCUSSION

Focal segmental glomerulosclerosis is one of the most difficult and enigmatic diseases in nephrology and the last 4 decades its incidence has been increasing in virtually all ethnic groups, across the entire age spectrum, and around the world, being one important cause of acquired chronic kidney disease (CKD) in children and adults. This analysis concerns one of the largest cohorts reporting outcomes on patients with primary FSGS over the span of 38 years.

In our study, complete and partial response were strongly associated with preserved kidney function and the administration of immunosuppressive regimens, while older patients seemed to achieve more often complete over partial remission or none response. This is probably explained by the fact that kidney function declines with age (age becomes significant only when adjustment for the levels of GFR are made). Complete responders had a well-preserved renal function at the time of diagnosis, with optimal levels of serum creatinine and GFR, but were those with severe FSGS, presented with nephrotic syndrome, a finding which has been reported in different cohorts (Troyanov *et al.*, 2005). In our study, patients who achieved complete remission had notably greater levels of GFR than those with partial remission and it is a finding not well depicted in other cohorts analysed to date. A possible explanation of the above is the bigger sample size of the Greek registry.

The characteristics of the patients who received or not immunosuppression were recorded and compared. It comes as a conclusion that those who presented with severe FSGS, heavier proteinuria and hypoalbuminemia were those in whom physicians used immunosuppressants, even when kidney function was well preserved at the initial assessment. Patients who were treated with immunosuppressants had optimal BMI and statistically significant greater possibility to achieve complete, rather than partial or none response, when adjustments for the severity of the disease (proteinuria, serum albumin) were

made. This evidence strongly supports a common recommendation in the treatment of FSGS, which suggests the use of immunosuppressants, because those left untreated are at high risk for a worse prognosis.

We also recorded the different characteristics of the patients, who after obtaining a remission, experienced a relapse. In fact, 57% of patients with a remission experienced at least one relapse, finding which comes in total accordance with the results of a recent study on patients with FSGS (Jauhal *et al.*, 2022). BMI was higher among those who relapsed at least once after either remission and had more severe disease at the time of the diagnosis, with heavier proteinuria and more severe hypoalbuminemia than those who never relapsed. Studies have suggested that obesity might be an important risk factor for progression of renal disease (Hall *et al.*, 2003), playing a role in the pathogenesis of the disease. In the cohort of Jauhal et al., 2022, in which the authors examine the impact of remissions and relapses on kidney function decline and ESRD, there are no identifying differences between the two groups while in their nephrotic period, but this time information is not available in our cohort. The patients in the Greek Registry who relapsed at least once after remission were more likely to be on immunosuppressants, a common finding with those patients from the Toronto Registry (Jauhal *et al.*, 2022). As far as the treatment of relapses, in Greece, clinicians follow the KDIGO recommendations (Rovin *et al.*, 2021), with the administration of corticosteroids and CNIs, while MMF was a potential drug of choice (Cattran *et al.*, 2004).

The findings of our study suggest that either complete or partial remission confers an excellent long-term prognosis. Glomerular filtration rate (GFR), when adjustments for the response status were made, was strongly related with slower progression to ESRD. These findings are comparable with those previously evaluated in large cohorts of patients with primary FSGS (Troyanov *et al.*, 2005). A noteworthy finding was that baseline proteinuria showed a strong correlation with the progression to ESRD, with higher levels of urine protein excretion at diagnosis

to be associated with shorter time to the adverse outcome, even if the result near misses its statistical significance. It is a conclusion not previously underlined in different groups of patients, in which proteinuria reduction is a main goal towards the preservation of kidney function (Troost *et al.*, 2021).

In our study, 18% of patients reached the composite outcome (as defined by ESRD or death), in a median follow up time of 5 years. Several studies have identified that not only the complete, but also the partial response, are both associated with a slower rate of renal function decline and a reduced risk for renal failure (Pei *et al.*, 1987). This was featured in our cohort, with the induction of either response to strongly improve patients' and renal survival. The only baseline parameter that could serve as a predictor of progression to ESRD or death was the levels of GFR at the diagnosis, while urine protein excretion showed a weak (p=0.06) effect on the prevention of renal damage, in the multivariate analysis. BMI has been associated with a better renal survival and a slower rate of renal function decline (Troyanov *et al.*, 2005), but this was not shown in our study.

Our analysis is subject to several limitations; to note, no biopsy data was included in the analysis. Kidney biopsies were interpreted by different pathologists from multiple centers, across a big time period, in which new insights of the disease arised. Moreover, the unknown chronicity status of the disease at the time of diagnosis, may affected the administration of treatment in the patients. As a result, no valid evaluation between histopathological parameters and the clinical outcome could be made, in a disease which is mainly a histologic entity.

Our study could be also subject to misclassification issues; all patients registered had biopsy-proven FSGS and no evidence of secondary etiology of the disease were apparent. However, patients with other forms may have been included in the analysis, as genetic FSGS, in particular, is increasingly been recognized and a careful evaluation of the patients is required (Shabaka, Tato Ribera and Fernández-Juárez, 2020).

Time to various critical end-points was also unknown. In particular, no information was available for the time to induction of the treatment and the remission. The former could be related with fibrotic lesions in the renal tissue in cases of late induction of immunosuppression, predisposing to progression to ESRD and resistant disease. As far as the time to remission is concerned, shorter time to either remission is of paramount clinical importance and a therapeutic goal for clinicians, as it is related to better prognosis (Rydel *et al.*, 1995).

In conclusion, in our retrospective cohort study of 580 patients with primary FSGS, age, BMI, GFR and immunosuppressive therapy were strongly related with achievement of complete response, rather than partial or no remission. GFR and either remission were significant predictors of shorter time to ESRD or death, even in the subgroups of those who were treated or those with severe nephrotic-range proteinuria. Since most data derive from retrospective studies and not well-designed trials (Hodson, Sinha and Cooper, 2022), research on biomarkers and genetic testing towards an early diagnosis and valid estimation of the prognosis in FSGS, as well as clinical trials (De Vriese *et al.*, 2021) evaluating new therapeutic protocols in the disease are needed.

VIII. SUPPLEMENTARY MATERIALS

Supplementary Table 1. Characteristics (demographic and laboratory), exposure to antihypertensive and immunosuppressive agents and disease progression (relapsing disease, death, ESRD) among patients with primary FSGS and different response status (Complete Remission Vs. Partial Remission Vs. None Response).

Variable	CR N=173	PR N=212	NR N=107	p-value
Age (years) (Mean ± SD)	45 / 28	46 / 21	48 / 25.5	0.85
Gender (Female) (N/%)	68 / 39	73 / 34	27 / 25	0.05
BMI (kg/m^2) (Mean ± SD)	26.1 / 6.9	27 / 6.1	29 / 8	**0.02**
Serum Creatinine (mg/dl) (Mean ± SD)	1 / 0.5	1.2 / 0.66	1.6 / 0.9	**<0.001**
eGFR [CKD-EPI (ml/min)] (Mean ± SD)	79 / 51	72.6 / 45.5	48 / 43	**<0.001**
eGFR [CKD-EPI (ml/min)] >60 (N/%)	102 / 70	106 / 61	34 / 35	
30 – 60 (N/%)	33 / 23	56 / 32	44 / 45	**<0.001**
< 30 (N/%)	10 / 7	11 / 7	19 / 20	
Urine Protein (g/day) (Median/IQR)	4.7 / 5.3	3.5 / 3.5	3.6 / 3.5	**0.03**
Proteinuria >3.5 (g/dL) (N/%)	112 / 65	107 / 51	56 / 53	**0.01**
Serum Albumin (g/dL) (Mean ± SD)	3 / 1.6	3.7 / 1.1	3.7 / 1.4	**<0.001**
Serum Albumin < 3.5 (g/dL) (N/%)	98 / 60	84 / 40	37 / 36	**<0.001**
Hypertension (N/%)	99 / 60	138 / 67	87 / 85	**<0.001**
ACEi / ARB (N/%)	120 / 87	171 / 92	75 / 78	**0.005**
Immunosuppression (Any form) (N/%)	127 / 76	127 / 61	52 / 51	**<0.001**

Steroids only (N/%)	55 / 62	43 / 48	27 / 71	**0.03**
Cyclosporine ± Steroids (N/%)	34 / 38	46 / 51	11 / 29	
Relapsing Disease (N/%)	87 / 59	92 / 55		0.54
ESRD (N/%)	4 / 2	22 / 10	49 / 45	**<0.001**
Death (N/%)	5 / 3	8 / 4	7 / 7	0.3

ΕΥΧΑΡΙΣΤΙΕΣ

Έχοντας ολοκληρώσει τη διπλωματική μου διατριβή, θα ήθελα να ευχαριστήσω θερμά τον επιβλέποντα μου, κύριο Φίλιππο Ορφανό, για την καθοδήγηση και τις χρήσιμες συμβουλές του καθ΄όλη τη διάρκεια των μεταπτυχιακών μου σπουδών, από την πρώτη έως και την τελευταία ημέρα. Ήταν ιδιαίτερη τιμή για εμένα να έχω την καθηγήτρια μου, κυρία Παγώνα Λάγιου, στην επιτροπή της διπλωματικής μου εργασίας και να έχω τη στήριξή της, τόσο στην εκπόνηση της διατριβής μου, όσο και στα επόμενα βήματά μου στην επαγγελματική μου πορεία. Ένα μεγάλο ευχαριστώ ανήκει επίσης σε όλα τα νεφρολογικά κέντρα στην Ελλάδα για τη συμβολή τους στη συλλογή των δεδομένων ενός τόσου μεγάλου δείγματος ασθενών.

Θερμή εκτίμηση και ευγνωμοσύνη οφείλω στη νεφρολογική κλινική του Λαϊκού Νοσοκομείου, το νεφρολόγο κύριο Κομποτιάτη και την καθηγήτρια μου, κυρία Μαρινάκη, οι οποίοι αφιέρωσαν χρόνο και μου προσέφεραν πολύτιμες κλινικές - και όχι μόνο – υποδείξεις, με σκοπό το βέλτιστο αποτέλεσμα.

Τέλος, το μεγαλύτερο ευχαριστώ ανήκει στον καθηγητή μου, κύριο Ιωάννη Μπολέτη, ο οποίος ήταν το πρόσωπο εκείνο το οποίο με παρότρυνε να ακολουθήσω το Μεταπτυχιακό Πρόγραμμα της Επιδημιολογίας και Μεθοδολογίας της Έρευνας, μου προσέφερε συνεχώς ευκαιρίες για συνεργασία και τη δυνατότητα να αναλύσω βάσεις δεδομένων νεφρολογικών ασθενών όντας ακόμη φοιτητής και τελικά μου εμπιστεύθηκε τη διαχείριση και ανάλυση του πανελληνίου αρχείου καταγραφής ασθενών με FSGS.

Με εκτίμηση,

Ιωάννης Ελ. Μιχελάκης

IX. REFERENCES

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