PO1530

Proteinuria Endpoints and Association with Renal Survival in FSGS: Analysis of the UK National RaDaR Idiopathic Nephrotic Syndrome Cohort

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Introduction

Background

- Focal segmental glomerulosclerosis (FSGS) is one of the most common histopathologic lesions of glomerular injury in patients with nephrotic syndrome (NS), often following a progressive course to established kidney failure over a period of months to years[1,2]
- Proteinuria contributes to podocyte dysfunction[3] and has been suggested to be predictive of a poor prognosis and a biomarker of disease severity,[4] with remission of proteinuria beneficial in slowing disease progression[5,6]
- We have analysed data from a large national cohort of patients with FSGS, adult and paediatric, with comprehensive long-term follow up

Objective

- To test for associations between complete or partial remission of proteinuria within 12 months of disease onset and long-term renal survival in adult and paediatric patients with FSGS

Methods

Data Source

- Data were analysed from the National Registry of Rare Kidney Diseases (RaDaR), which is a UK Kidney Association (UKKA) initiative that collects and pools retrospective and prospective data from patients with certain rare kidney diseases in the United Kingdom (UK)
- The Idiopathic Nephrotic Syndrome Rare Disease Group (RaDaR-INS) includes 3,907 patients with NS not attributable to glomerulonephritis or systemic disorders
- Recruitment began in 2010 to RaDaR-INS and is ongoing in 107 adult and paediatric kidney units across the UK

Definitions and Clinical Measures

- Disease onset was defined as the first occurrence of positive diagnostic renal biopsy, primary renal diagnosis, symptom presentation, initiation of immunosuppression, or first recorded proteinuria >1 g/g
- Baseline pertains to first nephrotic range proteinuria value (≥3.0 g/g) at or after disease onset
- Proteinuria endpoints (see Table 2) were based on proteinuria measured during follow-up, which was assessed at 6-12 months from first nephrotic-range proteinuria value
- End-stage kidney disease (ESKD) was defined as chronic kidney disease (CKD) stage 5 (confirmed eGFR <15 mL/min/1.73m^2 or CKD stage 5 recorded in RaDaR) or receiving chronic dialysis or kidney transplant
- Renal survival was defined as absence of ESKD or death with survival time calculated from baseline to ESKD onset date/death date or last follow-up

Eligibility Criteria

- Patients with idiopathic biopsy-proven or monogenic FSGS and ≥12 months observation from disease onset were included
- A nephrotic range proteinuria value (≥3.0 g/g) at disease onset or during follow-up, and a subsequent follow-up proteinuria value within 6-12 months from the first nephrotic range proteinuria value was required
- Patients with ESKD at or prior to disease onset as defined were excluded

Statistical Analyses

- Comparisons across groups were evaluated via Chi-square test, a two-sample t-test, or Wilcoxon-Mann-Whitney test, as appropriate
- Time to ESKD or death was analysed using accelerated failure time modelling of the Weibull distribution and Kaplan-Meier estimates of cumulative incidence

RaDaR, the UK Rare Renal Disease Registry (www.rarerenal.org), was established by the UK Kidney Association (https://ukkidney.org) in 2010 and now includes more than 26,000 patients at over 100 UK hospitals who have been diagnosed with one of 30 categories of rare kidney disease and who have provided written informed consent to participate. It is hosted by the UK Renal Registry (https://ukkidney.org/about-us/who-we-are/uk-renal-registry) and incorporates links to other national databases and, for the majority of participants, automated upload of biochemical and other hospital medical record data.

DISCLOSURES & FUNDING

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Results

Table 1. Demographics and follow-up of paediatric and adult patients with FSGS

	Overall (N=270)	Paediatrics (<18 years) (n=120)	Adults (≥18 years) (n=150)	P-Value
Age, Median (IQR)	22.3 (7.4-50.2)	6.6 (3.0-12.3)	44.8 (29.7-59.2)	
Sex (F), %	46.7	51.7	42.7	0.14*
Time from Disease Onset to First Nephrotic Range Proteinuria Value (years)†, Median (IQR)	0.5 (0.1-4.7)	0.5 (0.1-7.0)	0.5 (0.0-4.0)	0.04**
Duration of Follow-up from Nephrotic Range Proteinuria Value† (years)†, Median (IQR)	2.9 (1.5-5.9)	2.9 (1.6-5.9)	2.9 (1.5-5.9)	0.93**

Abbreviations: IQR, interquartile range. *Chi-square; **Mann-Whitney; †Defined as protein to creatine ratio (PCR) ≥3.0 g/g. Albumin to creatine ratio (ACR) values converted to PCR by applying a factor of 1.43.

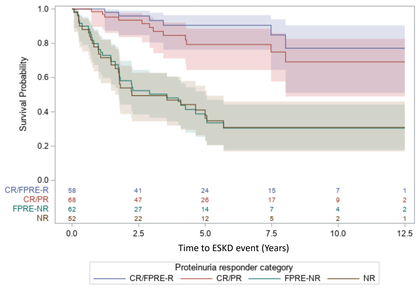
Table 2. Achievement of proteinuria endpoints and ESKD/death events in paediatric and adult patients with FSGS

	Proteinuria endpoints: PCR during follow-up (6-12 months from first nephrotic range PCR value)	Patients achieving proteinuria endpoint n (%)			ESKD/death events n (% of events of n in responder category)		
		Overall (n=270)	Paediatrics (n=120)	Adults (n=150)	Overall (n=90)	Paediatrics (n=42)	Adults (n=48)
CR/PR	PCR <3.0 g/g AND 50% decrease in PCR	165 (61.1)	68 (56.7)	97 (64.7)	34 (20.6)	12 (17.6)	22 (22.7)
NR	Not achieving PCR <3.0 g/g AND 50% decrease in PCR	105 (38.9)	52 (43.3)	53 (35.3)	56 (53.3)	30 (57.7)	26 (49.1)
CR/FPRE-R	PCR <1.5 g/g AND 40% decrease in PCR	137 (50.7)	58 (48.3)	79 (52.7)	20 (14.6)	6 (10.3)	14 (17.7)
FPRE-NR	Not achieving PCR <1.5 g/g AND 40% decrease in PCR	133 (49.3)	62 (51.2)	71 (47.3)	70 (52.6)	36 (58.1)	34 (47.9)

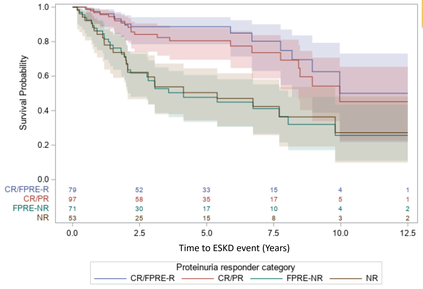
Abbreviations: CR, complete remission; **ESKD**, end-stage kidney disease; **FPRE**, FSGS partial remission of proteinuria endpoint; **NR**, non-responder; **PCR**, urine protein to creatinine ratio; **PR**, partial remission; **R**, responder.

Figure 1. Kaplan-Meier renal survival curves (incl. 95% CI) for proteinuria endpoints in patients with FSGS

A. Paediatric patients (<18 years)



B. Adult patients (≥18 years)



Abbreviation: CI, confidence interval.

Table 3: Median time to ESKD event or death by accelerated failure time modelling in paediatric and adult patients with FSGS by proteinuria responder category

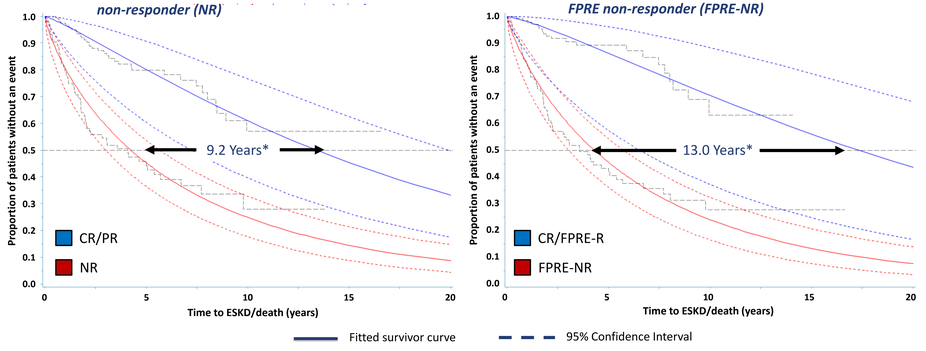
	Median time to ESKD/death (Years) (95% CI)*		
	Overall	Paediatrics	Adults
CR/PR	13.4 (9.4-19.1)	17.4 (8.9-34.3)	11.2 (7.3-17.2)
NR	4.2 (3.1-5.9)	3.5 (2.2-5.6)	5.1 (3.2-7.9)
CR/FPRE-R	17.3 (10.5-28.4)	22.4 (8.5-58.7)	14.4 (8.3-25.0)
FPRE-NR	4.3 (3.3-5.7)	3.8 (2.5-5.7)	4.8 (3.3-6.9)

Abbreviations: CI, confidence internal; **CR**, complete remission; **ESKD**, end-stage kidney disease; **FPRE**, FSGS partial remission of proteinuria endpoint; **NR**, non-responder; **PR**, partial remission.

Figure 2. Time to ESKD event or death by accelerated failure time modelling in FSGS patients by proteinuria responder category (paediatrics and adults combined)

A. Complete or partial remission (CR/PR) vs non-responder (NR)

B. Complete remission or FPRE-R (CR/FPRE-R) vs FPRE non-responder (FPRE-NR)



*Statistically significant difference in median survival for CR/PR vs NR and CR/FPRE-R vs FPRE-NR (p<0.0001; Chi-square test).

Conclusion

Summary and Discussion

- A greater proportion of adults achieved remission definitions than paediatric patients, however, the frequency of ESKD/death events in responders was lower in children
- For patients achieving CR/PR, 21% progressed to ESKD/death, while the proportion was lower at 15% for patients achieving CR/FPRE-R, based on proteinuria level
- Failure to achieve remission definitions was associated with very poor outcomes, with median time to ESKD/death of <5 years
- A higher probability for survival was observed among patients achieving remission definitions, extending median time to ESKD/death by ≈9 years for CR/PR vs NR, and ≈13 years for CR/FPRE-R vs NR, independent of initial proteinuria level

Strengths and Limitations

- This study utilized large sample sizes with comprehensive data collection, representing a nationwide database and involving a large proportion of UK renal centres
- Data were presented from both paediatric and adult FSGS populations with lengthy follow-up and automatic laboratory feeds for updating many test results in RaDaR
- Selection of patients with 6-12 months of follow-up proteinuria data may create a bias in the analysis as this group may not be a random selection of the full RaDaR-INS FSGS cohort

Conclusions

- Achieving partial or complete remission of proteinuria is associated with an important and clinically meaningful increase in the time FSGS patients are alive and free from ESKD

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