

# Mortality and Kidney Failure among Adults with Primary Podocytopathies

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## Abstract

**Introductions:** Patients with primary podocytopathies such as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) with nephrotic syndrome are at risk for adverse outcomes. This study reports on the long-term outcomes, specifically kidney failure and death among patients treated for primary podocytopathies in a tertiary centre in Singapore. **Materials and Methods:** This was a single-centre, retrospective cohort study of all adults aged  $\geq 21$  years old diagnosed between 2016 and 2020 with MCD and FSGS with nephrotic-range proteinuria. We excluded patients with membranous nephropathy and secondary glomerulonephritides (lupus nephritis, ANCA-associated vasculitis, membranoproliferative glomerulonephritis, and diabetic nephropathy). Socio-demographic, comorbidity, laboratory and pharmacotherapy data were retrieved from the electronic medical records. The outcomes assessed were incidence of death or kidney failure (estimated glomerular filtration function [eGFR]  $< 15$  ml/min/1.73 m<sup>2</sup> or required kidney replacement therapy). **Results:** Sixty patients (Chinese 80%, Malay 6%, Indian 3% and other races 3%) with MCD (37 patients) and FSGS (23 patients) were included. The morphological lesions in FSGS included cellular (n=2), tip (n=2), perihilar (n=7), collapsing (n=3) and not otherwise specified (n=17). At a median follow-up of 26.3 (8.9, 50.3) months, 12 (20%) outcomes were recorded, 11 (47.8%; death 6 and kidney failure 5) in the FSGS group and 1 (2.7%; died) in the MCD group. The causes of death were attributed to kidney failure (n=1), cardiovascular disease (n=1), infection (n=3); and unknown (n=2). The Kaplan-Meier survival curve showed that patients with MCD had better patient and kidney outcomes than those with FSGS (log rank  $p < 0.001$ ). Cox regression analysis (adjusted for age) found that FSGS was significantly associated with death or kidney failure (adjusted hazard ratio 18.17, 95% confidence interval 2.28-145.07,  $p = 0.006$ ), compared with MCD. **Conclusion:** Adults with severe primary podocytopathy due to FSGS had worse patient and kidney outcomes than MCD.

**Keywords:** Kidney disease; Glomerulonephritides; Death; Outcomes.

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**INTRODUCTION**

Podocytopathies are a spectrum of primary glomerular diseases resulting from podocyte injury, that commonly presents as nephrotic syndrome. Nephrotic syndrome is clinically characterised by severe proteinuria (greater than 3g per day), hypoalbuminemia (serum albumin 30g/L), hyperlipidaemia, and oedema. Nephrotic syndrome, if persistent or progressive, can contribute to the development of chronic kidney disease (CKD) and may ultimately result in end stage renal disease (ESRD) and is associated with higher risk of cardiovascular disease and mortality.

The common primary podocytopathies that cause nephrotic syndrome in adults are Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS).<sup>1</sup> Both FSGS and MCD are the most frequent histopathologic findings of podocyte injury leading to nephrotic syndrome. The incidence of adult MCD is 10-25% of all nephrotic syndromes, whereas primary FSGS is reported in 20-30% of adult nephrotic syndrome patients.<sup>2,3</sup>

Primary FSGS are more likely to resemble MCD by the absence of immune-type electron-dense deposits and the presence of widespread foot process effacement. Although FSGS and MCD are defined as different types of primary glomerular diseases, they both share overlapping clinical and pathological entities.<sup>4</sup> A limited renal biopsy sample may lead to a misdiagnosis of FSGS as MCD and MCD may evolve into FSGS over years.<sup>5</sup> MCD and FSGS thus, could represent, in a proportion of patients, two phases of the same disease.<sup>6</sup>

Both MCD and FSGS can lead to adverse renal outcomes, with FSGS potentially having a higher risk of progression to ESRD and death. The prevalence of FSGS, relative to other glomerular disease, seems to be increasing worldwide and major contributors to ESRD.<sup>7</sup> Based on Singapore's renal biopsy data over four decades between year 1976 and 2018, FSGS has become increasingly prevalent cause of nephrotic syndrome from 5% in the 1<sup>st</sup> decade to 25% on the 4<sup>th</sup> decade.<sup>8</sup>

Both are primarily treated with immunosuppressive therapy (IST), with corticosteroids being the initial treatment in most cases. Thus, early and accurate diagnosis of both MCD and FSGS is crucial for effective treatment and management. Characterizing the long-term health course of primary podocytopathies is

crucial for risk profiling, risk factors optimisation, and potentially slow down or prevent development of ESRD.

Previous Study comparing kidney outcomes between patients with MCD and FSGS in Southeast Asian Cohort mainly evaluated treatment response and treatment-related toxicities.<sup>9</sup> There is scarce data that investigates the clinical profile, risk of mortality and kidney failure of adult Southeast Asian patients with nephrotic syndrome caused by MCD and FSGS.

Therefore, the purpose of this study is to further evaluate the characteristics, long-term renal and patient outcomes for both adult MCD and FSGS individuals in Southeast Asian population. We hope that this study will confer additional understanding in identifying individuals who are at higher risk of kidney disease progression to allow early intervention and mitigate CKD progression into ESRD.

**MATERIAL AND METHODS****Study Design and Patient Selection**

This was a retrospective observational cohort study of individuals aged  $\geq 21$  years old with nephrotic-range proteinuria (urine protein: creatinine ratio [UPCR]  $>3$  g/g) and hypoalbuminemia (serum albumin  $<30$  g/L) and histopathological findings of MCD and FSGS on renal biopsy treated in tertiary referral centre (Singapore General Hospital) between January 2016 and December 2020. Individuals with multiple biopsies were included only once in the data collection, i.e. the first index biopsy within the study period. Patients lost to follow up were censored/screened at their last clinic review/visit. Enrolled patients were followed up until December 2023. Kidney biopsies are routinely assessed for sampling adequacy by medical laboratory technologists at the time of kidney biopsy. The medical laboratory technologist uses microscope to assess number of glomeruli and proportion of cortex and medulla at bedside during the kidney biopsy procedure to assess adequacy. In general, 10 glomeruli considered adequate sample.

Inclusion criteria were individuals  $\geq 21$  years of age and had nephrotic-range proteinuria (urine protein: creatinine ratio [UPCR]  $>3$ g/g) and hypoalbuminemia (serum albumin  $<30$  g/L). Patients with membranous nephropathy and secondary glomerulonephritides (lupus

nephritis, ANCA-associated vasculitis, membranoproliferative glomerulonephritis, and diabetic nephropathy) are excluded. Patients who received a kidney transplant are also excluded.

### Outcome parameters

The outcomes were the incidence of death or development of kidney failure (estimated glomerular filtration function [eGFR]<15 ml/min/1.73 m<sup>2</sup> or required kidney replacement therapy).

Demographic and clinical data included age at diagnosis, gender, ethnicity, comorbidities i.e. diabetes, hypertension and hyperlipidaemia, body mass index (BMI), and eGFR. Clinical presentation included blood pressure, presence of nephrotic syndrome, presence of haematuria, acute kidney disease (AKD), severe AKD requiring RRT, serum creatinine, serum albumin, random urine protein-to-creatinine ratio (UPCR), and 24-h urinary protein excretion, Hb<sub>A1c</sub>, fasting glucose, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL), percentage of global glomerulosclerosis at the time of biopsy.

For statistical analysis, analysis was performed using SPSS 25.0. Categorical variables presented as number (column percentage) and compared using the chi square test or Fisher's exact test. Continuous variables presented as median (25th centile, 75th centile) and compared using the Mann-Whitney U test. Statistical significance was defined as  $p < 0.05$ . Kaplan-Meier survival curve analysis was used to assess death or kidney failure among adults with primary podocytopathies and comparison by histology.

This study was approved by the SingHealth Centralised Institutional Ethics Review Board (CIRB Ref: 2024-3941) and included waiver of informed consent based on ethical consideration.

## RESULTS

### Baseline and Demographic Characteristics

The study included 60 adults (80% Chinese, 6% Malay, 3% Indian, 3% other races) with MCD (37 patients) and FSGS (23 patients). The morphological lesions in FSGS included cellular (2 patients), tip (2 patients), perihilar (7 patients), collapsing (3 patients) and not otherwise specified (17 patients). The median age was 53.8 (interquartile range 35.7, 71.2) years. Ischaemic heart disease, cerebrovascular disease and liver cirrhosis were present in 8.3%, 5.0% and 1.7%, respectively.

**Table I** shows that compared with the MCD group,

patients with FSGS had significantly older age and poorer baseline kidney function. The FSGS group had higher levels of serum creatinine, haematuria and global glomerulosclerosis at presentation; fewer had lipid assessment but had lower total and LDL-cholesterol, than the MCD group. Twelve patients (20.0%) died or had kidney failure during the median follow-up of 26.3 (interquartile range 25<sup>th</sup> centile, 75<sup>th</sup> centile: 8.9, 50.3) months.

**Figure 1** showed that the death or kidney failure rate was highest in the first 9 months after diagnosis. Five (8.3%) had kidney failure at 2.8 (1.1, 11.9) months after diagnosis and 7 (11.7%) died at median 6.4 (4.1, 32.6) months after diagnosis. The causes of death were attributed to kidney failure (1 patient), cardiovascular disease (1 patient), infection (3 patients); and unknown (2 patients).

Among the group with FSGS, 11 patients (47.8%) died or had kidney failure during median follow-up of 11.1 (3.8, 44.0) months. Among the group with MCD, 1 patient (2.7%), died or had kidney failure during median follow-up of 33.4 (13.9, 52.6) months. The Kaplan-Meier survival curve for death or kidney failure (**Figure 2**) showed that patients with MCD had better patient and kidney outcomes than those with FSGS (log rank  $p < 0.001$ ). Cox regression analysis (adjusted for age) found that FSGS was significantly associated with death or kidney failure (adjusted hazard ratio 18.17, 95% confidence interval 2.28-145.07,  $p = 0.006$ ), compared with MCD.

## DISCUSSION

In the present study, we retrospectively evaluated the clinical characteristics and long-term kidney and patient outcomes with histological diagnosis of FSGS (N = 23) and MCD (N = 37) in Southeast Asian cohort at our centre. Of the 37 patients with MCD, 17 were male and 20 were female. The median age at diagnosis is 46.6 years (IQR 31.9, 67.6). Of the 23 patients with FSGS, 12 were male and 11 were female. The median age at diagnosis is 61.3 years (52.4, 76.8). Study looking at demographics of Japanese patients with primary NS showed the median (IQR) age of onset was also lower for MCD 31 [16-49] as compared with FSGS 39 [19-55].<sup>10</sup> However, in our cohort the FSGS group were significantly older compared with MCD group.

Microscopic haematuria was present in 10% of our MCD cohort, and 13% of our FSGS cohort which was similar to that in previous studies (10-30%).<sup>11</sup> Study on prevalence of hypertension across primary GN showed

	All N = 60 (25%, 75% interquartile range)	Type of histological lesion		
		MCD, N = 37 (25%, 75% interquartile range)	FSGS, N = 23 (25%, 75% interquar- tile range)	P value
<b>Comorbidities</b>				
Age, years	53.8 (35.7, 71.2)	46.6 (31.9, 67.6)	61.3 (52.4, 76.8)	0.051
Male, n (%)	29 (48.3)	17 (45.9)	12 (52.2)	0.64
BMI, kg/m <sup>2</sup>	24.0 (22.1, 27.2)	23.4 (21.6, 26.1)	25.5 (23.0, 28.6)	0.058
Diabetes mellitus, n (%)	10 (16.7)	4 (10.8)	6 (26.1)	0.16
- Glucose-lowering therapy, n (%)	3 (5.0)	1 (2.7)	2 (8.7)	<b>0.08</b>
Hypertension, n (%)	28 (46.7)	15 (40.5)	13 (56.5)	0.23
- RAS blocker therapy, n (%)	27 (45.0)	18 (48.6)	9 (39.1)	0.52
- MRA therapy, n (%)	3 (5.0)	1 (2.7)	2 (8.7)	<b>0.08</b>
Hyperlipidemia, n (%)	27 (45.0)	16 (43.2)	11 (47.8)	0.73
Baseline eGFR past 1 year, ml/min/1.73 m <sup>2</sup>	96.3 (82, 112)	98.8 (88.4, 114.8)	89.8 (78.6, 98.9)	<b>0.03</b>
<b>Clinical presentation</b>				
Systolic BP, mmHg	126 (114, 133)	124 (113, 132)	128 (114, 141)	0.38
Diastolic BP, mmHg	70 (64, 78)	71 (65, 80)	69 (59, 72)	0.16
Microscopic hematuria, n (%)	23 (38.3)	10 (27.0)	13 (56.5)	0.07
Urine RBC, number per high-power field	3 (0, 16)	0 (0, 7)	10 (0, 93)	<b>0.005</b>
Nephrotic syndrome, n (%)	56 (93.3)	36 (97.3)	20 (87.0)	0.17
Acute kidney disease, n (%)	17 (28.3)	7 (18.9)	10 (43.5)	<b>0.049</b>
Severe AKD requiring KRT, n (%)	4 (6.7)	3 (8.1)	1 (4.3)	0.61
Serum creatinine, mcml/L	94 (68, 223)	78 (57, 154)	158 (88, 322)	<b>0.02</b>
Serum albumin, g/L	19 (17, 22)	18 (17, 22)	20 (17, 25)	0.09
UCPR, g/g	9.8 (7.4, 15.9)	9.9 (8.1, 14.4)	9.6 (7.4, 17.8)	0.86
TUP <sup>^</sup> , g/day	8.8 (5.9, 12.1)	7.8 (5.8, 13.8)	9.6 (5.7, 11.6)	0.71
HbA1c assessed, n (%)	37 (61.7)	23 (85.2)	14 (63.6)	0.08
HbA1c level, %	5.9 (5.5, 6.7)	5.9 (5.5, 6.5)	6.0 (5.5, 6.8)	0.70
Fasting glucose assessed, n (%)	38 (63.3)	24 (64.9)	14 (60.9)	0.23
Fasting glucose level, mmol/L	5.3 (4.7, 6.4)	5.4 (4.9, 5.9)	5.6 (4.5, 6.9)	0.96
Fasting lipid assessed, n (%)	54 (90.0)	35 (94.6)	19 (82.6)	<b>0.02</b>
Total cholesterol level, mmol/L	8.92 (6.36, 11.94)	10.60 (8.22, 12.52)	7.12 (5.22, 8.73)	<b>0.001</b>
LDL-cholesterol level, mmol/L	6.01 (4.23, 8.48)	8.01 (5.22, 8.89)	4.23 (3.10, 5.93)	<b>&lt;0.001</b>
HDL-cholesterol level, mmol/L	1.37 (0.79, 1.64)	1.57 (1.33, 3.15)	0.79 (0.7, 1.3)	0.059
Global glomerulo-sclerosis, percentage	11.4 (0.9, 27.2)	4.2 (0, 12.5)	22.2 (12.8, 36.8)	<b>&lt;0.001</b>
<b>Outcomes</b>				
Follow-up, months	26.3 (8.9, 50.3)	33.4 (13.9, 52.6)	11.1 (3.8, 44.0)	<b>0.02</b>
Death or kidney failure, n (%)	12 (20.0)	1 (2.7)	11 (47.8)	<b>&lt;0.001</b>

AKD, acute kidney disease; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAS, renin-angiotensin system; RBC, red blood cells; TUP, total urine protein; UPCr, urine protein-to-creatinine ratio.

<sup>^</sup>TUP was performed in 44 patients (73.3%).

Categorical variables presented as number (column percentage) and compared using the chi square test or Fisher's exact test. Continuous variables presented as median (25th centile, 75th centile) and compared using the Mann-Whitney U test. Statistical significance was defined as p <0.05.

that the odds of hypertension were 3.8 times greater in FSGS compared to MCD.<sup>12</sup> The rates of hypertension were 40% in our MCD and 56% in our FSGS groups.

FSGS group had poorer baseline kidney function with higher serum creatinine compared with MCD group. Lower eGFR at baseline could be caused by

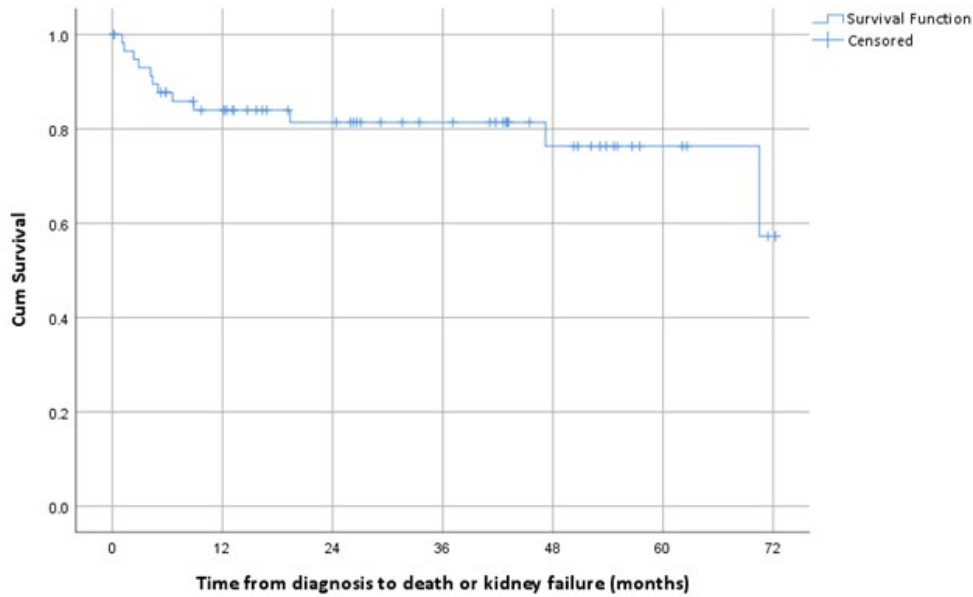


Fig. 1. Kaplan-Meier survival curve for death or kidney failure among adults with primary podocytopathies.

underlying chronic kidney dysfunction and AKI. AKI was observed in 20%–40% of adult MCD and 44% of FSGS with NS.<sup>13,14</sup> Of the 60 of our patients, 17 (28.3%) had acute kidney disease (AKD). Among the FSGS group, 10 out of 23 patients (43.5%) had AKD, of which one required RRT. Among the MCG group, seven out of 37 patients (18.9%) had AKD of which four required RRT.

Overall 56 (93.3%) had NS. In the MCD group 97.3% (36 out of 37 patients) and in the FSGS group 87% (20 out of 23 patients). Initial levels of proteinuria in patients with FSGS (9.6 g/24h) were higher than those with MCD (7.8 g/24h). Higher serum creatinine levels and the degree of proteinuria at diagnosis, as well as more severe glomerular sclerosis rate and interstitial fibrosis, are known predictors of renal survival,

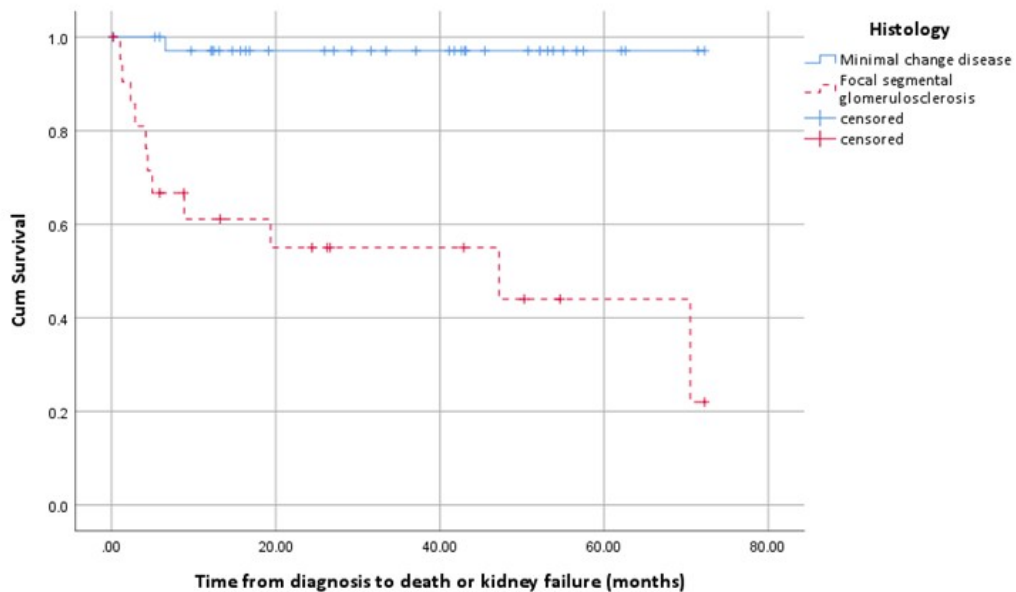


Fig. 2. Kaplan-Meier survival curve for death or kidney failure, compared by histology.

and faster progression to kidney failure.<sup>2</sup> In our study, the percentage of global glomerulosclerosis is higher 22.2% in the FSGS group compared to 4.2% in the MCD group.

In our study with a median follow-up of 26.3 months, 20.0% of patients experienced death or kidney failure. The highest rate of death or kidney failure occurred within the first 9 months after diagnosis. Specifically, 8.3% of patients developed kidney failure at a median of 2.8 months, and 11.7% died at a median of 6.4 months.

In primary podocytopathies, while podocyte injury is the initiating factor, main causes of death are related to kidney disease progression and its complications, including infections, cardiovascular disease and ESRD.<sup>11</sup> This was observed in our study where the causes of death were attributed to kidney failure (1 patient), cardiovascular disease (1 patient), infection (3 patients); and unknown (2 patients). CKD progression to ESRD is rare in patients with MCD, and when reported, most were cases that did not respond to corticosteroids or that were related to the diagnosis of FSGS in biopsies performed at a later stage in the evolution of the disease.<sup>15</sup> In our study, 11 out of 23 patients with FSGS (47.8%) died or had kidney failure during median follow-up of 11.1 (3.8, 44.0) months. As to be expected, among the group with MCD, only 1 out of 37 patients (2.7%), died or had kidney failure during median follow-up of 33.4 (13.9, 52.6) months.

MCD, in general, has more favorable renal and patient outcome in comparison to primary FSGS. In large US cohort study on incident ESRD and mortality, highest ESRD incidence (per 100 person-years) was observed in FSGS which was 8.72 (95% CI, 3.93-16.72), and MCD was 1.67 (95% CI, 0.15-6.69).<sup>16</sup> Two studies on long term outcomes of patients with primary GN in Taiwanese Chinese population and in the Korean population showed patients with MCD had best renal outcome and patient survival, whilst FSGS patients had worst renal survival with highest incidence of ESRD.<sup>17,18</sup>

The Kaplan-Meier survival curve for death or kidney failure in our study showed that patients with MCD had better patient and kidney outcomes than those with FSGS (log rank  $p < 0.001$ ). Cox regression analysis (adjusted for age) found that FSGS was significantly associated with death or kidney failure (adjusted hazard ratio 18.17, 95% confidence interval 2.28-145.07,  $p = 0.006$ ), compared with MCD.

There are some limitations in this study: as a single-centre, retrospective observational study. Our sample size was relatively small, which may influence statistical power. Follow up data may be incomplete from disease onset or diagnosis. It is known that response to immunosuppressive therapy, that is, remission of proteinuria, is an important factor associated with renal prognosis for both FSGS and MCD. However, in this study, we have not included the use of immunosuppressive therapy.

## CONCLUSION

Southeast Asia carries a significant burden of kidney disease which includes Singapore, where glomerular diseases (GD) are one of the leading causes of CKD. This study analysed the long-term renal and patient outcomes of primary podocytopathies, MCD and FSGS, that are amongst the most common causes of primary GN. Both MCD and FSGS have similar clinical manifestations, often presenting as nephrotic syndrome and treatment approaches. Previous studies have consistently shown that adult MCD carries more favorable prognosis with fewer than 5% of patients progressing to kidney failure, whilst FSGS is associated with higher risk of kidney progression and thus are at increased risks of kidney failure and mortality. As evidenced in our study, adults with primary podocytopathy from FSGS had worse patient and kidney outcomes compared to MCD. Continued research into primary podocytopathies, diseases affecting kidney podocytes, is crucial for improving patient outcomes by enabling better disease management, the development of targeted therapies, and potentially slowing disease progression.

## Take Home Message

- Primary podocytopathies such as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are amongst the most common causes of primary GN which present with nephrotic syndrome.
- Nephrotic syndrome can lead to progressive kidney dysfunction, increasing the risk of CKD and ultimately ESRD with significant morbidity and mortality.
- MCD has more favourable renal and patient outcome compared to FSGS with lower mortality and kidney failure.
- Main causes of death include infections, cardiovascular disease and ESRD.

**Abbreviations**

<b>CKD</b>	Chronic kidney disease
<b>ESRD</b>	End stage renal disease
<b>MCD</b>	Minimal change disease
<b>FSGS</b>	Focal segmental glomerular sclerosis
<b>IST</b>	Immunosuppressive therapy
<b>eGFR</b>	Estimate glomerular filtration rate
<b>BMI</b>	Body mass index
<b>AKI</b>	Acute kidney injury
<b>RRT</b>	Renal replacement therapy
<b>AKD</b>	Acute kidney disease

**Declarations**

All the authors declared no competing interests.

**Ethical Consideration**

This study was approved by the SingHealth Central[1]ised Institutional Ethics Review Board (CIRB Ref: 2024 -3941) and included waiver of informed consent based on ethical consideration.

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