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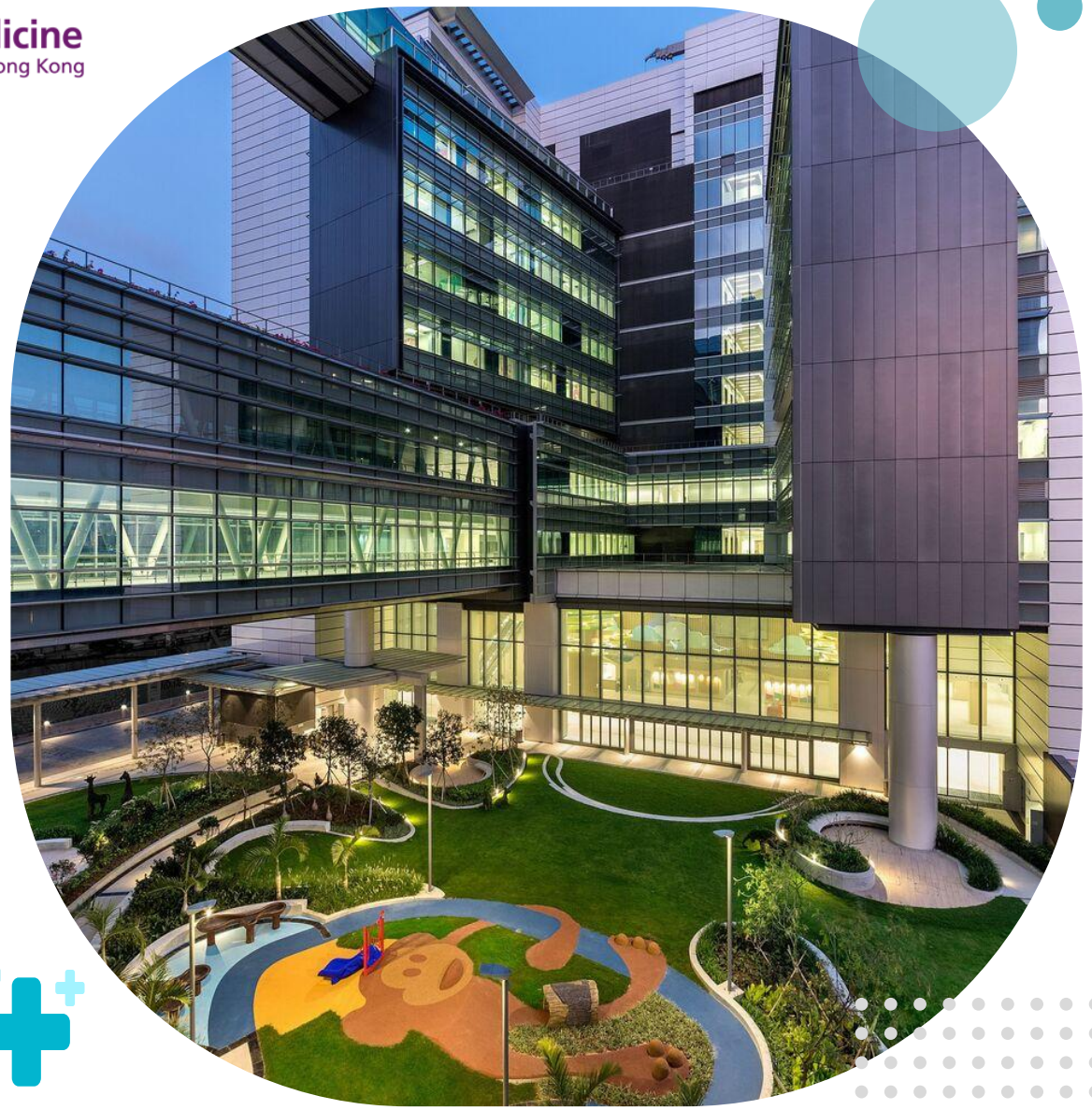
Use of Immunosuppression in severe IgA Nephropathy in children:

A multi-national and multicentre study



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Background

IgA Nephropathy (IgAN) is the most common primary Glomerulonephritis worldwide

- Affecting both adults and children
- Variation in the incidence/ prevalence of childhood IgAN - ethnicity/screening practices

Severe presentation in children

- Rapidly progressive Glomerulonephritis (RPGN) / Acute Nephritic syndrome
- Nephrotic syndrome
- Immunosuppressants (IS) are use often in children with severe presentation

Purpose of the Study

- To understand the long term outcome of children with severe IgAN who were on IS
- To understand the factors associated with poor kidney outcomes
- To investigate if there if any relationship between that phenotypes at presentation and the clincial outcomes
- Applicability of Partial remission as an intermediate group

Method

Multi-national Retrospective cohort study

- 50 tertiary paediatric nephrology centres across 25 countries from 2010-2020

Inclusion Criteria

- Children (< 18yo) with biopsy-proven Severe IgAN receiving immunosuppression
- Presentation
  - Acute nephritic syndrome /RPGN
    - Acute Nephritic syndrome: Children presenting with haematuria , proteinuria, and reduced GFR.
    - RPGN: Children with 50% or more decline in eGFR over the past 3 months
  - Nephrotic syndrome
    - NS: Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/l) or edema when serum albumin level is not available

Outcome Measures

Primary outcome

- Remission status according to the proposed criteria at different time points

Secondary Outcomes

- Event Free survival from
  - Advanced chronic kidney disease (CKD) stage 3-5
  - Kidney failure
- Factors associated with poor kidney outcome

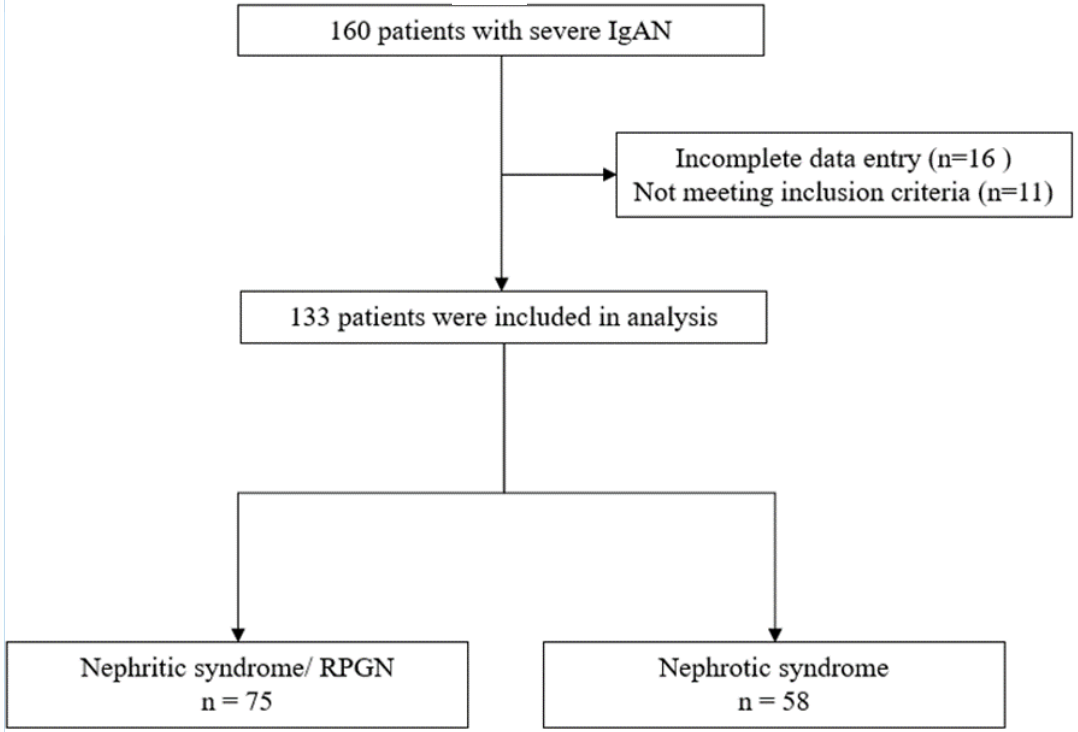
Presentation	Complete Remission (CR)	Partial Remission (PR)	Non-remission (NR)
Nephrotic syndrome	Absence of proteinuria (UPCR, <0.2mg/mg or 20mg/mmol, or urine dipsticks negative/trace	Sub-nephrotic-range proteinuria (UPCR >0.2 and <2mg/mg, >20mg/mmol and <200mg/mmol, or urine albustix 1+ to 2+) with a serum albumin level ≥30g/L.	Failure to attain CR and PR at the given time-points.
Acute nephritis syndrome/ RPGN	UPCR <0.5mg/mg[5]	Reduction in UPCR by >50% and <3mg/mg[5]	
	Require improvement or stabilization of kidney function (eGFR decrease of <15% at 6- or 12-months compared with baseline)[5]		

Definition of the remission by this study

Results

133 children (age, 10.2 years [IQR, 7.3-13.4]

- Follow up period : 55 months (IQR 34.5-92).
- M: F : 80: 53
- Nephritic/RPGN, n=75 Vs Nephrotic, n=58
- Immunosuppression
  - Nearly all received corticosteroids (96%)
  - 63% required additional immunosuppressants
  - 94% received ACEI



	All patients	Clinical Presentations	
		Nephritic syndrome/ RPGN	Nephrotic syndrome
(A) Baseline Characteristics	(N = 133)	(N = 75)	(N = 58)
Gender			
Male	80 (60)	44 (59)	36 (62)
Female	53 (40)	31 (41)	22 (38)
Ethnicity			
White	67 (50)	42 (56)	25 (43)
East Asian	43 (32)	15 (20)	28 (48)
South Asian	15 (11)	11 (15)	4 (7)
Black	2 (2)	2 (3)	0 (0)
Others	6 (5)	5 (7)	1 (2)
Median age at presentation, years (IQR)	10.5 (7.3–13.3)	11.7 (7.9–13.9)	8.2 (5.9–11.9)
Median age at biopsy, years (IQR)	10.6 (7.3–13.4)	11.7 (8.0–14.1)	8.3 (5.9 –11.9)
MEST score			
M[a]			
0	20 (16)	14 (19)	6 (11)
1	109 (84)	60 (81)	49 (89)
E[a]			
0	60 (47)	30 (41)	30 (55)
1	69 (53)	44 (59)	25 (45)
S[a]			
0	74 (57)	40 (54)	34 (62)
1	55 (43)	34 (46)	21 (38)
T[a]			
0	98 (78)	57 (78)	41 (79)
1	26 (21)	16 (22)	10 (19)
2	1 (1)	0 (0)	1 (2)

54%

(A) Baseline Characteristics (cont'd)	All patients (N = 133)	Clinical Presentations	
		Nephritic syndrome/ RPGN (N = 75)	Nephrotic syndrome (N = 58)
C[b]			
0	58 (46)	29 (41)	29 (53)
1	44 (35)	25 (35)	19 (34)
2	24 (19)	17 (24)	7 (13)
% crescent of glomeruli	25 (10-40)	20 (8-40)	25 (13-30)
Hypertension	43 (32)	28 (37)	15 (26)
Laboratory findings at baseline			
UPCR, mg/mg (IQR)	4.2 (2.2-7.6)	3.2 (1.3-5.4)	5.1 (3.6-9.8)
Serum albumin, g/L (IQR)	28.5 (20.0-37.5)	31.0 (23.0-40.0)	25.0 (19.5-32.1)
Serum creatinine, umol/L (IQR)	66.0 (45.0-107)	88.4 (61.9-150.3)	49.5 (34.5-70.9)
eGFR, ml/min/1.73m^2 (IQR)	73.0 (46.5-99.5)	57.0 (37.0-78.5)	85.5 (66.5-117.0)
Acute dialysis	8	6 (75)	2 (25)
Follow-up duration, months	55.0 (34.5-92.0)	49.0 (26.0-79.0)	71.0 (46.0-120.0)

	All patients	Clinical Presentations	
		Nephritic syndrome/ RPGN	Nephrotic syndrome
(B) Treatment Regimen (cont'd)	(N = 133)	(N = 75)	(N = 58)
Cyclophosphamide	25 (19)	16 (21)	9 (15)
Oral	11 (8)	8 (11)	3 (5)
Intravenous	14 (11)	8 (11)	6 (10)
Mycophenolate mofetil	49 (37)	32 (43)	17 (29)
Azathioprine	20 (15)	4 (5)	16 (28)
Calcineurin inhibitors	24 (18)	6 (8)	18 (31)
Cyclosporine A	19 (14)	5 (7)	14 (24)
Tacrolimus	4 (3)	1 (1)	3 (5)
Both (sequential use)	1 (1)	0 (0)	1 (2)
RAASi	125 (94)	71 (95)	54 (93)
Either ACEi or ARB	109 (82)	64 (85)	45 (78)
Dual RAAS blockade	16 (12)	7 (9)	9 (16)
Tonsillectomy	7 (5)	1 (1)	6 (11)
Other adjunctive treatments			
Anti-CD20 therapy	8 (6)	3 (4)	5 (9)
Therapeutic plasmapheresis	4 (3)	4 (5)	0 (0)
Omega-3	5 (4)	4 (5)	1 (2)
Mizoribine	3 (2)	0 (0)	3 (5)
Intravenous immunoglobulin	1 (1)	0 (0)	1 (2)
Chlorambucil	1 (1)	1 (1)	0 (0)

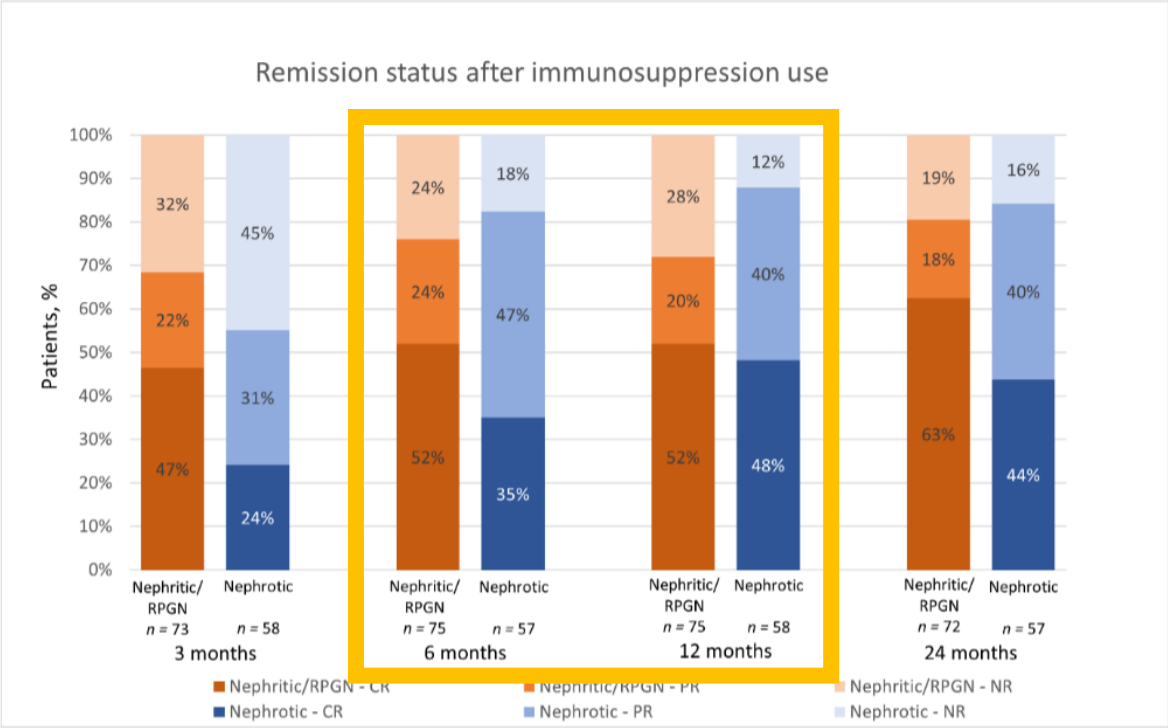
Results

	3m	6m	12m	24m
Remission (Complete/ Partial)	63%	79%	79%	82%
Non Remission	37%	21%	21%	18%

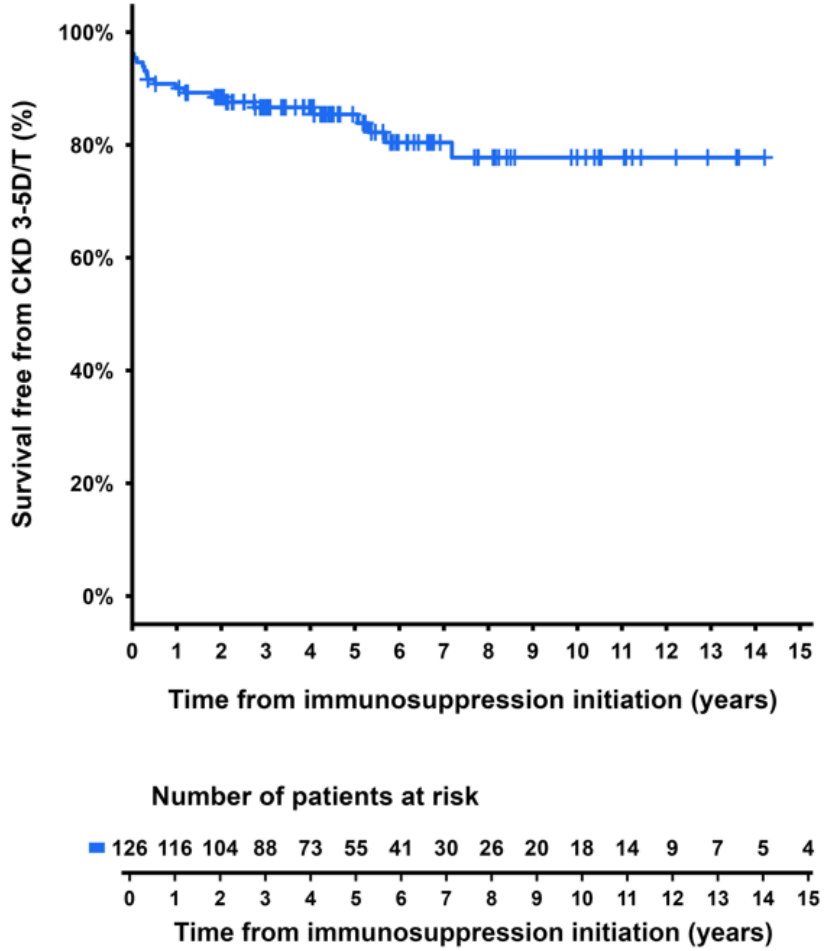
Based on the Remission criteria of the current study

Results- Remission status

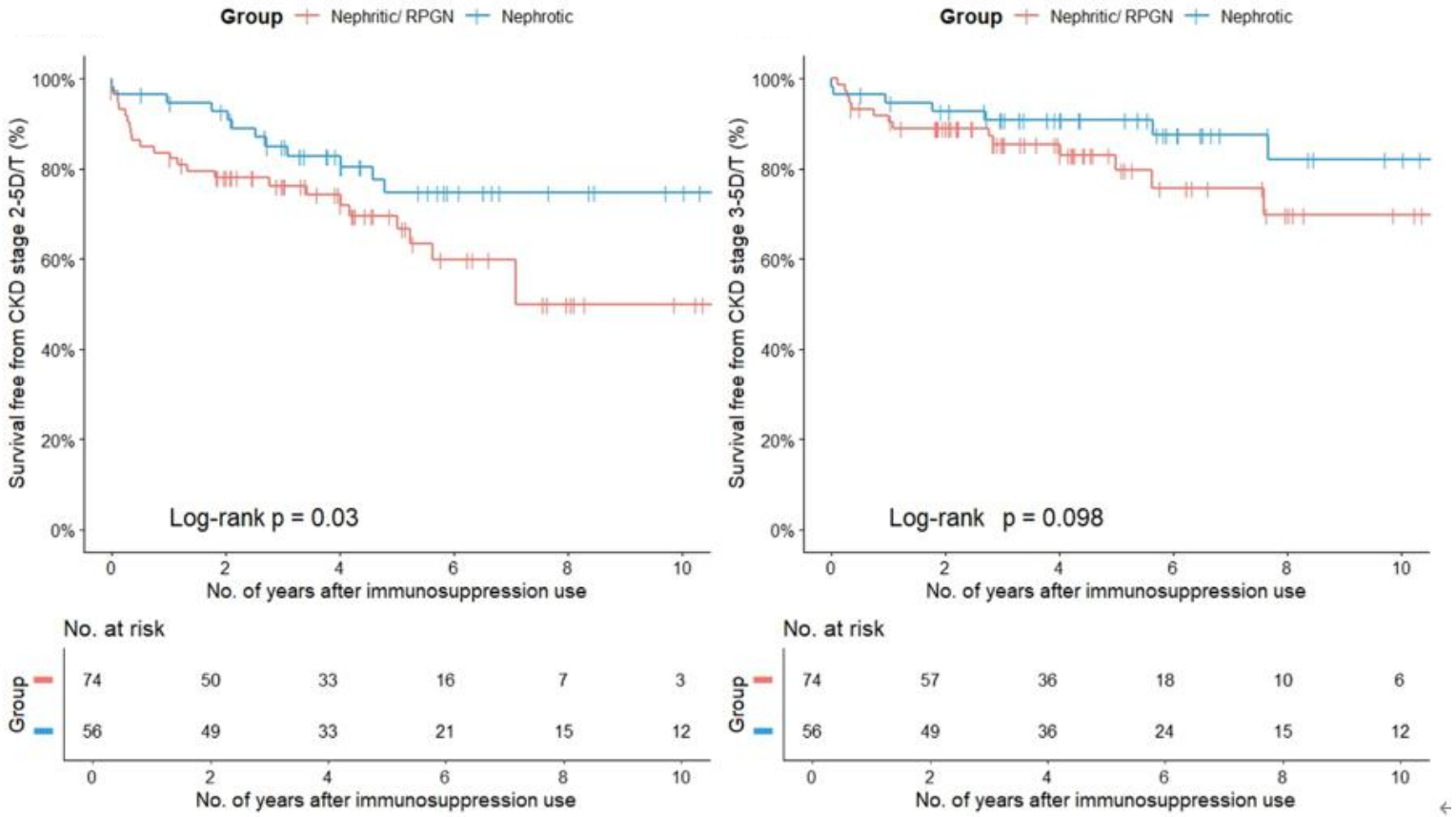
- Remission (CR/PR) was achieved more often in nephrotic syndrome than nephritic/RPGN
  - 6-months (82.5% [95% CI, 69.6-90.8] vs. 76.0% [95% CI, 64.5-84.8])
  - 12-months (87.9% [95% CI, 76.1-94.6] vs. 72.0% [95% CI, 60.3-81.5])



Overall picture -Survival Free from CKD III-V



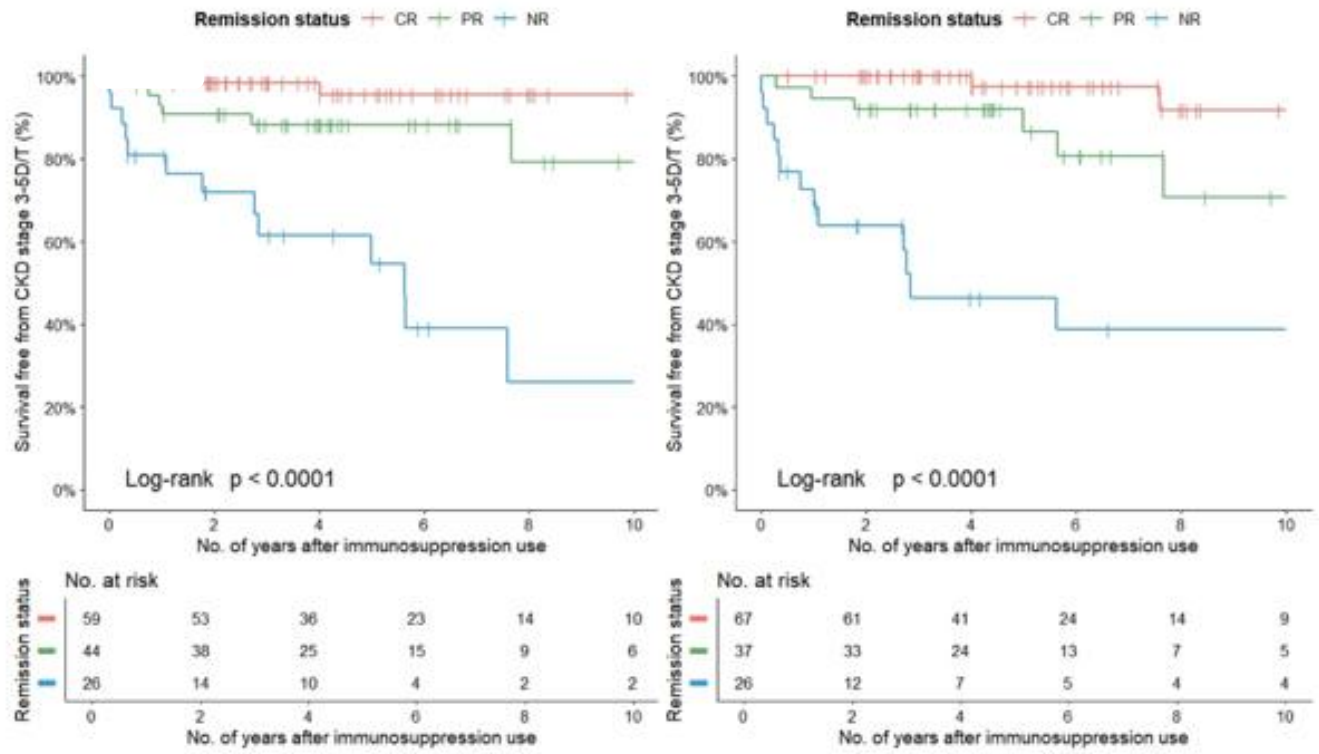
Results- Nephritic Vs Nephrotic presentation



Survival Free from CKD II-V

Survival Free from CKD III-V

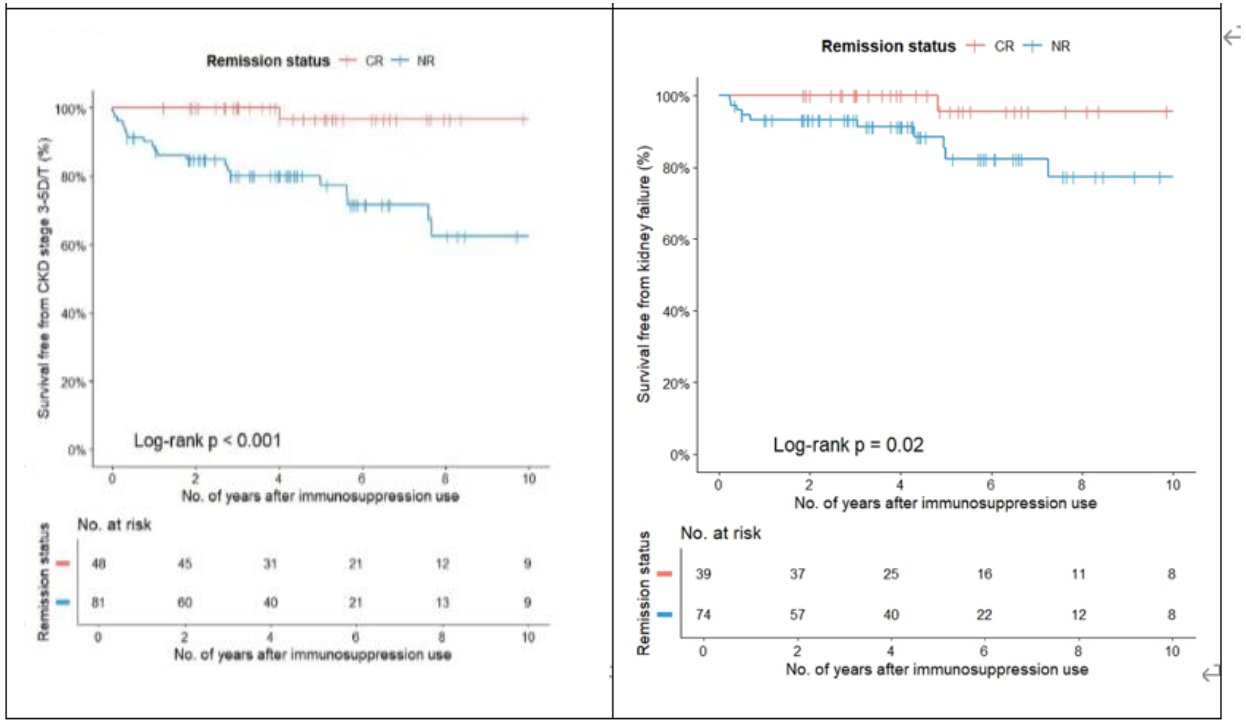
Results-6m Remission status and advanced CKD



CR, complete remission; PR, partial remission; NR, non remission

6 months **12 months**

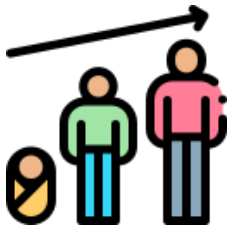
Results-6m Remission status and advanced CKD (IPNA criteria)



Survival Free from CKD III-V

Survival Free from Kidney Failure

Predictors of Advanced CKD



Older age at diagnosis

Lower baseline eGFR

Remission status

HR(Adj)	1.25 (95% CI 1.06-1.46)	0.97 95% CI, 0.96-0.09	PR at 6m :5.45, (95% CI, 1.10-27.02) NR at 6m : 12.52 (95% CI, 2.73-57.56)

Limitations

Retrospective nature, there is potential for selection and reporting bias

- Mitigation - consecutive recruitment, establishing well-defined inclusion and exclusion criteria with standardized reporting methods.

Not feasible to recruit a control group without immunosuppression

- Including patients with milder disease as controls was also inappropriate, given their markedly different clinical trajectory.

Heterogeneity in patient demographics and treatment protocols across centres and treatment periods

Clinical phenotypes could be overlapping

Small proportion of Black patients in our cohort- Limiting the generalisability of our findings to specific populations

Conclusion

Most patients with severe IgAN survive with reasonable kidney function

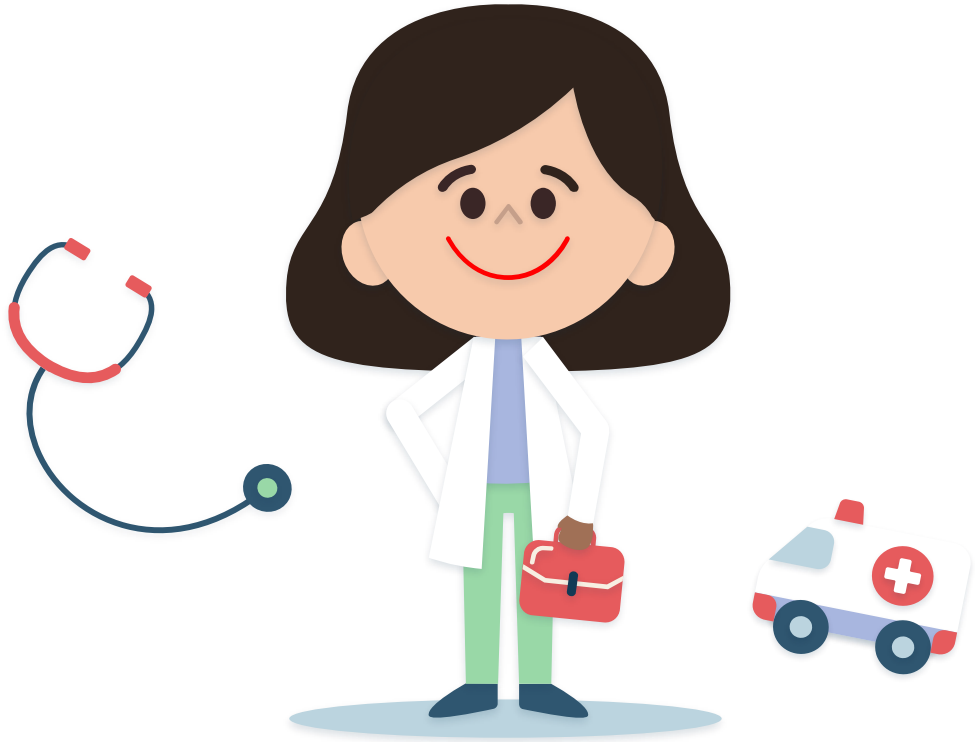
The presenting phenotypes of Nephritic/RPGN Vs nephrotic

- Might carry implications on the long term outcome

Risk factors for poor kidney outcome include older age at diagnosis, lower GFR at presentation and Remission status at 6m

Further studies are indicated !

THANK YOU



IPNA criteria of IgAN remission

- Resolution of proteinuria (UPCR < 0.2 mg/mg or 20 mg/mmol) or proteinuria < 100 mg/m2 per day or < 0.2 g/day in 24-h collection) based on at least two urine samples collected at least 1 month apart
- in the presence of normal (≥ 90 mL/min/1.73 m2) or stable eGFR. Complete remission includes
- in addition to these features, the resolution of hematuria, defined as a negative dipstick for blood and/or < 5 RBC/high-power microscopic field

IPNA remission criteria		
	Complete Remission (CR)	Non-remission (NR)
Any form of IgAN	Resolution of proteinuria (UPCR<0.2 mg/mg or 20 mg/mmol or proteinuria<100 mg/m^2 per day or<0.2 g/day in 24-h collection) based on at least two urine samples collected at least 1 month apart in the presence of normal (≥90 mL/min/1.73 m^2) or stable eGFR. *In the original description, complete remission includes the resolution of haematuria in additional to the above features. However, this was not included in the study due to the lack of standardisation in haematuria assessment, its uncertain prognostic value in IgAN, and its infrequent use as an outcome measure in current clinical trials.	Failure to attain remission at the given time-points.

Results

	6m	12m
Remission (Complete/ Partial)	36%	42%
Non Remission	63%	58%

IPNA criteria