Do Anti-Phospholipase A2 Receptor Antibodies Predict Recurrence of Membranous Nephropathy After Transplantation?

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Idiopathic Membranous Nephropathy

- One of the most common causes of nephrotic syndrome in adults
- MN can also be secondary to: infections, drugs, toxins, autoimmune disease, and cancer
- Idiopathic (primary) MN is the most common form (2/3 of biopsy-proven cases of MN)
- Current diagnosis of IMN relies exclusively on kidney biopsy
- IMN progresses to ESRD in 15-30%

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M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

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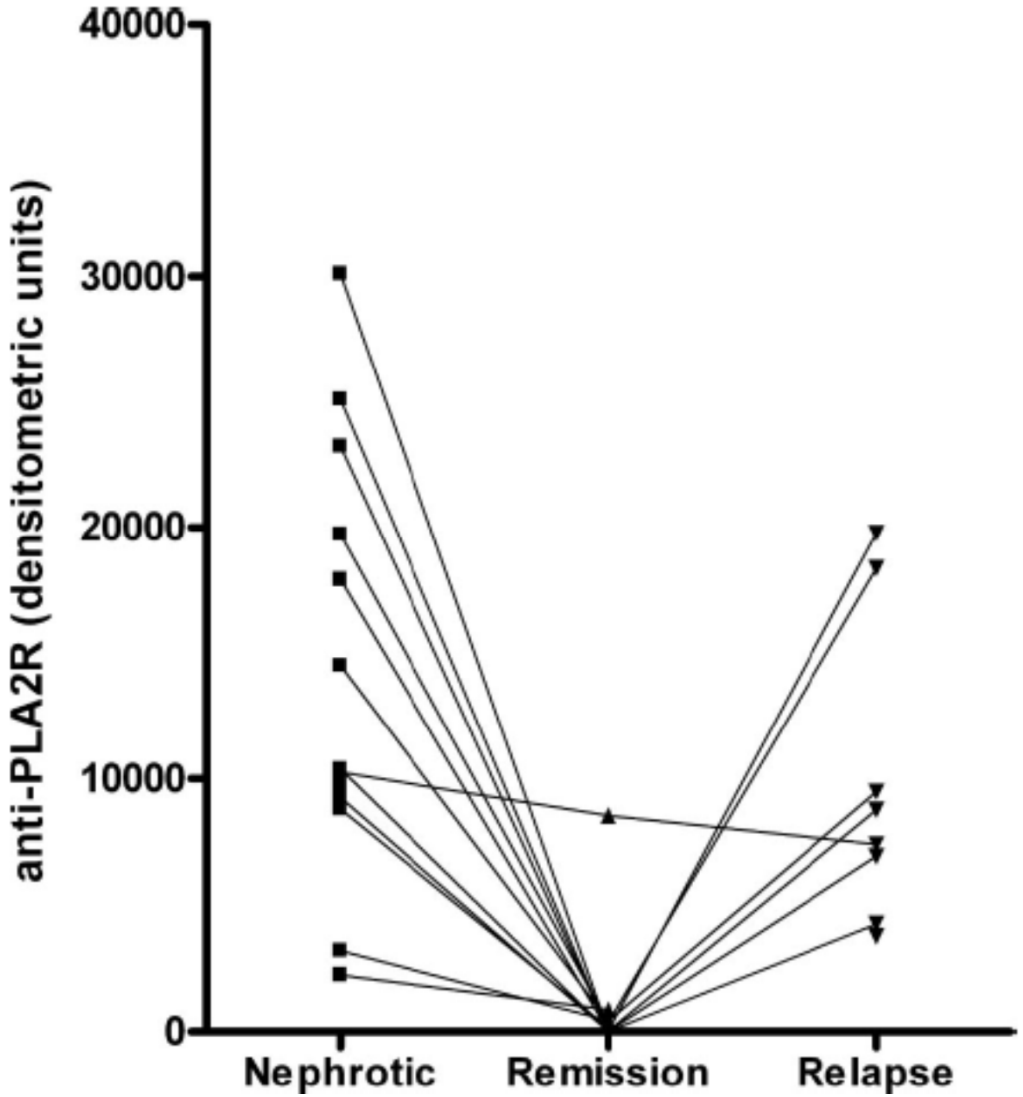
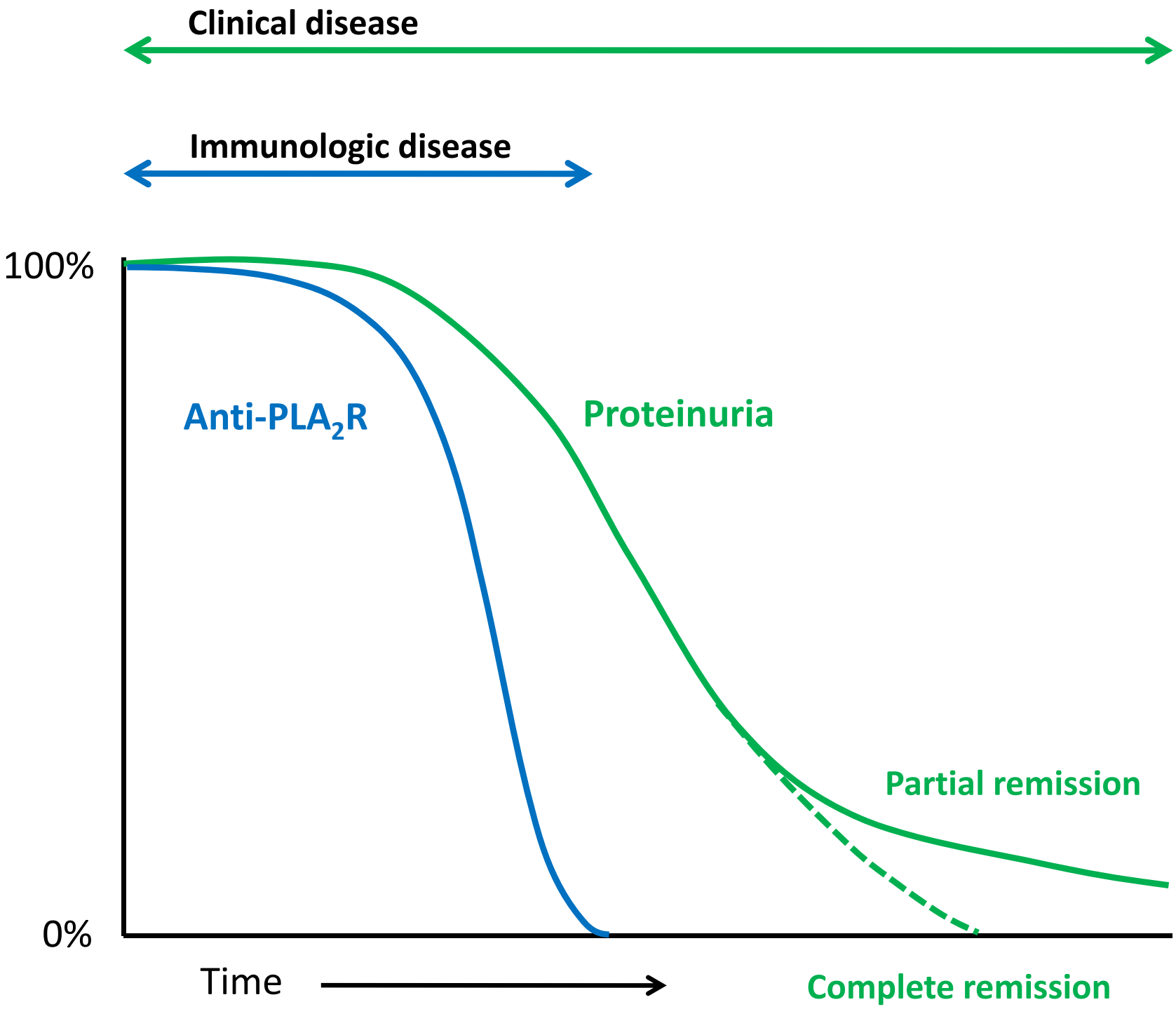
Idiopathic Membranous Nephropathy

- Growing data from American, European and Chinese cohorts show high prevalence (above 70%) of anti-PLA2R antibodies among patients with idiopathic MN while nearly all subjects with secondary MN were negative
- IgG4 is the dominant subclass in the majority of patients.
  - IgG4 has been linked to “tolerogenic” immune responses
  - IgG4 does not activate complement in the same way that other subclasses do

Presence of anti-PLA2R antibody correlates with clinical disease



Hofstra JM, et al. Clin J Am Soc Nephrol 6, 2011.



Beck LH, Salant DJ. KI (2010) 77, 765–770

Recurrent MN

- Incidence of recurrence: 10 to 45%
- Centers performing protocol biopsy report higher incidence and earlier recurrence
- Assessment of incidence rate is imperfect:
  - Patients who lose their allograft to rejection before developing rMN
  - Subclinical disease without substantial proteinuria
- The mean time for overt recurrence is 13-15 months
  - Kidney biopsy may show recurrence as soon as one week after transplantation*

* Blosser CD et al, *AJT* (2012) 12, 1359–1661

Anti-PLA2R and rMN

- The occasionally rapid recurrence of MN following transplantation suggests the presence of a circulating factor that may be present at the time of transplantation and raises 2 important questions:
  1. Does a positive anti-PLA2R at or just before transplantation predict recurrence?
  2. Can one use anti-PLA2R seropositivity post-transplant instead of surveillance biopsies to diagnose early recurrence?

Our Study

- We examined the relationship between anti-PLA2R antibodies and recurrence of MN in the allograft
- Retrospective analysis of anti-PLA2R by western blotting of sera from 70 patients
- To date we have obtained and analyzed pre-TP serum from 34 patients
- 25/34 are from the Mayo protocol biopsy group and 9/34 sporadic patients

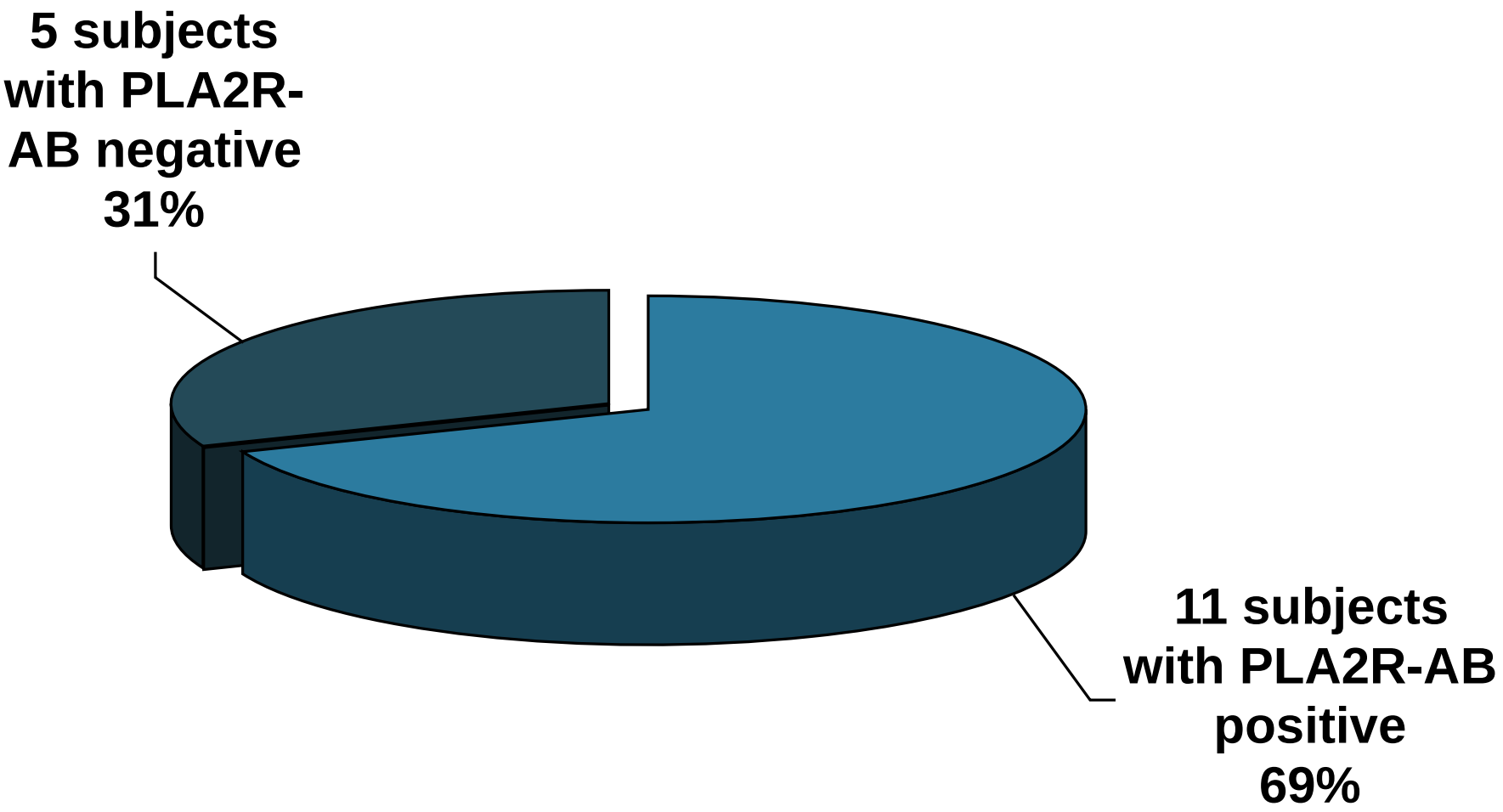
Pre-TP PLA2R as a predictor of recurrence

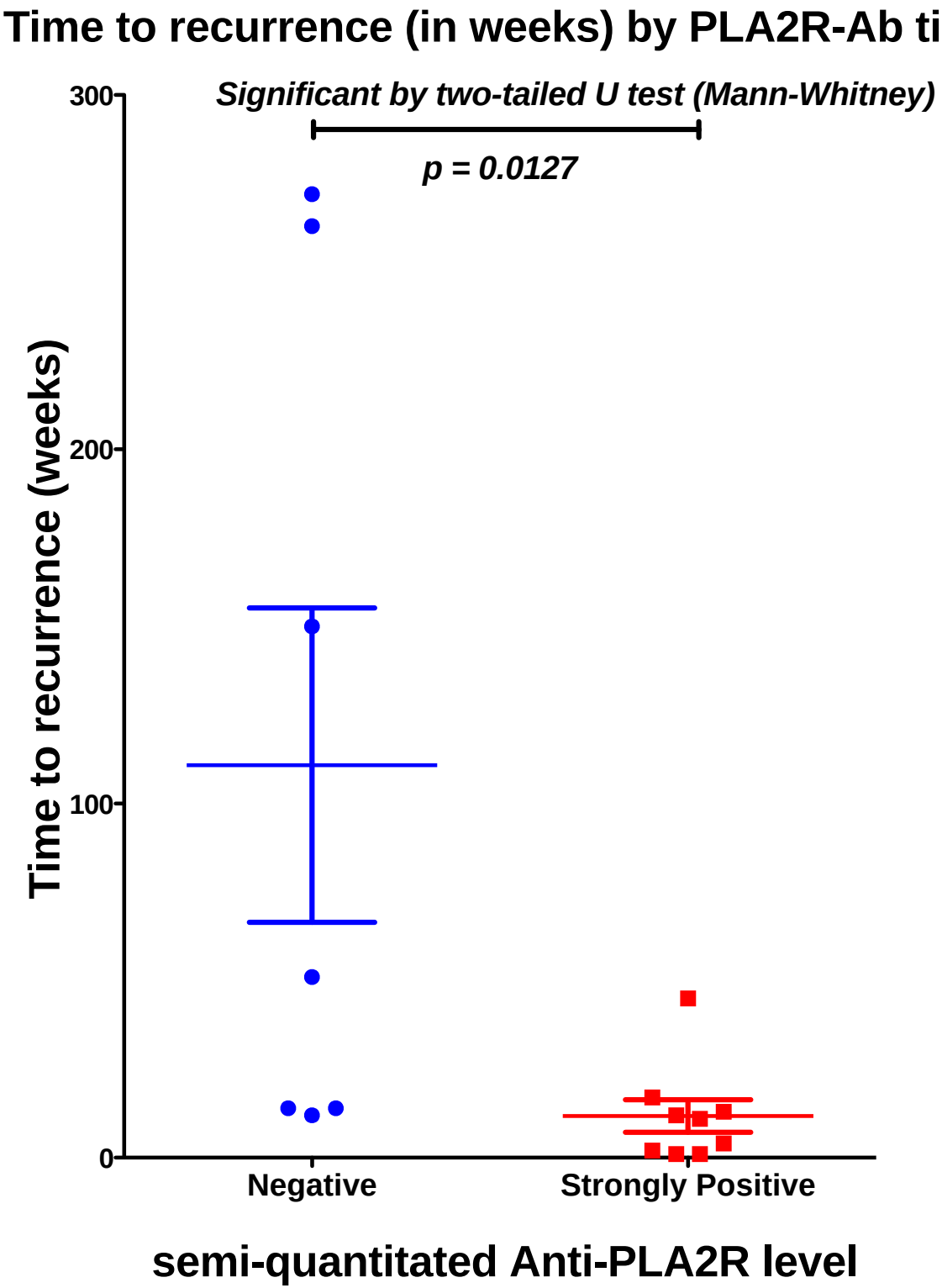
	Recurrence (+) n=25	Recurrence (-) n=9	
PLA2R Ab (+) n=23	17	6	Positive predictive value **74%**
PLA2R Ab (-) n=11	8	3	Negative predictive value **27%**
	Sensitivity **68%**	Specificity **33%**	

Pre-TP PLA2R as a predictor of recurrence among the Mayo protocol biopsy group

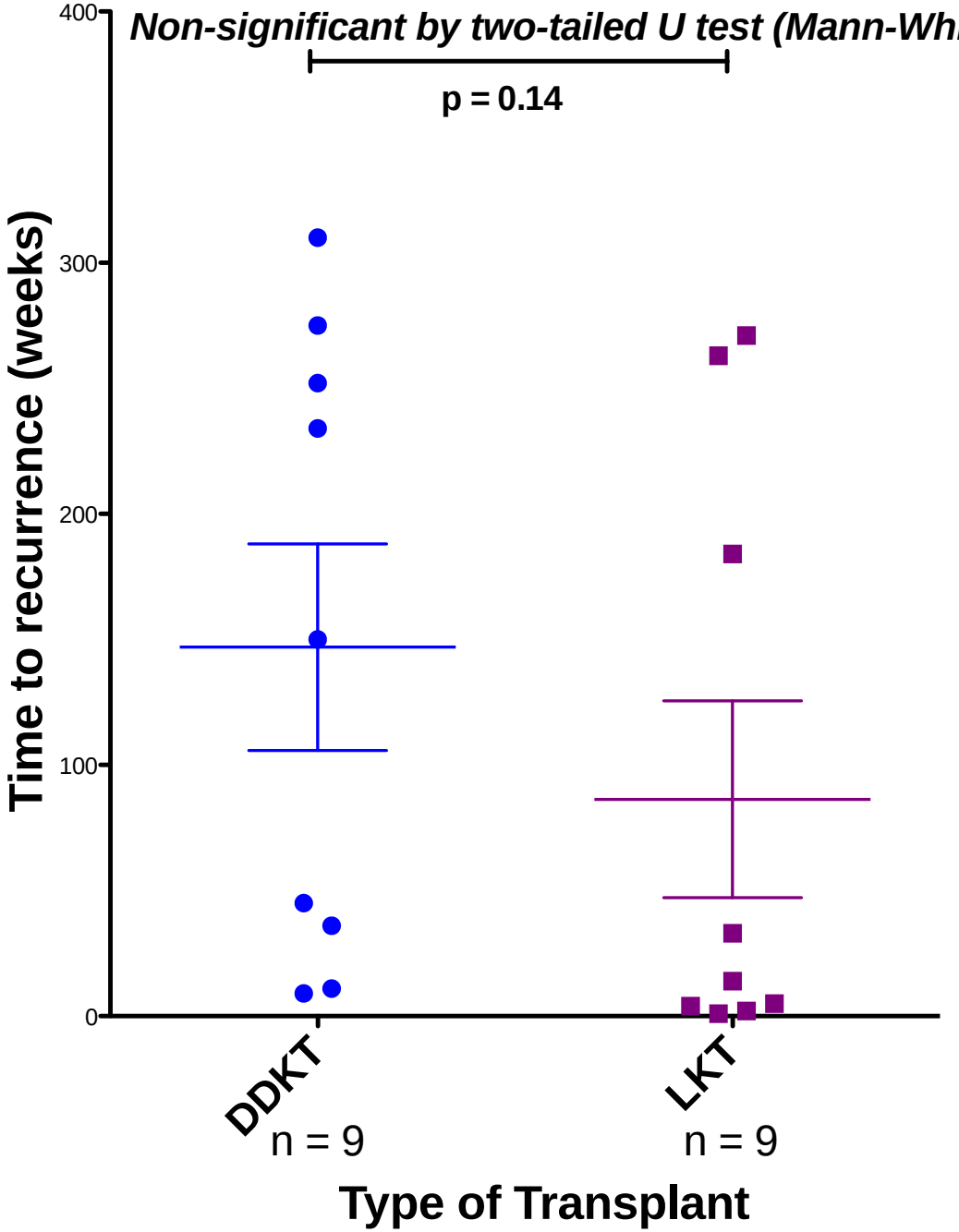
	Recurrence (+) n=18	Recurrence (-) n=7	
PLA2R Ab (+) n=16	12	4	Positive predictive value **75%**
PLA2R Ab (-) n=9	6	3	Negative predictive value **33%**
	Sensitivity **67%**	Specificity **43%**	

PLA2R-Ab within 4 month of recurrence as evident by biopsy/proteinuria




Time to recurrence (in weeks) by PLA2R-Ab titer
Significant by two-tailed U test (Mann-Whitney)
p = 0.0127
300
200
100
0
Time to recurrence (weeks)
Negative
Strongly Positive
semi-quantitated Anti-PLA2R level

Time to recurrence (in weeks) by type of transplant



DDKT = Deceased Kidney Transplant

LKT = Living Kidney Transplant (Related + Un-Related)

Conclusions

- This study does not represent the true incidence of rMN.
- Positive anti-PLA2R pre-TP predicts a high risk for recurrence but not all seropositive cases have recurred to date.
- The absence of pre-TP anti-PLA2R does not rule out future recurrence, which might be explained by post-TP reappearance of anti-PLA2R or other as yet unidentified antibodies.

Conclusions

- The prevalence of anti-PLA2R at the time of recurrence is similar to that seen in primary MN.
- Our results suggest that high pre-TP anti-PLA2R levels predict early recurrence.
- We propose that the presence of anti-PLA2R before or after transplantation merits close monitoring for recurrent MN.

THANK YOU

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