Predicting Post-Transplant Disease Recurrence in C3 Glomerulopathy

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Background

- C3 Glomerulopathy (C3G), defined by dominant C3 deposition on kidney biopsy, is a rare kidney disease characterized by persistent dysregulation of the alternative complement pathway.
- >50% of patients progress to ESKD within 10 years
- Post-transplant recurrence of disease manifests in nearly 67% of patients.
- We sought to examine demographic features, drivers of disease, and pre-transplant complement biomarkers in our cohort to identify parameters which may predict disease recurrence.

Methods

- Forty transplanted C3G patients from the University of Iowa's C3G Natural History Study were included in the cohort.
- Demographic data included sex, age at transplantation, race, transplant institution, time from diagnostic biopsy to transplant, and disease category (DDD vs C3GN).
- Clinical genes tested included *CFH, CFI, MCP, CFB, C3, CFHR5, DGKE, ADAMTS13, PLG,* and *THBD.*
- Biomarkers reviewed included C3, C3c, Bb, C5, C3Nef, C5Nef and sC5b-9. A C3c/C3 ratio was also calculated.
- The Mann-Whitney U test and chi-square analysis (95% CI) were applied. Receiver Operator Characteristic (ROC) curves were utilized to characterize each assay's diagnostic potential.
- Pre-transplant risk of recurrence (PTxRR) scores were calculated for each patient based on the extent of complement dysregulation as predicted by C3, C3c, C5, C3Nef, C5Nef, sC5b-9, and the genetic profile. Each parameter was chosen for their statistically significant difference between the study groups (recurrence vs. no recurrence). Abnormal values were assigned one point on a scale of zero to six.

Figure 1: Cohort Selection Flow Chart

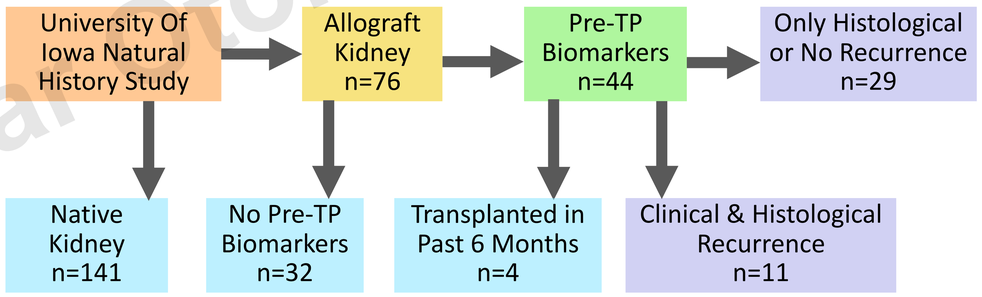

Figure 1- Blue boxes represent various exclusions from the cohort. The cutoff for date of transplant to be included in the cohort was 1/30/2022.

Results

- 11/40 (27.5%) patients in the cohort had documented recurrence.
- There were no significant differences in any of the demographic characteristics examined between groups.
- Compared to the non-recurrence group, recurrence patients had elevated C3Nef, C5Nef, C3c, C3c/C3 ratio, and sC5b-9, while C3 was depressed.
- Bb and C5 showed slight elevation and depression, respectively, in the recurrence group, but did not meet the threshold of statistical significance.
- Genetics were not a significant individual factor at the 95% confidence level but did increase the sensitivity of the PTxRR score when factored into the calculation.
- PTxRR scores were significantly higher for recurrence patients, with a median recurrence score of 4.5 points compared to the median non-recurrence score of 1 point.
- Utilizing a PTxRR score cutoff of ≥ 3 points identified 100% of individuals whose disease recurred after their tranpslant.

References

1. *Nat. Re. Nephrol.*, **15**, 129-143, (2019)
2. *J Am Soc Nephrol.*, **5**, 1110-7, (2014)

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Results

Figure 2: Complement Biomarker Estimation Plots and Median Differences

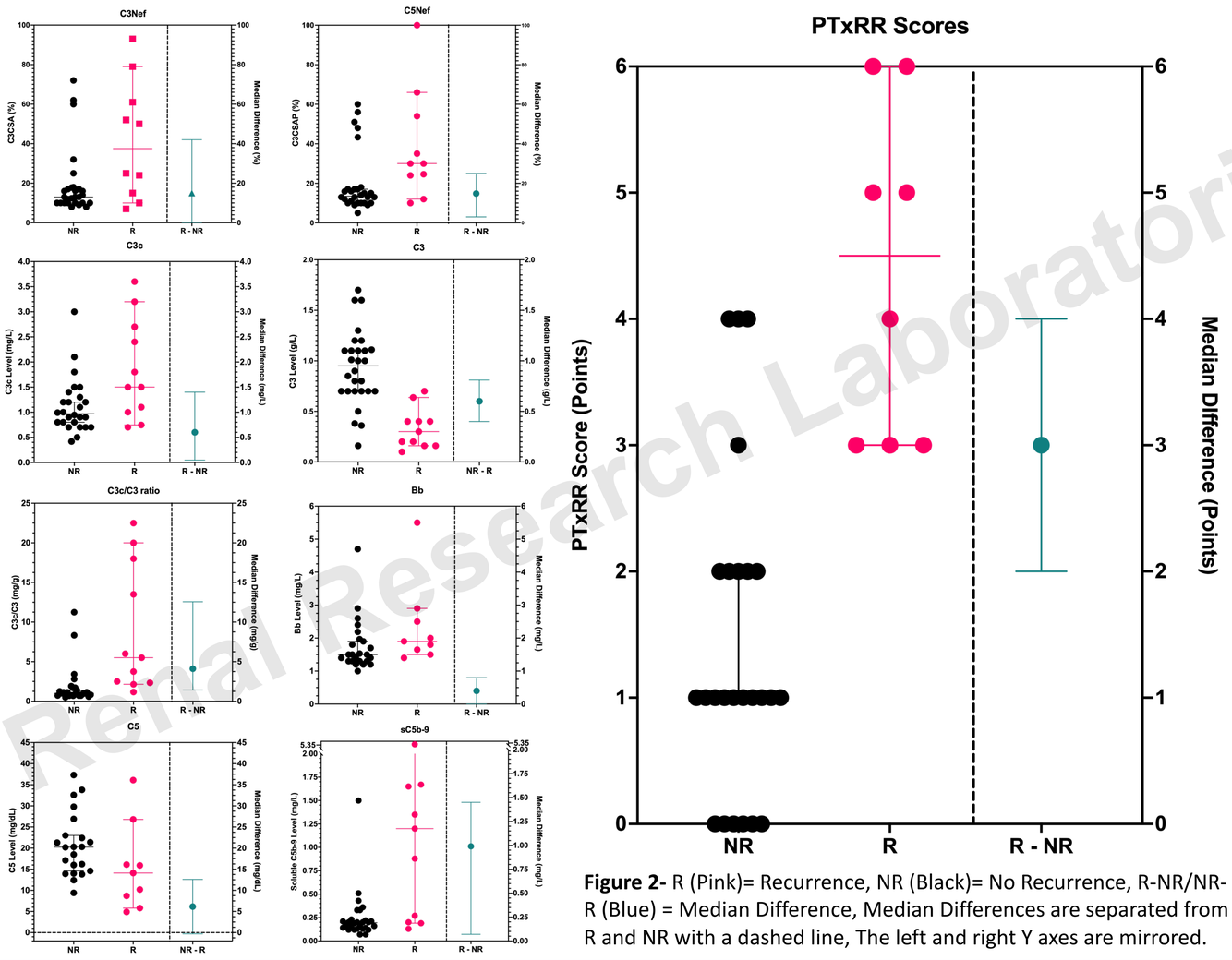

Figure 2- R (Pink)= Recurrence, NR (Black)= No Recurrence, R-NR/NR-R (Blue) = Median Difference, Median Differences are separated from R and NR with a dashed line, The left and right Y axes are mirrored.

Table 1: Recurrence and Non-Recurrence Demographic, Genetic, and Complement Biomarker Profiles

	Recurrence n		Non-Recurrence n		Yate's X^2 & z Statistic (df)		
Male/Female	8 / 3		13 / 16		2.49, 1.22 (1)		
White/Other Race	6 / 5		21 / 8		0.63, 0.70 (1)		
C3GN/DDD	9 / 2		18 / 11		0.66, 0.81 (1)		
Iowa/Other Institutions	2 / 9		9 / 20		0.17, 0.42 (1)		
+/- Genetics	6 / 3		8 / 21		2.99, 1.73 (1)		
	Recurrence n / Non-Recurrence n	Non-Recurrence Median [Range]	Recurrence Median [Range]	Difference Between Medians (95% CI)	Mann Whitney U Value & Z-Score	ROC AUC (95% CI)	Relative Risk (95% CI)
Age at Transplant (years)	11 / 29	25.5 [17.4-54.9]	22.0 [18.2-28.0]	3.5 (-4.3-8.7)	139, -0.61	0.56 (0.37-0.76)	X
Time from Diagnostic Bx to TP (years)	11 / 29	7.6 [2.0-12.1]	6.1 [4.1-9.3]	1.5 (-3.5-3.9)	146, -0.39	0.54 (0.33-0.75)	X
Time from Biomarkers to TP (years)	11 / 29	0.4 [1.3- 0.3]	1.8 [5.6- 0]	1.4 (2.9- 0)	102, 1.73	0.68 (0.46-0.90)	X
C3Nef (%) *	10 / 28	13.0 [10.0-17.0]	37.5 [10.0-79.0]	24.5 (0-42.0)	79, **-2.00**	0.72 (0.50-0.93)	5.1 (1.7-15.7)
C5Nef (%) *	10 / 28	13.5 [10.0-17.0]	30.0 [12.0-66.0]	16.5 (3.0-25.0)	68, **-2.37**	0.76 (0.57-0.94)	8.7 (2.5-32.6)
C3 (g/L) *	11 / 28	0.95 [0.70-1.10]	0.30 [0.16-0.64]	0.65 (0.40-0.81)	24, **4.04**	0.92 (0.84-1.00)	13.8 (2.0 - ∞)
C3c (mg/L) *	11 / 26	0.97 [0.80-1.20]	1.50 [0.75-3.20]	0.53 (0.05-1.40)	76.5, **-2.19**	0.73 (0.54-0.92)	3.0 (1.2-7.1)
C3c/C3 Ratio (mg/g) *	11 / 26	1.0 [.8-1.4]	5.5 [2.1-20.0]	4.5 (1.4-12.6)	27, **-3.84**	0.91 (0.81-1.00)	14.7 (2.9-84.5)
Bb (mg/L)	9 / 24	1.5 [1.3-1.9]	1.9 [1.5-2.9]	0.4 (0-0.8)	58.5, -1.97	0.73 (0.55-0.90)	1.9 (0.6-5.0)
C5 (mg/dL)	9 / 22	20.3 [14.6-23.0]	14.1 [5.8-26.8]	6.2 (-0.3-12.6)	57, 1.81	0.71 (0.48-0.94)	1.3 (0.5-3.9)
sC5b-9 (mg/L) *	11 / 28	0.20 [0.14-0.21]	1.20 [0.19-2.81]	1.00 (0.07-1.45)	57.5, **-3.00**	0.81 (0.65-0.98)	3.5 (1.3-9.6)
PTxRR Score (0-6 points) *	8 / 25	1.0 [1.0-2.0]	4.5 [3.0-6.0]	3.5 (2.0-4.0)	12, **-3.68**	0.94 (0.86-1.00)	28.0 [1] (1.8 - ∞)

Table 1- Statistically significant parameters are identified with an asterisk, a bolded title, and a bolded z score. Ranges are indicated with brackets and confidence intervals are indicated by parentheses. * = $p < 0.05$, [1] (with a cutoff of 3 points determined by ROC).

Conclusions

- Absolute risk of recurrence was lower than previously reported estimates but may represent better patient outcomes for patients closely monitored with complement biomarkers.
- Demographic characteristics **had no statistical value** for predicting recurrence of C3G.
- Carrying a genetic variant was not a good indicator of recurrence on its own but did enhance the diagnostic potential of the PTxRR score.
- Pre-transplant excess complement activity was associated **with increased post-transplant recurrence risk**, both cumulatively (PTxRR score) and individually (C3, C3c, C3Nef, C5Nef, sC5b-9, and C3c/C3 ratio).
- Our data suggests that the PTxRR score may be useful for identifying patients at higher risk of post-transplant C3G recurrence.
- Possible limitations include the timing of biomarker draws and the limited cohort size. Future directions include exploring the role of Factor H and other complement biomarkers in C3G recurrence, in addition to improving the PTxRR score's statistical power.