# Renal Pathology as a Predictor of Complement Dysregulation in $C_3$ Glomerulopathy


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## Background

C3 Glomerulopathy (C3G) is characterized by complement dysregulation and resulting C3 deposition in glomeruli. We reviewed the characteristics of the baseline kidney biopsy in a cohort of patients with C3G to determine if biopsy features of activity and chronicity correlate with complement dysregulation across the disease course.

## Methods

Patient data from the University of Iowa's C3G Natural History Study were used. Criteria for entry included baseline native biopsy diagnosis of C3G and complement biomarkers within one year of diagnostic biopsy. Patients with a history of dialysis, transplant, or anti-complement therapy were excluded. Significance was assessed using linear regression with two-tailed p values (95% confidence); results were considered statistically significant when p-values were less than 0.05.


We are grateful for the support of families with C3G, The Bruder Family and the NIDDK: R01 110023


MORL
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## References


1. Kidney Int. 93(4):977-985, 2018
2. Clin J Am Soc Nephrol. (7):994-1007, 2022
3. Am J Kidney Dis. 77(5):684-695.e1, 2021.


## Results

**Figure 1:**
**Significance and Directionality of Chronicity Score Correlation with Complement Biomarker Slope**

| Marker: | < 12yo at Onset | | 12-17yo at Onset | | 18yo ≤ at Onset | | All Ages | |
|---|---|---|---|---|---|---|---|---|
| | p-value: | $R^2$: | p-value: | $R^2$: | p-value: | $R^2$: | p-value: | $R^2$: |
| CFH Autoab (AU) | 0.8079 | 0.006915 | **0.0033** | **0.4983** | 0.3502 | 0.07299 | 0.6541 | 0.005338 |
| CFB Autoab (AU) | 0.8701 | 0.002542 | 0.4323 | 0.03460 | 0.7421 | 0.008621 | 0.5969 | 0.005996 |
| C3 Nef - C3CSA % | *0.0720* | *0.1882* | 0.8578 | 0.001644 | 0.1209 | 0.1527 | 0.1138 | 0.04484 |
| C5 Nef - C3CSAP% | **0.0236** | **0.2812** | 0.58961 | 0.01589 | 0.1414 | 0.1384 | 0.2261 | 0.02702 |
| C4 Nef% | 0.5178 | 0.03568 | *0.0639* | *0.1693* | 0.9175 | 0.0007393 | 0.1394 | 0.04317 |
| Hemolytic % | 0.5496 | 0.03349 | 0.5488 | 0.02447 | 0.9614 | 0.0003598 | 0.9343 | 0.0001678 |
| APFA% | 0.0945 | 0.2002 | 0.1363 | 0.1130 | 0.5837 | 0.01918 | 0.6507 | 0.003972 |
| CH50 (UEq/mL) | NI | NI | 0.9161 | 0.002474 | 0.1822 | 0.4992 | 0.4485 | 0.02520 |
| C3 (g/L) | 0.4897 | 0.04891 | 0.7249 | 0.007474 | 0.5106 | 0.03153 | 0.6832 | 0.003735 |
| C4 (g/L) | 0.8971 | 0.001962 | 0.1712 | 0.1210 | 0.8986 | 0.001202 | 0.2630 | 0.02974 |
| Factor B (mg/dL) | 0.2928 | 0.1098 | 0.2647 | 0.08215 | 0.2539 | 0.1164 | 0.6194 | 0.006224 |
| Factor H (mg/L) | NI | NI | 0.8306 | 0.003967 | 0.6229 | 0.02274 | 0.7801 | 0.002324 |
| Factor I (mg/L) | **0.0343** | **0.4479** | 0.2096 | 0.1278 | 0.4986 | 0.04262 | 0.1618 | 0.05516 |
| Ba (mg/L) | 0.7088 | 0.01455 | 0.3337 | 0.07197 | 0.0990 | 0.1954 | 0.2413 | 0.03416 |
| Bb (mg/L) | 0.4829 | 0.05043 | 0.4706 | 0.04076 | 0.2568 | 0.09767 | 0.9770 | 2.106e-5 |
| C3c (mg/L) | 0.5841 | 0.03457 | 0.9853 | 2.347e-5 | 0.3899 | 0.05738 | 0.5434 | 0.009076 |
| C5 (mg/dL) | 0.1230 | 0.3052 | 0.4856 | 0.04981 | 0.9401 | 0.001021 | 0.4851 | 0.01585 |
| Properdin (mg/L) | 0.2432 | 0.1333 | 0.3651 | 0.04578 | 0.3860 | 0.05411 | 0.9528 | 7.704e-5 |
| SC5b-9 (mg/L) | 0.5515 | 0.03033 | 0.3620 | 0.04170 | 0.2748 | 0.07772 | 0.5242 | 0.007696 |

**Figure 1:** Of the 59 subjects, 12 (20.3%) presented with a chronicity score ≥ 4, indicating an increased risk for progression to renal failure[1]. Among patients with disease onset before age 12 (n = 18), higher chronicity scores were associated with increased C5 nephritic factor (Figure 3) and increased Factor I (mg/L) levels over time. Of those with disease onset between ages 12 and 17 (n = 22), higher chronicity scores were associated with decreased Factor H autoantibody (AU) levels over time (Figure 4). At disease onset, chronicity scores were significantly correlated with Ba (mg/L) (p = 1.74e-09, R = 0.663) and APFA (%) (p = 0.002, R = 0.314); however, these associations did not persist across the disease course. No significant associations were observed between chronicity scores and changes in complement biomarkers over time in patients with disease onset at age 18 or older (n = 19) or in the overall cohort (n = 59).

**Figure 2:**
**Significance and Directionality of Activity Score Correlation with Complement Biomarker Slope**

| Marker: | < 12yo at Onset | | 12-17yo at Onset | | 18yo ≤ at Onset | | All Ages | |
|---|---|---|---|---|---|---|---|---|
| | p-value: | $R^2$: | p-value: | $R^2$: | p-value: | $R^2$: | p-value: | $R^2$: |
| CFH Autoab (AU) | 0.2912 | 0.1226 | 0.1164 | 0.1788 | 0.3036 | 0.0878 | 0.5232 | 0.01081 |
| CFB Autoab (AU) | *0.0736* | *0.2622* | 0.3051 | 0.05830 | 0.9863 | 2.168e-005 | 0.8506 | 0.0007624 |
| C3 Nef - C3CSA % | 0.7470 | 0.006690 | 0.2239 | 0.07302 | 0.2243 | 0.09674 | 0.1059 | 0.04684 |
| C5 Nef - C3CSAP% | 0.5260 | 0.02560 | 0.3428 | 0.04746 | 0.6344 | 0.01546 | 0.5093 | 0.008108 |
| C4 Nef% | 0.7889 | 0.006211 | 0.4541 | 0.02982 | 0.4326 | 0.04155 | 0.5713 | 0.006453 |
| Hemolytic % | 0.2597 | 0.1138 | 0.1932 | 0.1101 | 0.2932 | 0.1558 | 0.7658 | 0.002188 |
| APFA% | 0.6330 | 0.01806 | 0.6844 | 0.008885 | 0.9406 | 0.000358 | 0.6434 | 0.004152 |
| CH50 (UEq/mL) | 0.9666 | 0.0004969 | 0.7180 | 0.01720 | 0.6102 | 0.09689 | 0.8806 | 0.001001 |
| C3 (g/L) | 0.2728 | 0.1187 | 0.9069 | 0.0008278 | 0.7461 | 0.007730 | 0.3628 | 0.01843 |
| C4 (g/L) | 0.9255 | 0.001026 | 0.3631 | 0.05540 | 0.7354 | 0.008146 | 0.5087 | 0.01047 |
| FB (mg/dL) | 0.2880 | 0.1119 | 0.2907 | 0.07405 | 0.5658 | 0.03087 | 0.8010 | 0.001608 |
| FH (mg/L) | 0.9660 | 0.002783 | 0.4074 | 0.05786 | 0.9932 | 6.935e-6 | 0.6122 | 0.007642 |
| FI(mg/L) | 0.9166 | 0.001456 | 0.1863 | 0.1407 | 0.2804 | 0.1049 | 0.6633 | 0.005478 |
| Ba (mg/L) | 0.6236 | 0.02500 | 0.7677 | 0.006952 | **0.0302** | **0.3128** | *0.0562* | *0.08815* |
| Bb (mg/L) | 0.7145 | 0.01397 | 0.3983 | 0.05542 | 0.1840 | 0.1315 | 0.2185 | 0.03761 |
| C3c (mg/L) | 0.9727 | 0.0001375 | 0.8715 | 0.001802 | 0.3868 | 0.05811 | 0.9788 | 1.751e-5 |
| C5 (mg/dL) | 0.9832 | 6.8e-005 | 0.8453 | 0.003994 | 0.5759 | 0.05507 | 0.7935 | 0.002244 |
| Properdin (mg/L) | 0.2513 | 0.1291 | 0.7402 | 0.006258 | 0.3728 | 0.05709 | 0.7673 | 0.001922 |
| SC5b-9 (mg/L) | **0.0259** | **0.3497** | 0.5281 | 0.02020 | 0.3730 | 0.04694 | 0.8965 | 0.0003223 |

**Figure 2:** Of the 59 subjects, 35 (59.3%) presented with an activity score of ≥ 9 indicating increased risk for progression to renal failure[1]. Among patients with disease onset before age 12 (n = 18), higher activity scores were associated with decreased SC5b-9 (mg/L) levels over time (Figure 5). In those with disease onset at age 18 or older (n = 19), higher activity scores were associated with increased Ba (mg/L) levels over time (Figure 6); in the overall cohort, the relationship between Ba levels and activity scores approached significance. No significant associations were observed between activity scores and changes in complement biomarkers over time among patients with disease onset between ages 12 and 17 (n = 22). Additionally, no significant relationships were found between activity scores and complement biomarkers at disease onset.

**Figure 3 – Linear Regression: Chronicity Score vs. C5 Nephritic Factor for Onset <12 Years of Age**

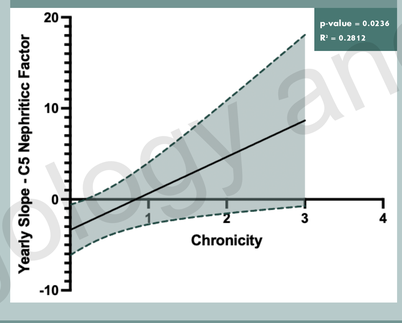



**Figure 4 – Linear Regression: Chronicity Score vs. Factor H Autoantibody for Onset 12-17 Years of Age**

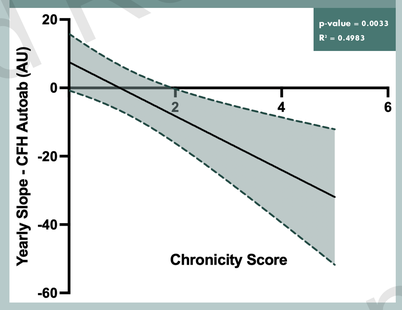



**Figure 5 – Linear Regression: Activity Score vs. SC5b-9 (mg/L) for Onset <12 Years of Age**

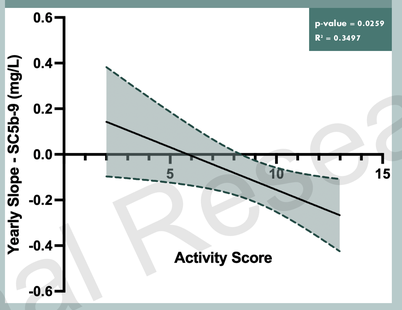
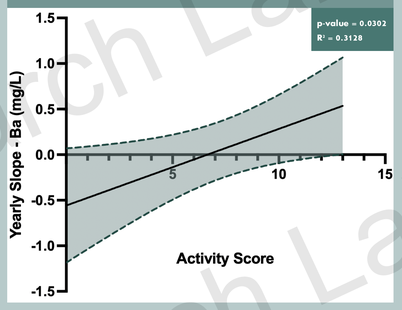
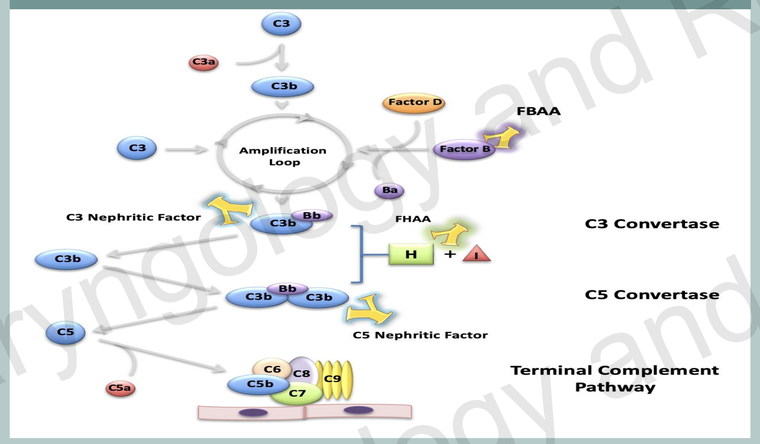



**Figure 6 – Linear Regression: Activity Score vs. Ba (mg/L) for Onset 18 ≤ Years of Age**




**Alternative Complement Pathway:**




## Conclusions

Previously, we reported that at disease onset, chronicity scores were significantly correlated with Ba and APFA. These associations did not persist over time. Over time, in the preadolescent group (< 12 years old), three findings were identified: a correlation between elevated C5Nef and FI with the chronicity score, and a correlation with elevated sC5b-9 and the activity score. Similarly, over time, in the adult group (>17yo), there was only one statistically significant correlation: a correlation between increasing Ba and the activity score. When considering a multiple comparisons model of evaluation, no significant correlations were found. A major limitation of this survey is undoubtedly the sample size.