Low Serum Levels of Complement C3c at Diagnosis Indicate Poor Outcome in Antineutrophil Cytoplasmic Antibody-Associated Glomerulonephritis

To the Editor: We read with great interest the recent study by Lionaki *et al.*[1] regarding the value of low serum complement C3 levels as an independent predictor of poor renal prognosis in patients with pauci-immune antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis.[1] We herein share our own experience with regard of low serum levels of complement C3c at diagnosis of ANCA glomerulonephritis.[2] Although only 5 of 38 patients (13.2%) had hypocomplementemia with C3c levels below the normal range (<0.82 g/l), patients who will experience requirement of kidney replacement therapy (13 of 38) or death (1 of 38) had significantly lower C3c levels ($P = 0.0265$; Figure 1a). According to median serum levels of C3c (1.295 g/l), low levels of C3c were associated with worse renal function reflected by median glomerular filtration rate (9.8 vs. 24.1 ml/min, $P = 0.0121$), higher urinary protein-to-creatinine ratio (1492 vs. 754 mg/g, $P = 0.0344$), and higher ANCA renal risk score (Figure 1b). During 40 days follow-up after diagnosis, low levels of C3c were more likely associated with early requirement of kidney replacement therapy or death ($P = 0.0093$; Figure 1c). In conclusion and confirmatory to the observations by Lionaki *et al.*,[1] low C3c levels within the normal range were associated with more severe deterioration of kidney function also reflected by higher ANCA renal risk score, associated with early requirement of kidney replacement therapy or death. These observations suggest that targeting the complement system might be especially beneficial in this patient subgroup. This is especially relevant because C5a receptor inhibitor avacopan and the monoclonal C5a antibody IFX-1 are currently in clinical development for ANCA-associated vasculitis.[3,4]

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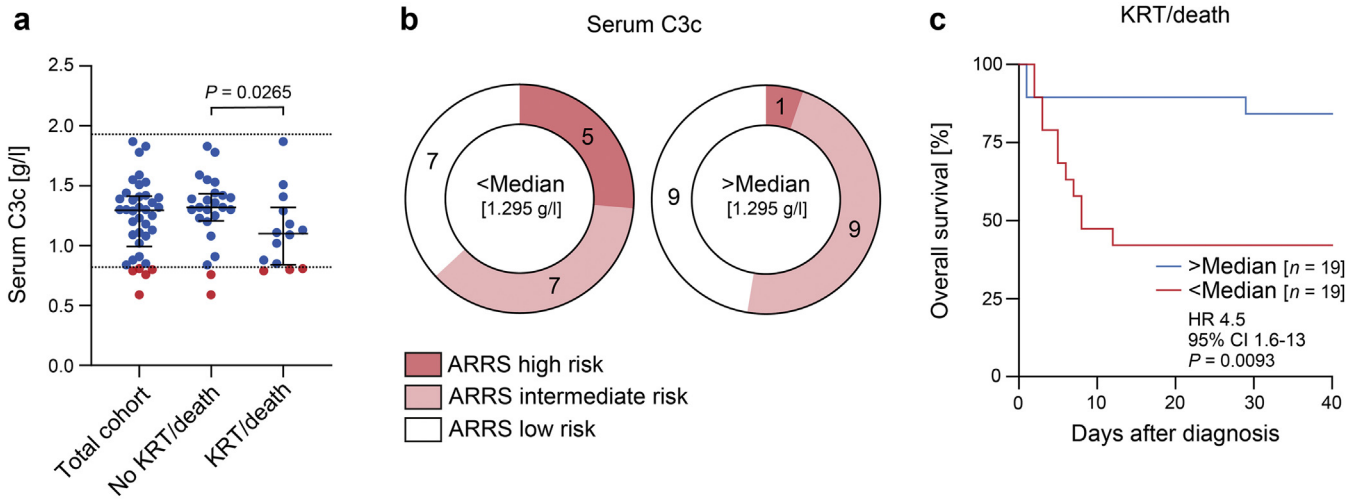

Figure 1. Low serum levels of complement C3c at diagnosis indicate poor outcome in ANCA GN. (a) Serum levels of complement C3c in the total cohort and according to requirement of KRT or death during follow-up. The scatter dot plots include median ± IQR compared with one-tailed Mann–Whitney *U* test; the dotted lines represent upper and lower normal ranges of serum C3c levels in our institution. (b) ARRS according to low and normal levels of serum C3c. (c) Overall survival (KRT/death) within 40 days after diagnosis according to low or normal levels of serum C3c. Comparison of survival curves was performed with log-rank (Mantel-Cox) testing. ANCA GN, antineutrophil cytoplasmic antibody-associated glomerulonephritis; ARRS, antineutrophil cytoplasmic antibody renal risk score; HR, hazard ratio; IQR, interquartile range; KRT, kidney replacement therapy.

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Désirée Tampe[1], Eva Baier[1], Samy Hakroush[2] and Björn Tampe[2]

[1]Department of Nephrology and Rheumatology, University Medical Center Göttingen, Göttingen, Germany and [2]Institute of Pathology, University Medical Center Göttingen, Göttingen, Germany

Correspondence: Björn Tampe, Department of Nephrology and Rheumatology, University Medical Center Göttingen, Germany. E-mail: bjoern.tampe@med.uni-goettingen.de

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Hypocomplementemia at Diagnosis of Antineutrophil Cytoplasmic Autoantibody Glomerulonephritis Is an Independent Risk Factor for a Worst Outcome

The Authors Reply: We appreciate the opportunity to respond to the report by Tampe *et al*.[1] regarding the prognostic significance of C3 hypocomplementemia in patients with pauci-immune antineutrophil cytoplasmic autoantibody glomerulonephritis.[2] Notably, this group of investigators, in agreement with our findings, revealed that 13.2% of patients had low serum C3c at diagnosis, while these patients had higher probability of experiencing requirement of kidney replacement therapy or death.[1] Low serum C3c levels were associated with worse renal function, reflected by median glomerular filtration rate, higher urinary protein-to-creatinine ratio, and higher antineutrophil cytoplasmic autoantibody renal risk score at diagnosis.[1] Although we do not know the precise reason why a relatively small proportion of patients with antineutrophil cytoplasmic autoantibody vasculitis present with low serum complement, and how this is connected with a worst outcome, it is becoming clear that this subgroup of patients follows a different pathway, in terms of pathophysiology and outcome, despite administration of standard therapy. One might speculate that either delayed diagnosis or a different pathogenetic background might explain this observation. In any case, its interpretation points toward an individualized approach in patients with antineutrophil cytoplasmic autoantibody vasculitis, and more importantly given the knowledge of the crucial role of complement activation in some of these patients, complement blockage, using C5a receptor inhibitor avacopan or the monoclonal C5a antibody IFX-1, should probably be used in clinical practice in conjunction with all or part of the current therapeutic scheme.

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Sophia Lionaki[1,2] and John N. Boletis[1,3]

[1]National and Kapodistrian University of Athens, Athens, Greece; [2]Department of Nephrology, Attikon Hospital, Athens, Greece; and [3]Department of Nephrology and Transplantation, Laiko Hospital, Athens, Greece

Correspondence: Sophia Lionaki, National and Kapodistrian University of Athens, Athens, Department of Nephrology, Attikon University Hospital, Athens, Rimini 1 street, 12462, Greece. E-mail: sophial@med.uoa.gr

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