SUPPLEMENTARY MATERIAL

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Supplementary methods

Patient selection

Patients with suspected complement-mediated glomerulonephritis, whose samples were sent to the complement diagnostic laboratory for complement protein, autoantibody and genetic analysis, were eligible for this study (n=205). Patients with an alternate diagnosis (n=21), secondary MPGN (n=2), or with missing clinical dataset (n=63) were excluded. From the 119 patients with diagnosed MPGN further 27 were excluded because of missing electron microscopy, immunofluorescence microscopy or lack of detailed description of light microscopy (the excluded patients were similar compared to the included study subjects in regards to their available characteristics). Finally, altogether 92 patients with histologically proven C3G (dominant glomerular C3 staining), IC-MPGN (MPGN pattern with significant Ig stain) were enrolled in the study from 34 centers in Central and Eastern Europe from January 2008 to May 2018 (Supplementary Figure 1, Table 1A&B). All of the 92 patients had a complete dataset for the cluster analysis, including electron microscopy analysis to further classify C3G as DDD or C3GN.

Relevant clinical and laboratory data were collected from the medical charts. Histology based diagnosis and detailed data were collected from pathologists (n=62), while if only biopsy descriptions were available (n=30) these were re-evaluated and scored using a standardized questionnaire. The retrospective study based on the clinical data of the patients was approved by the Medical Research Council of the Ministry of Human Capacities in Hungary (approval's number: 55381-1/2015/EKU).

Blood sampling and complement analysis

Peripheral blood samples were collected by venipuncture or from a central venous catheter. Serum and EDTA plasma samples were separated sent in cooled packages and stored in aliquots at −80°C until analysis. Cells of the EDTA-anticoagulated blood samples were used for DNA isolation.

Antigenic levels of C3 and C4 were measured by turbidimetry (Cobas Integra 400analyzer; Roche, Switzerland), whereas C3 nephritic factor (C3NeF) activity was determined by using a home-made hemolytic test in serum according to the method of Rother (1).

Total activity of the classical pathway was measured by a home-made hemolytic titration test using sheep erythrocytes based on Mayer's method (2), whereas activation of the alternative pathway was determined using a commercially available kit (Wieslab AP ELISA KITs, EuroDiagnostica, Malmö, Sweden) (3).

Plasma sC5b-9, C3a, Bb and C4d levels were measured using commercially available ELISA kits (MicroVue sC5b-9 Plus EIA, A029; MicroVue C3a-desArgEIA, A032; MicroVue Bb Plus EIA, A027; MicroVue C4d EIA, A008), along with the concentration of plasma factor D (HyCult Complement Factor D, Human, ELISA kitHK343-02), according to the manufacturer's instructions (3).

Concentrations of C1q, anti-C1q, anti-Factor H were measured with in-house ELISA methods (3-7).

Titers of anti-C3 and anti-Factor B were also measured with in-house ELISA methods: in brief, microtiter ELISA plates were coated with 1 μg/mL commercially available C3 or Factor-B (Quidel) in carbonate buffer overnight, followed by blocking with PBS and 0.5% BSA on the next day. Serum was diluted 1:50 in PBS 0.05% Tween-20 and added to the plate for 1 hour at room temperature. Bound antibodies were detected by adding anti-human IgG-horseradish peroxidase diluted to 1:2500 and followed by TMB substrate. The optical density (OD) was determined at 450/620 nm. The samples were compared to the different dilution of

normal human serum (NHS). Samples were regarded as positive for any of the antibodies if they had a significantly increased (>2SD) OD compared to the normal human serum with the same dilution, considered background (1:50).

Molecular genetic analysis

In order to screen for mutations, rare variations or risk polymorphisms, the whole coding regions of the genes encoding complement Factor H (*CFH*; MIM# 134370), Factor I (*CFI*; MIM#217030), membrane cofactor protein (*CD46*; MIM#120920), thrombomodulin (*THBD*; MIM#188040), Factor B (*CFB*, MIM#138470) and C3 (*C3*, MIM#120700) were analyzed by direct bidirectional DNA sequencing following PCR amplification, as described previously (8). Primer sequences and PCR conditions are available upon request. Polymorphic variants were numbered as +1 from the A of the ATG translation initiation site. Previously identified and functionally characterized missense, as well as nonsense and splice site mutations were categorized as likely pathogenic variants (LPV). In case of novel missense variations, they were regarded as LPVs if they were not found or found with a minor allele frequency of <0.1% in international databases (dbSNP (www.ncbi.nlm.nih.gov/snp)), Exome Variant Server (NHLBI GO ExomeSequencing Project (ESP), Seattle, WA (http://evs.gs.washington.edu/EVS/) and 1000Genomes Project phase 3 (http://browser.1000genomes.org/index.html)) and CADD score ≥10.

Statistical analysis

The continuous variables showed skewed distribution according to the results of Shapiro-Wilk's test. Therefore, for descriptive purposes, the values are given as median and 25th–75th percentiles. Categorical variables were shown as numbers and percent. The comparative analysis between the resulting clusters was performed using Kruskal-Wallis test and Dunn

post-hoc test in case of continuous variables and Pearson's Chi-square test was applied for categorical variables.

For cluster analysis we used the same method and variable set that was applied in the study of Iatropoulus et al. (9). The following set of variables (Supplementary Table 1) was used to reproduce the previously described cluster analysis on our independent cohort: gender, age at onset, hematuria, proteinuria, renal impairment, trigger event, familiarity, sclerotic glomeruli, crescent, degree of mesangial proliferation, endocapillary proliferation, interstitial inflammation, interstitial fibrosis, C3-, IgA-, IgG-, IgM- or C1q-staining on immunofluorescence microscopy, mesangial/subepithelial/subendothelial or intramembranous deposits on electron microscopy, serum C3 and C4 levels, plasma sC5b-9 concentration, activity of C3NeF, presence of likely pathogenic variants, common polymorphisms (*CFH* V62I and Y402H, *CD46* c.-366A>G, *CFB* R32Q/W, *C3* R102G, *THBD* A473V). Only one variable, namely the fibrinogen staining on immunofluorescence microscopy was excluded from our study because of the limited number of available data. In addition, we could not differentiate between granular and ribbon-like highly electron-dense intramembranous deposits, rather, this information is presented as one variable, "intramembranous dense deposit". We analyzed the presence of LPV and C3NeF as separate variables in our study, because their additive effect is not proved. The cluster analysis was performed with hierarchical clustering using Ward's method with squared Euclidean distance using IBM SPSS 20 program. Missing data occurred infrequently (generally <3%), and were input with linear interpolation. To check the stability of clustering random half-splitting (by 100 times) was used with subsequent repetition of clustering. Case membership in the repetition analysis was cross-checked with that of the original clustering each time, by calculating Cohen's kappa agreement rates. The mean 0.885 (95% CI of the mean 0.859-0.910) of kappa values obtained by Cohen's method indicated an almost perfect confirmity between the repetition and the

original observations. We repeated the analysis after performing principal component analysis based on the variables (to filter the "noise"), and the results were the same, except for four patients who were regrouped from cluster 1 to cluster 4. (See legend for Supplementary Figure 3.)

For analyzing the difference in renal survival between the different clusters Kaplan-Meier analysis was used.

A general classification and regression model, based on the above variable set as predictor variables and cluster numbers as categorical dependent variable, was also generated to predict membership of patients in the clusters, and to rank the above variables for importance. The 4 patients in cluster 2 were excluded from this analysis.

Two-tailed p-values were calculated and the significance level was determined at a value of $p < 0.05$, if not stated otherwise.

Supplementary results

Baseline characteristics of the cohort

Our study included a total of 92 patients with the diagnosis of C3G/IC-MPGN, of them 11 patients (12 %) had DDD, 37 (40.2%) had C3GN, 44 had IC-MPGN (47.8 %) Table 1A&B show the clinical, biochemical, genetic and histological characteristics of the cohort stratified according to renal pathology based groups. The gender and age distribution did not differ between the groups. IC-MPGN group was characterized by decreased C4 levels (p=0.02) and by significant immunoglobulin staining (for C3 p=0.047; IgA p=0.002; IgG p<0.0001; IgM p<0.0001; C1q p<0.0001), whereas all patients with DDD showed the presence of intramembranous electron dense deposits (p=0.001). C3G showed significantly higher prevalence of intramembranous dense deposits when compared to IC-MPGN, but prevalence of LPVs, C3NeF positivity or low serum C3 with normal C4 was similar across the histology

groups in our cohort (Table 1A&B). These data, in agreement with earlier results (10) including the Italian cohort (9) clearly document the lack of tight association between the key pathogenetic and pathognomic features of MPGN and the histology-based classification.

Comparison of the current validation cohort to the original cohort of Iatropoulos et al.

Next, to validate the results of the study of Iatropoulos et al (9) we analyzed and compared key features of the two cohorts. In our cohort 40.2% of the patients had C3GN, 12% had DDD and 47.8% were diagnosed with IC-MPGN compared to 39.3%, 14.5% and 46.2% in the Italian study. The mean age at onset was 24 vs. 18.9 years in the current and the original cohorts, with pediatric cases (<18 years) being 51% and 64% in the two cohorts, respectively. In the group of patients with C3GN a slight shift to higher mean age was observed in the validation cohort 28 vs. 18.2 years). The sex distribution with 0.50 and 0.56 male prevalence was also similar. The median time from onset to biopsy was within 1 year in patients with C3GN and IC-MPGN and was 1.1 year in patients with DDD which is longer than in our cohort where the biopsies were performed mostly at the time of diagnosis (Table 1B). Based on the prevalence of sclerotic glomeruli our cohort had a more severe disease at onset (16.4 vs. 4%), but without relevant difference in crescent formation (6.7% vs. 5.3%). End-stage renal disease (ESRD) at time of diagnosis was 12% in our cohort and 1.2 % in the Italian. Nearly 50% of the patients were followed for at least 5 or 2 years (range in the validation cohort 0.05-10.32 years, in original cohort ~0.1-10 years), respectively. During the follow-up period the incidence of ESRD was 10.9% and 8.6% in the two cohorts. Slight differences in the prevalence of LPVs (20.5% vs. 19.5%) or of C3NeF (25.3% vs. 44.7%) were also noted. Based on the comparison of key clinical, biochemical and genetic features (Supplementary Figure 2) the two cohorts can be considered to be similar.

Supplementary Table 1: Coding of variables used for the cluster construction

Variable	Code
gender	1:male 2:female
age at diagnosis	years
hematuria	0: none 1: microhematuria 2: gross hematuria
proteinuria	0: none 1: proteinuria 2: nephrotic syndrome
renal impairment	0: none 1: renal impairment GFR<60 mL/min/1.73 m2 2: renal failure GFR<15 mL/min/1.73 m2/TX/HD
trigger event	0:no 1:yes
familiarity	0:no 1:yes
sclerotic glomeruli %	%
crescent %	%
degree of mesangial proliferation on LM	0 to 3 + scale
degree of endocapillary proliferation on LM	0 to 3 + scale
degree of interstitial inflammation on LM	0 to 3 + scale
degree of interstitial fibrosis on LM	0 to 3 + scale
arteriolar sclerosis	0: no 1: yes
C3 on IF	0 to 3 + scale
IgA on IF	0 to 3 + scale
IgG on IF	0 to 3 + scale
IgM on IF	0 to 3 + scale
C1q on IF	0 to 3 + scale
mesangial deposits on EM	0: no 1: yes
subepithelial deposits on EM	0: no 1: yes
subendothelial deposits on EM	0: no 1: yes
intramembranosus deposits on EM	0: no 1: yes
serum C3	0: <0.5 g/L 1:≥0.5 g/L;<0.9 g/L 2: ≥0.9 g/L
serum C4	0: <0.1 g/L 1: ≥0.1 g/L;<0.2 g/L 2: ≥0.2 g/L
plasma sC5b-9	0: ≤303 ng/mL 1: ≥303 ng/mL≤800 ng/mL 2: >800 ng/mL

C3NeF	0: no 1: yes
LPV	0: no 1: yes
CFH V62I	N° of I alleles
CFH Y402H	N° of H alleles
CD46 c.-366A>G	N° of G alleles
CFB Q/W32R	N° of R alleles
C3 R102G	N° of G alleles
THBD A473V	N° of V alleles

Supplementary Table 2. Patients carrying at least one likely pathogenic variant in our cohort

Patient ID	Likely pathogenic variant	Allele frequency		CADD score	Previous functional studies	Histology group	Cluster	C3NeF, %	C3, g/l	TCC, ng/ml
		1000 Genomes Project	Exome VariantServer (all alleles)							
HUN152*	*CFH* C959S	0.0%	0.0%	22.5	None	C3GN	1	5.7	0.2	1282.5
HUN194	*THBD* A43T	0.3%	0.4%	11.52	Yes (11)	C3GN	4	4.7	0.89	-
HUN564	*CD46* A353V	0.4%	1.2%	0.001	Yes (12-14)	IC-MPGN	1	4.7	0.7	165.0
HUN633	*CFI* T203I	0.04%	0.05%	5.13	Yes (15)	DDD	4	14.0	0.2	453.0
HUN650	*CD46* A353V	0.4%	1.2%	0.001	Yes (12-14)	IC-MPGN	4	4.3	0.7	490.0
HUN779	*THBD* E361K	0.0%	0.0%	23.3	None	IC-MPGN	3	11.0	1.1	235.0
HUN851	*CD46* A353V	0.4%	1.2%	0.001	Yes (12-14)	C3GN	1	5.0	0.2	707.6
HUN944	*C3* K65Q	0.0%	0.0%	23.7	Yes (16)	DDD	1	10.0	0.1	-
	CFH D130N	0.0%	0.01%	22.6	None					
HUN1073	*THBD* P501L	0.12%	0.2%	1.046	Yes (11)	IC-MPGN	1	11.9	0.2	4614.0
HUN1093	C3 c.683-1G>A	0.0%	0.0%	29	None	IC-MPGN	1	2.8	0.2	259.0
	CFH D90G	0.0%	0.0%	25.5	Yes (17)					
HUN1109	*C3* K633R	0.02%	0.07%	9.69	Yes (18)	C3GN	1	10.2	0.1	661.0
HUN1179	*CD46* A353V	0.4%	1.2%	0.001	Yes (12-14)	C3GN	1	15	0.3	945.0
HUN1273	*CD46* A353V	0.4%	1.2%	0.001	Yes (12-14)	IC-MPGN	3	6.0	0.9	330.0
HUN1345	*CD46* E142Q	0.0%	0.007%	0.289	Yes (18)	C3GN	4	7.7	1.0	581.0
	THBD L563Q	0.0%	0.0%	25.6	None					

HUN1447	*C3* R315X	0.0%	0.0%	28.9	None	IC-MPGN	1	20.0	0.3	2575.0
HUN1502	*CD46* T383I	0.02%	0.05%	3.41	Yes (19)	IC-MPGN	4	5.9	0.2	261.0
HUN1575	*CFI* W353R	0.0%	0.0%	31	None	C3GN	1	27.8	1.1	326.0
HUN1591	*CD46* T383I	0.02%	0.05%	3.41	Yes (19)	C3GN	3	7.2	0.3	206.0
	CFB I469M	0.02%	0.02%	23.1	None					

**Patient HUN152 carried the observed CFH C959S in homozygous form.*

Supplementary Table 3. Ranking of predictor variables according to their predictor importance as determined by general classification and regression (decision tree) analysis

	Variables	Predictor importance	
		Variable Rank	Importance
1	sclerotic glomeruli	100	1.00
2	age at diagnosis	46	0.45
3	degree of interstitial fibrosis	33	0.32
4	degree of interstitial inflammation	20	0.20
5	sC5b-9 levels	20	0.20
6	arteriolar sclerosis	19	0.18
7	presence of renal failure	12	0.11
8	CFH Y402H	11	0.11
9	serum C4 level	11	0.11
10	C1q staining in immunofluorescence microscopy	11	0.10
11	IgM staining in immunofluorescence microscopy	10	0.10
12	CD46 c.-366A>G	10	0.09
13	intramembranous deposit on electron microscopy	9	0.09
14	crescent %	8	0.08
15	subepithelial deposit on electron microscopy	7	0.07
16	LPVs	7	0.07
17	IgG staining in immunofluorescence microscopy	7	0.06
18	trigger event	7	0.06
19	C3NeF positivity	6	0.06
20	subendothelial deposit on electron microscopy	6	0.05
21	serum C3 level	6	0.05
22	familiarity	5	0.05
23	gender	5	0.05
24	C3 R102G	5	0.04
25	degree of endocapillary proliferation	5	0.04
26	CFH V62I	4	0.04
27	degree of mesangial proliferation	4	0.04
28	presence of proteinuria	3	0.03
29	mesangial deposits on electron microscopy	3	0.02
30	IgA staining in immunofluorescence microscopy	3	0.02
31	C3 staining in immunofluorescence microscopy	2	0.02
32	THBD A473V	2	0.02
33	presence of hematuria	2	0.02
34	CFB Q/W 32R	1	0.01

Supplementary Table 4. Lack of association between histology based diagnosis and clusters

	cluster 1	cluster 2	cluster 3	cluster 4	p
C3GN	16	0	9	12	0.186
DDD	5	2	1	3	
IC-MPGN	24	2	7	11	

Data represent number of patients

Supplementary Table 5. Therapy of patients in different clusters

	cluster 1 n=45	cluster 2 n=2	cluster 3 n=17	cluster 4 n=26
ACE-I/ARB	28 (62.2)	1 (25)	10 (58.8)	12 (46.5)
steroid	22 (48.8)	3 (75)	11 (64.7)	13 (50)
cyclophosphamid	7 (15.5)	2 (50)	3 (17.6)	5 (19.2)
MMF	8 (17.7)	0 (0)	3 (17.6)	2 (7.7)
cyclosporin	1 (2.2)	0 (0)	1 (5.8)	2 (7.7)
plasmatherapy	2 (4.4)	1 (25)	3 (17.6)	1 (3.8)
rituximab	2 (4.4)	1 (25)	2 (11.7)	0 (0)
eculizumab	1 (2.2)	1 (25)	1 (5.8)	0 (0)
RRT	1 (2.2)	1 (25)	3 (17.6)	2 (7.7)
tacrolimus/azathioprin	1 (2.2)	0 (0)	0 (0)	2 (7.7)
combined therapy	22 (48.8)	2 (50)	8 (47)	10 (38.5)

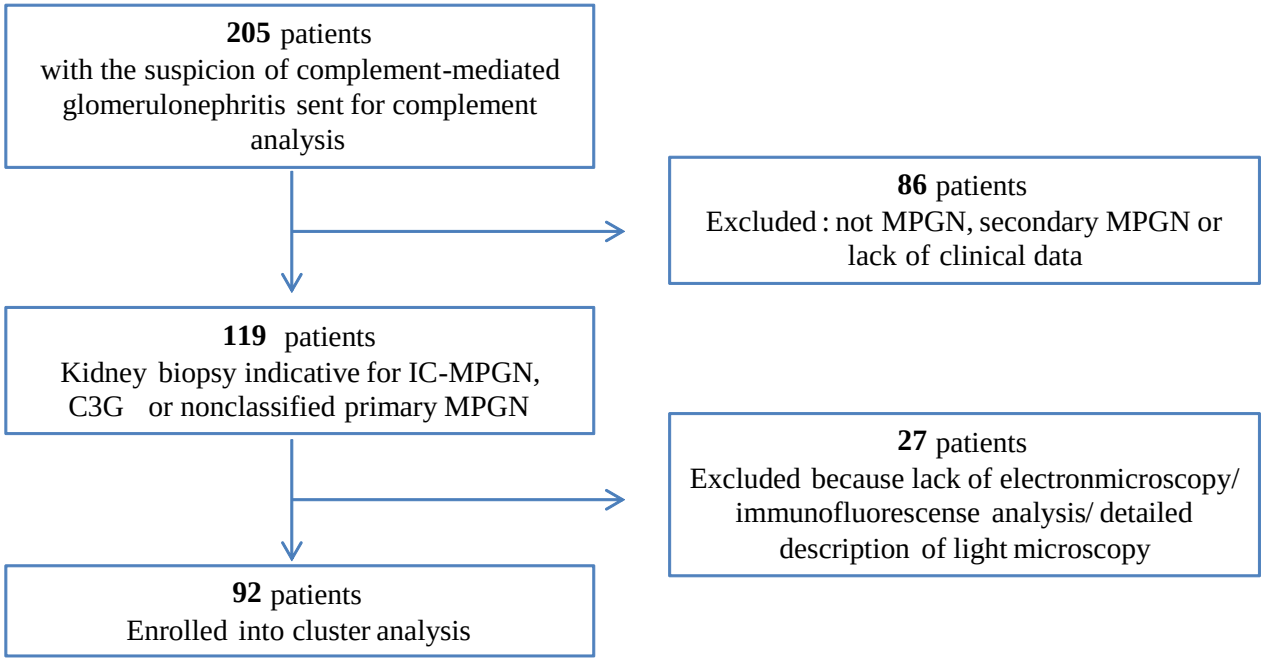
Abbrevations: ACE-I: angiotensine-converting enzyme-inhibitor; ARB: angiotensine-receptor-blocker; MMF: mycophenolat-mofetil; RRT: renal replacement therapy

Supplementary Table 6. Additional complement factors, activation markers and autoantibodies in the different histology-based groups

	C3GN	DDD	IC-MPGN	all	p
classical pathway activity CH50/mL	41.5 (19-62)	46 (21-57)	46 (25-61)	46 (21.5-61)	0.94
alternative pathway activity, %	67.5 (4-91.5)	1 (0.1-65)	67.5 (4-91.5)	51 (1-83.5)	0.06
C1q antigen mg/L	108 (84 -127)	96 (85-109.5)	99.5 (63.5-125)	100.5 (82.25-123.7)	0.66
anti-C1q positivity, present	4 (11.4)	1 (11.1)	8 (20)	13 (15.4)	0.55
anti-Factor H positivity, present	3 (8.3)	0 (0)	2 (4.5)	5 (5.5)	0.52
anti-C3 positivity, present	2 (6.3)	1 (9)	2 (45.4)	5 (5.7)	0.83
anti-Factor B positivity, present	3 (9.4)	2 (18.2)	1 (2.2)	6 (6.9)	0.14
Positivity for >1 complement autoantibody[1]	3 (8.8)	1 (11.1)	3 (7.5)	7 (8.4)	0.93
Factor D, µg/mL	1.76 (0.71-4.36)	2.43 (0.75-4.03)	1.85 (0.95-3.97)	1.85 (0.87-3.95)	0.96
C4d, µg/mL	5.9 (2.7-9.5)	6.6 (3.4-9.4)	4.3 (3.2-7.23)	5.21 (3.18-9.08)	0.54
Bb, µg/mL	1.4 (1.1-2.3)	1.76 (1.5-3.6)	1.4 (0.82-1.96)	1.48 (1.01-2.24)	0.19
C3a, ng/mL	173.5 (114-248)	201 (157-279)	124 (73-197)	144 (98-209)	0.04

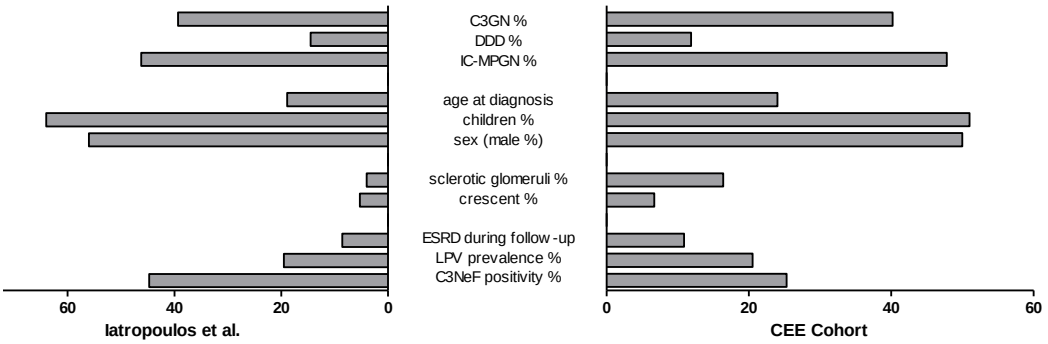
The data are given as median and interquartile range or number and percentages. P-values are given as the results of $\chi 2$ or Kruskal-Wallis tests of patients with IC-MPGN, DDD and C3GN.
[1]Out of C3NeF, anti-C1q, anti-Factor H, anti-C3 and anti-Factor B
Reference range:C1q antigen level 60-180 mg/L; C3a 70-270 ng/mL; C4d 0.7-6.3 μg/mL; Bb 0.49-1.42 μg/mL; Factor D 0.51-1.59 μg/mL
Some patients have missing values in the following data: C1q antigen, anti-C1q, anti-FH, anti-FH, anti-C3 and anti-FB, FD, C4d, Bb, C3

Supplementary Figure 1. Flow-chart of the study population



Abbreviations: MPGN: Membranoproliferative glomerulonephritis IC-MPGN: immunocomplex-mediated glomerulonephritis; C3G: C3-glomerulopathy

Supplementary Figure 2. Comparison of the baseline characteristics of the original (Iatropoulos et al, (9)) and of the current validation (Central and Eastern European, CEE) cohorts



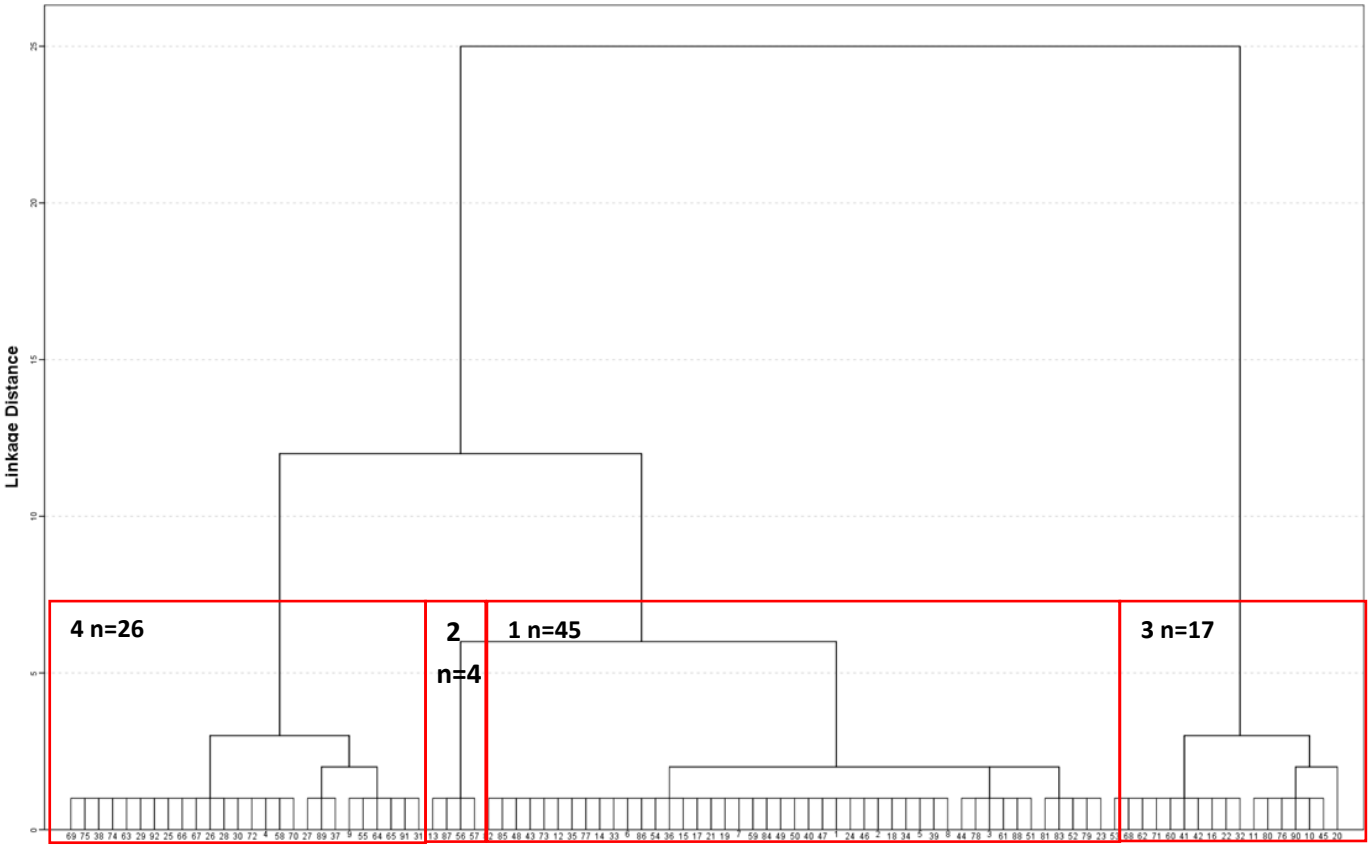
Supplementary Figure 3. Dendrogram of the identified 4 clusters defined with hierarchical clustering by Ward's method with squared euclidean distances

A: Clusters made by using the whole variable set

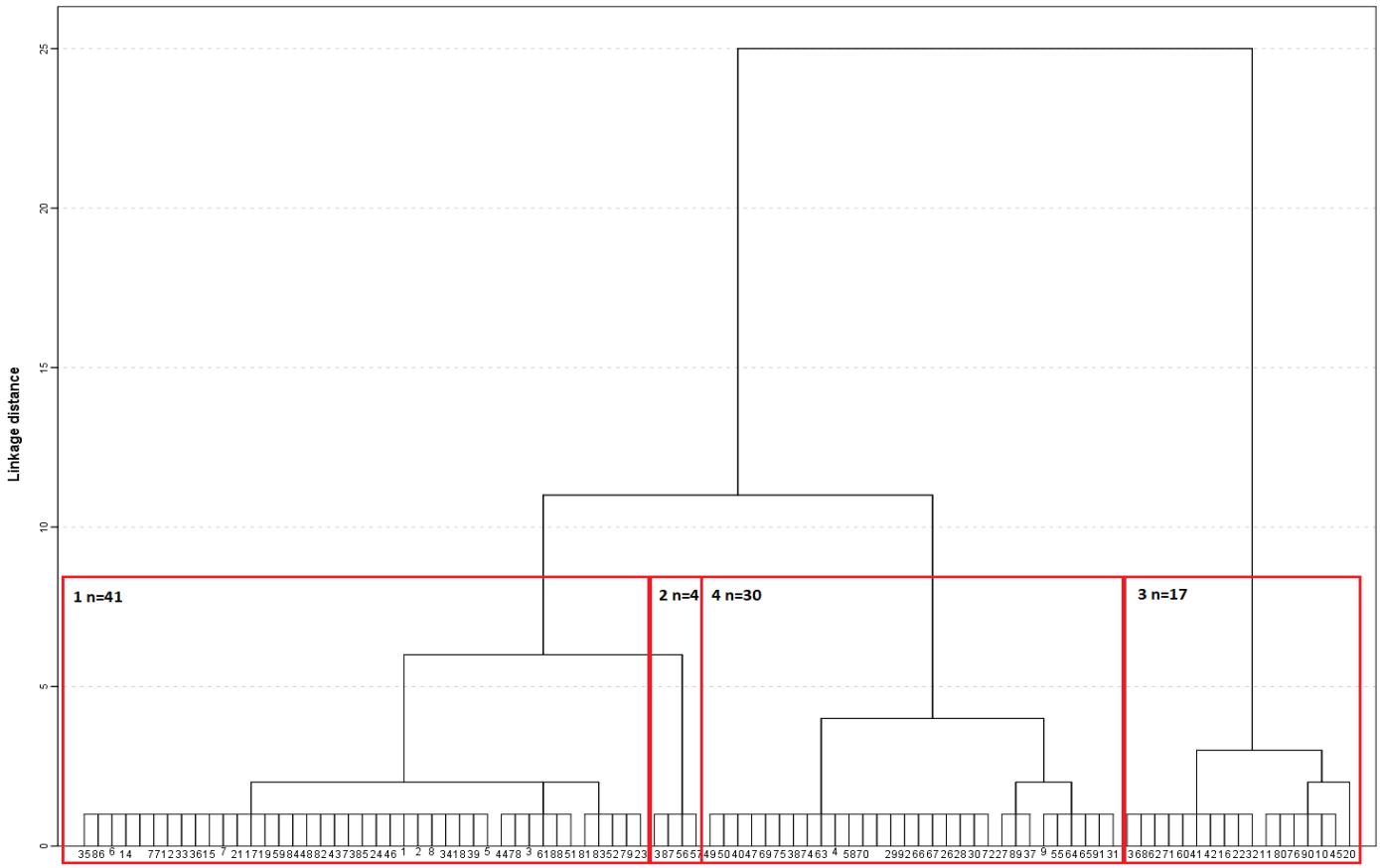
B: Cluster made by using the variables defined by principal component analysis.

Using these selected variables (assigned to PCs with >1 Eigenvalues) to the cluster analysis, the result was almost the same, 4 patients were regrouped from cluster 1 to cluster 4, which did not make big differences. We remained with our original (not filtered) set of variables for cluster analysis.

A

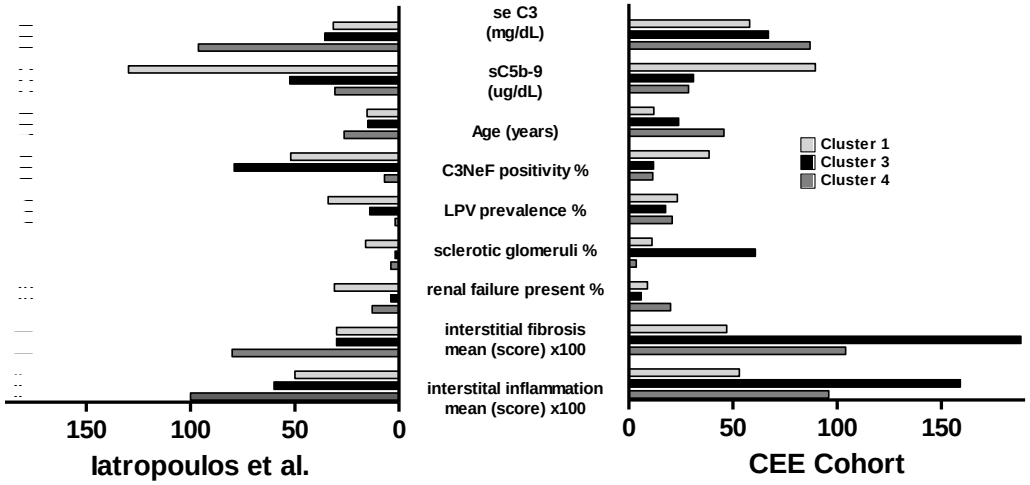


B



Each vertical line at the bottom of the dendrogram represents a patient. The boxes show the 4 different clusters.

Supplementary Figure 4. Comparison of selected cluster features of the original (Iatropoulos et al, (9) and of the current validation (Central and Eastern European, CEE) cohorts



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