

Supplemental material

Supplementary table 1: Defining criteria for the diagnosis of the five main established cystinosis extra-renal complications.

Supplementary table 2: Correlation analysis between the proposed biomarkers of macrophage activation and the number of extra-renal complications in the subgroup of patients harboring at least one extra-renal complication.

Supplementary figure 1: Median values for biomarkers of macrophage activation and WBC cystine values in ERC+ patients in relation to the number of extra-renal complications. Biomarker values (a: IL-1 β , b: IL-6, c: IL-18, d: chitotriosidase) and WBC cystine levels were categorized according to the number of extra-renal complications. P-values were based on Kruskal-Wallis test. Data is presented as median \pm IQR.

Table S1: Defining criteria for the diagnosis of the five main established cystinosis extra-renal complications

	Cystinosis extra-renal complication	Diagnostic criteria	Ref¹
1	Primary hypothyroidism	(1) Biochemical evidence for primary hypothyroidism (increased thyroid stimulating hormone (TSH) > 10 mIU/L combined with a decreased free thyroxin (FT4) level) and/or (2) Treatment with age- & weight appropriate dosage of L-thyroxin	(19-21)
2	Retinopathy	(1) Clinical signs and symptoms of nyctalopia, impaired color vision, visual field restriction and/or retinal blindness and/or (2) Fundoscopic findings of (peripheral) retinal pigmentary changes (incl. depigmentation and pigmentary mottling) and retinal degeneration, and/or findings of visual field restriction by perimetry	(22)
3	Insulin-dependent diabetes mellitus	(1) Biochemical evidence of insulin dependent diabetes mellitus (HbA1c > 6.5%, fasting glucose > 126mg/dl, C-peptide < 0.2 nmol/L) and/or (2) Treatment with appropriate dosages of insulin	(23)
4	Peripheral myopathy	Clinical signs of significant muscular atrophy of the thenar- and hypothenar musculature, combined with a history of reduced grip strength	(24-26)
5	Swallowing dysfunction	History of difficulties on swallowing solids and/or fluids	(27)

¹ Ref: reference

Table S2: Correlation analysis between the proposed biomarkers of macrophage activation and the number of extra-renal complications in the subgroup of patients harboring at least one extra-renal complication.

Variable	Spearman r	95% CI	<i>p</i>
# of extra-renal complications ERC+ patients (n=26)			
WBC cystine	0.39	-0.007 to 0.68	0.05
Chitotriosidase	0.55	0.2 to 0.78	0.004
IL-1 β	0.058	-0.35 to 0.45	0.78
IL-6	0.31	-0.096 to 0.63	0.12
IL-18	-0.079	-0.46 to 0.33	0.70

Of the biomarkers for macrophage activation studied, apart from WBC cystine, only chitotriosidase is significantly correlated with the number of extra-renal complications in the subgroup of patients harboring at least one extra-renal complication. The continuous variables studied, concern the 2-year average per subject.

Figure S1: Median values for biomarkers of macrophage activation and WBC cystine values in ERC+ patients in relation to the number of extra-renal complications

