

Electronic Supplementary Materials

Comparison of serum and urinary biomarker panels with albumin/creatinin ratio in the prediction of renal function decline in type 1 diabetes

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ESM Table 1: Median, interquartile range (IQR), range and intraclass correlations (ICC) for the biomarkers analyzed in the study

Biomarker	Laboratory	Unit	Median (IQR)	Range	ICC
Serum biomarkers					
Alpha-1-Microglobulin	Myriad RBM	µg/ml	18.0 (14.0, 23.0)	4.3 – 77.5	0.82
CD27 antigen	Corelabs	pg/ml	7144.8 (5555.8, 9619.2)	2689.3 – 41257.5	0.98
Clusterin	Myriad RBM	µg/ml	251.0 (196.0, 338.0)	52.0 – 1200.0	0.65
Cystatin-C	Myriad RBM	ng/ml	906.0 (709.0, 1160.0)	333.0 – 3280.0	0.78
Kidney Injury Molecule-1	Myriad RBM	pg/ml	115.0 (68.0, 214.0)	12.0 – 5830.0	0.99
Matrix Metalloproteinase-8	Corelabs	pg/ml	739.2 (493.2, 1105.5)	65.7 – 56998.6	0.94
Syndecan 1	Corelabs	pg/ml	1865.9 (1530.4, 2305.4)	516.6 – 7541.1	0.86
Thrombomodulin	Corelabs	pg/ml	6204.7 (4963.2, 7844.4)	274.6 – 64982.8	0.97
Tumour Necrosis Factor Receptor 1	Corelabs	pg/ml	986.8 (804.4, 1288.5)	361.7 – 5633.5	0.97
Urine biomarkers					
Amphiregulin	Myriad RBM	pg/ml	28.0 (28.0, 28.0)	28.0 – 382.0	0.97
EGF/MCP-1 ratio	Myriad RBM	ratio	121.2 (68.6, 214.0)	0.3 – 2225.9	—
Epidermal Growth Factor	Myriad RBM	pg/ml	18600.0 (8560.0, 35900.0)	433.0 – 86000.0	0.96
Epidermal Growth Factor Receptor	Myriad RBM	pg/ml	15.5 (15.5, 15.5)	15.5 – 450.0	0.76
Epiregulin	Myriad RBM	pg/ml	6.6 (3.2, 11.0)	3.2 – 484.0	0.96
Heparin-Binding EGF-Like Growth Factor	Myriad RBM	pg/ml	43.0 (39.0, 48.0)	15.0 – 64.0	0.66
Interleukin-18	Myriad RBM	pg/ml	23.0 (6.0, 49.0)	6.0 – 1460.0	0.98
Interleukin-4	Myriad RBM	pg/ml	9.0 (9.0, 9.0)	9.0 – 11100.0	—
Interleukin-6	Myriad RBM	pg/ml	0.8 (0.8, 0.8)	0.8 – 570.0	0.95
Interleukin-8	Myriad RBM	pg/ml	6.1 (1.6, 26.0)	0.7 – 3180.0	0.99
Macrophage Inflammatory Protein-1 beta	Myriad RBM	pg/ml	33.0 (17.0, 58.5)	8.0 – 661.0	0.92
Monocyte Chemotactic Protein 1	Myriad RBM	pg/ml	166.5 (74.0, 313.2)	27.0 – 4770.0	0.92
Placenta Growth Factor	Myriad RBM	pg/ml	52.0 (33.0, 80.0)	12.0 – 1070.0	0.92

Median, IQR and ranges for urine biomarkers are shown prior to normalization for urinary creatinine
 Intraclass correlations were computed over 48 blinded duplicate samples
 Interleukin-4 had no variation within the duplicate samples

ESM Table 2: Biomarkers removed from the analysis and reason

Biomarker	Laboratory	Reason
Serum biomarkers		
uPAR	Corelabs	Intraclass correlation < 0.4
Urine biomarkers		
Granulocyte-Macrophage Colony-Stimulating Factor	Myriad RBM	All identical readings
Interferon gamma	Myriad RBM	All identical readings
Interleukin-10	Myriad RBM	Excessive left censoring
Interleukin-2	Myriad RBM	Excessive left censoring
Interleukin-3	Myriad RBM	Excessive left censoring
Interleukin-5	Myriad RBM	Excessive left censoring
Interleukin-7	Myriad RBM	Excessive left censoring
Macrophage Inflammatory Protein-1 alpha	Myriad RBM	Excessive left censoring
Platelet-Derived Growth Factor BB	Myriad RBM	Excessive left censoring
Tenascin-C	Myriad RBM	Excessive left censoring
Tumour Necrosis Factor alpha	Myriad RBM	All identical readings
Tumour Necrosis Factor beta	Myriad RBM	Excessive left censoring

ESM Table 3: Associations of each biomarker (considered separately) with having an achieved eGFR < 30, overall and stratified by albuminuria status at study day

Biomarker	Overall (N=1627, 41 events)				Normo/micro (n=1571, 18 evs)				Macro (n=56, 23 events)			
	Basic covariates		Basic covariates + ACR		Basic covariates		Basic covariates		Basic covariates		Basic covariates	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Serum biomarkers												
Alpha-1-Microglobulin	2.43 (1.71, 3.47)	9.3×10^{-07}	1.46 (1.00, 2.23)	6.4×10^{-02}	2.15 (1.42, 3.12)	9.0×10^{-05}	0.97 (0.37, 2.42)	9.5×10^{-01}	47.3 (4.86, 2274.39)	0.60 (0.23, 1.38)	1.1×10^{-02}	1.1 $\times 10^{-02}$
CD27 antigen	15.8 (7.77, 35.60)	8.0×10^{-13}	9.43 (4.37, 22.23)	5.0×10^{-08}	8.08 (3.72, 19.29)	4.8×10^{-07}	0.60 (0.23, 1.38)	2.5×10^{-01}		1.13 (0.39, 2.96)	8.1×10^{-01}	8.1 $\times 10^{-01}$
Clusterin	1.01 (0.62, 1.62)	9.7×10^{-01}	0.88 (0.50, 1.53)	6.6×10^{-01}	1.20 (0.62, 2.23)	5.8×10^{-01}	1.42 (0.67, 3.32)	3.7×10^{-01}		0.81 (0.40, 1.56)	5.4×10^{-01}	5.4 $\times 10^{-01}$
Cystatin-C	1.83 (1.15, 2.98)	1.3×10^{-02}	1.44 (0.85, 2.48)	1.8×10^{-01}	1.89 (1.02, 3.65)	5.0×10^{-02}	1.42 (0.67, 3.32)	3.7×10^{-01}		4.79 (1.56, 20.92)	1.5×10^{-02}	1.5 $\times 10^{-02}$
Kidney Injury Molecule-1	3.12 (2.23, 4.50)	1.8×10^{-10}	2.05 (1.40, 3.08)	3.5×10^{-04}	3.10 (2.02, 4.93)	4.6×10^{-07}	1.64 (0.58, 5.24)	3.8×10^{-01}		14.7 (2.52, 206.31)	1.3×10^{-02}	1.3 $\times 10^{-02}$
Matrix Metalloproteinase-8	1.01 (0.71, 1.44)	9.6×10^{-01}	0.93 (0.63, 1.37)	7.2×10^{-01}	0.93 (0.57, 1.50)	7.5×10^{-01}						
Syndecan 1	4.71 (2.91, 7.98)	1.4×10^{-09}	3.32 (1.96, 5.86)	1.6×10^{-05}	3.43 (1.93, 6.40)	5.0×10^{-05}						
Thrombomodulin	2.83 (1.74, 4.80)	5.8×10^{-05}	2.01 (1.18, 3.63)	1.5×10^{-02}	2.59 (1.38, 5.15)	4.5×10^{-03}						
Tumour Necrosis Factor Receptor 1	12.1 (5.84, 27.50)	2.3×10^{-10}	5.80 (2.61, 14.08)	4.2×10^{-05}	4.73 (2.14, 11.20)	2.2×10^{-04}						
Urine biomarkers												
Amphiregulin	1.29 (0.86, 1.94)	2.1×10^{-01}	1.00 (0.67, 1.51)	9.9×10^{-01}	0.89 (0.51, 1.54)	6.8×10^{-01}	1.36 (0.60, 3.32)	4.7×10^{-01}		0.10 (0.02, 0.36)	2.5×10^{-03}	2.5 $\times 10^{-03}$
EGF/MCP-1 ratio	0.30 (0.19, 0.47)	4.2×10^{-07}	0.57 (0.33, 0.96)	3.8×10^{-02}	0.74 (0.42, 1.27)	2.8×10^{-01}	0.49 (0.16, 1.29)	1.7×10^{-01}		2.40 (1.06, 6.32)	4.9×10^{-02}	4.9 $\times 10^{-02}$
Epidermal Growth Factor	0.71 (0.44, 1.12)	1.4×10^{-01}	0.83 (0.49, 1.37)	4.7×10^{-01}	1.06 (0.57, 1.96)	8.5×10^{-01}	1.07 (0.49, 2.43)	8.6×10^{-01}		1.52 (0.63, 3.94)	3.7×10^{-01}	3.7 $\times 10^{-01}$
Epidermal Growth Factor Receptor	2.17 (1.49, 3.21)	6.6×10^{-05}	1.24 (0.84, 1.89)	2.9×10^{-01}	0.91 (0.52, 1.55)	7.2×10^{-01}	1.07 (0.49, 2.43)	8.6×10^{-01}		1.35 (0.63, 2.86)	4.3×10^{-02}	4.3 $\times 10^{-02}$
Epiregulin	1.35 (0.92, 2.01)	1.3×10^{-01}	0.99 (0.65, 1.51)	9.6×10^{-01}	1.18 (0.70, 2.00)	5.4×10^{-01}	1.52 (0.63, 3.94)	3.7×10^{-01}		2.50 (1.00, 8.14)	7.9×10^{-02}	7.9 $\times 10^{-02}$
Heparin-Binding EGF-Like Growth Factor	1.18 (0.80, 1.74)	3.9×10^{-01}	1.02 (0.67, 1.53)	9.4×10^{-01}	0.85 (0.50, 1.45)	5.6×10^{-01}	1.35 (0.63, 2.86)	4.3×10^{-01}		3.87 (1.53, 12.93)	1.1×10^{-02}	1.1 $\times 10^{-02}$
Interleukin-18	1.86 (1.26, 2.77)	2.0×10^{-03}	1.16 (0.75, 1.80)	5.0×10^{-01}	1.18 (0.70, 2.00)	5.4×10^{-01}	1.35 (0.63, 2.86)	4.3×10^{-01}		1.63 (0.66, 4.41)	3.0×10^{-01}	3.0 $\times 10^{-01}$
Interleukin-4	1.41 (0.97, 2.05)	7.5×10^{-02}	1.18 (0.78, 1.79)	4.3×10^{-01}	0.95 (0.56, 1.60)	8.3×10^{-01}	1.63 (0.66, 4.41)	3.0×10^{-01}		1.77 (0.72, 4.86)	2.4×10^{-01}	2.4 $\times 10^{-01}$
Interleukin-6	2.19 (1.50, 3.25)	7.1×10^{-05}	1.28 (0.84, 1.96)	2.5×10^{-01}	1.10 (0.63, 1.91)	7.3×10^{-01}	1.77 (0.72, 4.86)	2.4×10^{-01}		1.50 (0.72, 3.59)	3.1×10^{-01}	3.1 $\times 10^{-01}$
Interleukin-8	1.77 (1.15, 2.75)	1.0×10^{-02}	1.08 (0.65, 1.79)	7.5×10^{-01}	1.26 (0.70, 2.31)	4.5×10^{-01}						
Macrophage Inflammatory Protein-1 beta	1.47 (1.02, 2.13)	4.2×10^{-02}	0.92 (0.61, 1.40)	7.1×10^{-01}	1.04 (0.63, 1.73)	8.9×10^{-01}						
Monocyte Chemoattractant Protein 1	2.73 (1.86, 4.11)	5.5×10^{-07}	1.63 (1.05, 2.56)	3.2×10^{-02}	1.47 (0.89, 2.44)	1.3×10^{-01}						
Placenta Growth Factor	1.67 (1.18, 2.41)	4.7×10^{-03}	1.30 (0.90, 1.92)	1.7×10^{-01}	1.84 (1.12, 3.07)	1.7×10^{-02}						

Data includes only participants with eGFR > 30 at study day

Odds ratios are per unit of SD of Gaussianised biomarker

CI, confidence interval

Basic clinical covariates: age, sex, diabetes duration, study day eGFR, length of follow-up

ESM Table 4: Associations of each biomarker (considered separately) with having an achieved eGFR < 45, overall and stratified by albuminuria status at study day

Biomarker	Overall (N=1573, 74 events)			Normo/micro (n=1529, 53 evs)			Macro (n=44, 21 events)		
	Basic covariates		Basic covariates + ACR	Basic covariates		Basic covariates	Basic covariates		Basic covariates
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	
Serum biomarkers									
Alpha-1-Microglobulin	1.97 (1.54, 2.52)	6.6×10^{-08}	1.47 (1.11, 1.94)	6.5×10^{-03}	1.75 (1.30, 2.34)	1.6×10^{-04}	1.23 (0.53, 3.02)	6.3×10^{-01}	
CD27 antigen	3.80 (2.66, 5.55)	9.0×10^{-13}	2.64 (1.80, 3.93)	1.0×10^{-06}	3.02 (2.03, 4.59)	1.0×10^{-07}	3.18 (1.26, 11.29)	3.3×10^{-02}	
Clusterin	1.03 (0.72, 1.44)	8.8×10^{-01}	0.98 (0.66, 1.44)	9.2×10^{-01}	1.10 (0.72, 1.64)	6.5×10^{-01}	0.62 (0.24, 1.40)	2.7×10^{-01}	
Cystatin-C	1.80 (1.31, 2.50)	4.0×10^{-04}	1.53 (1.08, 2.18)	1.7×10^{-02}	1.99 (1.36, 2.98)	5.8×10^{-04}	0.71 (0.31, 1.50)	3.8×10^{-01}	
Kidney Injury Molecule-1	2.77 (2.15, 3.62)	1.3×10^{-14}	2.05 (1.55, 2.75)	7.8×10^{-07}	2.48 (1.86, 3.35)	9.9×10^{-10}	1.52 (0.70, 3.62)	3.0×10^{-01}	
Matrix Metalloproteinase-8	1.06 (0.81, 1.37)	6.8×10^{-01}	1.01 (0.77, 1.33)	9.4×10^{-01}	1.10 (0.81, 1.49)	5.4×10^{-01}	0.60 (0.26, 1.21)	1.8×10^{-01}	
Syndecan 1	2.46 (1.84, 3.34)	2.7×10^{-09}	1.91 (1.40, 2.62)	4.8×10^{-05}	2.21 (1.60, 3.12)	3.1×10^{-06}	1.11 (0.55, 2.35)	7.6×10^{-01}	
Thrombomodulin	1.88 (1.40, 2.56)	4.1×10^{-05}	1.46 (1.06, 2.03)	2.3×10^{-02}	1.57 (1.13, 2.20)	8.3×10^{-03}	1.11 (0.50, 2.68)	8.0×10^{-01}	
Tumour Necrosis Factor Receptor 1	4.39 (2.98, 6.64)	4.3×10^{-13}	2.87 (1.90, 4.44)	1.1×10^{-06}	3.23 (2.12, 5.05)	1.1×10^{-07}	1.99 (0.80, 6.25)	1.8×10^{-01}	
Urine biomarkers									
Amphiregulin	1.24 (0.92, 1.68)	1.6×10^{-01}	1.04 (0.78, 1.39)	8.0×10^{-01}	0.95 (0.67, 1.36)	7.9×10^{-01}	1.51 (0.67, 3.67)	3.3×10^{-01}	
EGF/MCP-1 ratio	0.36 (0.26, 0.49)	1.3×10^{-10}	0.53 (0.37, 0.75)	3.6×10^{-04}	0.51 (0.36, 0.72)	1.7×10^{-04}	0.26 (0.07, 0.67)	1.4×10^{-02}	
Epidermal Growth Factor	0.88 (0.65, 1.20)	4.3×10^{-01}	0.96 (0.70, 1.33)	8.2×10^{-01}	0.98 (0.68, 1.39)	8.9×10^{-01}	0.89 (0.37, 2.07)	7.8×10^{-01}	
Epidermal Growth Factor Receptor	1.43 (1.08, 1.90)	1.3×10^{-02}	1.00 (0.75, 1.34)	9.9×10^{-01}	0.77 (0.54, 1.09)	1.4×10^{-01}	2.40 (1.07, 6.54)	5.2×10^{-02}	
Epregrulin	1.47 (1.10, 1.96)	9.2×10^{-03}	1.15 (0.86, 1.55)	3.4×10^{-01}	1.34 (0.96, 1.87)	8.5×10^{-02}	1.50 (0.72, 3.45)	3.0×10^{-01}	
Heparin-Binding EGF-Like Growth Factor	1.05 (0.78, 1.40)	7.7×10^{-01}	0.92 (0.68, 1.23)	5.6×10^{-01}	0.84 (0.59, 1.18)	3.1×10^{-01}	1.72 (0.74, 4.38)	2.2×10^{-01}	
Interleukin-18	1.57 (1.19, 2.08)	1.7×10^{-03}	1.09 (0.81, 1.48)	5.5×10^{-01}	1.17 (0.84, 1.63)	3.5×10^{-01}	1.35 (0.65, 2.88)	4.2×10^{-01}	
Interleukin-4	0.97 (0.72, 1.30)	8.4×10^{-01}	0.86 (0.64, 1.16)	3.3×10^{-01}	0.78 (0.55, 1.11)	1.7×10^{-01}	1.99 (0.89, 5.29)	1.2×10^{-01}	
Interleukin-6	1.63 (1.23, 2.17)	7.8×10^{-04}	1.17 (0.88, 1.57)	2.8×10^{-01}	1.17 (0.83, 1.66)	3.6×10^{-01}	2.63 (1.17, 7.33)	3.4×10^{-02}	
Interleukin-8	2.05 (1.50, 2.80)	6.6×10^{-06}	1.45 (1.03, 2.03)	3.3×10^{-02}	1.65 (1.15, 2.39)	7.2×10^{-03}	1.99 (0.86, 5.22)	1.3×10^{-01}	
Macrophage Inflammatory Protein-1 beta	1.70 (1.31, 2.24)	1.0×10^{-04}	1.24 (0.94, 1.65)	1.4×10^{-01}	1.48 (1.09, 2.01)	1.3×10^{-02}	1.81 (0.82, 4.66)	1.7×10^{-01}	
Monocyte Chemoattractant Protein 1	2.40 (1.82, 3.21)	1.6×10^{-09}	1.70 (1.25, 2.33)	8.0×10^{-04}	1.80 (1.31, 2.51)	3.4×10^{-04}	3.50 (1.47, 10.67)	1.2×10^{-02}	
Placenta Growth Factor	1.35 (1.04, 1.77)	2.6×10^{-02}	1.15 (0.87, 1.52)	3.3×10^{-01}	1.33 (0.98, 1.82)	7.0×10^{-02}	2.02 (0.88, 5.71)	1.3×10^{-01}	

Data includes only participants with eGFR > 45 at study day

Odds ratios are per unit of SD of Gaussianised biomarker

CI, confidence interval

Basic clinical covariates: age, sex, diabetes duration, study day eGFR, length of follow-up