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Association between circulating ECM-associated molecules and cardiovascular outcomes in hemodialysis patients

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Objectives: The extracellular matrix (ECM) is a complex network of non-cellular components that provide structural support for the tissues. Circulating ECM-associated molecules are increased during cardiovascular (CV) remodeling process and can be potential biomarkers of adverse CV outcomes. However, their clinical significance in hemodialysis patients is unclear.

Methods: A total of 372 hemodialysis patients were enrolled from a prospective multicenter cohort study. We measured four plasma ECM-associated proteins: matrix metalloproteinase (MMP)-2, MMP-9, tenascin-C, and thrombospondin-2. The primary outcome was set as a composite of cardiac and noncardiac vascular events.

Results: Plasma MMP-2 levels were significantly higher in patients with future CV events than in those without (p = 0.004), while the others were not. All the measured molecules had significant correlations with NT-proBNP levels, but the correlation coefficient was most strong with plasma MMP-2 (Rho = 0.317, p < 0.001). In logistic regression analysis, elevated plasma MMP-2 levels were independently associated with LV diastolic dysfunction (adjusted odds ratio [OR] per standard deviation, 1.48; 95% confidence interval [CI], 1.05 – 2.08; p = 0.024). Cox regression analysis showed that plasma MMP-2 levels were associated with a 1.30-fold risk for the composite of CV events (per a standard deviation increase; 95% CI, 1.04 – 1.63; p = 0.022) after multivariable adjustments.

Conclusions: Plasma MMP-2 levels were independently associated with an increased risk of LV diastolic dysfunction and adverse CV outcomes in hemodialysis patients. Our results suggest that MMP-2 levels can be a useful biomarker in identifying hemodialysis patients at high risk of future CV events.

figure 1. Correlation of circulating ECM-associated molecules and cardiac biomarkers

Figure 1

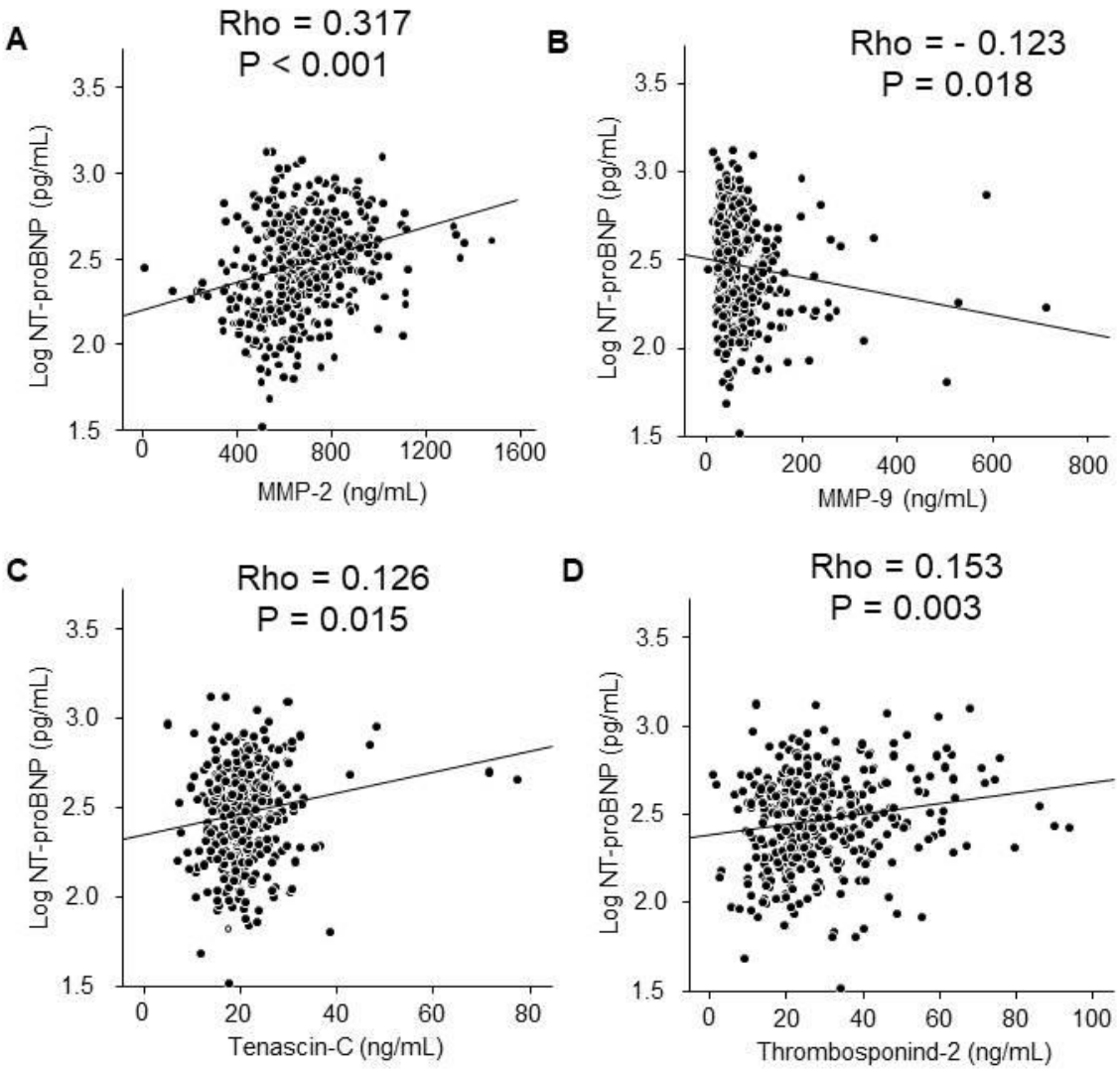

Table 1. Hazard ratios of ECM level for cardiovascular events

Table 3. Hazard ratios of ECM level for cardiovascular events

		Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Composite of CV event					
MMP-2	per 1 ng/mL	1.001 (1.000-1.002)	0.056	1.001 (1.000-1.002)	0.039
	per SD	1.27 (1.02-1.59)	0.033	1.30 (1.04-1.63)	0.022
MMP-9	per 1 ng/mL	1.002 (1.000-1.004)	0.107	1.002 (0.999-1.004)	0.152
	per SD	1.12 (0.94-1.33)	0.203	1.12 (0.94-1.32)	0.199
Tenascin-C	per 1 ng/mL	0.989 (0.953-1.027)	0.564	0.982 (0.940-1.026)	0.418
	per SD	0.91 (0.64-1.31)	0.625	0.85 (0.57-1.27)	0.431
Thrombospondin-2	per 1 ng/mL	0.998 (0.982-1.014)	0.799	0.998 (0.981-1.015)	0.822
	per SD	0.99 (0.96-1.03)	0.754	1.00 (0.96-1.03)	0.776
Cardiac event					
MMP-2	per 1 ng/mL	1.002 (1.000-1.003)	0.009	1.002 (1.000-1.003)	0.007
	per SD	1.40 (1.11-1.77)	0.004	1.43 (1.13-1.82)	0.003
MMP-9	per 1 ng/mL	1.002 (1.000-1.005)	0.042	1.002 (1.000-1.005)	0.051
	per SD	1.16 (0.97-1.38)	0.097	1.17 (0.98-1.38)	0.078
Tenascin-C	per 1 ng/mL	0.983 (0.942-1.026)	0.443	0.973 (0.926-1.022)	0.278
	per SD	0.85 (0.56-1.28)	0.435	0.78 (0.50-1.21)	0.262
Thrombospondin-2	per 1 ng/mL	0.992 (0.974-1.010)	0.388	0.991 (0.972-1.010)	0.356
	per SD	0.98 (0.94-1.02)	0.364	0.98 (0.94-1.02)	0.333

Multivariate analysis was adjusted for the following covariates: age, sex, BMI, Charlson comorbidity index, dialysis duration, LDL cholesterol, hsCRP, NT-pro BNP and spKt/V.
ECM, extraceullar matrix; *MMP,* matrix metalloproteinase; *HR,* hazard ratio; *CI,* confidence interval; *No,* number