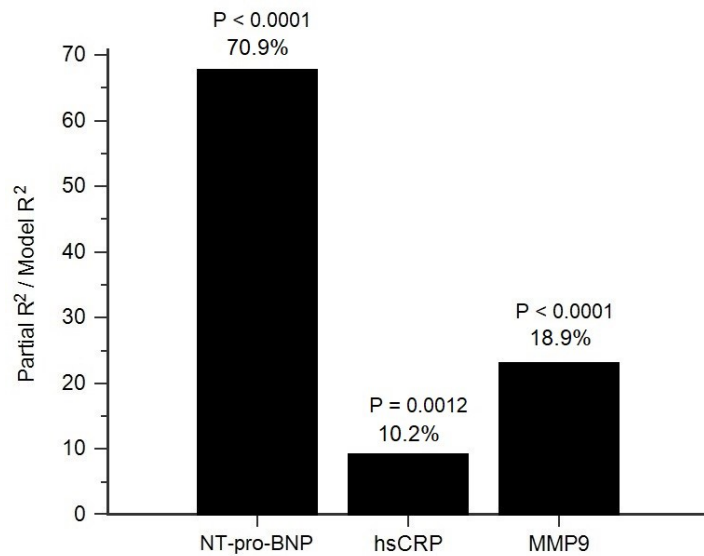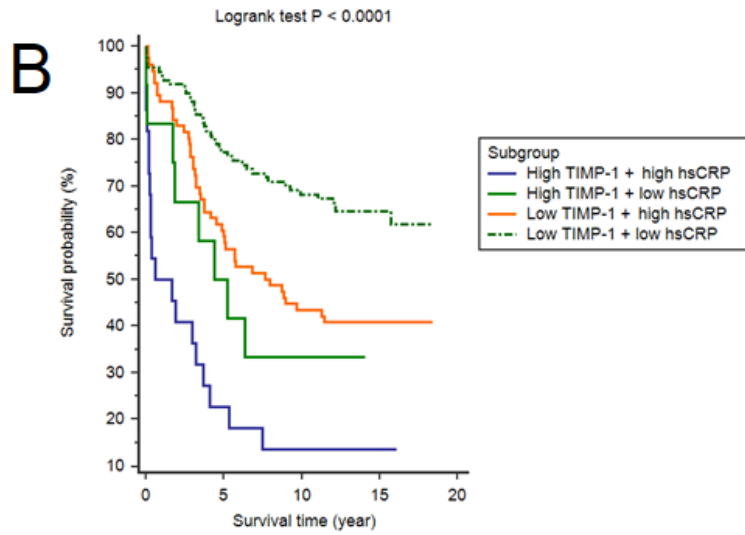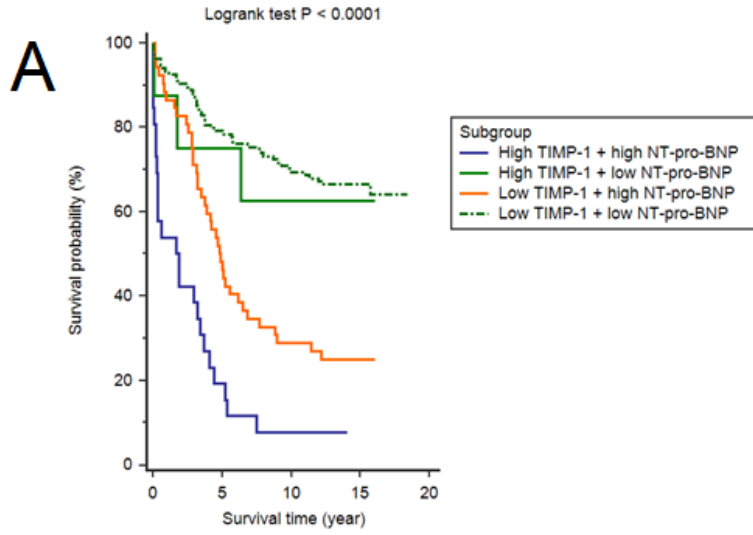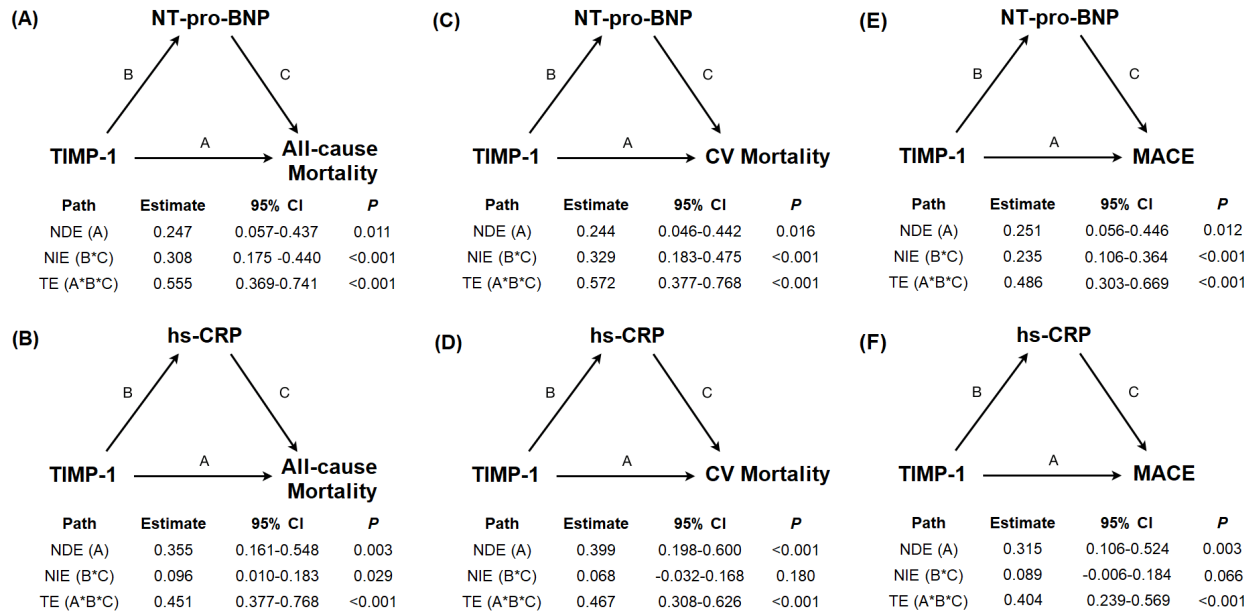## 146. Significance of TIMP-1 in Prognosis and Left Ventricle Remodeling of Patients Undergone Coronary Artery Bypass Surgery: A 12-Year Follow-Up Study

Jui-Tzu Huang, Shih-Hsien Sung, Chiao-Po Hsu, Chao-Yu Guo, Chern-En Chiang, Cheng-Hsiung Huang, Taipei General Veterans Hospital, Taipei, Taiwan

Body

Studies have suggested that matrix metalloproteinase (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) provide pathological effects on various cardiovascular diseases, post-cardiovascular surgical healing, and structural remodeling. However, the correlation between TIMP-1 and other biomarkers such as high-sensitive C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP), the proportion of TIMP-1 contributed to the remodeling process, and its prognostic value of post-cardiovascular surgery patients was still unclear. We, therefore, investigated the role of TIMP-1 in the prognosis of patients underwent coronary bypass surgery (CABG), and the causal relationship between TIMP-1, hs-CRP, and NT-pro-BNP. A total of 234 patients (52.9% male; mean age: 54.0 ± 15.0 years) recommended to receive CABG were prospectively enrolled. Every participant was operated by the same experienced surgeon. During a median follow-up of 12.1 years, 120 deaths (92 cardiovascular deaths) were confirmed from the National Death Registry. The major adverse cardiovascular events (MACE) were defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. Multivariable Cox models adjusting for age, sex, manifest acute coronary syndrome, estimated glomerular filtration rate, left ventricular ejection fraction, total cholesterol and triglycerides revealed that pre-operative serum TIMP-1 (HR=1.506; 95% CI 1.183-1.917), hs-CRP (HR=1.349; 95% CI 1.183-1.561), and NT-Pro-BNP (HR=1.707; 95% CI 1.326-2.199) were significantly associated with greater mortality risk. TIMP-1 was strongly correlated to inflammatory and cardiovascular markers including hs-CRP and NT-pro-BNP. Moreover, forward stepwise regression showed that NT-pro-BNP was a major determinant of TIMP-1, with 67.7% contributed. Mediation analysis revealed TIMP-1 was mediated by both NT-pro-BNP (87.75%) and hs-CRP (41.78%), and more by NT-pro-BNP in prediction of all-cause mortality and cardiovascular mortality. In conclusion, TIMP-1 was an independent predictor for long-term outcome after CABG and might play an important role in further cardiac tissue healing and structural remodeling after the surgery.

A

Logrank test P < 0.0001

Survival probability (%)

Survival time (year)

Subgroup
— High TIMP-1 + high NT-pro-BNP
— High TIMP-1 + low NT-pro-BNP
— Low TIMP-1 + high NT-pro-BNP
--- Low TIMP-1 + low NT-pro-BNP

B

Logrank test P < 0.0001

Survival probability (%)

Survival time (year)

Subgroup
— High TIMP-1 + high hsCRP
— High TIMP-1 + low hsCRP
— Low TIMP-1 + high hsCRP
--- Low TIMP-1 + low hsCRP

P < 0.0001
70.9%

P = 0.0012
10.2%

P < 0.0001
18.9%

Partial R^2 / Model R^2

NT-pro-BNP   hsCRP   MMP9

(A) NT-pro-BNP

TIMP-1 → All-cause Mortality (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.247	0.057-0.437	0.011
NIE (B*C)	0.308	0.175 -0.440	<0.001
TE (A*B*C)	0.555	0.369-0.741	<0.001

(C) NT-pro-BNP

TIMP-1 → CV Mortality (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.244	0.046-0.442	0.016
NIE (B*C)	0.329	0.183-0.475	<0.001
TE (A*B*C)	0.572	0.377-0.768	<0.001

(E) NT-pro-BNP

TIMP-1 → MACE (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.251	0.056-0.446	0.012
NIE (B*C)	0.235	0.106-0.364	<0.001
TE (A*B*C)	0.486	0.303-0.669	<0.001

(B) hs-CRP

TIMP-1 → All-cause Mortality (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.355	0.161-0.548	0.003
NIE (B*C)	0.096	0.010-0.183	0.029
TE (A*B*C)	0.451	0.377-0.768	<0.001

(D) hs-CRP

TIMP-1 → CV Mortality (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.399	0.198-0.600	<0.001
NIE (B*C)	0.068	-0.032-0.168	0.180
TE (A*B*C)	0.467	0.308-0.626	<0.001

(F) hs-CRP

TIMP-1 → MACE (paths A, B, C)

Path	Estimate	95% CI	P
NDE (A)	0.315	0.106-0.524	0.003
NIE (B*C)	0.089	-0.006-0.184	0.066
TE (A*B*C)	0.404	0.239-0.569	<0.001

Clinical Implications: We investigated the post-operative long-term prognostic value of TIMP-1 and its relationship with different biomarkers by applying the mediation analysis. Our major result is compatible with recent studies that serum TIMP-1 level provides prognostic value in patients with coronary disease by multivariable Cox regression analysis, and attributed to NT-pro-BNP and hs-CRP significantly. TIMP-1 served as a robust marker in predicting long-term all-cause mortality and MACE in CAD patients elected for CABG, jointly influencing post-surgical tissue inflammation and structural remodeling.