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OSTEO18, a novel urinary proteomic signature, associated with osteoporosis in heart transplant recipients

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Background: Immunosuppressive treatment in heart transplant (HTx) recipient causes osteoporosis. The urinary proteomic profile (UPP) includes peptide fragments derived from the bone extracellular matrix.

Purpose: Study aims were to develop and validate a multidimensional UPP biomarker for osteoporosis in HTx patients from single sequenced urinary peptides identifying the parent proteins.

Methods: A single-center HTx cohort was analyzed. Urine samples were measured by capillary electrophoresis coupled with mass spectrometry. Cases with osteoporosis and matching controls were randomly selected from all available 389 patients. In derivation case-control dataset, 1576 sequenced peptides detectable in ≥30% of patients. Applying statistical analysis on these, an 18-peptide multidimensional osteoporosis UPP biomarker (OSTEO18) was generated by support vector modeling. The 2 replication datasets included 118 and 94 patients. For further validation, the whole cohort was analyzed. Statistical methods included logistic regression and receiver operating characteristic curve (ROC) analysis.

Results: In derivation dataset, the AUC, sensitivity and specificity of OSTEO18 were 0.83 (95% CI: 0.76-0.90), 74.3% and 87.1%, respectively. In replication datasets, results were confirmatory. In the whole cohort (154 osteoporotic patients [39.6%]), the ORs for osteoporosis increased ($p < 0.0001$) across OSTEO18 quartiles from 0.39 (95% CI: 0.25-0.61) to 3.14 (2.08-4.75). With full adjustment for known osteoporosis risk factors, OSTEO18 improved AUC from 0.708 to 0.786 ($p = 0.0003$) for OSTEO18 categorized (optimized threshold: 0.095) and to 0.784 ($p = 0.0004$) for OSTEO18 as continuously distributed classifier.

Conclusion: OSTEO18 is a clinically meaningful novel biomarker indicative of osteoporosis in HTx recipients and is being certified as in-vitro diagnostic.

[A]

Osteoporosis (n/N = 154/389)

	AUC (95% CI)	*p*-value
Base model 1	0.632 (0.574, 0.689)	
Base model 2	0.708 (0.655, 0.760)	0.0026
+OSTEO18		
Continuous	0.786 (0.740, 0.832)	0.0003
Categorized threshold, 0.095	0.784 (0.737, 0.831)	0.0004

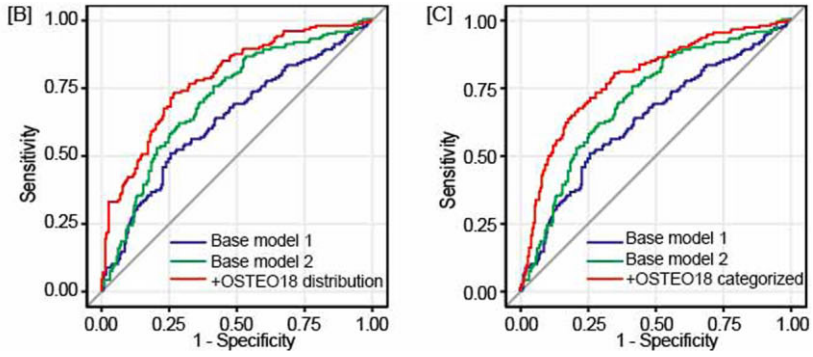

Figure 1