A novel prognostic model to predict the incidence of radiographic knee osteoarthritis

Supplemental Material

Supplementary Tables

Supplementary Table 1. Proteotypic peptides altered in the sera of patients with rKOA (KL≥ 2) compared to healthy controls, and their corresponding proteins.

Peptide sequence	Protein
QLTPYAQRMER	APOA4
ELQQRLEPYADQLR	APOA4
LHELQEKLSPLGEEMR	APOA1
QKLHELQEKLSPLGEEMR	APOA1
LHELQEKLSPLGEEMRDR	APOA1
ARAHVDALRTHLAPYSDELR	APOA1
LHELQEKLSPLGEEMRDRAR	APOA1
QKLHELQEKLSPLGEEMRDR	APOA1
QKLHELQEKLSPLGEEMRDRAR	APOA1
DSFHLDEQFTVPVEMMQAR	A2AP
QKWEAEPVYVQR	AZGP

Supplementary Table 2. Predictive capacity in the development phase of the clinical model (age, sex, BMI and WOMAC pain at baseline) and the clinical model in combination with the biomarkers in patients with KL=0 at baseline.

	AUC	IC95%	
Clinical model	**0.702**	**0.598**	**0.805**
Clinical model + APOA1	0.739	0.643	0.836
Clinical model + ZA2G	0.738	0.640	0.836
Clinical model + A2AP	0.732	0.634	0.829
Clinical model + APOA4	0.708	0.605	0.811
Clinical model + ZA2G + A2AP (optimal model)	**0.820**	**0.734**	**0.906**

Clinical model + APOA1 + ZA2G + A2AP (best performance model)	**0.831**	**0.750**	**0.913**
Clinical model + APOA1 + ZA2G + APOA4	0.785	0.696	0.873
Clinical model + APOA1 + A2AP + APOA4	0.778	0.693	0.863
Clinical model + ZA2G + A2AP + APOA4	0.816	0.730	0.902
Clinical model + APOA1 + ZA2G + A2AP + APOA4	0.826	0.745	0.908

Supplementary Table 3. Internal validation of the prognostic models developed in the OAI cohort using bootstrap techniques, showing with AUC, sensitivity, and specificity parameters. The NRI was calculated comparing the best performance and optimal models with the clinical model.

Estimate	**Clinical model (CM)** (age, sex, BMI and WOMAC)	**Best performance model** (CM+APOA1+ZA2G+A2AP)	**Optimal model** (CM+ZA2G+A2AP)
AUC (95% CI)	0.702 (0.598-0.905)	0.831 (0.750-0.913)	0.820 (0.734-0.906)
Bootstrap-corrected AUC (95% CI)	0.675 (0.575-0.764)	0.793 (0.716-0.873)	0.797 (0.726-0.879)
Sensitivity (95% CI)	0.759 (0.586-0.897)	0.929 (0.821-1.000)	0.828 (0.689-0.966)
Specificity (95% CI)	0.585 (0.526-0.644)	0.672 (0.608-0.733)	0.731 (0.676-0.787)
NRI(>0) (95% CI)		0.856 (0.528-1.184)	0.839 (0.559-1.118)

CI, confidence interval; AUC, area under the ROC curve; NRI(>0): Category-free net reclassification improvement.

Supplementary Table 4. Reclassification table for non-incident and incident events in the OAI cohort.

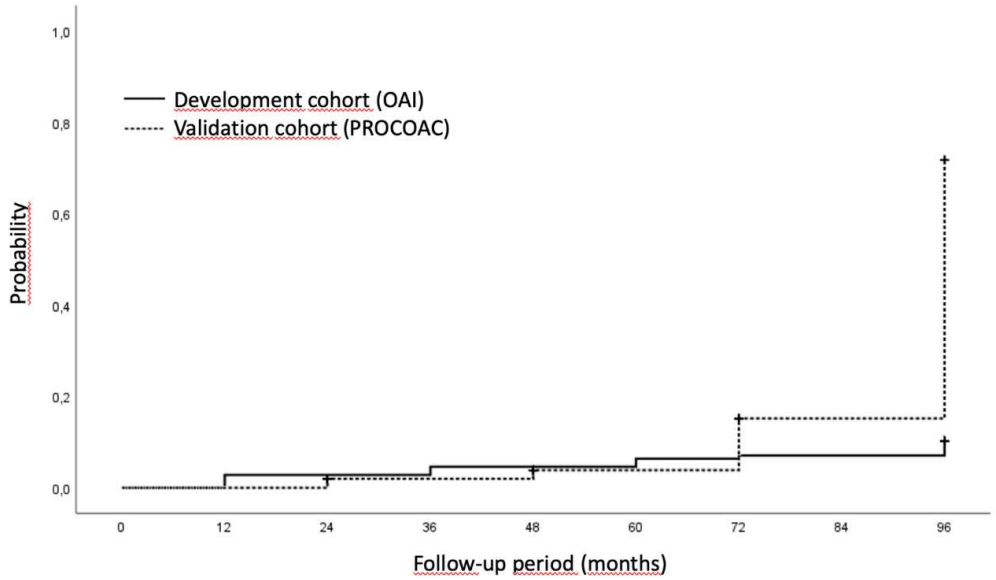
		Optimal model			
	Total	**Up***	**Down***	**P(up)**	**NRI(0.1-0.3)**
Non-incident	253	27	30	0.1067	-0.012
Incident	29	12	1	0.4138	0.379
Global					0.391 (0.182-0.600)
		Best performance model			
	Total	**Up***	**Down***	**P(up)**	**NRI(0.1-0.3)**
Non-incident	253	25	35	0.0988	-0.039
Incident	29	16	2	0.5517	0.483
Global					0.522 (0.281-0.763

Upward (up) and downward (down) movements were defined based on the algorithm developed in this study.
*up: represents the number of patients that change into a higher category based on the optimal and best performance models; down: represents the number of movements as a change in the opposite direction. NRI(0.1-0.3): categorical net reclassification index, established by cut-off points 0.1 and 0.3.

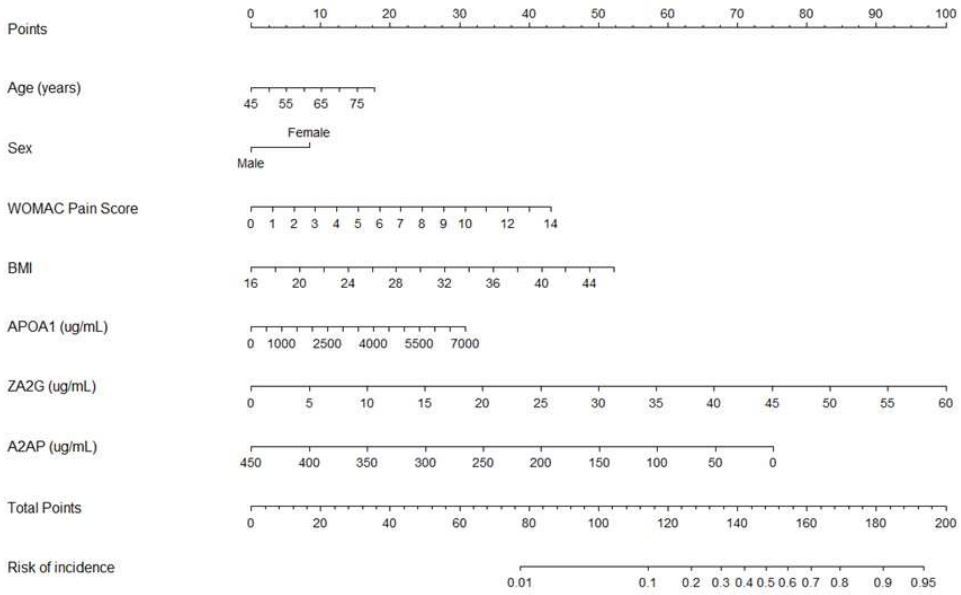
Supplementary Table 5. Mathematical expression for the prognostic models described in the development phase.

Model	Model	Mathematical expression
Clinical model	Age, sex, BMI and WOMAC	ODDs=exp(-6.889+0.028*age+0.106*BMI+0.156*WOMAC-0.265*male)
Best model	Clinical model + ZA2G + A2AP + APOA1	ODDs=exp(-7.483+0.033*age+0.113*BMI+0.200*WOMAC-0.547*male+0.108*ZA2G(ug/mL)-0.011*A2AP(ug/mL)+0.0003*APOA1(ug/mL))
Optimal model	Clinical model + ZA2G + A2AP	ODDs=exp(-7.147+0.032*age+0.115*BMI+0.187*WOMAC-0.439*male+0.117*ZA2G(ug/mL)-0.011*A2AP(ug/mL)

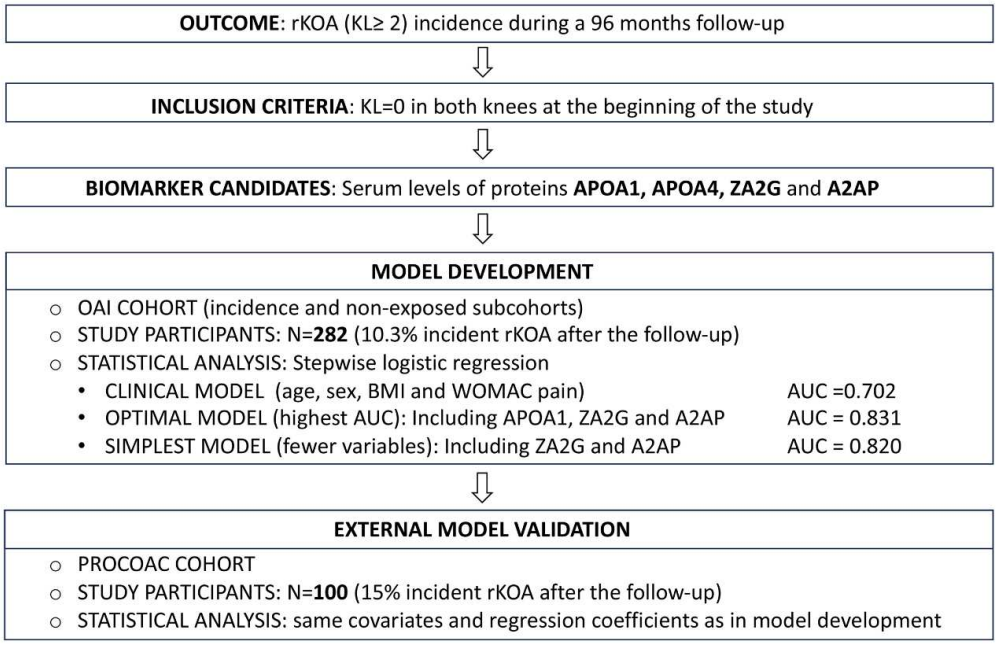
Supplementary Figures



Supplementary Figure 1. Probability of rKOA incidence during the 96 months follow-up in the development (OAI) and validation (PROCOAC) study populations.



Supplementary Figure 2. A translational prognostic tool for predicting rKOA in individuals with KL=0. The provided nomogram plot is based on the parameters of the prognostic model including basic clinical variables (age, sex, BMI and WOMAC) and serum levels of the 3 protein biomarker candidates that were included in the best performance model (APOA1, ZA2G and A2AP). To use the nomogram, a straight edge on the top of the figure identifies the value on the points scale that corresponds to the score for each predictor. In addition, the total points scale is aligned with the risk of incidence to determine the risk of incidence at the bottom of the nomogram, once all the points for each predictor are summed. The resulted value reports the probability of developing rKOA (KL ≥2) within a period of 96 months.



Supplementary Figure 3. Flow and analysis of the present study.