**Supplementary materials**

|  |  |
| --- | --- |
| **Outcome**  | **Criteria** |
| K&L grades | Grades ≥ 2 |
| JSN medial | OARSI grade ≥ 1 |
| JSN lateral | OARSI grade ≥ 1 |
| Osteophytes medial  | OARSI grade ≥ 1 |
| Osteophytes lateral | OARSI grade ≥ 1 |
| WOMAC pain score | ≥ 3 |
| WOMAC stiffness score | ≥ 3  |

***Supplementary table 1. Criteria for the association of baseline biomarkers with radiographic and clinical outcome.***

|  |
| --- |
| How the baseline biomarkers predict OA over four years?  |
| **Population** | Everyone. Mixed of people with OA and without OA |
| **Intervention** | Biomarkers |
| **Comparison/ Outcome** | OA progression |

***Supplementary table 2. The association of baseline biomarkers and radiographic/clinical outcome.***

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Types** | **Functions in OA** | **Measured in** |
| ***Cartilage markers*** |  |  |  |
| C2C | Type II collagen | Type II collagen degradation | Serum and Urine |
| CTXII | Type II collagen | Type II collagen degradation | Urine |
| Coll2-1 NO2 | Type II collagen | Type II collagen degradation | Serum and Urine |
| C1,2C | Type II collagen | Type I and II collagen marker degradation | Serum and Urine |
| CPII | Type II collagen | Type II collagen synthesis | Serum |
| PIIANP | Type II collagen | Cartilage turnover | Serum |
| COMP | Extracellular matrix protein | Cartilage degradation | Serum |
| CS846 | Proteoglycan Aggrecan | Cartilage turnover | Serum |
| ***Bone markers*** |  |  |  |
| CTX-I | Type I collagen | Type I collagen degradation | Serum |
| NTXI | Type I collagen | Type I collagen degradation | Serum and Urine |
| ***Proteases*** |  |  |  |
| MMP 3 | Matrix Metallopeptidase | Extracellular matrix degradation | Serum |
| HA | Glycosaminoglycans | Maintain high fluid viscosity  | Serum |

***Supplementary Table 3. Thirteen of the biomarkers used in the study that have been measured in either urine or serum.***

|  |
| --- |
| **K&L grade outcome** |
| **Multivariate** |
|  | **OR (95% CI)** | **P - value** | **Likelihood-ratio test** |
| ***Follow up*** |  |  |  |
| 12 Months | 5.2455 (1.82829,15.04974) | 0.002 |  |
| 24 Months | 7.0396 (2.38145,20.80916) | 0.000 |  |
| 36 Months | 15.97259 (4.92149,51.83871) | 0.000 |  |
| 48 Months | 21.78328 (6.47551,73.27791) | 0.000 |  |
| ***Predictors*** |  |  |  |
| sC1,2C | 0.90412 (0.81457,1.00352) | 0.058 | 0.396 |
| sC2C | 1.00721 (0.97384,1.04173) | 0.676 | 0.009 |
| sCPII | 1.00003 (0.99998,1.00008) | 0.206 | 0.226 |
| sPIIANP | 1.00198 (1.00046,1.00349) | 0.011 | 0.178 |
| sColl2-1 NO2 | 1.72176 (1.22544,2.4191) | 0.002 | 0.724 |
| sCS846 | 0.99215 (0.96965,1.01517) | 0.501 | 0.493 |
| sMMP3 | 1.00161 (0.90377,1.11003) | 0.976 | 0.982 |
| sCTXI | 0.09029 (0.00001,578.3737) | 0.591 | 0.439 |
| sCOMP | **0.94934 (0.91164,0.98861)** | **0.012** | **0.000** |
| sHA | 1.00253 (0.96802,1.03828) | 0.887 | 0.046 |
| uCTXII | 1.14977 (1.02962,1.28396) | 0.013 | 0.271 |
| uC1,2C | 0.89288 (0.25443,3.13341) | 0.860 | 0.183 |
| uNTXI | 1.00309 (0.89848,1.11988) | 0.956 | 0.302 |
| uCreatinine | 1.16887 (0.76915,1.77633) | 0.465 | 0.323 |
| Age | 4.54812 (0.91744,22.54674) | 0.064 | 0.028 |
| Race | 1.1316 (0.05652,22.65787) | 0.936 | 0.652 |
| Gender | 0.23031 (0.01323,4.00953) | 0.314 | 0.429 |
| BMI | 10.60795 (2.77042,40.61787) | 0.001 | 0.291 |

***Supplementary Table 4. Multivariate model. The association of baseline biomarkers and K&L grade. Likelihood ratio test is to test for the evidence of time interaction with the biomarkers and <0.050 is considered as significant.***