

Supplementary Table S1. Cytokines quantifications in the patients series by Knee Osteoarthritis Inflammatory Phenotypes (**KOIP**). Cells show medians and median absolute deviations (continuous) and absolute frequencies and percentages (categorical) for the 13 cytokines evaluated in plasma and synovial fluid samples of the patients' cohort. Statistical significance was assessed using a Kruskal-Wallis (continuous) or a Fisher's test for contingency tables (categorical variables). **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | | All 168 (100%) | KOIP-1 55 (32.7%) | KOIP-2 51 (30.4%) | KOIP-3 27 (16.1%) | KOIP-4 35 (20.8%) | P-value |
|----------------|-------------------------------------|----------------------------------|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|---------|
| SYNOVIAL FLUID | C-reactive protein (mg/L) | 1.23 [0.03, 9.64] | 1.52 [0.27, 6.02] | 0.78 [0.03, 4.10] | 1.61 [0.27, 9.64] | 0.98 [0.15, 4.76] | <0.0001 |
| | Tumor Necrosis Factor alpha (pg/mL) | 9.02 [1.19, 127.49] | 9.09 [1.19, 127.49] | 8.14 [2.00, 18.17] | 9.90 [2.19, 22.16] | 8.90 [1.78, 17.98] | 0.1239 |
| | Interleukin 6 (pg/mL) | 116.33 [0.11, 15683.26] | 208.03 [7.55, 15683.26] | 91.67 [0.11, 1857.83] | 222.45 [22.77, 5820.23] | 71.56 [4.01, 652.84] | 0.0012 |
| | Interleukin 8 (pg/mL) | 6.21 [0.04, 881.40] | 8.00 [0.44, 881.40] | 6.21 [0.11, 278.44] | 8.21 [0.04, 145.52] | 3.92 [0.44, 29.02] | 0.0012 |
| | Nerve Growth Factor (pg/mL) | 2.26 [0.01, 21.63] | 2.26 [0.01, 21.63] | 2.26 [0.46, 8.25] | 2.20 [0.46, 6.90] | 2.20 [0.72, 12.17] | 0.038 |
| | Calprotectin (ng/mL) | 576.06 [36.79, 5957.01] | 763.04 [60.31, 5376.84] | 599.99 [36.79, 5957.01] | 759.60 [197.72, 4129.89] | 420.07 [36.79, 2447.75] | 0.0006 |
| | Leptin (pg/mL) | 36160.71 [1928.12, 522278.22] | 54016.11 [14014.43, 522278.22] | 23126.79 [5335.19, 58808.60] | 39506.85 [1928.12, 79207.03] | 34888.07 [1928.12, 101330.36] | <0.0001 |
| | Irisin (ng/mL) | 695.95 [61.56, 3099.45] | 938.23 [315.26, 3099.45] | 422.07 [61.56, 983.08] | 701.88 [161.47, 1270.77] | 686.28 [242.12, 1527.24] | <0.0001 |
| | Adiponectin (ng/mL) | 2420.01 [300.19, 70423.60] | 1937.73 [300.19, 6721.39] | 3047.42 [689.12, 14901.06] | 3372.91 [1194.76, 70423.60] | 1501.12 [370.24, 3730.72] | <0.0001 |
| | Omentin (pg/mL) | 4292.68 [0.45, 28995.97] | 3073.42 [0.45, 9401.45] | 6648.21 [496.86, 28995.97] | 6943.02 [1081.05, 25688.53] | 2787.84 [130.78, 11575.06] | <0.0001 |
| | Osteopontin (ng/mL) | 47.95 [0.78, 3253.98] | 48.55 [6.88, 3253.98] | 46.75 [0.78, 441.11] | 103.82 [15.18, 1400.55] | 36.02 [6.88, 180.41] | 0.0013 |
| | Visfatin (ng/mL) | 2.07 [0.13, 553.81] | 2.28 [0.49, 70.61] | 1.88 [0.13, 553.81] | 2.11 [0.42, 7.53] | 1.90 [0.53, 12.96] | 0.5075 |
| | Resistin (pg/mL) | 1480.20 [32.46, 53485.59] | 1692.08 [83.70, 53485.59] | 1390.64 [52.92, 10386.82] | 1242.23 [83.70, 18547.89] | 1329.84 [32.46, 14574.82] | 0.421 |
| PLASMA | C-reactive protein (mg/L) | 4.26 [0.42, 66.38] | 6.87 [1.44, 66.38] | 2.59 [0.42, 20.38] | 6.00 [0.42, 27.13] | 2.90 [0.42, 19.50] | <0.0001 |
| | Interleukin 6 (pg/mL) | 2.01 [0.08, 51.18] | 2.28 [0.08, 42.02] | 1.55 [0.12, 51.18] | 2.45 [0.16, 8.28] | 1.27 [0.08, 11.19] | 0.0149 |
| | Interleukin 8 (pg/mL) | 3.19 [0.56, 402.21] | 3.21 [0.93, 24.91] | 3.79 [0.91, 13.13] | 3.52 [0.56, 402.21] | 2.30 [0.83, 8.22] | 0.0152 |
| | Tumor Necrosis Factor alpha (pg/mL) | 6.37 [1.77, 22.13] | 7.18 [1.77, 22.13] | 6.18 [2.94, 14.66] | 6.70 [2.59, 10.74] | 6.08 [2.63, 8.86] | 0.0997 |
| | Nerve Growth Factor (pg/mL) | 1.52 [0.22, 14.81] | 1.52 [0.40, 14.81] | 1.52 [0.22, 5.19] | 1.69 [0.40, 8.31] | 1.52 [0.44, 6.52] | 0.2699 |
| | Calprotectin (ng/mL) | 694.27 [205.01, 12307.99] | 851.11 [287.17, 6607.95] | 613.63 [205.01, 1837.92] | 800.12 [365.98, 12307.99] | 588.54 [342.92, 1291.50] | <0.0001 |
| | Leptin (pg/mL) | 36688.11 [4039.08, 173177.01] | 54392.71 [23739.58, 173177.01] | 23566.59 [4039.08, 54817.52] | 39809.19 [5017.56, 68130.76] | 35530.72 [6972.63, 78971.55] | <0.0001 |
| | Irisin (ng/mL) | 707.78 [15.67, 1181.91] | 859.25 [421.34, 1181.91] | 437.22 [15.67, 884.41] | 727.20 [234.19, 1059.97] | 726.02 [116.43, 1105.78] | <0.0001 |
| | Adiponectin (ng/mL) | 16406.09 [1450.48, 59716.25] | 11544.55 [1450.48, 52203.90] | 22357.78 [10162.63, 59716.25] | 21707.37 [7771.73, 40371.01] | 11562.39 [4997.58, 42515.20] | <0.0001 |
| | Omentin (pg/mL) | 26859.10 [40.42, 114068.21] | 22317.93 [40.42, 55037.25] | 44069.15 [2444.37, 114068.21] | 41837.49 [2444.37, 114068.21] | 22449.96 [2444.37, 68850.68] | <0.0001 |
| | Osteopontin (ng/mL) | 13.71 [3.40, 64.53] | 12.52 [3.40, 64.53] | 14.12 [4.78, 55.83] | 16.40 [4.91, 43.44] | 12.10 [5.55, 29.52] | 0.1872 |
| | Visfatin (ng/mL) | 4.01 [2.20, 12.58] | 4.02 [2.20, 12.58] | 4.23 [2.42, 8.37] | 4.01 [2.59, 6.04] | 3.74 [2.26, 6.93] | 0.281 |
| | Resistin (pg/mL) | 2115.23 [791.02, 10079.62] | 2389.10 [791.02, 8829.96] | 1891.16 [958.55, 4435.30] | 2657.56 [1045.95, 10079.62] | 1874.89 [1194.29, 3812.08] | 0.0001 |

Supplementary Table S2. Cytokines and Knee Osteoarthritis (**KOA**) outcomes evaluated in the patients series. g: parameter value for a Tukey ladder of powers transformation applied to continuous variables (when necessary) to symmetrize their distribution and make them more suitable for graphical representation and linear models for ELISA batch correction.

| Set | Variable type | Variable (units / values) | Type (transformation parameter) |
|---------------------------------------|---|---|------------------------------------|
| Cytokines | Inflammation markers - synovial fluid | C-reactive protein - synovial fluid (mg/L) | Continuous (g = 0.25) |
| | | Interleukin 6 - synovial fluid (pg/mL) | Continuous (g = 0) |
| | | Interleukin 8 - synovial fluid (pg/mL) | Continuous (g = 0) |
| | | Tumor Necrosis Factor alpha - synovial fluid (pg/mL) | Continuous (g = 0) |
| | | Nerve Growth Factor - synovial fluid (pg/mL) | Continuous (g = 0.25) |
| | | Calprotectin - synovial fluid (ng/mL) | Continuous (g = 0.25) |
| | Adipocytokines / Myokines - synovial fluid | Leptin - synovial fluid (pg/mL) | Continuous (g = 0.25) |
| | | Irisin - synovial fluid (ng/mL) | Continuous (g = 0) |
| | | Adiponectin - synovial fluid (ng/mL) | Continuous (g = -0.25) |
| | | Omentin - synovial fluid (pg/mL) | Continuous (g = 0.25) |
| | | Osteopontin - synovial fluid (ng/mL) | Continuous (g = 0) |
| | | Visfatin - synovial fluid (ng/mL) | Continuous (g = 0) |
| | Inflammation markers - plasma | Resistin - synovial fluid (pg/mL) | Continuous (g = 0) |
| | | C-reactive protein - plasma (mg/L) | Continuous (g = 0) |
| | | Interleukin 6 - plasma (pg/mL) | Continuous (g = 0) |
| | | Interleukin 8 - plasma (pg/mL) | Continuous (g = -0.25) |
| | | Tumor Necrosis Factor alpha - plasma (pg/mL) | Continuous (g = 0) |
| | | Nerve Growth Factor - plasma (pg/mL) | Continuous (g = 0.25) |
| KOA severity and progression | Radiography - baseline | Calprotectin - plasma (ng/mL) | Continuous (g = -0.50) |
| | | Leptin - plasma (pg/mL) | Continuous (g = 0.25) |
| | | Irisin - plasma (ng/mL) | Continuous (g = 0.75) |
| | Clinical severity - baseline | Adiponectin - plasma (ng/mL) | Continuous (g = 0) |
| | | Omentin - plasma (pg/mL) | Continuous (g = 0.50) |
| | | Osteopontin - plasma (ng/mL) | Continuous (g = -0.25) |
| | Ultrasound - baseline | Visfatin - plasma (ng/mL) | Continuous (g = -0.25) |
| | | Resistin - plasma (pg/mL) | Continuous (g = -0.50) |
| | | Kellgren-Lawrence radiographic grade (1-4) | Categorical - four categories |
| | Radiographic progression (2 years follow-up) | Osteophytes score (0-10) | Continuous |
| | | Joint space narrowing (0-4) | Categorical - five categories |
| | | KOOS - pain (reversed, 0-100) | Continuous |
| | | KOOS - symptoms (reversed, 0-100) | Continuous |
| | | KOOS - functional disability (reversed, 0-100) | Continuous |
| | | Joint effusion (mm) | Continuous |
| | | Synovial tissue thickness (mm) | Continuous |
| | | Kellgren-Lawrence radiographic progression (Yes / No) | Binary |
| | | Osteophytes radiographic progression (Yes / No) | Binary |
| | | Joint space narrowing radiographic progression (Yes / No) | Binary |

Supplementary Table S3. Association between cytokines and Knee Osteoarthritis (**KOA**) outcomes in the **complete female KOA patients series**. Table cells show non-parametric correlation-like measures and 95% Confidence Intervals (95%CI) between cytokines and clinical, radiographic and ultrasound severity at baseline and radiographic progression. Correlation-like measures are: Spearman correlation (continuous or ordinal outcomes) and Glass rank biserial correlation (binary outcomes). Radiographic progression according to Kellgren-Lawrence staging and joint space narrowing were treated as ordinal in these analyses. Red color indicates positive correlation, blue represents negative correlation, and color intensity expresses more extreme values of the correlation coefficients. Color intensities were saturated to 0.5 and -0.5 for positive and negative correlation, respectively. **IL-6:** Interleukin 6; **IL-8:** Interleukin 8; **TNF-alpha:** Tumor Necrosis Factor alpha; **NGF:** Nerve Growth Factor; **CRP:** C-Reactive Protein; **KOA:** Knee Osteoarthritis. **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | KOOS pain | KOOS symptoms | KOOS functional disability | Joint effusion | Synovial tissue thickness | Kellgren-Lawrence Baseline | Osteophytes Baseline | Joint space narrowing Baseline | Kellgren-Lawrence Progression | Osteophytes Progression | Joint space narrowing Progression |
|--------------------------------------|---------------------------------------|--|--|--|---------------------------------------|---------------------------------------|--|--|---|--|--|
| CRP - synovial fluid | 0.106 [-0.065, 0.273] 0.172647 | 0.055 [-0.09, 0.218] 0.480493 | 0.121 [-0.035, 0.272] 0.1183501 | 0.037 [-0.123, 0.192] 0.631780 | 0.027 [-0.142, 0.178] 0.737452 | 0.079 [-0.066, 0.229] 0.308226 | -0.015 [-0.157, 0.142] 0.848850 | 0.069 [-0.093, 0.231] 0.3730562 | 0.143 [-0.064, 0.343] 0.1718505 | 0.073 [-0.130, 0.271] 0.476703 | 0.161 [-0.039, 0.364] 0.115263 |
| CRP - plasma | 0.092 [-0.068, 0.250] 0.233347 | 0.008 [-0.163, 0.171] 0.917722 | 0.138 [-0.028, 0.297] 0.0746962 | -0.033 [-0.187, 0.126] 0.675439 | 0.003 [-0.159, 0.157] 0.974419 | 0.068 [-0.076, 0.211] 0.384565 | 0.003 [-0.151, 0.162] 0.970962 | 0.019 [-0.131, 0.186] 0.8021990 | 0.068 [-0.129, 0.283] 0.5162111 | 0.023 [-0.166, 0.218] 0.824084 | 0.032 [-0.179, 0.252] 0.755686 |
| IL-6 - synovial fluid | 0.097 [-0.053, 0.252] 0.213718 | 0.135 [-0.010, 0.280] 0.082567 | 0.125 [-0.022, 0.273] 0.1064135 | 0.193 [-0.036, 0.323] 0.012246 | 0.051 [-0.102, 0.195] 0.517584 | 0.052 [-0.102, 0.204] 0.501415 | -0.106 [-0.255, 0.051] 0.172672 | -0.015 [-0.163, 0.138] 0.8470682 | -0.018 [-0.230, 0.196] 0.8606411 | 0.162 [-0.036, 0.369] 0.117072 | 0.200 [-0.007, 0.410] 0.049446 |
| IL-6 - plasma | 0.005 [-0.154, 0.159] 0.943831 | -0.003 [-0.149, 0.151] 0.973303 | 0.036 [-0.111, 0.176] 0.6409276 | 0.038 [-0.107, 0.200] 0.622594 | -0.083 [-0.269, 0.077] 0.290938 | 0.006 [-0.157, 0.166] 0.942834 | -0.114 [-0.267, 0.052] 0.145264 | -0.017 [-0.173, 0.137] 0.8284591 | 0.056 [-0.164, 0.240] 0.5968512 | -0.228 [-0.412, -0.032] 0.026496 | -0.004 [-0.215, 0.219] 0.965771 |
| IL-8 - synovial fluid | 0.130 [-0.036, 0.286] 0.096622 | 0.196 [-0.034, 0.338] 0.011760 | 0.145 [-0.019, 0.303] 0.0636919 | 0.009 [-0.139, 0.161] 0.908944 | 0.054 [-0.094, 0.216] 0.498515 | 0.176 [-0.038, 0.313] 0.203867 | 0.089 [-0.074, 0.240] 0.256650 | 0.139 [-0.010, 0.293] 0.0760077 | 0.117 [-0.083, 0.321] 0.2662429 | 0.055 [-0.158, 0.259] 0.593650 | 0.241 [-0.053, 0.444] 0.018825 |
| IL-8 - plasma | 0.033 [-0.109, 0.192] 0.671038 | 0.060 [-0.072, 0.210] 0.442820 | 0.021 [-0.137, 0.156] 0.699391 | 0.030 [-0.131, 0.191] 0.518432 | 0.051 [-0.123, 0.213] 0.581276 | 0.043 [-0.093, 0.196] 0.578107 | 0.009 [-0.137, 0.150] 0.906812 | 0.045 [-0.104, 0.212] 0.5629462 | 0.004 [-0.186, 0.212] 0.9733046 | 0.114 [-0.087, 0.307] 0.266360 | 0.089 [-0.110, 0.258] 0.379714 |
| TNF-alpha - synovial fluid | 0.061 [-0.091, 0.233] 0.452481 | 0.064 [-0.098, 0.221] 0.425905 | 0.094 [-0.076, 0.263] 0.2471124 | 0.009 [-0.154, 0.179] 0.907790 | -0.031 [-0.192, 0.127] 0.710042 | -0.003 [-0.159, 0.162] 0.969022 | -0.078 [-0.223, 0.083] 0.337730 | -0.084 [-0.265, 0.069] 0.2958517 | 0.052 [-0.163, 0.257] 0.984160 | -0.002 [-0.209, 0.205] 0.159725 | 0.148 [-0.078, 0.355] 0.282672 |
| TNF-alpha - plasma | -0.019 [-0.180, 0.133] 0.802994 | -0.004 [-0.164, 0.162] 0.962353 | -0.026 [-0.183, 0.142] 0.3787056 | 0.080 [-0.088, 0.233] 0.302833 | 0.012 [-0.144, 0.163] 0.261137 | -0.087 [-0.241, 0.068] 0.046935 | -0.154 [-0.248, 0.065] 0.2563597 | -0.088 [-0.167, 0.233] 0.7339591 | 0.036 [-0.167, 0.233] 0.910722 | 0.101 [-0.220, 0.183] 0.3257003 | 0.101 [-0.103, 0.307] 0.325744 |
| NGF - synovial fluid | 0.048 [-0.106, 0.198] 0.545127 | 0.064 [-0.094, 0.225] 0.414522 | 0.106 [-0.051, 0.257] 0.1789914 | -0.013 [-0.175, 0.155] 0.8686187 | -0.050 [-0.216, 0.110] 0.529795 | 0.047 [-0.116, 0.196] 0.829499 | -0.017 [-0.164, 0.140] 0.9299662 | 0.007 [-0.144, 0.155] 0.426160 | -0.046 [-0.246, 0.160] 0.6589828 | 0.111 [-0.110, 0.305] 0.282672 | 0.054 [-0.151, 0.280] 0.602053 |
| NGF - plasma | -0.078 [-0.224, 0.071] 0.313855 | -0.091 [-0.246, 0.062] 0.241721 | -0.099 [-0.260, 0.047] 0.2034301 | 0.077 [-0.079, 0.211] 0.3242948 | 0.087 [-0.054, 0.224] 0.2727677 | 0.023 [-0.129, 0.174] 0.768014 | -0.027 [-0.178, 0.125] 0.727082 | 0.070 [-0.087, 0.213] 0.3653970 | -0.006 [-0.206, 0.194] 0.9567602 | -0.125 [-0.321, 0.077] 0.223902 | 0.062 [-0.127, 0.250] 0.538461 |
| Calprotectin - synovial fluid | 0.088 [-0.066, 0.247] 0.262794 | 0.142 [-0.014, 0.300] 0.070438 | 0.129 [-0.032, 0.283] 0.0989424 | 0.116 [-0.038, 0.265] 0.140374 | 0.135 [-0.031, 0.295] 0.0900812 | -0.017 [-0.163, 0.135] 0.831931 | -0.016 [-0.171, 0.146] 0.8353508 | -0.053 [-0.214, 0.109] 0.4966793 | 0.124 [-0.102, 0.325] 0.2420335 | 0.164 [-0.038, 0.375] 0.112762 | 0.164 [-0.024, 0.347] 0.113266 |
| Calprotectin - plasma | 0.050 [-0.107, 0.211] 0.519412 | -0.006 [-0.152, 0.134] 0.938829 | 0.067 [-0.086, 0.223] 0.3912433 | 0.023 [-0.135, 0.177] 0.768682 | 0.047 [-0.195, 0.102] 0.549679 | -0.002 [-0.181, 0.157] 0.984388 | -0.013 [-0.169, 0.135] 0.864959 | 0.001 [-0.158, 0.155] 0.9862902 | 0.153 [-0.062, 0.361] 0.1439470 | -0.007 [-0.185, 0.194] 0.948872 | 0.063 [-0.164, 0.279] 0.533744 |
| Leptin - synovial fluid | 0.135 [-0.013, 0.279] 0.881013 | 0.088 [-0.060, 0.242] 0.254356 | 0.225 [-0.072, 0.366] 0.0033520 | 0.090 [-0.116, 0.190] 0.245064 | 0.043 [-0.116, 0.190] 0.583333 | 0.105 [-0.175, 0.254] 0.575552 | -0.042 [-0.198, 0.096] 0.5868616 | 0.121 [-0.031, 0.275] 0.1179575 | 0.172 [-0.026, 0.383] 0.1001374 | 0.067 [-0.120, 0.250] 0.513072 | 0.157 [-0.050, 0.361] 0.123332 |
| Leptin - plasma | 0.106 [-0.040, 0.244] 0.173251 | 0.029 [-0.115, 0.195] 0.705549 | 0.176 [-0.040, 0.317] 0.0227427 | -0.001 [-0.152, 0.159] 0.984908 | -0.040 [-0.209, 0.127] 0.611528 | 0.121 [-0.022, 0.268] 0.119502 | -0.019 [-0.178, 0.131] 0.804121 | 0.137 [-0.022, 0.288] 0.0769468 | 0.113 [-0.102, 0.327] 0.2809827 | 0.095 [-0.117, 0.311] 0.357184 | 0.046 [-0.197, 0.253] 0.649196 |
| Irisin - synovial fluid | 0.115 [-0.034, 0.268] 0.141464 | 0.105 [-0.056, 0.264] 0.177834 | 0.172 [-0.019, 0.317] 0.2027393 | 0.090 [-0.078, 0.251] 0.251526 | 0.133 [-0.029, 0.286] 0.093369 | 0.166 [-0.017, 0.306] 0.3023891 | 0.078 [-0.088, 0.213] 0.320152 | 0.150 [-0.011, 0.297] 0.0552518 | 0.076 [-0.128, 0.307] 0.4720448 | 0.001 [-0.214, 0.202] 0.989492 | 0.111 [-0.103, 0.298] 0.277614 |
| Irisin - plasma | 0.020 [-0.139, 0.189] 0.799933 | 0.008 [-0.151, 0.163] 0.918325 | 0.144 [-0.018, 0.292] 0.0635070 | -0.006 [-0.165, 0.155] 0.943256 | -0.026 [-0.183, 0.137] 0.744818 | 0.134 [-0.024, 0.283] 0.085793 | 0.001 [-0.160, 0.151] 0.986551 | 0.159 [-0.001, 0.301] 0.0407500 | 0.072 [-0.144, 0.275] 0.4913428 | 0.080 [-0.129, 0.273] 0.437514 | -0.044 [-0.230, 0.175] 0.668025 |
| Adiponectin - synovial fluid | 0.027 [-0.120, 0.169] 0.725210 | 0.050 [-0.106, 0.211] 0.517209 | -0.012 [-0.151, 0.135] 0.3735796 | 0.162 [-0.033, 0.268] 0.052435 | 0.152 [-0.033, 0.287] 0.1046330 | 0.126 [-0.145, 0.161] 0.950345 | 0.005 [-0.101, 0.207] 0.4777987 | 0.055 [-0.133, 0.078] 0.2206489 | -0.128 [-0.188, 0.282] 0.436538 | 0.080 [-0.108, 0.282] 0.436539 | 0.003 [-0.194, 0.202] 0.976359 |
| Adiponectin - plasma | -0.051 [-0.210, 0.109] 0.510409 | -0.052 [-0.206, 0.108] 0.505660 | -0.079 [-0.239, 0.083] 0.3085893 | -0.012 [-0.217, 0.105] 0.882101 | -0.055 [-0.217, 0.105] 0.489390 | -0.084 [-0.278, 0.084] 0.278785 | 0.082 [-0.289, 0.244] 0.289479 | 0.072 [-0.355, 0.291] 0.3552915 | -0.217 [-0.414, 0.161] 0.0382159 | -0.042 [-0.261, 0.166] 0.679950 | -0.160 [-0.360, 0.035] 0.114326 |
| Omentin - synovial fluid | 0.042 [-0.117, 0.205] 0.587873 | 0.095 [-0.076, 0.246] 0.225457 | -0.003 [-0.167, 0.165] 0.9726616 | 0.126 [-0.029, 0.195] 0.0645883 | 0.037 [-0.164, 0.160] 0.958346 | 0.004 [-0.164, 0.160] 0.586035 | -0.043 [-0.204, 0.118] 0.5916123 | -0.042 [-0.194, 0.195] 0.9415448 | -0.008 [-0.207, 0.202] 0.9415448 | 0.017 [-0.210, 0.238] 0.869613 | 0.056 [-0.148, 0.265] 0.584155 |
| Omentin - plasma | -0.096 [-0.238, 0.055] 0.214799 | -0.071 [-0.233, 0.093] 0.2360105 | -0.105 [-0.250, 0.051] 0.1764601 | -0.037 [-0.183, 0.105] 0.634172 | 0.019 [-0.143, 0.190] 0.805377 | 0.143 [-0.011, 0.296] 0.064701 | 0.112 [-0.151, 0.271] 0.151278 | 0.078 [-0.079, 0.232] 0.3179424 | -0.222 [-0.429, -0.009] 0.0338698 | -0.006 [-0.232, 0.214] 0.952276 | -0.187 [-0.387, 0.027] 0.065546 |
| Osteopontin - synovial fluid | 0.193 [-0.050, 0.338] 0.012093 | 0.096 [-0.047, 0.243] 0.217753 | 0.163 [-0.015, 0.304] 0.0349961 | 0.107 [-0.043, 0.254] 0.168054 | -0.087 [-0.231, 0.058] 0.267754 | 0.089 [-0.214, 0.086] 0.4954547 | -0.053 [-0.208, 0.115] 0.533669 | -0.048 [-0.221, 0.078] 0.3493345 | 0.055 [-0.156, 0.263] 0.6000368 | 0.055 [-0.303, 0.095] 0.331758 | 0.174 [-0.031, 0.377] 0.086380 |
| Osteopontin - plasma | 0.119 [-0.042, 0.277] 0.125627 | 0.046 [-0.097, 0.207] 0.555586 | 0.132 [-0.043, 0.277] 0.0875631 | 0.003 [-0.143, 0.158] 0.965672 | -0.038 [-0.188, 0.110] 0.631939 | 0.119 [-0.029, 0.278] 0.124017 | 0.152 [-0.006, 0.303] 0.050165 | 0.147 [-0.007, 0.301] 0.0569692 | -0.155 [-0.351, 0.061] 0.1391145 | -0.154 [-0.359, 0.051] 0.133487 | 0.078 [-0.117, 0.294] 0.441023 |
| Vifatini - synovial fluid | 0.071 [-0.085, 0.233] 0.361786 | 0.088 [-0.062, 0.247] 0.258380 | 0.092 [-0.061, 0.233] 0.2352516 | 0.036 [-0.119, 0.197] 0.645365 | 0.089 [-0.061, 0.259] 0.255956 | 0.151 [-0.001, 0.295] 0.0506360 | 0.092 [-0.061, 0.243] 0.239091 | 0.136 [-0.006, 0.270] 0.0794944 | -0.019 [-0.235, 0.185] 0.8583501 | 0.069 [-0.130, 0.275] 0.499395 | 0.089 [-0.117, 0.298] 0.382014 |
| Vifatini - plasma | 0.025 [-0.123, 0.170] 0.749365 | -0.012 [-0.157, 0.150] 0.879680 | 0.038 [-0.145, 0.159] 0.934747 | 0.006 [-0.145, 0.159] 0.271426 | 0.087 [-0.152, 0.151] 0.968803 | -0.003 [-0.152, 0.099] 0.513867 | -0.051 [-0.198, 0.106] 0.5941026 | -0.041 [-0.213, 0.072] 0.3236576 | -0.125 [-0.313, 0.097] 0.300889 | -0.106 [-0.364, 0.019] 0.103136 | -0.166 [-0.364, 0.019] 0.0103136 |
| Resistin - synovial fluid | 0.094 [-0.059, 0.252] 0.227636 | 0.049 [-0.106, 0.207] 0.527293 | 0.182 [-0.036, 0.324] 0.0182285 | -0.066 [-0.218, 0.093] 0.391851 | -0.106 [-0.255, 0.051] 0.176498 | -0.026 [-0.179, 0.120] 0.741997 | 0.003 [-0.155, 0.163] 0.972354 | -0.023 [-0.169, 0.130] 0.7654880 | -0.149 [-0.330, 0.053] 0.1564857 | 0.1 | |

Supplementary Table S4. Association between cytokines and Knee Osteoarthritis (**KOA**) outcomes in the **KOIP-1 group**. Table cells show non-parametric correlation-like measures and 95% Confidence Intervals (95%CI) between cytokines and clinical, radiographic and ultrasound severity at baseline and radiographic progression. Correlation-like measures are: Spearman correlation (continuous or ordinal outcomes) and Glass rank biserial correlation (binary outcomes). Radiographic progression according to Kellgren-Lawrence staging and joint space narrowing were treated as ordinal in these analyses. Red color indicates positive correlation, blue represents negative correlation, and color intensity expresses more extreme values of the correlation coefficients. Color intensities were saturated to 0.5 and -0.5 for positive and negative correlation, respectively. **IL-6:** Interleukin 6; **IL-8:** Interleukin 8; **TNF-alpha:** Tumor Necrosis Factor alpha; **NGF:** Nerve Growth Factor; **CRP:** C-Reactive Protein; **KOA:** Knee Osteoarthritis. **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | KOOS pain | KOOS symptoms | KOOS functional disability | Joint effusion | Synovial tissue thickness | Kellgren-Lawrence Baseline | Osteophytes Baseline | Joint space narrowing Baseline | Kellgren-Lawrence Progression | Osteophytes Progression | Joint space narrowing Progression |
|--------------------------------------|--|---------------------------------------|--|---------------------------------------|--|---------------------------------------|--|---|--|--|---------------------------------------|
| CRP - synovial fluid | 0.057 [-0.212, 0.338] 0.680475 | 0.169 [-0.099, 0.453] 0.217488 | 0.037 [0.265, 0.324] 0.7880936 | 0.088 [-0.192, 0.374] 0.524307 | 0.008 [0.287, 0.289] 0.953269 | [0.201, 0.316] 0.685440 | 0.245 [-0.037, 0.482] 0.071720 | -0.057 [0.312, 0.225] 0.6782933 | 0.322 [-0.023, 0.620] 0.623661 | -0.033 [0.519, 0.439] 0.8768724 | 0.013 [-0.318, 0.364] 0.936124 |
| CRP - plasma | 0.018 [-0.254, 0.283] 0.8941563 | 0.084 [0.203, 0.368] 0.541826 | 0.092 [-0.198, 0.374] 0.5044741 | -0.152 [0.440, 0.135] 0.268012 | -0.096 [0.350, 0.169] 0.491954 | -0.014 [0.271, 0.234] 0.0919239 | 0.079 [0.193, 0.325] 0.565797 | -0.169 [0.399, 0.071] 0.2181278 | 0.025 [0.318, 0.360] 0.8860196 | 0.089 [0.311, 0.508] 0.6795200 | -0.110 [0.449, 0.226] 0.508546 |
| IL-6 - synovial fluid | -0.122 [0.364, 0.153] 0.3763797 | 0.060 [-0.194, 0.328] 0.661141 | -0.041 [0.304, 0.222] 0.7636312 | 0.031 [-0.232, 0.289] 0.821858 | -0.139 [0.378, 0.135] 0.316026 | 0.117 [0.153, 0.368] 0.393270 | -0.165 [0.429, 0.095] 0.228933 | 0.027 [0.263, 0.297] 0.8453379 | 0.029 [0.319, 0.373] 0.8686328 | 0.033 [0.378, 0.467] 0.8768849 | 0.304 [0.202, 0.603] 0.068297 |
| IL-6 - plasma | 0.007 [-0.293, 0.277] 0.9621484 | 0.088 [0.190, 0.339] 0.521256 | 0.113 [0.164, 0.376] 0.4132549 | 0.078 [-0.215, 0.333] 0.573820 | 0.072 [-0.225, 0.328] 0.604131 | 0.108 [0.167, 0.369] 0.434161 | -0.083 [0.340, 0.206] 0.547407 | -0.052 [0.335, 0.225] 0.7068630 | 0.055 [0.292, 0.436] 0.7491395 | -0.058 [0.436, 0.333] 0.7863020 | 0.130 [0.229, 0.433] 0.434612 |
| IL-8 - synovial fluid | 0.030 [-0.266, 0.345] 0.8320551 | 0.314 [0.058, 0.556] 0.202651 | 0.199 [0.110, 0.466] 0.1488220 | 0.082 [0.234, 0.372] 0.5533226 | 0.145 [0.142, 0.404] 0.301267 | 0.103 [0.166, 0.345] 0.459411 | -0.081 [0.353, 0.179] 0.558649 | 0.093 [0.167, 0.344] 0.5039524 | -0.101 [0.429, 0.255] 0.5616879 | -0.006 [0.442, 0.469] 0.7989212 | 0.049 [0.270, 0.389] 0.771999 |
| IL-8 - plasma | 0.038 [-0.235, 0.309] 0.7821161 | 0.192 [0.064, 0.444] 0.160820 | 0.164 [0.102, 0.424] 0.2326517 | 0.058 [0.215, 0.346] 0.675558 | -0.121 [0.434, 0.170] 0.383941 | 0.165 [0.109, 0.434] 0.228820 | 0.028 [0.242, 0.296] 0.8470407 | 0.065 [0.200, 0.303] 0.6360916 | -0.112 [0.459, 0.268] 0.5153208 | 0.225 [0.186, 0.544] 0.2956847 | 0.164 [0.167, 0.465] 0.326266 |
| TNF-alpha - synovial fluid | 0.028 [-0.272, 0.286] 0.8418532 | 0.124 [0.164, 0.388] 0.370218 | 0.155 [0.139, 0.421] 0.646216 | 0.107 [0.151, 0.356] 0.439213 | -0.067 [0.339, 0.213] 0.634666 | 0.103 [0.173, 0.350] 0.702761 | -0.053 [0.340, 0.229] 0.9470219 | 0.009 [0.273, 0.303] 0.560, 0.119 | -0.236 [0.342, 0.400] 0.9683949 | 0.009 [0.180, 0.485] 0.1777694 | 0.154 [0.180, 0.485] 0.362595 |
| TNF-alpha - plasma | 0.019 [-0.251, 0.305] 0.8908295 | 0.070 [0.216, 0.370] 0.6096631 | 0.028 [0.285, 0.291] 0.8368486 | 0.028 [0.072, 0.480] 0.126986 | 0.032 [0.226, 0.288] 0.3090, 0.19534 | 0.038 [0.321, 0.269] 0.7808635 | -0.019 [0.293, 0.279] 0.9884097 | 0.002 [0.293, 0.279] 0.6197631 | 0.086 [0.300, 0.615] 0.4086700 | 0.178 [0.200, 0.455] 0.127874 | 0.254 [0.044, 0.575] 0.127874 |
| NGF - synovial fluid | 0.028 [-0.274, 0.309] 0.8436937 | 0.012 [0.287, 0.304] 0.929738 | 0.072 [0.227, 0.369] 0.6101472 | 0.033 [0.201, 0.295] 0.814862 | 0.033 [0.248, 0.306] 0.816196 | -0.001 [0.303, 0.279] 0.994785 | 0.060 [0.194, 0.323] 0.670694 | -0.121 [0.385, 0.170] 0.3861629 | -0.139 [0.471, 0.219] 0.4262136 | 0.462 [0.036, 0.843] 0.0311171 | 0.040 [0.304, 0.375] 0.812906 |
| NGF - plasma | -0.211 [-0.445, 0.022] 0.1257097 | -0.158 [0.417, 0.145] 0.2536636 | 0.181 [0.469, 0.099] 0.1898111 | 0.188 [0.087, 0.414] 0.173928 | 0.129 [0.136, 0.403] 0.357335 | 0.148 [0.128, 0.413] 0.286865 | -0.125 [0.376, 0.150] 0.306, 0.150 | 0.141 [0.135, 0.376] 0.3107590 | -0.250 [0.567, 0.084] 0.1492430 | -0.262 [0.683, 0.197] 0.2218059 | -0.033 [0.370, 0.310] 0.843722 |
| Calprotectin - synovial fluid | 0.167 [-0.104, 0.427] 0.2374352 | 0.222 [0.061, 0.463] 0.113881 | 0.136 [0.160, 0.404] 0.3347281 | -0.033 [0.298, 0.222] 0.8194296 | 0.196 [0.090, 0.462] 0.1669779 | -0.009 [0.286, 0.268] 0.951929 | -0.047 [0.310, 0.204] 0.741342 | -0.021 [0.295, 0.242] 0.8831276 | -0.039 [0.430, 0.339] 0.8265385 | -0.147 [0.569, 0.297] 0.4975183 | -0.002 [0.365, 0.325] 0.991202 |
| Calprotectin - plasma | -0.013 [-0.293, 0.283] 0.9252163 | 0.197 [0.083, 0.469] 0.148790 | 0.133 [0.160, 0.428] 0.3312908 | -0.048 [0.317, 0.215] 0.725346 | -0.075 [0.336, 0.213] 0.588316 | 0.070 [0.177, 0.300] 0.609572 | 0.090 [0.182, 0.334] 0.5151535 | 0.005 [0.244, 0.278] 0.9729602 | 0.181 [0.420, 0.259] 0.2948672 | 0.130 [0.211, 0.512] 0.4346242 | 0.130 [0.190, 0.452] 0.4346242 |
| Leptin - synovial fluid | -0.076 [-0.386, 0.223] 0.5800336 | -0.102 [0.393, 0.231] 0.457513 | -0.024 [0.325, 0.263] 0.8604284 | -0.159 [0.426, 0.116] 0.245836 | -0.152 [0.422, 0.119] 0.272638 | 0.154 [0.120, 0.419] 0.894325 | -0.018 [0.318, 0.236] 0.261320 | 0.165 [0.106, 0.426] 0.2289894 | 0.017 [0.313, 0.347] 0.9209499 | 0.483 [0.077, 0.841] 0.0246829 | -0.043 [0.396, 0.297] 0.794529 |
| Leptin - plasma | -0.110 [-0.404, 0.180] 0.4294761 | -0.077 [0.374, 0.219] 0.579981 | 0.015 [0.252, 0.288] 0.9156144 | -0.158 [0.413, 0.125] 0.2535359 | -0.258 [0.462, -0.022] 0.061894 | 0.072 [0.186, 0.326] 0.604795 | -0.025 [0.303, 0.244] 0.7859740 | 0.100 [0.166, 0.204] 0.4703454 | -0.044 [0.364, 0.341] 0.8023873 | 0.402 [0.031, 0.762] 0.0625738 | -0.061 [0.385, 0.294] 0.717928 |
| Irisin - synovial fluid | -0.086 [-0.335, 0.188] 0.5414083 | -0.032 [0.318, 0.259] 0.822072 | -0.011 [0.263, 0.236] 0.9387161 | -0.077 [0.365, 0.207] 0.582651 | 0.103 [0.178, 0.387] 0.468699 | 0.268 [0.007, 0.532] 0.052470 | 0.182 [0.124, 0.435] 0.192753 | 0.231 [0.074, 0.515] 0.0935657 | -0.433 [0.717, -0.112] 0.0141964 | 0.158 [0.328, 0.578] 0.4652117 | -0.364 [0.076, -0.011] 0.032935 |
| Irisin - plasma | -0.164 [-0.440, 0.115] 0.2365206 | -0.090 [0.354, 0.182] 0.517385 | -0.098 [0.375, 0.191] 0.4823262 | -0.016 [0.299, 0.275] 0.907568 | 0.055 [0.194, 0.307] 0.697348 | 0.198 [0.078, 0.462] 0.151702 | 0.094 [0.189, 0.355] 0.500657 | 0.242 [0.030, 0.315] 0.0777908 | -0.038 [0.424, 0.320] 0.8287400 | 0.483 [0.205, 0.743] 0.1145426 | -0.238 [0.346, 0.512] 0.157131 |
| Adiponectin - synovial fluid | -0.115 [-0.390, 0.148] 0.4034340 | -0.007 [0.295, 0.287] 0.961767 | -0.055 [0.320, 0.223] 0.6902647 | -0.022 [0.293, 0.272] 0.871413 | 0.009 [0.196, 0.349] 0.947383 | 0.080 [0.331, 0.250] 0.860097 | -0.024 [0.217, 0.287] 0.6660781 | 0.059 [0.217, 0.287] 0.6667851 | -0.139 [0.484, 0.188] 0.4208492 | 0.608 [0.326, 0.844] 0.0046935 | 0.070 [0.268, 0.405] 0.673965 |
| Adiponectin - plasma | -0.251 [-0.482, 0.004] 0.0641210 | -0.163 [0.430, 0.110] 0.234760 | -0.197 [0.439, 0.074] 0.2344749 | -0.163 [0.424, 0.111] 0.211267 | -0.173 [0.430, 0.116] 0.0874643 | 0.022 [0.249, 0.287] 0.879067 | 0.021 [0.243, 0.280] 0.3070675 | 0.140 [0.132, 0.404] 0.5011969 | -0.116 [0.427, 0.231] 0.5011969 | 0.311 [0.101, 0.705] 0.1482014 | 0.167 [0.158, 0.498] 0.316503 |
| Omentin - synovial fluid | -0.265 [-0.501, 0.001] 0.0503973 | -0.064 [0.341, 0.218] 0.643342 | -0.218 [0.462, 0.037] 0.1100286 | -0.145 [0.425, 0.406] 0.289727 | -0.030 [0.257, 0.242] 0.805986 | 0.034 [0.279, 0.280] 0.984379 | -0.003 [0.267, 0.317] 0.7237695 | 0.049 [0.149, 0.531] 0.0440146 | 0.208 [0.089, 0.735] 0.0440146 | 0.433 [0.089, 0.735] 0.0440146 | 0.435 [0.144, 0.723] 0.09020205 |
| Omentin - plasma | -0.233 [-0.484, 0.053] 0.0866440 | -0.060 [0.327, 0.224] 0.665615 | -0.106 [0.371, 0.172] 0.44045165 | -0.072 [0.337, 0.169] 0.601943 | -0.095 [0.061, 0.555] 0.4926416 | 0.327 [0.061, 0.555] 0.093683 | 0.228 [0.121, 0.431] 0.794522 | 0.365 [0.146, 0.322] 0.8082729 | -0.105 [0.460, 0.216] 0.5442162 | 0.506 [0.421, 0.216] 0.0187931 | -0.043 [0.400, 0.310] 0.7794529 |
| Osteopontin - synovial fluid | 0.097 [-0.183, 0.352] 0.4815616 | 0.116 [0.149, 0.364] 0.398835 | 0.109 [0.146, 0.350] 0.4303205 | -0.013 [0.309, 0.266] 0.922385 | -0.092 [0.348, 0.166] 0.506222 | -0.149 [0.411, 0.118] 0.278336 | -0.120 [0.379, 0.161] 0.381101 | -0.168 [0.435, 0.133] 0.2193841 | 0.042 [0.314, 0.377] 0.8082729 | 0.211 [0.209, 0.599] 0.3262690 | 0.244 [0.092, 0.582] 0.143416 |
| Osteopontin - plasma | 0.134 [-0.176, 0.392] 0.3281943 | -0.067 [0.318, 0.212] 0.900667 | 0.078 [0.216, 0.367] 0.5728687 | -0.181 [0.424, 0.085] 0.187217 | -0.130 [0.377, 0.130] 0.348827 | -0.047 [0.341, 0.226] 0.662141 | -0.060 [0.311, 0.174] 0.9978536 | 0.000 [0.272, 0.264] 0.662141 | -0.322 [0.574, 0.380] 0.0623984 | -0.117 [0.289, 0.364] 0.5876686 | 0.047 [0.289, 0.364] 0.779119 |
| Vistatin - synovial fluid | -0.073 [-0.443, 0.215] 0.5950288 | -0.009 [0.292, 0.271] 0.949144 | -0.009 [0.277, 0.292] 0.9484762 | -0.075 [0.324, 0.214] 0.5844413 | 0.147 [0.102, 0.420] 0.287949 | 0.158 [0.121, 0.431] 0.248905 | 0.036 [0.219, 0.294] 0.794522 | 0.088 [0.146, 0.322] 0.5216160 | -0.149 [0.489, 0.189] 0.3897290 | -0.058 [0.456, 0.378] 0.7862967 | 0.065 [0.303, 0.407] 0.696040 |
| Vistatin - plasma | 0.084 [-0.197, 0.379] 0.5431717 | 0.017 [0.283, 0.318] 0.900667 | -0.038 [0.312, 0.284] 0.7831750 | -0.150 [0.357, 0.126] 0.797978 | 0.036 [0.256, 0.309] 0.662137 | 0.060 [0.219, 0.334] 0.894325 | 0.018 [0.221, 0.278] 0.8820434 | -0.020 [0.299, 0.231] 0.7491395 | -0.055 [0.396, 0.294] 0.5876590 | -0.117 [0.523, 0.274] 0.333, 0.309 | -0.013 [0.333, 0.309] 0.936129 |
| Resistin - synovial fluid | -0.035 [-0.283, 0.225] 0.7977216 | -0.069 [0.326, 0.188] 0.615256 | 0.066 [0.220, 0.316] 0.6297848 | -0.060 [0.341, 0.243] 0.662958 | -0.095 [0.225, 0.328] 0.637103 | -0.036 [0.323, 0.249] 0.791860 | 0.023 [0.243, 0.295] 0.869784 | -0.066 [0.35 | | | |

Supplementary Table S5. Association between cytokines and Knee Osteoarthritis (**KOA**) outcomes in the **KOIP-2 group**. Table cells show non-parametric correlation-like measures and 95% Confidence Intervals (95%CI) between cytokines and clinical, radiographic and ultrasound severity at baseline and radiographic progression. Correlation-like measures are: Spearman correlation (continuous or ordinal outcomes) and Glass rank biserial correlation (binary outcomes). Radiographic progression according to Kellgren-Lawrence staging and joint space narrowing were treated as ordinal in these analyses. Red color indicates positive correlation, blue represents negative correlation, and color intensity expresses more extreme values of the correlation coefficients. Color intensities were saturated to 0.5 and -0.5 for positive and negative correlation, respectively. **IL-6:** Interleukin 6; **IL-8:** Interleukin 8; **TNF-alpha:** Tumor Necrosis Factor alpha; **NGF:** Nerve Growth Factor; **CRP:** C-Reactive Protein; **KOA:** Knee Osteoarthritis. **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | KOOS pain | KOOS symptoms | KOOS functional disability | Joint effusion | Synovial tissue thickness | Kellgren-Lawrence Baseline | Osteophytes Baseline | Joint space narrowing Baseline | Kellgren-Lawrence Progression | Osteophytes Progression | Joint space narrowing Progression |
|--------------------------------------|--|--------------------------------------|--------------------------------------|---------------------------------------|--|--------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|--|---------------------------------------|
| CRP - synovial fluid | -0.192 [0.472, 0.122 0.181226] | 0.006 [0.320, 0.331 0.968923] | -0.145 [0.422, 0.148 0.315037] | 0.022 [0.286, 0.329 0.878007] | 0.175 [0.123, 0.454 0.233185] | 0.068 [0.261, 0.370 0.636945] | -0.065 [0.337, 0.217 0.651815] | 0.109 [0.219, 0.412 0.449363] | 0.046 [0.457, 0.503 0.834243] | 0.025 [0.326, 0.405 0.8967512] | 0.268 [0.243, 0.731 0.2203176] |
| CRP - plasma | -0.005 [-0.268, 0.258 0.972142] | 0.028 [0.273, 0.308 0.845896] | 0.005 [0.273, 0.274 0.973821] | -0.107 [0.399, 0.172 0.456404] | 0.011 [0.291, 0.300 0.941143] | -0.083 [0.347, 0.198 0.563137] | 0.020 [0.304, 0.322 0.891247] | -0.020 [0.347, 0.283 0.886972] | 0.187 [0.346, 0.641 0.390714] | -0.195 [0.543, 0.150 0.3015557] | 0.082 [0.404, 0.523 0.6950003] |
| IL-6 - synovial fluid | 0.068 [0.230, 0.373 0.637689] | 0.176 [0.108, 0.467 0.222709] | 0.139 [0.188, 0.437 0.335177] | 0.101 [0.198, 0.394 0.484166] | 0.190 [0.083, 0.437 0.194681] | -0.080 [0.367, 0.216 0.581477] | -0.089 [0.394, 0.218 0.540704] | -0.102 [0.390, 0.211 0.480385] | 0.138 [0.683, 0.171 0.256604] | 0.138 [0.468, 0.364 0.4752297] | -0.061 [0.7737450 0.2203176] |
| IL-6 - plasma | 0.033 [-0.288, 0.330 0.820779] | 0.153 [0.171, 0.426 0.283983] | 0.083 [0.196, 0.360 0.564384] | 0.108 [0.193, 0.377 0.448654] | -0.118 [0.396, 0.148 0.418774] | -0.103 [0.398, 0.198 0.471828] | -0.076 [0.347, 0.197 0.597763] | -0.116 [0.414, 0.182 0.417632] | 0.098 [0.335, 0.528 0.651887] | -0.305 [0.790, -0.150 0.0075425] | -0.138 [0.590, 0.333 0.5103045] |
| IL-8 - synovial fluid | 0.084 [0.213, 0.360 0.564403] | 0.068 [0.235, 0.348 0.640122] | 0.096 [0.512996 0.042035] | -0.292 [0.349, -0.201 0.445407] | -0.114 [0.374, 0.142 0.812890] | 0.035 [0.250, 0.339 0.617389] | 0.160 [0.153, 0.454 0.273189] | 0.069 [0.212, 0.330 0.637051] | 0.347 [0.150, 0.743 0.114358] | -0.327 [0.655, 0.017 0.0876540] | 0.306 [0.126, 0.683 0.1478229] |
| IL-8 - plasma | 0.062 [0.183, 0.319 0.667046] | 0.084 [0.212, 0.253 0.558917] | 0.001 [0.286, 0.280 0.399320] | 0.157 [0.129, 0.431 0.473627] | 0.105 [0.164, 0.377 0.447476] | -0.109 [0.356, 0.140 0.217639] | -0.176 [0.439, 0.117 0.310341] | -0.145 [0.403, 0.143 0.158203] | -0.308 [0.619, 0.014 0.0554900] | 0.362 [0.018, 0.710 0.6141905] | -0.106 [0.488, 0.304 0.1619045] |
| TNF-alpha - synovial fluid | 0.186 [-0.110, 0.426 0.216900] | 0.149 [0.140, 0.396 0.322893] | 0.234 [0.057, 0.504 0.116843] | -0.095 [0.393, 0.243 0.528795] | 0.053 [0.225, 0.316 0.732315] | 0.019 [0.297, 0.312 0.902523] | -0.003 [0.305, 0.301 0.983231] | -0.186 [0.429, 0.108 0.215943] | 0.153 [NA, NA 0.508723] | -0.159 [0.548, 0.252 0.4594471] | 0.062 [0.419, 0.518 0.7722214] |
| TNF-alpha - plasma | -0.207 [0.480, 0.070 0.144965] | -0.140 [0.413, 0.151 0.327216] | -0.167 [0.451, 0.111 0.241859] | -0.141 [0.373, 0.118 0.642354] | -0.068 [0.369, 0.234 0.567212] | -0.082 [0.371, 0.214 0.451310] | -0.108 [0.369, 0.150 0.516493] | -0.093 [0.412, 0.229 0.550866] | -0.130 [0.560, 0.181 0.3134999] | -0.190 [0.724, 0.219 0.1976563] | -0.271 [0.249, 0.347 0.1976563] |
| NGF - synovial fluid | 0.113 [-0.174, 0.409 0.446692] | 0.127 [0.162, 0.396 0.390305] | 0.057 [0.248, 0.328 0.698342] | -0.029 [0.377, 0.330 0.844729] | -0.329 [0.566, -0.033 0.0258103] | -0.038 [0.316, 0.256 0.798773] | -0.167 [0.433, 0.136 0.256092] | -0.024 [0.301, 0.231 0.871516] | -0.201 [0.562, 0.185 0.359345] | -0.241 [0.613, 0.141 0.2093673] | -0.083 [0.467, 0.283 0.7044738] |
| NGF - plasma | 0.036 [-0.238, 0.304 0.800945] | 0.095 [0.190, 0.364 0.507137] | -0.043 [0.322, 0.275 0.763257] | -0.063 [0.362, 0.240 0.661225] | 0.042 [0.253, 0.327 0.772301] | -0.244 [0.499, 0.020 0.804875] | 0.035 [0.250, 0.319 0.806272] | -0.197 [0.439, 0.085 0.165288] | 0.102 [0.305, 0.494 0.640619] | -0.100 [0.455, 0.282 0.5956756] | 0.124 [0.295, 0.533 0.5553505] |
| Calprotectin - synovial fluid | 0.089 [-0.198, 0.372 0.537463] | 0.132 [0.175, 0.446 0.360214] | 0.083 [0.227, 0.376 0.568887] | 0.009 [0.266, 0.309 0.952726] | 0.103 [0.210, 0.403 0.486637] | -0.206 [0.472, 0.090 0.150516] | -0.028 [0.332, 0.282 0.844953] | -0.141 [0.431, 0.134 0.329142] | 0.359 [0.145, 0.767 0.100583] | 0.113 [0.242, 0.469 0.5510842] | 0.321 [0.118, 0.707 0.1275836] |
| Calprotectin - plasma | -0.054 [-0.359, 0.232 0.704307] | -0.048 [0.333, 0.230 0.348779] | -0.134 [0.376, 0.165 0.479215] | 0.101 [0.164, 0.359 0.443180] | -0.112 [0.397, 0.182 0.070478] | -0.255 [0.544, 0.050 0.525238] | -0.092 [0.357, 0.212 0.047015] | -0.279 [0.623, 0.511 0.737926] | -0.073 [0.638, 0.037 0.0963037] | -0.314 [0.790, 0.193 0.1040365] | -0.341 [0.295, 0.533 0.5553065] |
| Leptin - synovial fluid | -0.112 [-0.377, 0.161 0.432544] | -0.068 [0.326, 0.214 0.636232] | -0.074 [0.350, 0.187 0.607623] | -0.184 [0.443, 0.084 0.196678] | -0.054 [0.363, 0.234 0.711029] | 0.042 [0.243, 0.322 0.768883] | -0.125 [0.379, 0.138 0.383268] | -0.010 [0.280, 0.239 0.944671] | -0.333 [0.727, 0.125 0.126617] | -0.181 [0.534, 0.174 0.3382929] | -0.571 [0.361, 0.200 0.0685948] |
| Leptin - plasma | -0.076 [-0.322, 0.227 0.595469] | 0.024 [0.270, 0.318 0.8686906] | 0.023 [0.270, 0.288 0.874493] | -0.201 [0.472, 0.078 0.157256] | -0.103 [0.348, 0.181 0.480895] | -0.047 [0.333, 0.246 0.743424] | -0.088 [0.380, 0.216 0.540099] | -0.073 [0.358, 0.199 0.611502] | -0.187 [0.660, 0.313 0.390680] | -0.429 [0.536, 0.220 0.4421415] | -0.429 [0.835, 0.059 0.0408989] |
| Irisin - synovial fluid | 0.105 [-0.158, 0.374 0.469843] | 0.196 [0.095, 0.454 0.172175] | 0.142 [0.146, 0.406 0.446436] | -0.110 [0.210, 0.267 0.841649] | 0.030 [0.364, 0.162 0.496944] | -0.098 [0.364, 0.162 0.367196] | -0.130 [0.412, 0.167 0.204229] | -0.183 [0.378, 0.155 0.444781] | -0.196 [0.519, 0.222 0.3507954] | -0.177 [0.651, 0.129 0.2874759] | -0.224 [0.651, 0.129 0.2874759] |
| Irisin - plasma | -0.089 [-0.369, 0.196 0.533790] | 0.021 [0.281, 0.290 0.883898] | 0.067 [0.261, 0.369 0.638315] | -0.238 [0.532, 0.054 0.092753] | -0.091 [0.369, 0.210 0.530422] | -0.147 [0.413, 0.144 0.302119] | -0.186 [0.458, 0.096 0.190628] | -0.109 [0.378, 0.155 0.444781] | -0.137 [0.544, 0.300 0.531605] | -0.062 [0.432, 0.301 0.7432374] | -0.435 [0.829, 0.016 0.0382268] |
| Adiponectin - synovial fluid | 0.113 [-0.131, 0.374 0.429112] | 0.210 [0.095, 0.450 0.138468] | 0.132 [0.128, 0.390 0.355233] | 0.231 [0.082, 0.508 0.102952] | 0.314 [0.018, 0.573 0.028266] | 0.011 [0.258, 0.289 0.941083] | 0.086 [0.546396 0.749713] | -0.046 [0.321, 0.247 0.988393] | -0.003 [0.494, 0.456 0.1068209] | -0.035 [0.629, 0.028 0.2656, 0.600 0.3701570] | 0.188 [0.265, 0.560 0.3701570] |
| Adiponectin - plasma | 0.111 [-0.156, 0.378 0.439477] | 0.000 [0.315, 0.294 0.998736] | 0.079 [0.185, 0.344 0.582468] | 0.149 [0.126, 0.433 0.296014] | -0.026 [0.319, 0.291 0.859540] | -0.055 [0.310, 0.240 0.700631] | 0.186 [0.096, 0.453 0.190198] | -0.099 [0.384, 0.210 0.488163] | 0.333 [0.014, 0.645 0.126604] | -0.093 [0.506, 0.307 0.6231517] | 0.424 [0.124, 0.701 0.0437430] |
| Omentin - synovial fluid | 0.277 [-0.013, 0.550 0.048755] | 0.265 [0.033, 0.515 0.059832] | 0.228 [0.093, 0.527 0.107389] | 0.152 [0.166, 0.461 0.287255] | 0.106 [0.177, 0.414 0.470166] | -0.095 [0.383, 0.178 0.506556] | -0.022 [0.325, 0.268 0.880286] | -0.114 [0.388, 0.195 0.426190] | 0.162 [0.371, 0.682 0.458123] | -0.357 [0.687, 0.024 0.0583897] | 0.147 [0.340, 0.583 0.4838397] |
| Omentin - plasma | 0.171 [-0.113, 0.462 0.230413] | 0.150 [0.141, 0.416 0.293784] | 0.136 [0.145, 0.436 0.340476] | 0.096 [0.168, 0.363 0.501140] | 0.083 [0.228, 0.395 0.570988] | -0.086 [0.348, 0.198 0.546971] | 0.196 [0.412, 0.163 0.168473] | -0.134 [0.321, 0.247 0.348884] | 0.133 [0.412, 0.163 0.541179] | 0.103 [0.260, 0.528 0.5537400] | 0.283 [0.283, 0.482 0.6240523] |
| Osteopontin - synovial fluid | 0.183 [-0.102, 0.471 0.198656] | 0.064 [0.199, 0.346 0.654993] | 0.228 [0.041, 0.469 0.107057] | 0.014 [0.256, 0.302 0.923357] | -0.236 [0.476, 0.041 0.103114] | -0.210 [0.475, 0.076 0.138604] | -0.014 [0.305, 0.293 0.922460] | -0.104 [0.417, 0.198 0.465656] | 0.121 [0.344, 0.613 0.580254] | -0.371 [0.691, -0.021 0.0492861] | 0.029 [0.403, 0.509 0.8885989] |
| Osteopontin - plasma | 0.098 [-0.207, 0.379 0.494813] | 0.167 [0.110, 0.416 0.240444] | 0.169 [0.097, 0.410 0.237094] | 0.171 [0.083, 0.439 0.229920] | -0.085 [0.382, 0.228 0.561204] | 0.178 [0.114, 0.451 0.078544] | 0.249 [0.048, 0.501 0.166936] | 0.197 [0.091, 0.438 0.531605] | -0.137 [0.518, 0.289 0.531605] | -0.395 [0.738, -0.019 0.0364919] | -0.224 [0.590, 0.143 0.2872323] |
| Visfatin - synovial fluid | 0.089 [-0.179, 0.359 0.534199] | 0.135 [0.139, 0.395 0.345943] | 0.124 [0.152, 0.386 0.385418] | 0.197 [0.104, 0.513 0.166031] | 0.137 [0.114, 0.424 0.346373] | 0.126 [0.173, 0.424 0.376532] | 0.172 [0.129, 0.445 0.227533] | 0.196 [0.170, 0.445 0.167084] | 0.162 [0.245, 0.537 0.458107] | -0.143 [0.518, 0.289 0.458107] | -0.035 [0.383, 0.174 0.4496918] |
| Visfatin - plasma | -0.252 [-0.511, -0.004 0.074890] | -0.253 [0.442, 0.121 0.073414] | -0.156 [0.407, 0.403 0.275054] | 0.154 [0.371, 0.222 0.280186] | 0.208 [0.085, 0.646 0.152450] | 0.078 [0.382, 0.228 0.588722] | 0.007 [0.048, 0.501 0.961830] | -0.065 [0.412, 0.163 0.651418] | -0.537 [0.829, -0.179 0.013948] | -0.143 [0.561, 0.302 0.4496918] | -0.035 [0.383, 0.174 0.0055618] |
| Resistin - synovial fluid | 0.152 [-0.149, 0.425 0.285498] | -0.037 [0.313, 0.210 0.795390] | 0.127 [0.143, 0.403 0.375626] | -0.077 [0.371, 0.222 0.599027] | -0.249 [0.528, 0.057 0.084067] | -0.175 [0.438, 0.118 0.218957] | -0.034 [0.299, 0.236 0.811473] | -0.093 [0.383, 0.174 0.506133] | 0.162 [0.292, 0.579 0.457790] | 0.169 [0.197, 0.522 0.3706916] | 0.241 [0.225, 0.660 0.2505229] |
| Resistin - plasma | -0.064 [-0.320, 0.222 0.653606] | -0.181 [0.461, 0.145 0.202636] | -0.100 [0.355, 0.171 0.486370] | 0.113 [0.160, 0.350 0.429731] | 0.099 [0.174, 0.363 0.496551] | -0.112 [0.392, 0.191 0.435977] | -0.199 [0.482, | | | | |

Supplementary Table S6. Association between cytokines and Knee Osteoarthritis (**KOA**) outcomes in the **KOIP-3 group**. Table cells show non-parametric correlation-like measures and 95% Confidence Intervals (95%CI) between cytokines and clinical, radiographic and ultrasound severity at baseline and radiographic progression. Correlation-like measures are: Spearman correlation (continuous or ordinal outcomes) and Glass rank biserial correlation (binary outcomes). Radiographic progression according to Kellgren-Lawrence staging and joint space narrowing were treated as ordinal in these analyses. Red color indicates positive correlation, blue represents negative correlation, and color intensity expresses more extreme values of the correlation coefficients. Color intensities were saturated to 0.5 and -0.5 for positive and negative correlation, respectively. **IL-6:** Interleukin 6; **IL-8:** Interleukin 8; **TNF-alpha:** Tumor Necrosis Factor alpha; **NGF:** Nerve Growth Factor; **CRP:** C-Reactive Protein; **KOA:** Knee Osteoarthritis. **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | KOOS pain | KOOS symptoms | KOOS functional disability | Joint effusion | Synovial tissue thickness | Kellgren-Lawrence Baseline | Osteophytes Baseline | Joint space narrowing Baseline | Kellgren-Lawrence Progression | Osteophytes Progression | Joint space narrowing Progression |
|--------------------------------------|---------------------------------------|---|---|---------------------------------------|---------------------------------------|--|--|---------------------------------------|---|---|--|
| CRP - synovial fluid | 0.230 [-0.194, 0.591] 0.248541 | 0.012 [-0.402, 0.396] 0.952875 | 0.117 [-0.285, 0.504] 0.56014662 | 0.213 [-0.194, 0.534] 0.285651 | 0.078 [-0.345, 0.456] 0.698219 | 0.197 [-0.194, 0.531] 0.324519 | 0.006 [-0.410, 0.480] 0.974342 | -0.015 [-0.415, 0.392] 0.940895 | -0.582 [-0.182, 0.722] 0.035734 | 0.182 [-0.408, 0.706] 0.4813214 | 0.061 [-0.618, 0.706] 0.8229019 |
| CRP - plasma | 0.261 [-0.229, 0.596] 0.188318 | 0.157 [-0.266, 0.552] 0.435394 | 0.196 [-0.271, 0.595] 0.32842050 | 0.321 [-0.071, 0.599] 0.102142 | 0.354 [-0.002, 0.618] 0.069830 | 0.229 [-0.145, 0.565] 0.249803 | 0.095 [-0.320, 0.511] 0.6378534 | -0.058 [-0.487, 0.365] 0.773816 | -0.429 [-0.191, 0.131] 0.122289 | -0.109 [-0.636, 0.461] 0.6726548 | 0.204 [-0.455, 0.536] 0.4556390 |
| IL-6 - synovial fluid | 0.070 [-0.374, 0.513] 0.730124 | 0.099 [-0.294, 0.473] 0.621531 | -0.138 [-0.529, 0.286] 0.49322508 | 0.341 [-0.255, 0.731] 0.003598 | 0.125 [-0.318, 0.522] 0.533631 | 0.250 [-0.162, 0.562] 0.208900 | 0.002 [-0.309, 0.375] 0.9938882 | 0.102 [-0.294, 0.483] 0.612776 | -0.231 [-0.750, 0.333] 0.405381 | 0.273 [-0.245, 0.769] 0.2908457 | 0.184 [-0.408, 0.778] 0.5019387 |
| IL-6 - plasma | 0.098 [-0.367, 0.544] 0.634323 | 0.108 [-0.330, 0.487] 0.599393 | -0.213 [-0.505, 0.202] 0.29583152 | 0.067 [-0.345, 0.424] 0.746133 | -0.237 [-0.615, 0.168] 0.243464 | 0.070 [-0.300, 0.393] 0.7375083 | -0.069 [-0.483, 0.376] 0.995840 | 0.001 [-0.400, 0.397] 0.40514 | -0.024 [-0.514, 0.459] 0.932647 | -0.273 [-0.758, 0.309] 0.3050589 | 0.381 [-0.186, 0.493] 0.1869493 |
| IL-8 - synovial fluid | 0.222 [-0.229, 0.596] 0.265699 | 0.329 [-0.110, 0.657] 0.093377 | 0.062 [-0.429, 0.464] 0.75747769 | 0.373 [-0.039, 0.637] 0.055120 | 0.273 [-0.143, 0.613] 0.169035 | 0.215 [-0.203, 0.569] 0.281185 | 0.286 [-0.049, 0.584] 0.1483444 | 0.146 [-0.254, 0.518] 0.468515 | 0.363 [-0.187, 0.820] 0.191040 | 0.109 [-0.418, 0.655] 0.6726548 | 0.551 [-0.067, 0.918] 0.0439752 |
| IL-8 - plasma | 0.104 [-0.329, 0.494] 0.604240 | 0.045 [-0.314, 0.401] 0.821852 | -0.049 [-0.415, 0.353] 0.80987602 | -0.287 [-0.584, 0.068] 0.146647 | -0.144 [-0.618, 0.308] 0.474399 | -0.158 [-0.520, 0.229] 0.432082 | 0.200 [-0.192, 0.584] 0.3173169 | 0.084 [-0.285, 0.462] 0.675329 | 0.538 [-0.000, 0.938] 0.052204 | 0.055 [-0.469, 0.578] 0.8326894 | 0.531 [-0.022, 1.000] 0.0524134 |
| TNF-alpha - synovial fluid | -0.030 [-0.407, 0.374] 0.881729 | -0.018 [-0.415, 0.350] 0.929964 | -0.163 [-0.506, 0.286] 0.41540770 | -0.051 [-0.459, 0.376] 0.800525 | -0.093 [-0.481, 0.368] 0.646096 | -0.251 [-0.591, 0.093] 0.206947 | 0.020 [-0.329, 0.346] 0.921885 | -0.295 [-0.619, 0.057] 0.135553 | 0.275 [-0.238, 0.750] 0.321912 | 0.291 [-0.204, 0.763] 0.2598752 | 0.531 [-0.051, 0.534] 0.0524134 |
| TNF-alpha - plasma | -0.030 [-0.491, 0.267] 0.549462 | -0.018 [-0.291, 0.490] 0.643169 | -0.163 [-0.580, 0.213] 0.27036970 | -0.051 [-0.301, 0.492] 0.545621 | -0.093 [-0.364, 0.335] 0.925976 | -0.251 [-0.595, 0.105] 0.192837 | 0.020 [-0.329, 0.346] 0.921885 | -0.295 [-0.619, 0.057] 0.135553 | 0.275 [-0.238, 0.750] 0.321912 | 0.291 [-0.204, 0.763] 0.2598752 | 0.531 [-0.051, 0.534] 0.0524134 |
| NGF - synovial fluid | -0.148 [-0.530, 0.257] 0.461117 | 0.010 [-0.420, 0.461] 0.960321 | 0.172 [-0.272, 0.576] 0.39219769 | -0.014 [-0.434, 0.359] 0.946414 | 0.033 [-0.317, 0.370] 0.869517 | 0.144 [-0.475, 0.515] 0.475105 | 0.194 [-0.315, 0.539] 0.3310559 | 0.137 [-0.425, 0.486] 0.496702 | -0.088 [-0.625, 0.475] 0.747662 | -0.227 [-0.718, 0.275] 0.3726152 | -0.204 [-0.704, 0.275] 0.4498428 |
| NGF - plasma | -0.339 [-0.631, 0.037] 0.084025 | -0.478 [-0.784, -0.062] 0.0161621 | -0.621 [-0.800, -0.352] 0.0095403 | 0.284 [-0.139, 0.676] 0.150438 | 0.194 [-0.148, 0.513] 0.582444 | 0.111 [-0.273, 0.504] 0.6207338 | 0.141 [-0.311, 0.463] 0.482475 | -0.132 [-0.677, 0.437] 0.631365 | -0.145 [-0.654, 0.364] 0.5701812 | -0.145 [-0.731, 0.231] 0.3100560 | -0.276 [-0.731, 0.231] 0.3100560 |
| Calprotectin - synovial fluid | -0.070 [-0.502, 0.371] 0.727834 | 0.104 [-0.327, 0.509] 0.604377 | 0.047 [-0.419, 0.479] 0.81577987 | 0.255 [-0.119, 0.560] 0.199743 | 0.150 [-0.271, 0.518] 0.456147 | 0.069 [-0.331, 0.435] 0.733513 | 0.008 [-0.381, 0.376] 0.9682261 | -0.159 [-0.542, 0.261] 0.427295 | 0.011 [-0.531, 0.548] 0.968395 | 0.091 [-0.491, 0.618] 0.7247712 | 0.245 [-0.051, 0.548] 0.3706500 |
| Calprotectin - plasma | 0.014 [-0.370, 0.406] 0.944335 | -0.109 [-0.497, 0.267] 0.5859533 | -0.143 [-0.533, 0.294] 0.47691063 | -0.032 [-0.435, 0.386] 0.875019 | 0.096 [-0.309, 0.488] 0.634117 | 0.278 [-0.207, 0.665] 0.159925 | 0.450 [-0.096, 0.738] 0.0184255 | 0.364 [-0.001, 0.711] 0.061790 | 0.143 [-0.455, 0.750] 0.606498 | 0.473 [-0.000, 0.852] 0.0671207 | 0.265 [-0.293, 0.782] 0.33221157 |
| Leptin - synovial fluid | -0.013 [-0.409, 0.409] 0.946752 | 0.008 [-0.374, 0.397] 0.969782 | 0.114 [-0.312, 0.527] 0.57047679 | 0.057 [-0.280, 0.400] 0.778359 | -0.034 [-0.434, 0.354] 0.865467 | 0.070 [-0.334, 0.449] 0.727033 | -0.437 [-0.714, 0.319] 0.226561 | -0.071 [-0.487, 0.322] 0.723484 | -0.209 [-0.714, 0.319] 0.451566 | -0.082 [-0.740, 0.259] 0.3599647 | 0.082 [-0.174, 0.319] 0.7653835 |
| Leptin - plasma | -0.007 [-0.387, 0.379] 0.973362 | 0.068 [-0.303, 0.413] 0.735142 | 0.062 [-0.358, 0.451] 0.75866749 | -0.049 [-0.452, 0.367] 0.808731 | 0.126 [-0.288, 0.506] 0.532626 | 0.122 [-0.428, 0.565] 0.543971 | -0.448 [-0.694, 0.081] 0.602765 | -0.105 [-0.497, 0.302] 0.142650 | -0.407 [-0.788, 0.509] 0.0572650 | -0.491 [-0.904, 0.000] 0.6015081 | -0.143 [-0.788, 0.509] 0.6015081 |
| Irisin - synovial fluid | -0.013 [-0.410, 0.381] 0.947960 | 0.079 [-0.322, 0.472] 0.694270 | -0.097 [-0.450, 0.294] 0.63091845 | 0.224 [-0.170, 0.550] 0.262268 | 0.116 [-0.341, 0.496] 0.563177 | 0.144 [-0.325, 0.583] 0.473691 | -0.353 [-0.700, 0.069] 0.0713304 | -0.013 [-0.401, 0.409] 0.948429 | -0.319 [-0.450, 0.409] 0.250547 | -0.382 [-0.427, -0.150] 0.2024357 | 0.122 [-0.425, 0.615] 0.6544215 |
| Irisin - plasma | -0.112 [-0.491, 0.331] 0.579430 | 0.067 [-0.341, 0.463] 0.740877 | 0.049 [-0.337, 0.432] 0.80990452 | 0.124 [-0.277, 0.502] 0.537725 | -0.026 [-0.445, 0.425] 0.898903 | 0.206 [-0.212, 0.588] 0.302407 | -0.306 [-0.651, 0.076] 0.1204924 | 0.062 [-0.352, 0.460] 0.756950 | -0.429 [-0.868, 0.131] 0.122289 | -0.429 [-0.855, 0.133] 0.0910224 | -0.388 [-0.857, 0.206] 0.1563399 |
| Adiponectin - synovial fluid | 0.024 [-0.363, 0.358] 0.906950 | 0.055 [-0.290, 0.424] 0.783724 | -0.060 [-0.483, 0.346] 0.76791642 | 0.265 [-0.145, 0.608] 0.181916 | -0.129 [-0.492, 0.302] 0.522620 | 0.234 [-0.193, 0.641] 0.239710 | -0.078 [-0.480, 0.297] 0.6978681 | 0.267 [-0.183, 0.598] 0.178132 | -0.407 [-0.875, 0.140] 0.142650 | 0.182 [-0.353, 0.666] 0.142650 | -0.020 [-0.481, 0.522] 0.9405292 |
| Adiponectin - plasma | -0.033 [-0.417, 0.362] 0.869757 | 0.112 [-0.243, 0.437] 0.579028 | 0.156 [-0.481, 0.278] 0.635255 | -0.096 [-0.455, 0.280] 0.692335 | 0.280 [-0.201, 0.699] 0.157229 | -0.161 [-0.427, 0.256] 0.4172065 | 0.240 [-0.227, 0.604] 0.1427065 | -0.495 [-1.000, 0.042] 0.029318 | -0.551 [-0.596, 0.407] 0.6220655 | -0.127 [-0.497, 0.302] 0.074592 | -0.551 [-1.000, 0.050] 0.0439752 |
| Omentin - synovial fluid | 0.165 [-0.198, 0.486] 0.410943 | 0.266 [-0.172, 0.579] 0.2390323 | 0.227 [-0.166, 0.516] 0.643962 | 0.093 [-0.305, 0.462] 0.256878 | -0.226 [-0.427, 0.206] 0.426532 | 0.160 [-0.217, 0.537] 0.2721665 | -0.219 [-0.457, 0.198] 0.398809 | -0.169 [-0.416, 0.520] 0.451566 | -0.209 [-0.467, 0.646] 0.4813214 | 0.182 [-0.467, 0.646] 0.4813214 | -0.020 [-0.467, 0.646] 0.9405292 |
| Omentin - plasma | -0.190 [-0.550, 0.214] 0.341452 | 0.099 [-0.268, 0.449] 0.622610 | 0.066 [-0.337, 0.474] 0.74256026 | -0.041 [-0.402, 0.342] 0.840559 | -0.009 [-0.396, 0.392] 0.962609 | 0.235 [-0.178, 0.581] 0.238994 | -0.283 [-0.438, 0.137] 0.1523455 | 0.052 [-0.364, 0.439] 0.795726 | -0.604 [-1.000, 0.020] 0.2598752 | -0.291 [-0.799, 0.241] 0.1356745 | -0.408 [-0.799, 0.241] 0.1356745 |
| Osteopontin - synovial fluid | -0.078 [-0.478, 0.342] 0.699415 | -0.140 [-0.172, 0.593] 0.487456 | -0.129 [-0.524, 0.308] 0.52268434 | 0.184 [-0.220, 0.564] 0.401329 | 0.143 [-0.264, 0.545] 0.476928 | 0.035 [-0.387, 0.431] 0.8625164 | -0.045 [-0.485, 0.376] 0.822667 | 0.033 [-0.409, 0.246] 0.905383 | -0.236 [-0.714, 0.327] 0.3599647 | 0.714 [-0.345, 0.978] 0.0090234 | -0.143 [-0.714, 0.327] 0.3599647 |
| Osteopontin - plasma | 0.253 [-0.195, 0.619] 0.202447 | 0.079 [-0.344, 0.522] 0.694270 | 0.205 [-0.166, 0.516] 0.30587029 | 0.012 [-0.368, 0.412] 0.553929 | 0.119 [-0.291, 0.468] 0.010467 | 0.484 [-0.088, 0.759] 0.1366053 | 0.294 [-0.111, 0.609] 0.018620 | 0.450 [-0.071, 0.745] 0.191040 | -0.363 [-0.824, 0.187] 0.12747712 | -0.091 [-0.625, 0.442] 0.2631100 | 0.306 [-0.300, 0.827] 0.2631100 |
| Visfatin - synovial fluid | -0.112 [-0.467, 0.263] 0.577334 | -0.204 [-0.556, 0.251] 0.308513 | -0.156 [-0.404, 0.211] 0.43691518 | 0.010 [-0.481, 0.396] 0.961409 | -0.108 [-0.460, 0.257] 0.592386 | 0.236 [-0.127, 0.568] 0.4748702 | 0.144 [-0.404, 0.480] 0.242943 | 0.233 [-0.364, 0.581] 0.242943 | -0.231 [-0.799, 0.241] 0.2598752 | 0.309 [-0.218, 0.745] 0.4556390 | 0.204 [-0.618, 0.706] 0.4556390 |
| Visfatin - plasma | -0.193 [-0.281, 0.463] 0.584682 | 0.132 [-0.294, 0.513] 0.511300 | 0.241 [-0.172, 0.593] 0.22615963 | -0.146 [-0.549, 0.295] 0.466435 | -0.018 [-0.392, 0.429] 0.930092 | -0.085 [-0.425, 0.554] 0.672054 | 0.070 [-0.411, 0.246] 0.4748702 | 0.070 [-0.425, 0.554] 0.7276493 | -0.201 [-0.711, 0.327] 0.3599647 | 0.714 [-0.345, 0.978] 0.0090234 | 0.184 [-0.367, 0.725] 0.5017999 |
| Resistin - synovial fluid | -0.130 [-0.482, 0.261] 0.517024 | 0.132 [-0.294, 0.513] 0.308513 | 0.241 [-0.172, 0.593] 0.22615963 | -0.146 [-0.549, 0.295] 0.466435 | -0.018 [-0.392, 0.429] 0.930092 | -0.085 [-0.425, 0.554] 0.672054 | 0.070 [-0.411, 0.246] 0.4748702 | 0.070 [-0.425, 0.554] 0.7276493 | | | |

Supplementary Table S7. Association between cytokines and Knee Osteoarthritis (**KOA**) outcomes in the **KOIP-4 group**. Table cells show non-parametric correlation-like measures and 95% Confidence Intervals (95%CI) between cytokines and clinical, radiographic and ultrasound severity at baseline and radiographic progression. Correlation-like measures are: Spearman correlation (continuous or ordinal outcomes) and Glass rank biserial correlation (binary outcomes). Radiographic progression according to Kellgren-Lawrence staging and joint space narrowing were treated as ordinal in these analyses. Red color indicates positive correlation, blue represents negative correlation, and color intensity expresses more extreme values of the correlation coefficients. Color intensities were saturated to 0.5 and -0.5 for positive and negative correlation, respectively. **IL-6:** Interleukin 6; **IL-8:** Interleukin 8; **TNF-alpha:** Tumor Necrosis Factor alpha; **NGF:** Nerve Growth Factor; **CRP:** C-Reactive Protein; **KOA:** Knee Osteoarthritis. **KOIP:** Knee Osteoarthritis Inflammatory Phenotype.

| | KOOS pain | KOOS symptoms | KOOS functional disability | Joint effusion | Synovial tissue thickness | Kellgren-Lawrence Baseline | Osteophytes Baseline | Joint space narrowing Baseline | Kellgren-Lawrence Progression | Osteophytes Progression | Joint space narrowing Progression |
|--------------------------------------|--|---|---|--|---|--|--|---|---|--|---------------------------------------|
| CRP - synovial fluid | -0.051 [+0.370, 0.265] 0.773244 | -0.032 [-0.277, 0.313] 0.8549996 | 0.001 [0.328, 0.301] 0.994261 | -0.590 [-0.771, -0.327] 0.00010364 | -0.339 [-0.645, 0.018] 0.0539382 | -0.272 [-0.593, 0.087] 0.1145569 | -0.354 [-0.649, 0.009] 0.0399525 | -0.180 [-0.496, 0.179] 0.2996134 | -0.006 [+0.523, 0.523] 0.9812838 | -0.024 [-0.469, 0.412] 0.913073 | 0.026 [-0.458, 0.565] 0.908632 |
| CRP - plasma | -0.178 [-0.455, 0.152] 0.306912 | -0.226 [-0.518, 0.133] 0.1918653 | -0.074 [-0.393, 0.263] 0.673283 | -0.512 [-0.738, -0.209] 0.00016725 | -0.327 [-0.663, 0.030] 0.0630728 | -0.140 [-0.464, 0.215] 0.4217320 | -0.271 [-0.554, 0.063] 0.12169892 | -0.072 [-0.384, 0.256] 0.6809147 | -0.011 [-0.528, 0.456] 0.9625946 | 0.114 [-0.288, 0.567] 0.600471 | -0.284 [-0.731, 0.210] 0.215403 |
| IL-6 - synovial fluid | 0.165 [+0.126, 0.427] 0.0343170 | 0.299 [+0.021, 0.551] 0.0807111 | 0.275 [0.030, 0.559] 0.109906 | 0.218 [+0.134, 0.511] 0.20763705 | 0.037 [0.342, 0.376] 0.83559898 | -0.272 [-0.578, 0.087] 0.1139323 | -0.157 [-0.503, 0.172] 0.3742850 | -0.409 [-0.568, -0.124] 0.0147857 | 0.000 [+NA, NA] 1.0000000 | 0.314 [-0.121, 0.692] 0.149800 | 0.232 [-0.278, 0.700] 0.312769 |
| IL-6 - plasma | -0.405 [-0.695, -0.061] 0.015818 | -0.475 [-0.734, -0.142] 0.0039018 | -0.305 [-0.617, 0.032] 0.0746499 | -0.368 [-0.638, -0.039] 0.0192431 | -0.353 [-0.652, -0.006] 0.0377034 | -0.376 [-0.668, 0.015] 0.02824512 | -0.172 [-0.530, 0.203] 0.3236348 | -0.216 [-0.659, 0.250] 0.3728437 | -0.186 [-0.635, 0.327] 0.394683 | -0.442 [-0.768, -0.010] 0.053939 | |
| IL-8 - synovial fluid | -0.018 [+0.357, 0.318] 0.920388 | 0.204 [0.113, 0.523] 0.2402526 | -0.025 [0.362, 0.317] 0.888666 | -0.163 [0.488, 0.180] 0.35017725 | -0.094 [0.418, 0.278] 0.6013952 | 0.243 [0.068, 0.496] 0.1600003 | 0.157 [0.193, 0.458] 0.37622660 | 0.089 [0.270, 0.452] 0.6100978 | -0.153 [-0.560, 0.268] 0.5260091 | 0.233 [-0.202, 0.625] 0.284296 | 0.242 [-0.194, 0.667] 0.290449 |
| IL-8 - plasma | -0.092 [-0.416, 0.239] 0.598623 | -0.112 [-0.426, 0.218] 0.5220963 | -0.025 [0.390, 0.317] 0.888143 | 0.084 [0.282, 0.436] 0.63166748 | 0.482 [0.162, 0.687] 0.0054503 | 0.125 [0.192, 0.475] 0.4726442 | 0.125 [0.189, 0.458] 0.48140979 | 0.266 [0.071, 0.559] 0.1220068 | 0.159 [0.321, 0.602] 0.5114100 | 0.480 [0.829, -0.091] 0.021930 | 0.000 [0.478, 0.442] 1.000000 |
| TNF-alpha - synovial fluid | -0.111 [-0.408, 0.374] 0.952326 | -0.154 [-0.442, 0.369] 0.7865293 | -0.190 [-0.404, 0.210] 0.332823 | -0.111 [-0.483, 0.245] 0.42877646 | -0.130 [-0.463, 0.542] 0.4972278 | -0.511 [-0.742, 0.180] 0.0053414 | -0.619 [-0.772, -0.304] 0.00507890 | -0.415 [-0.703, -0.061] 0.2060098 | 0.426 [+NA, NA] 0.1251937 | 0.067 [-0.392, 0.587] 0.796253 | |
| TNF-alpha - plasma | 0.131 [-0.280, 0.493] 0.453390 | 0.009 [0.385, 0.361] 0.9597489 | 0.007 [0.348, 0.358] 0.9694047 | -0.076 [-0.437, 0.286] 0.66257103 | 0.090 [0.294, 0.462] 0.6184347 | -0.473 [-0.718, -0.170] 0.03113721 | -0.370 [-0.671, -0.017] 0.0119588 | -0.420 [-0.660, -0.093] 0.6390846 | 0.114 [+0.323, 0.534] 0.484991 | 0.152 [0.300, 0.562] 0.713570 | 0.084 [0.369, 0.158] 0.713570 |
| NGF-synovial fluid | -0.052 [+0.343, 0.269] 0.767597 | 0.111 [0.235, 0.420] 0.5246115 | 0.047 [0.257, 0.359] 0.787501 | -0.206 [-0.511, 0.108] 0.23442602 | 0.068 [0.243, 0.364] 0.85887336 | -0.031 [0.303, 0.320] 0.83824586 | -0.036 [0.394, 0.311] 0.92120038 | -0.017 [-0.342, 0.335] 0.6213281 | 0.119 [0.361, 0.575] 0.264448 | 0.243 [0.212, 0.619] 0.231269 | 0.274 [0.183, 0.695] 0.231269 |
| NGF - plasma | -0.012 [+0.322, 0.308] 0.045470 | 0.034 [0.294, 0.348] 0.8479228 | 0.109 [0.211, 0.433] 0.5347378 | -0.139 [-0.463, 0.203] 0.42455463 | -0.064 [0.436, 0.310] 0.72251819 | -0.067 [-0.410, 0.253] 0.7036402 | -0.094 [-0.457, 0.254] 0.59867690 | 0.175 [0.167, 0.496] 0.3142315 | 0.341 [+NA, NA] 0.1579582 | 0.048 [0.394, 0.490] 0.826712 | 0.316 [0.188, 0.756] 0.166987 |
| Calprotectin - synovial fluid | -0.122 [-0.411, 0.203] 0.484876 | 0.158 [-0.168, 0.464] 0.3660033 | 0.061 [-0.249, 0.354] 0.7227834 | 0.195 [-0.138, 0.548] 0.26129604 | 0.006 [-0.350, 0.366] 0.9719816 | -0.099 [-0.467, 0.220] 0.5070765 | 0.015 [0.381, 0.391] 0.93120018 | -0.259 [-0.567, 0.083] 0.1328285 | -0.250 [-0.655, 0.227] 0.13202798 | 0.000 [+0.132, 0.856] 0.015401 | -0.211 [-0.478, 0.467] 1.000000 |
| Calprotectin - plasma | -0.141 [-0.472, 0.216] 0.418902 | -0.243 [-0.358, 0.094] 0.1669044 | -0.210 [-0.354, 0.118] 0.2261111 | -0.336 [-0.551, -0.038] 0.04875032 | -0.304 [-0.620, 0.044] 0.0853108 | -0.381 [-0.681, -0.029] 0.0240987 | -0.334 [-0.619, 0.006] 0.1569812 | -0.244 [-0.570, 0.080] 0.5735882 | -0.136 [-0.627, 0.333] 0.275234 | -0.238 [-0.615, 0.190] 0.275234 | -0.211 [-0.590, 0.217] 0.358795 |
| Leptin - synovial fluid | 0.209 [-0.147, 0.493] 0.227269 | 0.325 [-0.044, 0.637] 0.0570118 | 0.295 [-0.049, 0.585] 0.085203 | 0.405 [-0.090, 0.659] 0.01568681 | 0.410 [-0.059, 0.689] 0.0179554 | -0.079 [-0.403, 0.277] 0.6516151 | -0.063 [-0.329, 0.437] 0.72252699 | -0.055 [-0.401, 0.304] 0.7541151 | 0.284 [-0.250, 0.769] 0.2410174 | -0.143 [-0.558, 0.276] 0.512691 | 0.295 [-0.155, 0.733] 0.198887 |
| Leptin - plasma | 0.008 [+0.321, 0.318] 0.961480 | -0.030 [-0.369, 0.320] 0.8638458 | 0.031 [-0.260, 0.339] 0.860739 | 0.344 [0.013, 0.584] 0.40297202 | 0.192 [0.183, 0.520] 0.2853605 | 0.079 [0.274, 0.430] 0.6515922 | 0.276 [0.065, 0.602] 0.11040039 | 0.116 [0.241, 0.462] 0.5068793 | 0.205 [0.273, 0.660] 0.3985263 | 0.000 [0.442, 0.444] 1.000000 | -0.005 [-0.529, 0.522] 0.981695 |
| Irisin - synovial fluid | 0.048 [+0.310, 0.396] 0.786235 | 0.183 [-0.177, 0.523] 0.2924295 | 0.170 [-0.156, 0.514] 0.3282870 | 0.405 [-0.154, 0.616] 0.01589698 | 0.263 [-0.154, 0.616] 0.1397877 | 0.160 [-0.154, 0.783] 0.3593482 | 0.547 [-0.113, 0.513] 0.00081581 | 0.201 [-0.113, 0.513] 0.2477904 | 0.767 [-0.071, 0.977] 0.0015457 | 0.138 [+0.318, 0.571] 0.526793 | 0.553 [+0.083, 0.900] 0.015989 |
| Irisin - plasma | -0.069 [+0.420, 0.280] 0.699734 | -0.095 [-0.427, 0.259] 0.59488377 | 0.022 [-0.298, 0.352] 0.901609 | 0.119 [-0.424, 0.450] 0.50237127 | -0.050 [-0.452, 0.390] 0.7864792 | 0.190 [-0.187, 0.521] 0.2826495 | 0.309 [-0.163, 0.615] 0.08008344 | 0.185 [-0.146, 0.508] 0.2906624 | -0.083 [-0.584, 0.479] 0.7325198 | 0.087 [-0.372, 0.562] 0.695928 | -0.244 [-0.661, 0.273] 0.291178 |
| Adiponectin - synovial fluid | 0.014 [+0.399, 0.396] 0.938297 | 0.150 [-0.222, 0.508] 0.413901 | -0.143 [-0.481, 0.241] 0.14437156 | 0.252 [-0.136, 0.598] 0.17163438 | 0.244 [-0.133, 0.569] 0.16428179 | 0.081 [-0.262, 0.400] 0.75593000 | 0.056 [-0.288, 0.391] 0.7428617 | -0.057 [-0.400, 0.337] 0.8145036 | 0.057 [-0.412, 0.510] 0.710489 | 0.081 [-0.351, 0.524] 0.710489 | 0.211 [-0.345, 0.623] 0.358943 |
| Adiponectin - plasma | 0.174 [-0.217, 0.512] 0.381717 | 0.130 [-0.221, 0.495] 0.4572707 | 0.065 [0.285, 0.397] 0.712335 | 0.100 [-0.295, 0.451] 0.56767561 | 0.123 [-0.266, 0.489] 0.49722926 | 0.329 [-0.031, 0.630] 0.036746 | 0.430 [-0.103, 0.718] 0.01107059 | 0.420 [-0.068, 0.703] 0.0120269 | -0.250 [-0.444, 0.220] 0.4989268 | 0.000 [-0.457, 0.452] 1.000000 | -0.347 [-0.705, 0.066] 0.129986 |
| Omentin - synovial fluid | 0.151 [-0.240, 0.529] 0.410803 | 0.351 [-0.099, 0.723] 0.0486118 | 0.099 [-0.341, 0.494] 0.588345 | 0.363 [-0.022, 0.642] 0.2182067 | 0.232 [-0.166, 0.550] 0.9811311 | 0.004 [-0.324, 0.344] 0.27392591 | 0.203 [-0.179, 0.520] 0.4098268 | -0.124 [-0.446, 0.220] 0.4989268 | 0.099 [-0.444, 0.630] 0.6904043 | 0.161 [-0.321, 0.612] 0.487739 | 0.071 [-0.400, 0.565] 0.765189 |
| Omentin - plasma | 0.097 [-0.272, 0.473] 0.508470 | -0.201 [-0.360, 0.187] 0.2471811 | -0.054 [-0.370, 0.271] 0.759071 | -0.150 [-0.502, 0.222] 0.38595955 | 0.175 [-0.235, 0.555] 0.3297701 | 0.227 [-0.165, 0.577] 0.1982307 | 0.242 [-0.121, 0.668] 0.1618564 | -0.066 [-0.141, 0.599] 0.9812901 | -0.006 [-0.402, 0.642] 0.359338 | 0.200 [-0.260, 0.642] 0.765492 | -0.068 [-0.534, 0.467] 0.765492 |
| Osteopontin - synovial fluid | 0.411 [+0.108, 0.668] 0.014083 | 0.386 [-0.042, 0.678] 0.0219505 | 0.210 [-0.097, 0.949] 0.225970 | 0.094 [-0.263, 0.412] 0.5127265 | -0.118 [-0.433, 0.239] 0.4528285 | -0.107 [-0.398, 0.316] 0.66545335 | -0.077 [-0.473, 0.160] 0.2971746 | -0.181 [-0.468, 0.344] 0.982579 | -0.244 [-0.409, 0.441] 0.3103088 | -0.205 [-0.654, 0.309] 0.370641 | |
| Osteopontin - plasma | 0.020 [+0.315, 0.376] 0.911244 | 0.051 [-0.264, 0.369] 0.444344 | 0.134 [-0.197, 0.439] 0.32828734 | -0.044 [-0.372, 0.319] 0.94263559 | -0.023 [-0.350, 0.306] 0.89855330 | -0.003 [-0.313, 0.343] 0.9856129 | 0.235 [-0.070, 0.495] 0.180895912 | 0.052 [-0.285, 0.381] 0.7653307 | 0.091 [-0.363, 0.534] 0.7075242 | 0.124 [-0.305, 0.538] 0.570465 | 0.295 [-0.188, 0.988] 0.198887 |
| Visfatin - synovial fluid | 0.236 [-0.134, 0.553] 0.173074 | 0.260 [-0.103, 0.559] 0.1321914 | 0.183 [-0.114, 0.557] 0.291861 | 0.013 [-0.035, 0.283] 0.78927343 | 0.061 [-0.052, 0.093] 0.1655403 | 0.046 [-0.262, 0.413] 0.6128236 | 0.089 [-0.208, 0.261] 0.72701323 | -0.184 [-0.428, 0.381] 0.6555455 | 0.068 [-0.444, 0.630] 0.487739 | 0.133 [-0.186, 0.644] 0.238415 | 0.105 [-0.343, 0.522] 0.646355 |
| Visfatin - plasma | 0.267 [-0.049, 0.565] 0.120680 | 0.266 [-0.222, 0.393] 0.122476 | -0.026 [-0.318, 0.421] 0.72655629 | -0.008 [-0.396, 0.363] 0.9646272 | -0.024 [-0.525, 0.116] 0.1530834 | -0.024 [-0.453, 0.099] 0.19795756 | -0.184 [-0.427, 0.294] 0.2893346 | -0.059 [-0.446, 0.159] 0.8146050 | -0.068 [-0.454, 0.432] 0.8146050 | -0.248 [-0.487, -0.107] 0.520637 | -0.168 [-0.343, 0.304] 0.520637 |
| Resistin - synovial fluid | 0.195 [-0.161, 0.509] 0.260592 | 0.167 [-0.177, 0.496] 0.151854 | 0.247 [-0.114, 0.557] 0.78927343 | -0.047 [-0.352, 0.283] 0.5089355 | -0.247 [-0.456, 0.093] 0.1655403 | 0.089 [-0.268, 0.261] 0.6128236 | -0.062 [-0.280, 0.445] 0.1332518 | -0.074 [-0.477, 0.079] 0.1332518 | -0. | | |

Supplementary Table S8. Association of synovial and plasma cytokines with clinical severity in Knee Osteoarthritis Inflammatory Phenotypes (KOIP), adjusted for age, time of disease's evolution and Body Mass Index (BMI). The table presents Spearman correlation coefficients, 95% confidence intervals (95% CI) and p-values, illustrating the association between Knee Osteoarthritis (KOA) severity measures (KOOS-pain, KOOS-functional disability, and ultrasound joint effusion) and selected cytokines analyzed in the study. The analyses are adjusted for age, disease duration, and BMI. Results are presented for the entire patient cohort as well as for individual KOIP groups. **KOA:** Knee Osteoarthritis; **KOIP:** Knee Osteoarthritis Inflammatory Phenotypes (KOIP); **KOOS:** Knee injury and Osteoarthritis Outcome Scores (reversed scores); **95%CI:** 95% confidence interval.

| KOA Severity | Cytokine | All | | KOIP-1 | | KOIP-2 | | KOIP-3 | | KOIP-4 | |
|--|--|------------------------------|-----------|------------------------------|----------|------------------------------|----------|------------------------------|-------------|------------------------------|------------|
| | | Spearman correlation [95%CI] | P-value | Spearman correlation [95%CI] | P-value | Spearman correlation [95%CI] | P-value | Spearman correlation [95%CI] | P-value | Spearman correlation [95%CI] | P-value |
| KOOS - Pain (reversed, 0-100) | Omentin - synovial fluid (pg/mL) | 0.099 [-0.057, 0.249] | 0.21221 | -0.241 [-0.487, 0.040] | 0.092329 | 0.300 [-0.025, 0.567] | 0.070156 | 0.146 [-0.209, 0.467] | 0.42272 | 0.231 [-0.199, 0.586] | 0.29104 |
| | Osteopontin - synovial fluid (ng/mL) | 0.206 [0.055, 0.348] | 0.007798 | 0.118 [-0.176, 0.393] | 0.43198 | 0.114 [-0.207, 0.413] | 0.48995 | 0.098 [-0.349, 0.508] | 0.67805 | 0.461 [0.153, 0.687] | 0.0044899 |
| | Interleukin 6 - plasma (pg/mL) | 0.007 [-0.147, 0.160] | 0.93076 | 0.047 [-0.240, 0.327] | 0.75032 | 0.027 [-0.261, 0.310] | 0.85728 | 0.130 [-0.366, 0.568] | 0.61906 | -0.328 [-0.634, 0.067] | 0.10145 |
| KOOS - Functional Disability (reversed, 0-100) | Omentin - synovial fluid (pg/mL) | 0.060 [-0.095, 0.213] | 0.44518 | -0.202 [-0.446, 0.069] | 0.14207 | 0.247 [-0.079, 0.524] | 0.13584 | 0.194 [-0.207, 0.539] | 0.34369 | 0.206 [-0.241, 0.581] | 0.36769 |
| | Interleukin 6 - plasma (pg/mL) | 0.029 [-0.124, 0.182] | 0.70824 | 0.164 [-0.122, 0.425] | 0.26152 | 0.067 [-0.211, 0.335] | 0.64094 | -0.215 [-0.587, 0.233] | 0.34812 | -0.299 [-0.565, 0.023] | 0.068168 |
| Ultrasound Joint Effusion (mm) | C-reactive protein - synovial fluid (mg/L) | 0.007 [-0.146, 0.160] | 0.926 | 0.059 [-0.238, 0.346] | 0.70114 | 0.041 [-0.251, 0.326] | 0.78781 | 0.324 [-0.062, 0.626] | 0.097677 | -0.570 [-0.763, -0.284] | 0.00035628 |
| | C-reactive protein - plasma (mg/L) | -0.029 [-0.181, 0.124] | 0.70813 | -0.146 [-0.403, 0.133] | 0.30445 | -0.041 [-0.329, 0.254] | 0.78949 | 0.412 [0.089, 0.657] | 0.013912 | -0.538 [-0.748, -0.231] | 0.0012901 |
| | Leptin - synovial fluid (pg/mL) | 0.058 [-0.095, 0.209] | 0.45711 | -0.123 [-0.410, 0.187] | 0.43981 | -0.184 [-0.440, 0.099] | 0.2007 | 0.030 [-0.410, 0.458] | 0.89965 | 0.429 [0.091, 0.678] | 0.014337 |
| | Leptin - plasma (pg/mL) | -0.062 [-0.213, 0.093] | 0.4338 | -0.166 [-0.418, 0.110] | 0.23865 | -0.194 [-0.458, 0.101] | 0.19584 | -0.034 [-0.420, 0.363] | 0.87195 | 0.253 [-0.099, 0.548] | 0.15632 |
| | Irisin - synovial fluid (ng/mL) | 0.019 [-0.136, 0.173] | 0.81176 | -0.183 [-0.434, 0.095] | 0.19624 | -0.107 [-0.420, 0.228] | 0.53419 | 0.259 [-0.151, 0.593] | 0.2124 | 0.326 [-0.021, 0.603] | 0.064766 |
| | Interleukin 6 - synovial fluid (pg/mL) | 0.236 [0.086, 0.376] | 0.0023444 | 0.103 [-0.169, 0.361] | 0.45915 | 0.157 [-0.144, 0.430] | 0.30618 | 0.634 [0.390, 0.795] | 0.000012813 | 0.355 [0.035, 0.608] | 0.030222 |
| | Interleukin 6 - plasma (pg/mL) | 0.055 [-0.099, 0.206] | 0.48514 | 0.118 [-0.169, 0.387] | 0.42041 | 0.142 [-0.149, 0.409] | 0.33893 | 0.051 [-0.351, 0.437] | 0.80907 | -0.321 [-0.598, 0.025] | 0.068546 |
| | Calprotectin - plasma (ng/mL) | -0.003 [-0.156, 0.150] | 0.96899 | -0.044 [-0.306, 0.224] | 0.75206 | 0.141 [-0.132, 0.394] | 0.3115 | -0.052 [-0.438, 0.349] | 0.8052 | -0.308 [-0.554, -0.013] | 0.040914 |
| | Omentin - synovial fluid (pg/mL) | 0.162 [0.008, 0.308] | 0.040004 | 0.098 [-0.190, 0.370] | 0.50697 | 0.129 [-0.184, 0.418] | 0.42145 | 0.123 [-0.270, 0.480] | 0.54479 | 0.362 [0.021, 0.628] | 0.038155 |

Supplementary Table S9. Association of synovial and plasma cytokines with radiographic progression in Knee Osteoarthritis Inflammatory Phenotypes (KOIP), adjusted for age, time of disease's evolution and Body Mass Index (BMI). The table presents fold-changes, 95% confidence intervals (95% CI) and p-values, illustrating the association between Knee Osteoarthritis (KOA) progression according to different radiographic criteria (Kellgren-Lawrence, Osteophytes and Joint Space Narrowing) and selected cytokines analyzed in the study. Positive fold-changes indicate a higher level of the cytokine in progressors, while negative fold-changes represents a higher level of the cytokine in non-progressors. The analyses are adjusted for age, disease duration, and BMI. Results are presented for the entire patient cohort as well as for individual KOIP groups. **KOA:** Knee Osteoarthritis; **KOIP:** Knee Osteoarthritis Inflammatory Phenotypes (KOIP); **95%CI:** 95% confidence interval.

| KOA Radiographic Progression | Cytokines | All | | KOIP-1 | | KOIP-2 | | KOIP-3 | | KOIP-4 | |
|---|--|-------------------------|----------|-------------------------|----------|-------------------------|-----------|-------------------------|------------|------------------------|-----------|
| | | Fold-Change [95%CI] | P-value | Fold-Change [95%CI] | P-value | Fold-Change [95%CI] | P-value | Fold-Change [95%CI] | P-value | Fold-Change [95%CI] | P-value |
| Kellgren-Lawrence Radiographic Progression | Resistin - synovial fluid (pg/mL) | -1.24 [-1.74, 1.18] | 0.24462 | -2.08 [-3.65, -1.20] | 0.012175 | 1.51 [-1.41, 2.89] | 0.27554 | 1.31 [-2.27, 3.79] | 0.58863 | -1.24 [-2.91, 1.88] | 0.63494 |
| | C-reactive protein - synovial fluid (mg/L) | 1.12 [-1.16, 1.49] | 0.39035 | 1.51 [1.05, 2.19] | 0.037626 | 1.06 [-1.70, 1.81] | 0.85564 | -1.57 [-2.92, 1.13] | 0.11665 | 1.11 [-1.82, 2.06] | 0.75714 |
| | Omentin - plasma (pg/mL) | -1.26 [-1.64, 1.04] | 0.076489 | -1.40 [-2.20, 1.07] | 0.12058 | 1.06 [-1.45, 1.56] | 0.81773 | -2.70 [-7.00, -1.31] | 0.009627 | 1.05 [-1.66, 1.70] | 0.86185 |
| | Irisin - synovial fluid (ng/mL) | -1.04 [-1.18, 1.10] | 0.60394 | -1.25 [-1.47, -1.06] | 0.008212 | -1.07 [-1.49, 1.30] | 0.68488 | -1.16 [-1.74, 1.31] | 0.47166 | 1.39 [1.14, 1.66] | 0.0012974 |
| Osteophytes Radiographic Progression | Osteopontin - synovial fluid (ng/mL) | -1.21 [-1.63, 1.10] | 0.19176 | 1.37 [-1.36, 2.54] | 0.33122 | -1.45 [-2.30, 1.09] | 0.12429 | -1.10 [-2.64, 2.15] | 0.78894 | -1.10 [-1.78, 1.41] | 0.64559 |
| | Osteopontin - plasma (ng/mL) | -1.14 [-1.37, 1.04] | 0.14962 | -1.05 [-1.58, 1.40] | 0.78026 | -1.42 [-1.98, -1.04] | 0.031466 | -1.38 [-2.66, 1.42] | 0.33039 | 1.11 [-1.27, 1.60] | 0.55478 |
| | Omentin - synovial fluid (pg/mL) | 1.02 [-1.32, 1.42] | 0.88754 | 1.85 [1.08, 3.37] | 0.028051 | -1.72 [-2.92, -1.06] | 0.03584 | 1.05 [-3.20, 3.59] | 0.90198 | 1.41 [-1.36, 2.79] | 0.28672 |
| | Omentin - plasma (pg/mL) | 1.02 [-1.25, 1.31] | 0.86418 | 1.86 [1.10, 3.64] | 0.030952 | -1.15 [-1.64, 1.26] | 0.46302 | -1.76 [-5.02, 1.61] | 0.24345 | 1.36 [-1.17, 2.15] | 0.19517 |
| | Leptin - synovial fluid (pg/mL) | 1.05 [-1.19, 1.30] | 0.68843 | 1.74 [1.03, 2.94] | 0.034066 | -1.15 [-1.53, 1.19] | 0.38946 | -1.08 [-2.10, 1.75] | 0.80688 | -1.41 [-2.35, 1.16] | 0.19797 |
| | Leptin - plasma (pg/mL) | 1.05 [-1.14, 1.26] | 0.61333 | 1.43 [1.02, 2.01] | 0.044663 | -1.05 [-1.50, 1.39] | 0.84667 | -1.69 [-3.47, 1.37] | 0.1892 | 1.02 [-1.37, 1.43] | 0.92611 |
| | Irisin - synovial fluid (ng/mL) | -1.08 [-1.22, 1.05] | 0.27223 | 1.09 [-1.13, 1.34] | 0.40431 | -1.19 [-1.61, 1.12] | 0.23591 | -1.68 [-2.64, -1.09] | 0.031111 | 1.19 [-1.00, 1.43] | 0.066103 |
| | Irisin - plasma (ng/mL) | -1.03 [-1.17, 1.11] | 0.66774 | 1.17 [-1.02, 1.41] | 0.087542 | -1.15 [-1.59, 1.25] | 0.41349 | -1.34 [-2.34, 1.24] | 0.22328 | 1.02 [-1.23, 1.28] | 0.84938 |
| | Interleukin 8 - plasma (pg/mL) | 1.21 [-1.09, 1.55] | 0.1495 | 1.25 [-1.40, 2.05] | 0.35809 | 1.53 [1.06, 2.23] | 0.026868 | 1.49 [-2.98, 6.09] | 0.57305 | -1.55 [-2.44, 1.01] | 0.045448 |
| | Calprotectin - synovial fluid (ng/mL) | 1.33 [-1.06, 1.91] | 0.12387 | -1.30 [-2.31, 1.46] | 0.41521 | 1.45 [-1.50, 3.34] | 0.3442 | 2.30 [-1.03, 5.71] | 0.066658 | 2.09 [1.05, 4.29] | 0.041223 |
| Joint Space Narrowing Radiographic Progression | Adiponectin - synovial fluid (ng/mL) | 1.14 [-1.16, 1.48] | 0.36748 | 1.66 [1.07, 2.51] | 0.032595 | -1.47 [-2.35, 1.06] | 0.099879 | -1.05 [-2.86, 2.52] | 0.90321 | 1.16 [-1.47, 2.06] | 0.54318 |
| | Osteopontin - synovial fluid (ng/mL) | 1.26 [-1.04, 1.68] | 0.108 | 1.31 [-1.28, 2.14] | 0.25957 | 1.02 [-1.62, 1.79] | 0.87745 | 2.59 [1.68, 3.99] | 0.00034539 | -1.32 [-2.04, 1.17] | 0.20825 |
| | JoOmentin - synovial fluid (pg/mL) | 1.24 [-1.08, 1.65] | 0.16296 | 1.67 [1.12, 2.50] | 0.010921 | 1.22 [-1.57, 2.07] | 0.50537 | -1.04 [-2.67, 2.33] | 0.94272 | 1.05 [-1.90, 1.98] | 0.89549 |
| | Leptin - synovial fluid (pg/mL) | -1.04 [-1.30, 1.22] | 0.74315 | -1.06 [-1.56, 1.34] | 0.73046 | -1.67 [-2.30, -1.20] | 0.0013274 | 1.15 [-1.43, 1.84] | 0.59876 | 1.16 [-1.59, 1.97] | 0.54063 |
| | Leptin - plasma (pg/mL) | -1.14 [-1.42, 1.05] | 0.15722 | -1.07 [-1.44, 1.22] | 0.55993 | -1.60 [-2.32, -1.09] | 0.016944 | -1.26 [-2.31, 1.41] | 0.46167 | -1.07 [-1.54, 1.32] | 0.66752 |
| | Irisin - synovial fluid (ng/mL) | 1.01 [-1.11, 1.14] | 0.84859 | -1.12 [-1.30, 1.06] | 0.15696 | -1.14 [-1.55, 1.21] | 0.40734 | 1.20 [-1.23, 1.76] | 0.34398 | 1.26 [1.05, 1.49] | 0.012932 |
| | Irisin - plasma (ng/mL) | -1.16 [-1.33, -1.02] | 0.021346 | -1.10 [-1.24, 1.03] | 0.14487 | -1.54 [-2.67, -1.01] | 0.045653 | -1.22 [-1.92, 1.20] | 0.28199 | -1.15 [-1.51, 1.11] | 0.26456 |