

Supplementary Dataset

Clinically useful biomarker in osteoarthritis (OA): urinary CTXII is the best-qualified marker for evaluation of OA?

Yulia Liem¹, Andy Judge¹, John Kirwan², Khadija Ourradi¹, Yunfei Li¹ and Mohammed Sharif^{1*}

Corresponding Author:

*Dr Mohammed Sharif

Translational Health Sciences

Bristol Medical School

Musculoskeletal Research Unit

University of Bristol

Learning and Research Building (Level 2)

Southmead Hospital

Bristol

BS10 5NB

United Kingdom

Contact: +44 (0) 117 41 47926, Email: mo.sharif@bristol.ac.uk

Affiliations:

¹Translational Health Science, Bristol Medical School, Musculoskeletal Research Unit, Learning & Research, Southmead Hospital, University of Bristol, Bristol, United Kingdom

²Emeritus Professor at University of Bristol

Age	Frequencies	Percentage (%)
40 - 50	510	11.36
50 - 60	1566	34.87
60 - 70	1369	30.48
70 - 80	1046	23.29
Total	4491	100
Gender	Frequencies	Percentage (%)
Male	1881	41.88
Female	2610	58.12
Total	4491	100
Race	Frequencies	Percentage (%)
White / Caucasian	3600	80.16
Black / African American	780	17.37
Asian	38	0.85
Others	69	1.54
Missing	4	0.09
Total	4491	100
Body Mass Index	Frequencies	Percentage (%)
Underweight	11	0.24
Normal	1069	23.8
Overweight	1764	39.28
Class I Obese	1178	26.23
Class II Obese	392	8.73
Class II Obese	77	1.71
Total	4491	100

Supplementary table 1. Demographics data of the entire OAI cohort

Biomarkers		Serum											Urine							
		C12C	C2C	CPII	PIIANP	Coll2-1 NO2	CS846	MMP3	CTXI	COMP	HA	NTXI	CTXII	C12C	C2C	NTXI	CTX1 alpha	CTX1 beta	Coll2-1 NO2	Creatinine
Serum	C12C	1-0000																		
	C2C	0-4028	1-0000																	
	CPII	0-3880	0-3772	1-0000																
	PIIANP	0-0849	0-1239	0-0715	1-0000															
	Coll2-1 NO2	0-2812	0-3547	0-3783	-0-0249	1-0000														
	CS846	0-0052	-0-0029	-0-0477	-0-0644	0-0047	1-0000													
	MMP3	-0-0280	-0-2263	-0-2100	-0-1038	-0-1641	-0-0250	1-0000												
	CTXI	0-0599	0-0219	-0-0232	0-0099	-0-0005	0-1719	-0-0517	1-0000											
	COMP	0-0913	0-1218	0-1248	0-0720	0-0848	-0-0170	0-1963	0-0475	1-0000										
	HA	0-0653	0-0570	0-0099	-0-0598	0-0391	-0-0618	0-1316	0-0696	0-2707	1-0000									
NTXI	-0-1154	-0-0869	-0-0508	0-0170	0-0402	0-1082	-0-0131	0-6108	0-0938	0-1200	1-0000									
Urine	CTXII	0-1244	0-1637	0-0756	0-0773	0-1690	-0-0728	-0-1627	0-3026	0-1043	0-3274	0-2254	1-0000							
	C12C	-0-0378	0-0577	-0-0562	-0-1576	0-0072	0-0432	-0-0189	-0-0751	0-0053	-0-0284	-0-1021	-0-0272	1-0000						
	C2C	0-1332	0-1241	0-0559	0-0671	0-1220	-0-0454	-0-0323	0-1173	0-1389	0-4113	0-1072	0-6991	-0-0263	1-0000					
	NTXI	0-0586	0-0880	-0-0153	-0-0133	0-0719	0-1330	-0-2207	0-7474	-0-0187	0-1099	0-4949	0-4113	0-1359	0-2815	1-0000				
	CTX1 alpha	0-0783	0-1069	0-0303	0-0330	0-0605	0-1570	-0-1768	0-8210	-0-0270	0-1009	0-5364	0-4190	0-0089	0-2739	0-8661	1-0000			
	CTX1 beta	0-0563	0-0602	-0-0335	0-0083	0-0437	0-1891	-0-2118	0-8230	-0-0816	0-0255	0-5058	0-3203	0-0834	0-1452	0-8586	0-8991	1-0000		
	Coll2-1 NO2	0-0683	0-0190	0-0871	-0-0689	-0-0318	-0-0947	-0-0573	-0-0597	0-0832	0-0790	-0-0758	0-1007	0-3069	0-1674	0-1526	-0-0004	0-0262	1-0000	
Creatinine	-0-0940	-0-0139	-0-1245	-0-0467	-0-0955	0-0653	0-0985	0-0645	0-0338	-0-0359	0-0223	-0-0523	0-2843	-0-2706	-0-1185	-0-0749	0-0310	-0-0812	1-0000	

Supplementary table 2: Spearman correlations between biomarkers for checking collinearity at baseline.

Univariate models (K&L grade)									
N=300 - 600	Baseline			12 Months			24 Months		
	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC
Serum C12C	1.0040 (0.9841, 1.0244)	0.696	0.506	0.9957 (0.9754, 1.0164)	0.679	0.536	0.9974 (0.9760, 1.0192)	0.813	0.498
Serum C2C	1.0075 (1.0009, 1.0142)	0.025	0.597	1.0019 (0.9949, 1.0089)	0.601	0.511	0.9999 (0.9934, 1.0064)	0.972	0.522
Serum CPII	1.0012 (1.0002, 1.0022)	0.024	0.599	1.0000 (0.9990, 1.0010)	0.949	0.486	1.0003 (0.9993, 1.0013)	0.569	0.528
Serum PIIANP	1.0003 (0.9999, 1.0007)	0.150	0.569	1.0004 (0.9999, 1.0009)	0.094	0.578	1.0115 (0.9508, 1.0761)	0.718	0.505
Serum Coll21NO2	1.1054 (1.0246, 1.1926)	0.010	0.607	1.0563 (0.9778, 1.1412)	0.165	0.558	1.0115 (0.9508, 1.0761)	0.718	0.487
Serum CS846	0.9989 (0.9939, 1.0039)	0.660	0.507	0.9978 (0.9926, 1.0029)	0.392	0.587	0.9997 (0.9938, 1.0056)	0.920	0.511
Serum MMP3	0.9968 (0.9762, 1.0177)	0.759	0.521	1.0111 (0.9776, 1.0458)	0.520	0.520	1.0019 (0.9733, 1.0313)	0.899	0.486
Serum CTXI	0.9995 (0.9982, 1.0009)	0.506	0.492	0.9984 (0.997, 0.9998)	0.029	0.550	0.9989 (0.9975, 1.0003)	0.133	0.546
Serum COMP	0.9998 (0.9988, 1.0007)	0.651	0.513	1.0002 (0.9991, 1.0012)	0.770	0.518	0.9999 (0.9988, 1.0009)	0.808	0.499
Serum HA	1.0114 (1.0002, 1.0228)	0.046	0.623	1.0155 (1.0012, 1.0299)	0.034	0.630	1.0184 (1.0035, 1.0335)	0.015	0.656
Serum NTXI	0.9872 (0.9369, 1.0401)	0.628	0.502	1.0301 (0.9586, 1.107)	0.419	0.534	1.0284 (0.9580, 1.1039)	0.440	0.545
Urine CTXII	1.0317 (1.0090, 1.0550)	0.006	0.671	1.0225 (0.9996, 1.0458)	0.054	0.635	1.0335 (1.0070, 1.0607)	0.013	0.655
Urine C12C	1.1367 (0.8600, 1.5024)	0.368	0.546	1.3294 (0.9633, 1.8347)	0.083	0.574	1.1437 (0.8240, 1.5875)	0.422	0.536
Urine C2C	1.0012 (0.9980, 1.0043)	0.475	0.591	1.0030 (0.9987, 1.0073)	0.173	0.614	1.0074 (1.0022, 1.0126)	0.005	0.649
Urine NTXI	1.0003 (0.9832, 1.0177)	0.970	0.519	0.9895 (0.9739, 1.0054)	0.194	0.494	0.9938 (0.9727, 1.0154)	0.573	0.493
Urine CTX1alpha	0.9996 (0.9989, 1.0003)	0.240	0.479	0.9996 (0.9987, 1.0005)	0.365	0.475	0.9996 (0.9985, 1.0006)	0.444	0.481
Urine CTX1beta	0.9999 (0.9998, 1.0001)	0.379	0.532	0.9999 (0.9997, 1.0000)	0.138	0.524	0.9999 (0.9997, 1.0001)	0.456	0.510
Urine Coll21NO2	0.9981 (0.9735, 1.0234)	0.885	0.456	0.9846 (0.9693, 1.0002)	0.053	0.607	0.9980 (0.9696, 1.0272)	0.891	0.442
Urine Creatinine	1.0369 (0.9749, 1.1029)	0.250	0.554	1.0374 (0.9703, 1.1091)	0.282	0.538	1.0439 (0.9687, 1.1250)	0.260	0.561

Supplementary table 3 Univariate logistic regression model for biomarker associations with KL grade at Baseline, 12 months and 24 months. Unit of measurements of some biomarkers (serum C12C, COMP, CTXI and urinary CTXII, C12C, Coll2-1 NO2, CTXII alpha and beta) were adjusted to the power of 10, 100, 1000 and logarithmically

Adjusted Multivariate (K&L grade)									
n=546	Baseline			12 Months			24 Month:		
	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC
Serum C12C	0.9812 (0.954, 1.0093)	0.187		0.97976 (0.95078, 1.00963)	0.182		0.97103 (0.93788, 1.00536)	0.097	
Serum C2C	1.0048 (0.996, 1.0137)	0.282		1.00126 (0.99153, 1.01109)	0.801		1.00486 (0.99401, 1.01581)	0.382	
Serum CPII	1.0008 (0.9994, 1.0022)	0.275		1.00005 (0.99874, 1.00136)	0.943		1.00104 (0.99925, 1.00282)	0.255	
Serum PIIANP	1.0003 (0.9998, 1.0007)	0.257		1.00038 (0.99987, 1.00090)	0.145		1.00016 (0.99961, 1.00071)	0.563	
Serum Coll21NO2	1.1340 (1.0298, 1.2488)	0.011		1.09907 (0.98637, 1.22464)	0.087		1.12359 (1.00045, 1.26188)	0.049	
Serum CS846	0.9977 (0.9917, 1.0038)	0.462		0.99723 (0.9909, 1.00361)	0.394		0.99568 (0.98885, 1.00255)	0.217	
Serum MMP3	0.9982 (0.9728, 1.0243)	0.894		0.99743 (0.95914, 1.03725)	0.898		0.99642 (0.96548, 1.02834)	0.823	
Serum CTXI	1.0009 (0.9979, 1.0038)	0.566		0.99600 (0.99262, 0.99938)	0.020		1.00081 (0.99712, 1.00451)	0.668	
Serum COMP	0.9987 (0.9976, 0.9999)	0.029	0.7980	0.99935 (0.99811, 1.00060)	0.311	0.7800	0.99829 (0.99695, 0.99963)	0.013	0.8234
Serum HA	1.0012 (0.9898, 1.0127)	0.84		1.01066 (0.99274, 1.02890)	0.246		1.01503 (0.99574, 1.03471)	0.128	
Serum NTXI	0.9948 (0.9285, 1.0658)	0.882		1.13945 (1.00703, 1.28929)	0.038		1.01946 (0.92198, 1.12724)	0.707	
Urine CTXII	1.0700 (1.0270, 1.1148)	0.001		1.01889 (0.98335, 1.05571)	0.302		1.06842 (1.01538, 1.12424)	0.011	
Urine C12C	0.9731 (0.6612, 1.4322)	0.89		1.45672 (0.95100, 2.23136)	0.084		0.94022 (0.58042, 1.52308)	0.802	
Urine C2C	0.9985 (0.9938, 1.0032)	0.528		1.00033 (0.99467, 1.00603)	0.909		0.99837 (0.99228, 1.00451)	0.602	
Urine NTXI	1.0219 (0.9674, 1.0795)	0.439		0.97537 (0.93669, 1.01565)	0.227		1.03897 (0.96960, 1.11330)	0.278	
Urine CTX1alpha	0.9985 (0.9960, 1.0010)	0.238		1.00192 (0.99924, 1.00460)	0.161		0.99799 (0.99477, 1.00123)	0.224	
Urine CTX1beta	0.9998 (0.9995, 1.0002)	0.314		0.99989 (0.99948, 1.00031)	0.610		0.99966 (0.99921, 1.00011)	0.136	
Urine Creatinine	1.0155 (0.9318, 1.1067)	0.726		0.98874 (0.90873, 1.07578)	0.792		0.98688 (0.89406, 1.08933)	0.793	

Supplementary table 4 Multivariate model for biomarker associations with KL grade at baseline, 12 months and 24 months. Unit of measurements of some biomarkers (serum C12C, COMP, CTXI and urinary CTXII, C12C, Coll21 NO2, CTXII alpha and beta) were adjusted to the power of 10, 100, 1000 and logarithmically transformed. The data was adjusted for age, BMI, gender and race. Urinary Coll2-1 NO2 was removed due to missing data.

Final multivariate model (K&L grade)									
<i>n=547</i>	Baseline			12 Months			24 Months		
	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC	Odd Ratio (95% CI)	P value	AUC
Serum C12C	0.9816 (0.9546, 1.0093)	0.191	0.7856	0.97930 (0.95108, 1.00835)	0.161	0.775	0.97174 (0.93924, 1.00535)	0.098	0.8052
Serum C2C	1.0036 (0.9951, 1.0121)	0.407		0.99983 (0.99074, 1.00899)	0.970		1.00285 (0.9925, 1.0133)	0.591	
Serum CPII	1.0008 (0.9994, 1.0023)	0.254		0.99987 (0.9986, 1.00114)	0.837		1.00108 (0.99933, 1.00284)	0.227	
Serum PIIANP	1.0003 (0.9998, 1.0007)	0.252		1.00041 (0.9999, 1.00092)	0.118		1.00019 (0.99965, 1.00074)	0.488	
Serum Coll21NO2	1.1316 (1.0289, 1.2445)	0.011		1.11319 (1.00225, 1.23641)	0.045		1.11904 (0.99887, 1.25367)	0.052	
Serum CS846	0.9972 (0.9913, 1.0032)	0.364		0.99818 (0.99203, 1.00437)	0.564		0.99531 (0.98865, 1.00201)	0.17	
Serum MMP3	0.9992 (0.9737, 1.0253)	0.950		1.00051 (0.96272, 1.03978)	0.979		0.99938 (0.96843, 1.03133)	0.969	
Serum CTXI	0.9996 (0.9971, 1.0021)	0.761		0.99813 (0.99569, 1.00057)	0.133		0.99929 (0.99627, 1.00232)	0.645	
Serum COMP	0.9988 (0.9977, 0.9999)	0.036		0.99940 (0.99818, 1.00062)	0.335		0.99837 (0.99706, 0.99969)	0.015	
Serum HA	1.0011 (0.9898, 1.0125)	0.851		1.00953 (0.99236, 1.02700)	0.279		1.01517 (0.99577, 1.03494)	0.126	
Urine CTXII	1.0607 (1.0231, 1.0996)	0.001		1.02424 (0.99375, 1.05566)	0.120		1.05914 (1.01327, 1.1071)	0.011	
Urine C12C	0.9837 (0.6802, 1.4226)	0.930		1.34530 (0.8794, 2.05804)	0.171		0.94176 (0.59899, 1.48067)	0.795	
Urine NTXI	0.9933 (0.9609, 1.0268)	0.691		0.99595 (0.96468, 1.02823)	0.803		0.9939 (0.9544, 1.03503)	0.767	
Urine Creatinine	1.0208 (0.9381, 1.1107)	0.633		0.98596 (0.90896, 1.06949)	0.733		0.99452 (0.9024, 1.09604)	0.912	

Supplementary table 5. Multivariate logistic regression model for biomarker associations with KL grade at baseline, 12 months and 24 months. Unit of measurements of some biomarkers (serum C12C, COMP, CTXI and urinary CTXII, C12C, Coll21 NO2, CTXII alpha and beta) were adjusted to the power of 10, 100, 1000 and logarithmically transformed. The data was adjusted for age, BMI, gender and race.