

1 Title: Correlation between clinical and radiological outcome following matrix-induced
2 autologous chondrocyte implantation in the femoral condyles.

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4 Running Title: Correlation of clinical and radiological outcome following MACI.

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25

26 TITLE

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28 Correlation of clinical and radiological outcome following matrix-induced autologous
29 chondrocyte implantation in the tibiofemoral joint.

30

31 ABSTRACT

32

33 **Background:** Matrix-induced autologous chondrocyte implantation (MACI) is an established
34 technique for the repair of knee chondral defects, though the correlation between clinical and
35 radiological outcome following surgery is poorly understood.

36 **Purpose:** The aim of this study was to determine the correlation between clinical and
37 radiological outcomes throughout the post-operative time line to five years following MACI.

38 **Study Design:** Retrospective study.

39 **Methods:** This retrospective study was undertaken in 83 patients (53 males, 30 females) with
40 complete clinical and radiological follow up at 1, 2 and 5 years following MACI. The mean
41 age of patients was 38.9 years (range, 13-62 years), with a mean body mass index (BMI) of
42 26.6 (range, 16.8-34.8), defect size of 3.3cm² (range, 1-9) and pre-operative duration of
43 symptoms of 9.2 years (range, 1-46). Patients indicated for MACI in this follow-up were 13-
44 65 years of age, though excluded if they had a BMI > 35, had undergone a prior extensive
45 meniscectomy or had ongoing progressive inflammatory arthritis. Patients were assessed
46 clinically using the Knee Injury and Osteoarthritis Outcome Score (KOOS). Magnetic
47 resonance imaging (MRI) was used to evaluate graft assessment using a 1.5 T or 3 T clinical
48 scanner. MRI assessment included eight parameters of graft repair (infill, signal intensity,
49 border integration, surface contour, structure, subchondral lamina, subchondral bone and
50 effusion) based on the magnetic resonance observation of cartilage repair tissue (MOCART),
51 as well as an MRI composite score. Spearman's correlation coefficient (SCC) assessed the

52 degree of association between the MRI parameters KOOS subscales at each post-operative
53 time point, and significance was determined at $p < 0.05$. Ethics approval was obtained from
54 the appropriate hospital and university Human Research Ethics Committees, and informed
55 consent was gathered from all patients.

56 **Results:** The only MRI parameter displaying consistent evidence of association with KOOS
57 subscales was effusion, with a pattern of increasing strength of correlations over time, and
58 statistically significant associations at 5 years with Pain (SCC 0.25, $p=0.020$), Activities of
59 Daily Living (SCC 0.26, $p=0.018$) and Sport (SCC 0.32, $p=0.003$). Apart from a significant
60 correlation between subchondral lamina and KOOS Sport at 1 year (SCC 0.27, $p=0.016$), no
61 further significant findings were observed.

62 **Conclusion:** Apart from some consistent evidence of association between the KOOS and
63 effusion, this analysis demonstrated limited correlative capacity between clinical and
64 radiological outcomes up to 5 years post-surgery.

65 **Keywords:** matrix-induced autologous chondrocyte implantation, post-operative assessment,
66 clinical outcome, radiological outcome, magnetic resonance imaging, correlation.

67 **What is known about this subject:** Matrix-induced autologous chondrocyte implantation
68 (MACI) has demonstrated good clinical efficacy for the repair of full thickness articular
69 cartilage defects in the knee. However, the correlation between clinical and radiological
70 outcome following MACI surgery is poorly understood. This is an area that requires
71 investigation, and may provide further insight into which MRI-based parameters are most
72 associated with certain clinical outcomes. In time, this may provide further insight into which
73 MRI-based parameters of evaluating graft repair are most important after MACI (as well as
74 other types of cartilage repair), and how MRI may be used to predict longer-term maintenance
75 of the repair, as well as the future progression/reoccurrence of pain/symptoms.

76

77 **What this study adds to existing knowledge:** While understanding the association between
78 clinical and MRI-based outcomes after cartilage repair is important in treating these patients,
79 there is a paucity of evidence currently available. There is currently no study of this size,
80 specifically evaluating the correlation of a commonly used patient-reported outcome (PRO)
81 measure (i.e. KOOS), with the most commonly employed MRI scoring system (MOCART)
82 for evaluating cartilage repair, in patients following MACI.

83 INTRODUCTION

84

85 Matrix-induced autologous chondrocyte implantation (MACI) has become an established
86 technique for the repair of full thickness chondral defects in the knee,^{6, 8, 23} and involves
87 isolating and culturing a patient's own chondrocytes *in vitro*, and then re-implanting those
88 cells into the cartilage defect. In order to evaluate patient outcome after MACI, there has been
89 an increasing need to develop accurate, yet non-invasive ways to assess patient-reported pain
90 and function, as well as the quality of tissue repair after surgery.

91

92 Several commonly used patient-reported outcome (PRO) measures have been employed to
93 evaluate outcome after MACI, including: the Knee Injury and Osteoarthritis Outcome Score
94 (KOOS)^{19, 23, 33, 45, 50}; the Lysholm score;^{6, 8, 31, 33, 45} the Tegner activity scale;^{6, 8, 31, 32, 45} the
95 Visual Analogue Pain Scale (VAS);^{19, 27, 63} the International Knee Documentation Committee
96 (IKDC) Subjective Knee Form;^{27, 33} the Cincinnati Knee Rating System^{5, 45} and; the Short
97 Form Health Survey (SF-36).^{4, 19, 31} Furthermore, magnetic resonance imaging (MRI) has also
98 demonstrated efficacy in the evaluation of tissue repair^{1, 16, 39, 40, 47, 59} and, while a number of
99 MRI scoring systems have been reported,^{29, 40, 47, 59} the magnetic resonance observation of
100 cartilage repair tissue (MOCART)^{39, 40} classification has been the most common system
101 utilized for cartilage repair.¹⁰

102

103 While clinical and radiological improvement has been well documented after MACI, the
104 correlation between clinical and MRI-based outcome is poorly understood. Better
105 understanding of this link may provide further insight into which MRI-based parameters are
106 most associated with clinical outcomes and which are most important after MACI, and how
107 MRI may be used to predict longer-term maintenance of the MACI graft repair, as well as the
108 future reoccurrence of pain and/or symptoms. Two recent systematic reviews have

109 highlighted the paucity and heterogeneity of studies currently available,^{10, 15} as well as the
110 need for more robust studies with longitudinal clinical and MRI follow-up after various
111 cartilage repair techniques,¹⁰ in order to better define the correlation between these outcomes.
112 The aim of this study was to determine the correlation between clinical and radiological
113 outcome throughout the post-operative time line to five years following MACI.

114 MATERIALS AND METHODS

115

116 Patients

117

118 This retrospective analysis consisted of 83 patients (53 males, 30 females) that underwent
119 MACI to address femoral condylar defects (62 medial, 21 lateral), between June 2002 and
120 June 2007. All patients had complete clinical and radiological follow up at 1, 2 and 5 years
121 post-surgery. Prior to MACI, none of the patients had undergone prior extensive
122 meniscectomy or had ongoing progressive inflammatory arthritis. Patients indicated for
123 MACI in this follow-up were 13-65 years of age and all suffered from persistent pain
124 associated with grade III or IV chondral lesions, assessed with the International Cartilage
125 Repair Society (ICRS) chondral defect classification system.¹² Patients with ligamentous
126 instability or varus/valgus abnormalities ($> 3^\circ$ tibiofemoral anatomic angle) underwent
127 MACI, provided these were addressed prior to or at the time of MACI grafting. Patients were
128 further excluded if they had a body mass index (BMI) > 35 , had undergone a prior extensive
129 meniscectomy or had ongoing progressive inflammatory arthritis.

130

131 The mean age of patients in this retrospective analysis was 38.9 years (range, 13-62 years),
132 the mean body mass index (BMI) was 26.6 (range, 16.8-34.8) and the mean defect size at
133 implantation was 3.3cm^2 (range, 1-9). The pre-operative duration of symptoms was 9.2 years
134 (range, 1-46) and, on average, patients had undergone 1.4 prior procedures (range, 0-4). At
135 the time of surgery, 7 of the 83 patients had concomitant documented procedures at the time
136 of MACI grafting, including high tibial osteotomy (n, 1), partial meniscectomy (n, 2), anterior
137 cruciate ligament (ACL) reconstruction (n, 3) and posterior cruciate ligament (PCL)
138 reconstruction (n, 1). Ethical approval was obtained from the appropriate hospital and

139 university Human Research Ethics Committees, and all patients had provided signed informed
140 consent to allow their clinical data to be de-identified and used for research programmes.

141

142 The MACI Surgical Technique

143

144 The MACI technique has been previously described.^{19, 23} MACI is a 2-stage technique, where
145 arthroscopic surgery was initially performed to harvest a sample of normal articular cartilage
146 from a non weight-bearing area of the knee. After harvest, chondrocytes were isolated,
147 cultured and seeded onto a type I/III collagen membrane (ACI-Maix, Matricel GmbH,
148 Herzogenrath, Germany) ex vivo over a 6- to 8-week period. At the time of second-stage
149 implantation, the chondral defect was prepared via an open mini-arthrotomy by removing all
150 damaged cartilage down to, but not through, the subchondral bone plate. The defect was
151 measured and used to shape the membrane, which was secured to the bone using fibrin glue.
152 The wound was closed after assessment of graft stability.

153

154 Outcome Measures

155

156 *Clinical Assessment*

157 All patients in this cohort completed the Knee Injury and Osteoarthritis Outcome Score
158 (KOOS) at 1, 2 and 5 years after MACI. The KOOS is a knee specific questionnaire which
159 includes 42 questions in five individual subscales: Pain, Symptoms, Activities of Daily Living
160 (ADL), Sport and Recreation (Sport/Rec) and Knee Related Quality of Life (QOL).⁵⁰ Each of
161 these five subscales is scored from 0 (worst) to 100 (best). The KOOS has been recommended
162 for use with cartilage repair patients⁴⁹ and, more recently, has demonstrated validity and
163 reliability in patients after the surgical treatment of focal cartilage lesions.⁹ It has been used
164 extensively in patients following ACI.^{7, 17, 19, 23, 33, 43, 45, 48, 51, 65, 66}

165

166 *Radiological Assessment*

167 All patients underwent MRI scans on their operated knee at 1, 2 and 5 years after MACI,
168 performed using 1.5 T or 3 T clinical scanners (Siemens, Erlangen, Germany; Philips, Best,
169 the Netherlands; General Electric, Milwaukee, WI, USA). All examinations were performed
170 using a dedicated knee coil with 4, 8 or 16 receiver channels, depending on the particular
171 scanner. Standardized proton density and T2-weighted fat-saturated images were obtained in
172 coronal and sagittal planes (slice thickness 3 mm, field of view 14-15 cm, 512 matrix in at
173 least one axis for proton density images with a minimum 256 matrix in one axis for T2-
174 weighted images). Additional axial proton density fat-saturated images were obtained (slice
175 thickness 3-4 mm, field of view 14-15 cm, minimum 224 matrix in at least one axis).

176

177 Radiological assessment of the post-operative MACI grafts in this study was assessed in two
178 ways. Firstly, we employed the magnetic resonance observation of cartilage repair tissue
179 (MOCART) scoring system,^{39, 40} whereby eight pertinent parameters of graft repair (signal
180 intensity, graft infill, border integration, surface contour, structure, subchondral lamina,
181 subchondral bone and effusion) were selected to best describe the morphology and signal
182 intensity of the repair tissue, each scored individually from 1-4 (1=poor; 2=fair; 3=good;
183 4=excellent) in comparison to the native cartilage (Figure 1). An additional score of 3.5 for
184 'graft infill' was awarded for a fifth level (very good) corresponding with 'graft hypertrophy'
185 (Figure 2).^{40, 61} Secondly, an MRI composite score was calculated by multiplying each of the
186 eight individual scores by a weighting factor,⁴⁸ and summing the weighted scores.^{18, 48} This
187 composite score also ranged from 1-4 (1=poor; 2=fair; 3=good; 4=excellent). MRI evaluation
188 was performed by an independent, experienced musculo-skeletal radiologist, with almost 10
189 years of experience with the MOCART scoring system for cartilage repair since its initial
190 publication in 2004.

191

192 Statistical Analysis

193

194 Firstly, the kappa coefficient was used to assess intra-observer reliability for the eight
195 pertinent morphological MRI scores, while the intra-class correlation coefficient was used for
196 the continuous MRI composite score. This was achieved by re-scoring 20 randomly selected
197 MRI images filtered through a second time to the radiologist. Due to the ordinal nature of the
198 MRI scoring system subscales, Spearman's correlation coefficient (SCC) with associated 95%
199 confidence interval (CI), was used to assess the degree of association between each of the
200 eight individual morphological MRI parameters, as well as the MRI composite score, with
201 each of the five KOOS subscales at 1, 2 and 5 years after MACI. Analysis was performed
202 using Stata/IC 13.1 for Windows (StataCorp LP, College Station, TX, USA).

203 RESULTS

204

205 Evaluation of intra-observer reliability for the MRI scoring system indicated perfect
206 agreement for six of the eight individual MRI parameters (graft infill = 1.00; signal intensity =
207 1.00; border integration = 0.93; surface contour = 1.00; structure = 0.92; subchondral lamina
208 = 1.00; subchondral bone = 1.00 and; effusion = 1.00), and an intra-class correlation
209 coefficient for the MRI composite score of 0.996 (95%CI: 0.991 – 0.999), for the 20
210 randomly selected image pairs.

211

212 Figures 1 to 5 present the Spearman correlation coefficients with 95% confidence intervals
213 and p-values for the association between each of the eight individual morphological MRI
214 parameters, as well as the MRI composite score, with the KOOS subscales of Pain (Figure 3),
215 Symptoms (Figure 4), ADL (Figure 5), Sport/Rec (Figure 6) and QOL (Figure 7), at each
216 post-operative assessment time point (1, 2 and 5 years post-surgery). The only MRI parameter
217 displaying consistent evidence of association with KOOS subscales was ‘effusion’, with a
218 pattern of increasing strength of correlations over time, and statistically significant
219 associations at 5 years with KOOS Pain (SCC 0.25, CI 0.04 to 0.45, p=0.020) (Figure 3),
220 ADL (SCC 0.26, CI 0.05 to 0.45, p=0.018) (Figure 5) and Sport/Rec (SCC 0.32, CI 0.12 to
221 0.50, p=0.003) (Figure 6). Additionally, a significant correlation was observed between
222 subchondral lamina with KOOS Sport-Rec at 1 year (SCC 0.27, CI 0.05 to 0.46, p=0.016)
223 (Figure 6), though no further significant findings were observed.

224

225 Insert Figures 1-5.

226 DISCUSSION

227

228 In this study, limited correlative capacity was demonstrated between clinical and radiological
229 outcomes up to 5 years post-surgery. The only morphological MRI scoring variable that was
230 consistently associated with the KOOS was effusion, with the strength of the association
231 between the two becoming stronger with time. Previous research has demonstrated significant
232 associations between clinical scores and effusion (assessed via MRI) for osteochondral
233 autologous transplantation^{38, 56} and microfracture,³⁵ with only one study to the best of our
234 knowledge in ACI³⁴ patients and all studies using the IKDC as the clinical measure. However,
235 the clinical relevance of effusion to the graft must be evaluated with caution, given that the
236 MOCART system (and all reported MRI-based scoring systems) specifically aims to score the
237 graft repair, rather than the knee in general. Effusion may not be associated with the graft
238 itself, rather a further unrelated knee condition, or ongoing knee degeneration. This may also
239 reflect the increasing strength of the association throughout the post-operative time line.

240

241 Conflicting outcomes exist with respect to the correlation between clinical and MRI-based
242 outcome after cartilage repair, at least in the limited and poorly reported literature specifically
243 on correlative outcomes. This is highlighted by the findings of two recent systematic reviews
244 on the topic;^{10, 15} one of which concluded that graft hypertrophy and signal intensity were the
245 strongest MRI-based correlates with clinical outcome after ACI,¹⁰ the other found that the
246 overall MRI score and graft infill were found to correlate most often with clinical outcome,¹⁵
247 albeit after a range of cartilage repair procedures. We observed no correlations between graft
248 infill, signal intensity or the composite score with KOOS domains, as outlined by these
249 systematic reviews. Furthermore, we did not specifically evaluate graft hypertrophy as a
250 parameter on its own, rather it was incorporated into the overall MRI composite score.
251 Several studies specifically using the MOCART scoring system to evaluate ACI have

252 reported no correlation between clinical and radiological outcomes, using varied PRO clinical
253 measures and across varied post-operative time points.^{18, 20, 23, 26, 46, 52, 54, 65, 67}
254

255 While the MOCART classification has been the most common system utilized for cartilage
256 repair,¹⁰ there are a number of issues in using these morphological scoring systems for the
257 purposes in this study. Firstly, clearly the post-operative timeline will play an important role
258 in graft maturity and integration, with Blackman et al.¹⁰ reporting that the most consistent
259 correlations between clinical and MRI-based assessments occur between 6-36 months. They
260 suggested the earliest time point with clinical utility is six months, given the MRI findings
261 that are considered abnormal before this time though are a normal part of the repair/healing
262 process. They also suggested the poor longer term correlations observed in their review may
263 reflect the potential for degenerative changes in the knee or a new (though unrelated) knee
264 injury. Second, given the most clinically relevant MRI parameters appear to differ between
265 different cartilage repair methods,¹⁰ it is possible that they also differ between different
266 generations of ACI (periosteal, collagen-covered and matrix-induced ACI, as well as
267 arthroscopic methods of performing the technique). Therefore, the association between
268 clinical and MRI-based outcome may differ from one ACI patient to the next, depending on
269 the surgical and implantation method. Thirdly, using a composite score to evaluate MRI-
270 based outcome may disturb its use in predicting clinical outcome, given the large number of
271 variables that combine to make such a score.¹⁴ Fourthly, the clinical significance of many of
272 these individual MRI-based variables is not completely understood, with particular reference
273 to subchondral bone and lamina.^{32, 41} Furthermore, other factors not included in these
274 combined MRI-based scores, or even visible on MRI, such as inflammation, increased
275 vascular penetration and nerve growth, may also influence clinical outcome.^{2, 3, 14} Finally, any
276 predictive value of MRI may prove difficult given the wide array of variables that may
277 influence patient outcome, including age,^{13, 18, 19, 31, 36} BMI,^{18, 30} chondral defect size,^{18, 20, 24}

278 location^{11, 42, 44} and aetiology,⁴⁶ joint degeneration⁵³ at the time of surgery, pre-operative
279 duration of symptoms,^{24, 36, 46, 51} number of prior knee surgeries³⁶ and post-operative
280 rehabilitation.^{19, 21, 22, 24}

281

282 A number of limitations existed within this retrospective study. Firstly, we employed the
283 KOOS as our method of clinical assessment, though a number of other clinically important
284 PROs have been employed to assess the effectiveness of ACI.⁶² At present, there is currently
285 no agreement on a ‘gold standard’ PRO measure for the evaluation of cartilage repair
286 surgery,²⁸ let alone ACI. Tanner et al.⁵⁵ have reported that the KOOS and IKDC contain the
287 most items important to post-operative knee patients, including ACL reconstruction, meniscal
288 tears and osteoarthritis. However, all five KOOS subscales have previously demonstrated
289 large effect sizes,^{25, 49} while certain aspects of the KOOS such as the Sport/Rec and QOL
290 subscales have scored higher in mean importance to patients, when compared with the
291 IKDC.²⁸ Furthermore, the KOOS (in particular the Sport/Rec and QOL subscales) has shown
292 to be very responsive to improvement after MACI surgery.²⁵

293

294 Secondly, for the assessment of radiological outcome we employed a morphological scoring
295 system,^{39, 48, 61, 64} whereby morphological parameters may be less consistent and contingent on
296 graft maturity.^{14, 53, 58} While the MOCART classification has been the most common system
297 utilized for cartilage repair,¹⁰ new methods of assessing the biochemical characteristics of
298 repair tissue are emerging.^{37, 57, 60} This may assist in evaluating the ‘ultra-structure’ of the
299 repair tissue¹⁶ and, in time, may reflect a more accurate assessment of MRI-based outcome,
300 thereby altering the correlation between MRI-based and patient-reported clinical outcomes.
301 Thirdly, the outcomes of this retrospective analysis are limited to patients undergoing MACI
302 to the femoral condyles. It has been shown that the most clinically relevant MRI parameters

303 differ between different cartilage repair methods¹⁰ and, therefore, they may also differ
304 between different generations of ACI and specific graft locations.

305

306 To the best of our knowledge, this is the first study to specifically determine the correlation of
307 a commonly used PRO measure (i.e. KOOS), with the most commonly employed MRI
308 scoring system (MOCART) for evaluating cartilage repair, in MACI patients to five years
309 post-surgery. Apart from consistent evidence of association between KOOS subscales and
310 effusion, with a pattern of increasing strength of correlations over time, this analysis
311 demonstrated limited correlative capacity between clinical and radiological outcomes. Further
312 research through larger prospective trials is required to better evaluate these associations in
313 patients following varied generations of ACI, as well as different cartilage repair methods.

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- 530

531 FIGURE LEGENDS

532

533 FIGURE 1. Proton density fast spin echo magnetic resonance image of a MACI graft
534 (between white arrows) to the medial femoral condyle at 5 years post-surgery, demonstrating
535 equivalent signal and infill characteristics, as well as good integration with the adjacent native
536 cartilage and underlying bone.

537

538 FIGURE 2. Proton density fast spin echo magnetic resonance image of a hypertrophic MACI
539 graft (between white arrows) to the medial femoral condyle at 5 years post-surgery.

540

541 FIGURE 3. Spearman correlation coefficients with 95% confidence intervals (CI) and p-
542 values for the association between each of the eight individual morphological MRI
543 parameters, as well as the MRI composite score, with KOOS Pain at 1 year (1y), 2 years (2y)
544 and 5 years (5y) after MACI.

545

546 FIGURE 4. Spearman correlation coefficients with 95% confidence intervals (CI) and p-
547 values for the association between each of the eight individual morphological MRI
548 parameters, as well as the MRI composite score, with KOOS Symptoms at 1 year (1y), 2
549 years (2y) and 5 years (5y) after MACI.

550

551 FIGURE 5. Spearman correlation coefficients with 95% confidence intervals (CI) and p-
552 values for the association between each of the eight individual morphological MRI
553 parameters, as well as the MRI composite score, with KOOS ADL at 1 year (1y), 2 years (2y)
554 and 5 years (5y) after MACI.

555

556 FIGURE 6. Spearman correlation coefficients with 95% confidence intervals (CI) and p-
557 values for the association between each of the eight individual morphological MRI
558 parameters, as well as the MRI composite score, with KOOS Sport/Rec at 1 year (1y), 2 years
559 (2y) and 5 years (5y) after MACI.

560

561 FIGURE 7. Spearman correlation coefficients with 95% confidence intervals (CI) and p-
562 values for the association between each of the eight individual morphological MRI
563 parameters, as well as the MRI composite score, with KOOS QOL at 1 year (1y), 2 years (2y)
564 and 5 years (5y) after MACI.

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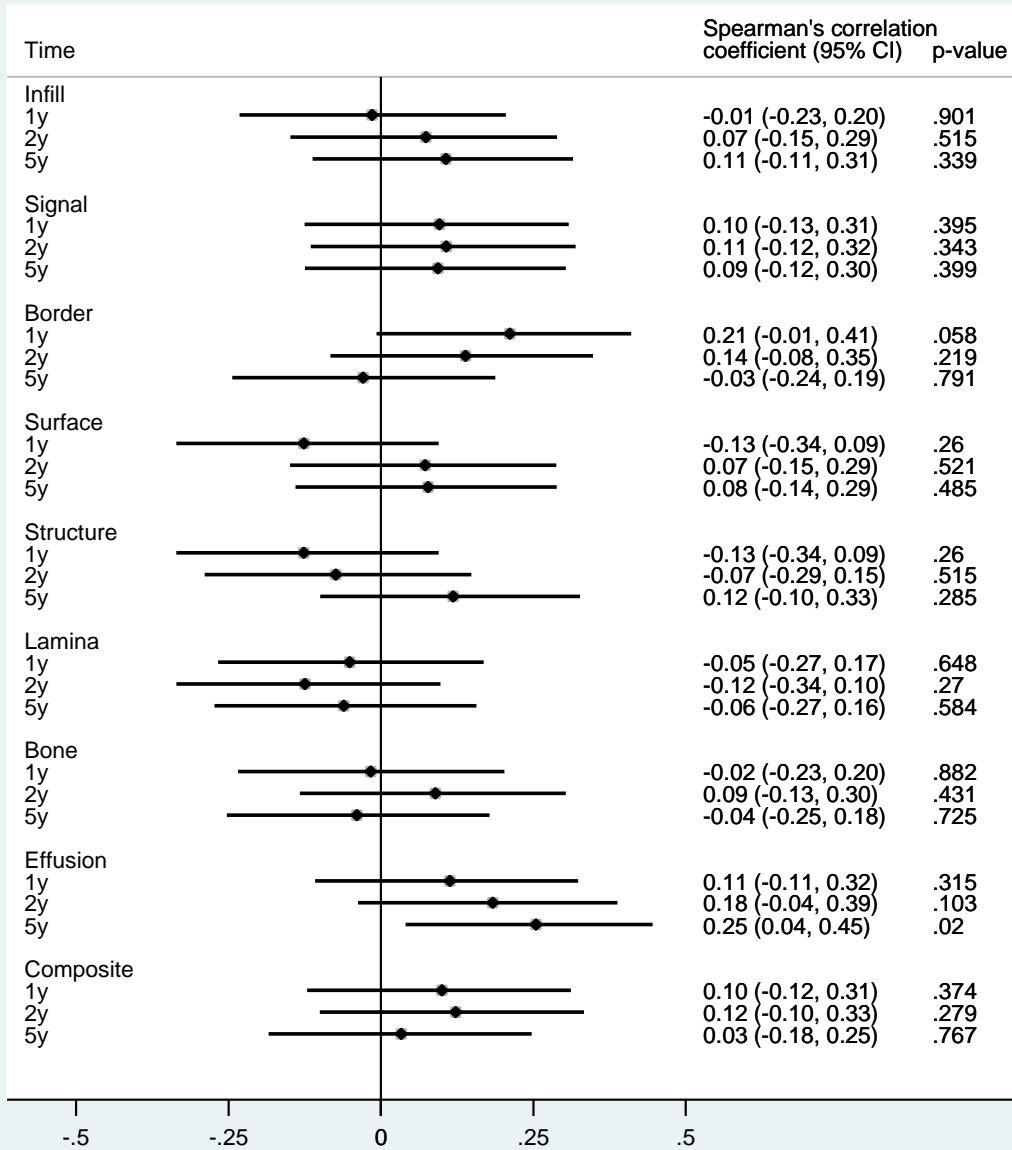
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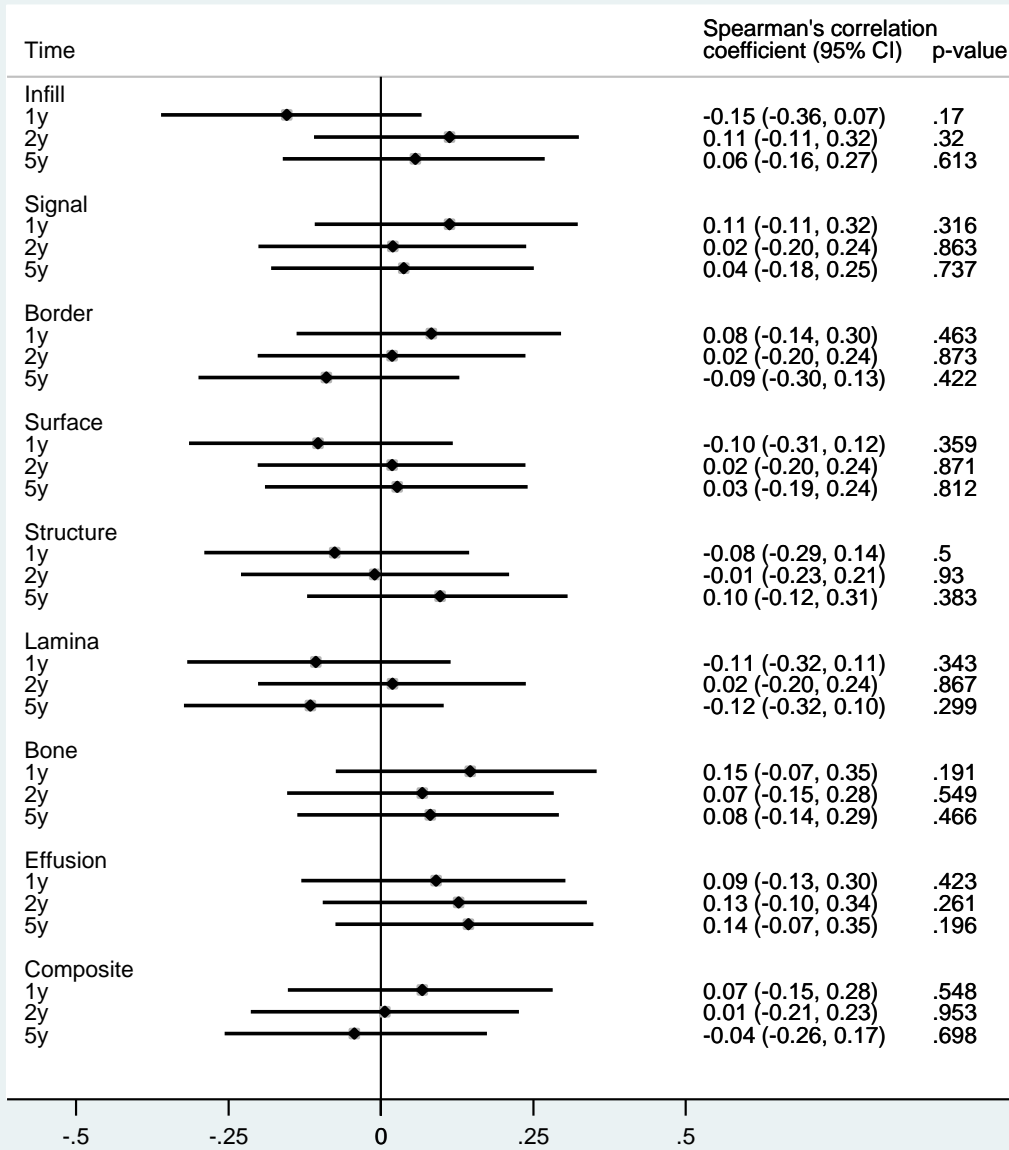
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KOOS Pain



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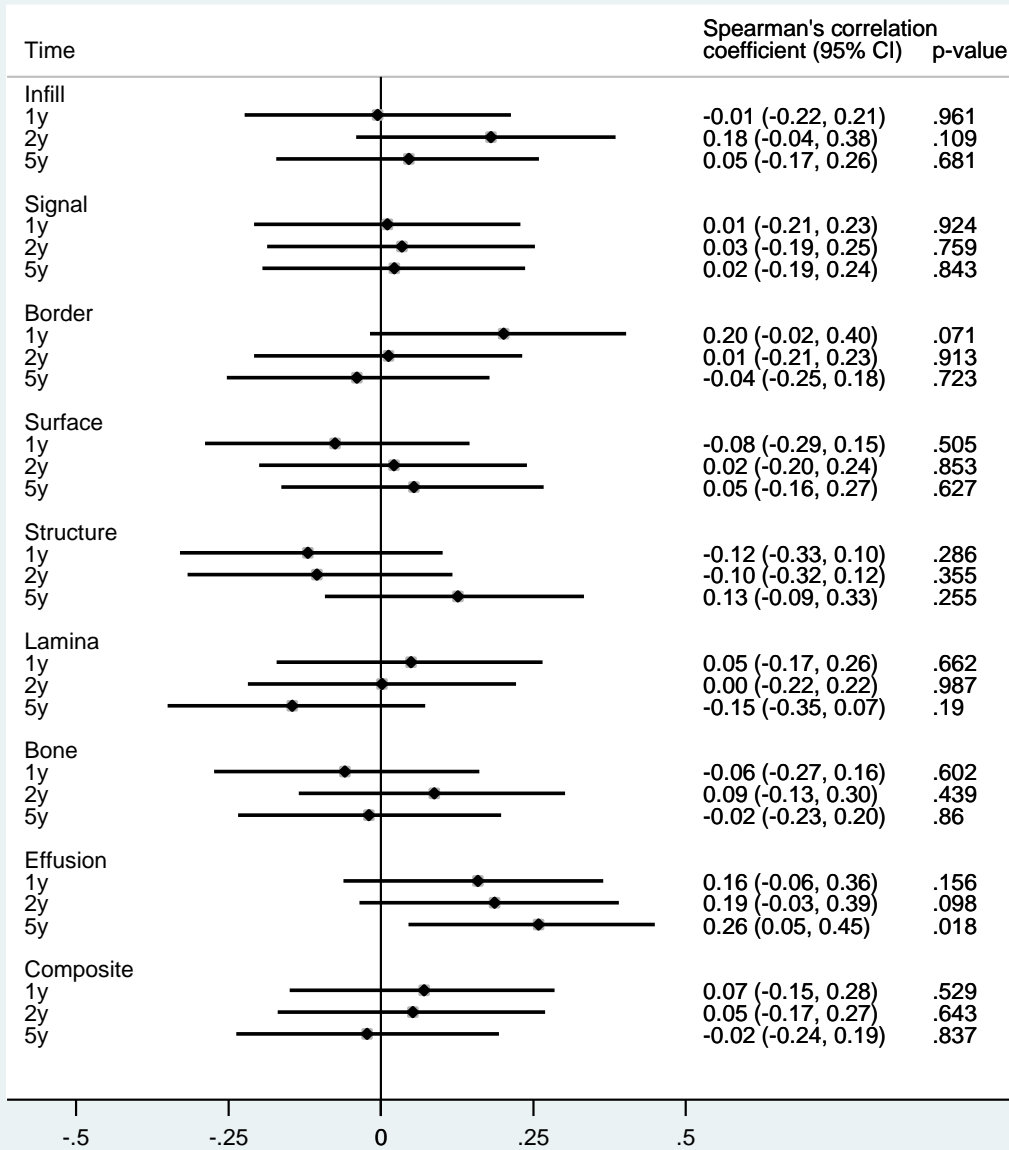
KOOS Symptoms



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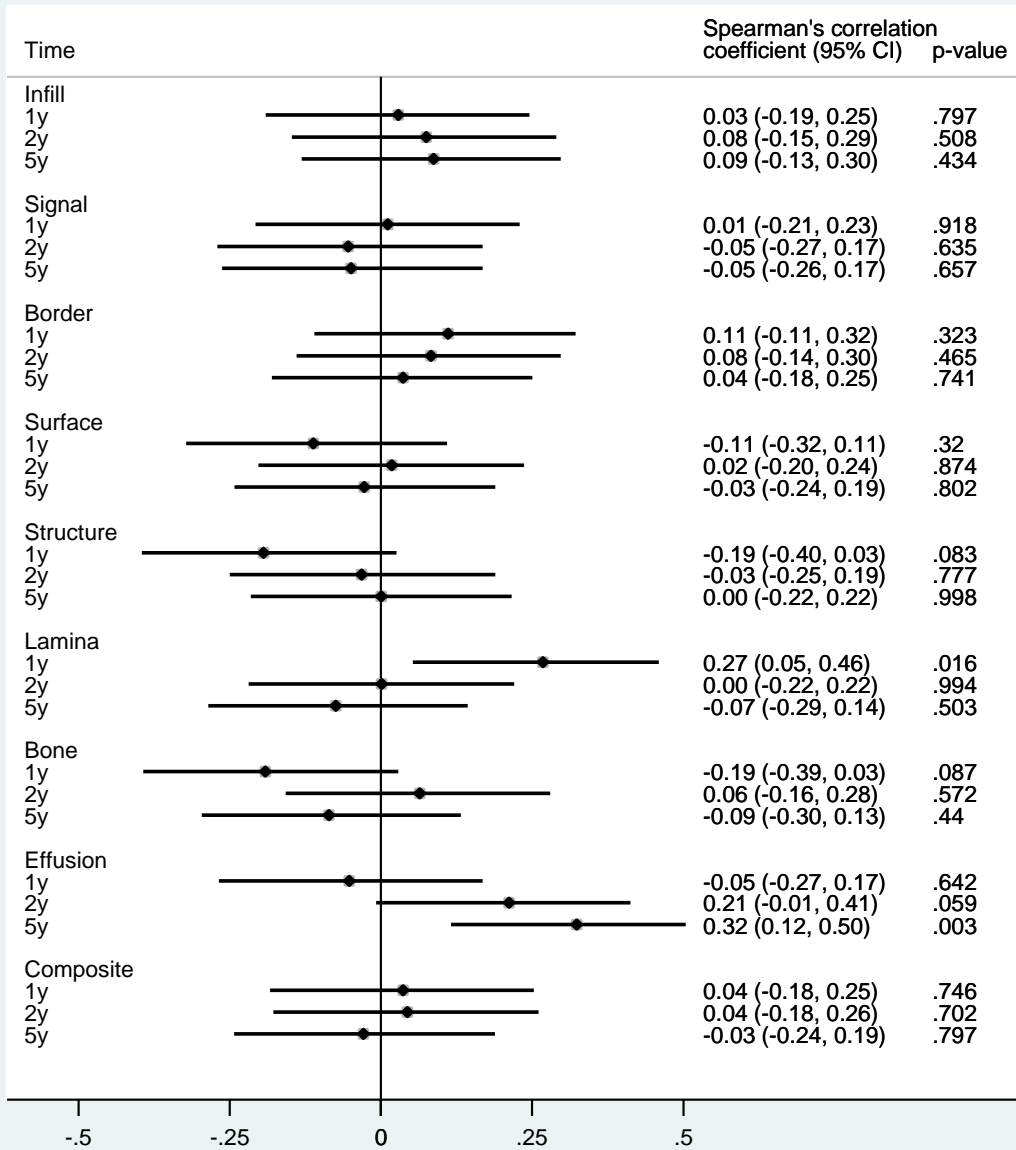
KOOS Activities of Daily Living



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KOOS Sport & Recreation



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KOOS Quality of Life

