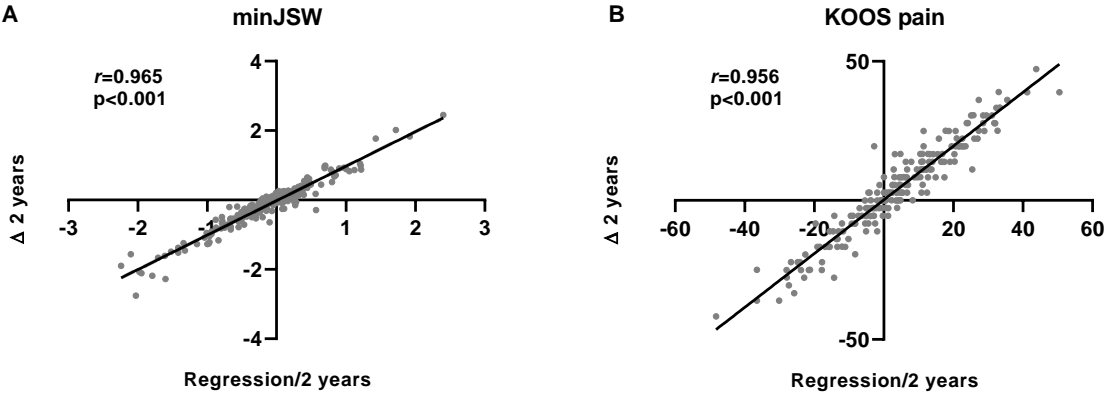


Supplementary Data S1: Correlations between absolute change and regression over 2 years

Figure S1. Correlations between absolute change and regression



Correlation between absolute change in 2 years and regression over 2 years of (A) minJSW (B) KOOS pain

Supplementary Data S2: Cut-off points for the P progression score in patients with *pain increase* and *stable significant pain*

Table S1a. Possible cut-off points for the P progression score in patients with *pain increase*

Cut-offs are based on percentile of the progression score. With a cut-off of 0.158 (10th percentile) 90% will be classified as progressor. With a cut-off of 0.742 (90th percentile) 10% will be classified as progressor, etc.

P score Cut-off*	Δ KOOS pain		Regression KOOS pain	
	Sensitivity	Specificity	Sensitivity	Specificity
0.158	100.0%	12.2%	100.0%	12.4%
0.198	96.0%	23.5%	96.4%	23.9%
0.240	96.0%	34.4%	96.4%	34.9%
0.300	84.0%	43.4%	85.7%	44.0%
0.407	68.0%	53.4%	71.4%	57.8%
0.492	60.0%	62.9%	67.9%	64.2%
0.580	36.0%	71.5%	46.4%	72.9%
0.663	32.0%	80.1%	39.3%	81.2%
0.742	24.0%	91.4%	21.4%	91.3%

Table S1b: Possible cut-off points for P progression score in patients with *stable significant pain*

Cut-offs are based on percentile of the progression score. With a cut-off of 0.158 (10th percentile) 90% will be classified as progressor. With a cut-off of 0.742 (90th percentile) 10% will be classified as progressor, etc.

P score Cut-off	Δ KOOS pain		Regression KOOS pain	
	Sensitivity	Specificity	Sensitivity	Specificity
0.158	100.0%	13.1%	100.0%	13.0%
0.198	100.0%	25.7%	100.0%	25.6%
0.240	97.5%	36.9%	97.4%	37.2%
0.300	95.0%	47.6%	94.9%	47.3%
0.407	92.5%	59.7%	92.3%	59.4%
0.492	82.5%	68.9%	82.1%	68.6%
0.580	70.0%	78.6%	69.2%	78.3%
0.663	60.0%	86.4%	59.0%	86.0%
0.742	27.5%	93.2%	28.2%	93.2%

Supplementary Data S3: Analyses using WOMAC pain scores instead of KOOS pain scores

Observed number of pain progressors

Table S2a. Pain progressors

Number of patients n(%)	Total	Non- progressors	Pain progressors		
			Pain increase	Stable significant pain	
ΔWOMAC pain	246	176 (71.5%)	70 (28.5%)	44 (62.9%)	26 (37.1%)
Regression WOMAC pain	246	182 (74.0%)	64 (26.0%)	36 (56.3%)	28 (43.7%)

Pain progressors according to the definition described in the study protocol and above. The total cohort consisted of 297 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 83% of patients for analyses.

Table S2b. Radiographic and/or pain progressors in the IMI-APPROACH cohort

Number of patients n (%)	Total	Non- progressors	Radiographic progressors	Pain progressors	Radiographic + pain progressors
Δ	221	125 (56.6%)	31 (14.0%)	56 (25.3%)	9 (4.1%)
Regression	242	133 (55.0%)	46 (19.0%)	54 (18.2%)	9 (3.7%)

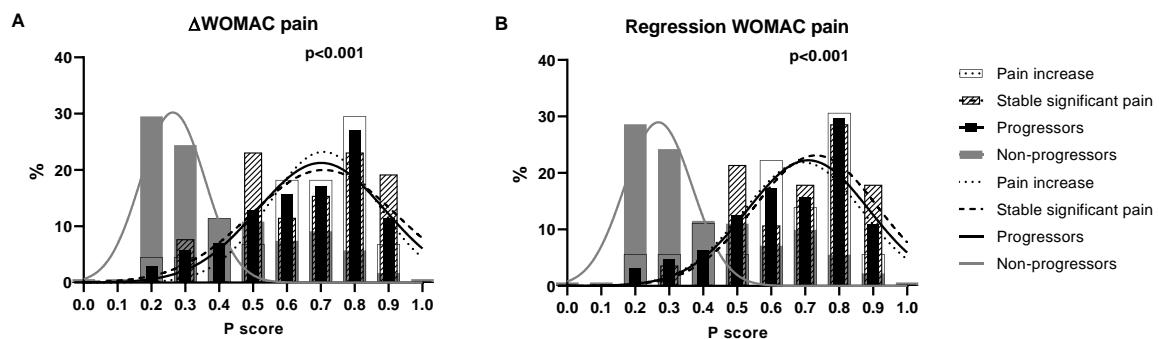
Radiographic and/or pain progressors in the IMI-APPROACH cohort. The total cohort consisted of 297 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 74% of patients for analyses using Δ and 81% for analyses using regression.

Differences in P progression score between pain progressors and non-progressors

Table S3. mean P progression scores

	Δ WOMAC pain	Regression WOMAC pain
Non-progressors	0.351±0.198	0.358±0.202
Progressors	0.602±0.180	0.607±0.176
<i>Pain increase</i>	0.587±0.186	0.574±0.189
<i>Stable significant pain</i>	0.627±0.170	0.650±0.150

Figure S2. P progression of pain progressors and non-progressors



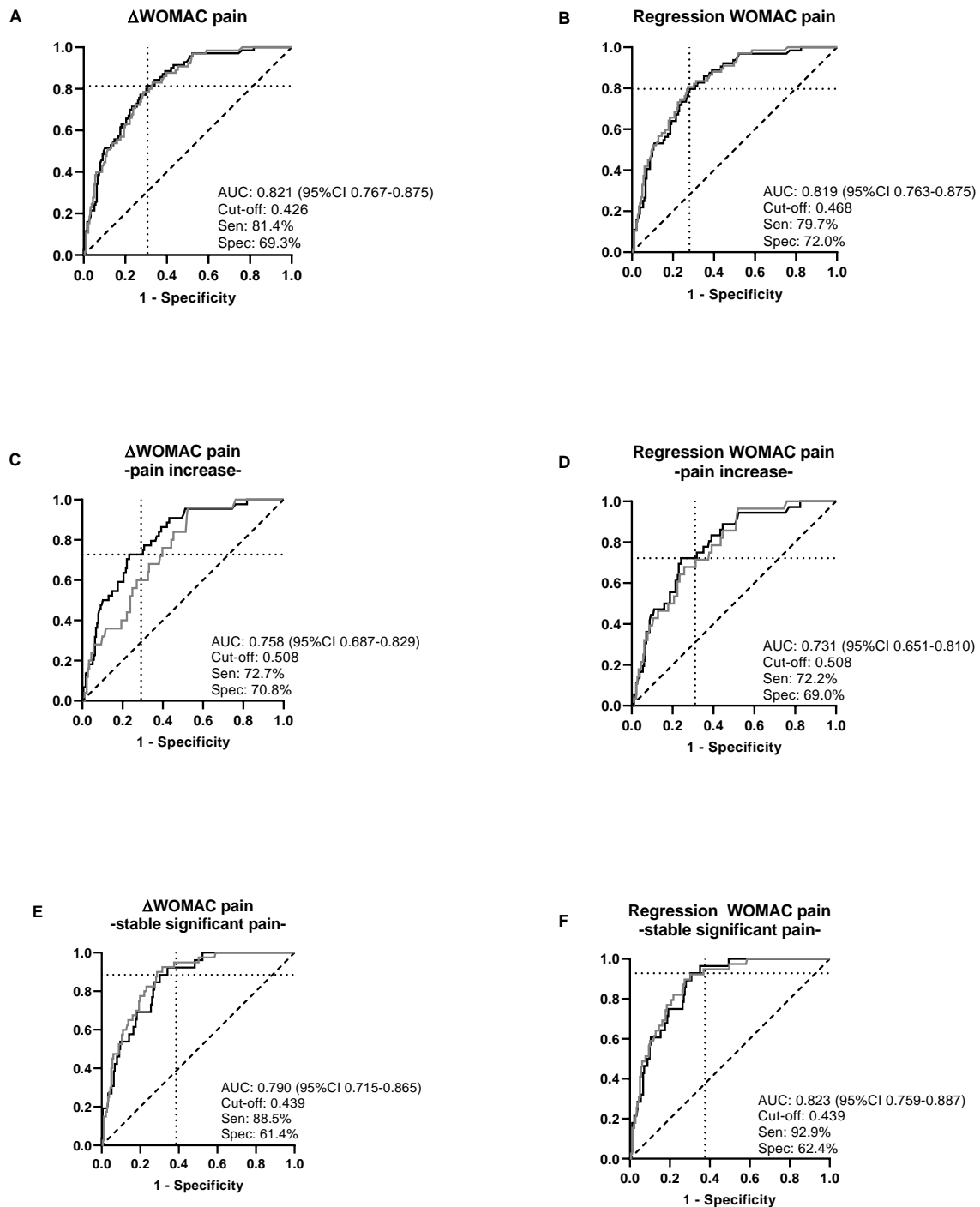
(A) P progression scores for actual pain progressors (n=70; black) and non-progressors (n=176; grey), as well as for patients with *pain increase* (n=44; dotted) and patients with *stable significant pain* (n=26; dashed) using the absolute decrease during the 2-year follow-up period

(B) P progression scores for actual pain progressors (n=64; black) and non-progressors (n=182; grey), as well as for patients with *pain increase* (n=36; dotted) and patients with *stable significant pain* (n=28; dashed) using the regression over 2 years of each individual patient.

Ability of P progression score to identify pain progressors

Figure S3. P progression of pain progressors and non-progressors

The black curves represent the ROC curves using WOMAC pain. The grey curves represent the ROC curves using KOOS pain.



ROC curves for Δ WOMAC pain and regression WOMAC pain for total progressors (A+B), patients with *pain increase* (C+D), and patients with *stable significant pain* (E+F)

AUC: area under the curve, Sen: sensitivity, Spec: specificity

Supplementary Data S4: Analyses including only CHECK patients or excluding CHECK patients

Observed numbers of radiographic and pain progressors in the IMI-APPROACH cohort

Table S4a. Radiographic progressors including only CHECK patients

Number of patients n (%)	Total	Progressors	Non-progressors
Δ minJSW	124	24 (19.4%)	100 (80.6%)
Regression minJSW	143	32 (22.4%)	111 (77.6%)

Radiographic progressors according to the definition described in the study protocol. The total cohort consisted of 153 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 81% of patients for analyses using Δ minJSW and 93% for analyses using regression minJSW.

Table S4b. Radiographic progressors excluding CHECK patients

Number of patients n (%)	Total	Progressors	Non-progressors
Δ minJSW	100	17 (17.0%)	83 (83.0%)
Regression minJSW	123	31 (25.2%)	92 (74.8%)

Radiographic progressors according to the definition described in the study protocol. The total cohort consisted of 144 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 69% of patients for analyses using Δ minJSW and 85% for analyses using regression minJSW.

Table S4c. Pain progressors including only CHECK patients

Number of patients n (%)	Total	Non-progressors	Pain progressors		
			Pain increase	Stable significant pain	
Δ KOOS pain	131	108 (82.4%)	23 (17.6%)	8 (34.8%)	15 (65.2%)
Regression KOOS pain	131	107 (81.7%)	24 (18.3%)	9 (37.5%)	15 (62.5%)

Pain progressors according to the definition described in the study protocol. The total cohort consisted of 153 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 86% of patients for analyses.

Table S4d. Pain progressors excluding CHECK patients

Number of patients n (%)	Total	Non-progressors	Pain progressors		
			Pain increase	Stable significant pain	
Δ KOOS pain	115	73 (63.5%)	42 (36.5%)	17 (40.5%)	25 (59.5%)
Regression KOOS pain	115	72 (62.6%)	43 (37.4%)	19 (44.2%)	24 (55.8%)

Pain progressors according to the definition described in the study protocol. The total cohort consisted of 144 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 80% of patients for analyses.

Table S4e. Radiographic and/or pain progressors including only CHECK patients

Number of patients n (%)	Total	Non- progressors	Radiographic progressors	Pain progressors	Radiographic + pain progressors
Δ	122	81 (66.4%)	19 (15.6%)	18 (14.8%)	4 (3.3%)
Regression	130	80 (61.5%)	26 (20.0%)	20 (15.4%)	4 (3.1%)

Radiographic and/or pain progressors in the IMI-APPROACH cohort. The total cohort consisted of 153 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 80% of patients for analyses using Δ and 85% for analyses using regression.

Table S4f. Radiographic and/or pain progressors excluding CHECK patients

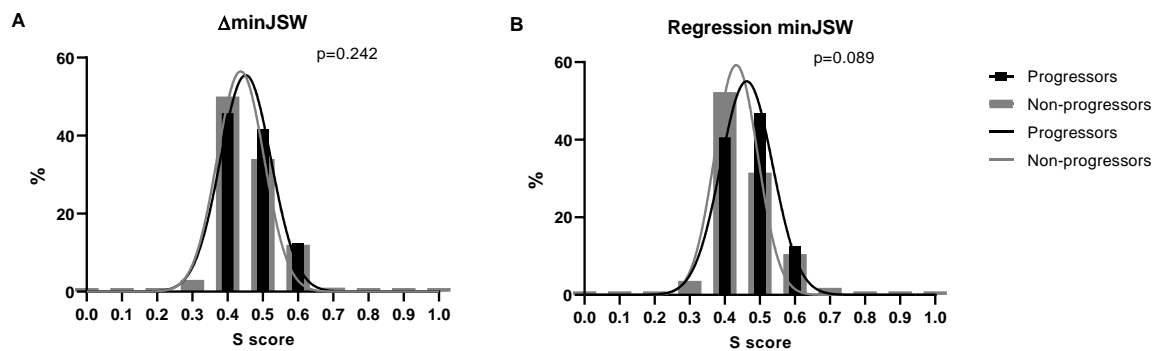
Number of patients n (%)	Total	Non- progressors	Radiographic progressors	Pain progressors	Radiographic + pain progressors
Δ	99	46 (46.5%)	12 (12.1%)	36 (36.4%)	5 (5.1%)
Regression	112	50 (44.6%)	19 (17.0%)	37 (33.0%)	6 (5.4%)

Radiographic and/or pain progressors in the IMI-APPROACH cohort. The total cohort consisted of 144 patients; because of the COVID-19 pandemic a relatively large number of M024 visits were missed leaving 69% of patients for analyses using Δ and 78% for analyses using regression.

Differences in S/P progression score between radiographic/pain progressors and non-progressors
Figure S4a. S progression score of radiographic progressors and non-progressors including only CHECK patients

Mean S progression scores

	Δ minJSW	Regression minJSW
Non-progressors	0.407±0.073	0.406±0.074
Progressors	0.425±0.065	0.429±0.064

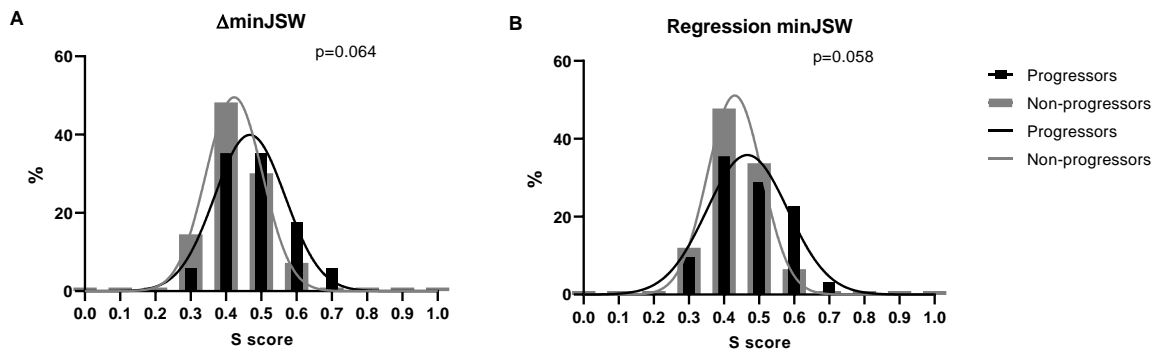


- (A) S progression scores for actual radiographic progressors (absolute decrease in 2 year ≥ 0.6 mm, n=24) and non-progressors (n=100)
- (B) S progression scores for actual radiographic progressors (regression of each patient ≥ 0.6 mm/2 year, n=32) and non-progressors (n=111)

Figure S4b. S progression score of radiographic progressors and non-progressors excluding CHECK patients

Mean S progression scores

	Δ minJSW	Regression minJSW
Non-progressors	0.382±0.077	0.386±0.075
Progressors	0.428±0.090	0.425±0.103



- (A) S progression scores for actual radiographic progressors (absolute decrease in 2 year ≥ 0.6 mm, n=17) and non-progressors (n=83)
- (B) S progression scores for actual radiographic progressors (regression of each patient ≥ 0.6 mm/2 year, n=31) and non-progressors (n=92)

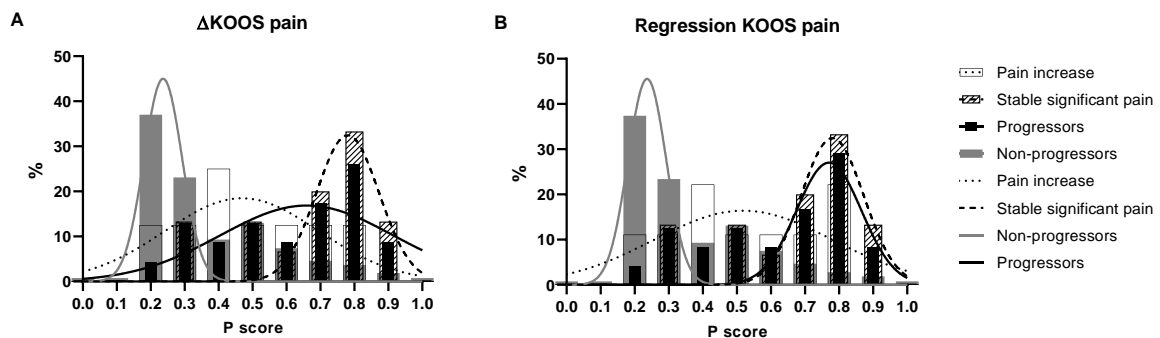
Figure S4c. P progression score of pain progressors and non-progressors including only CHECK patients

Mean P progression scores

	Δ KOOS pain	Regression KOOS pain
Non-progressors	0.317±0.185	0.314±0.182
Progressors	0.562±0.206	0.568±0.203
<i>Pain increase</i>	0.444±0.189	0.473±0.197
<i>Stable significant pain</i>	0.625±0.191	0.625±0.191

Comparison of P progression scores between different pain progression groups.

	Δ KOOS pain	Regression KOOS pain
Progressors vs non-progressors	p<0.001	p<0.001
<i>Pain increase</i> vs non-progressors	p=0.104	p=0.043
<i>Stable significant pain</i> vs non-progressors	p<0.001	p<0.001



- (A) P progression scores for actual pain progressors (n=23; black) and non-progressors (n=108; grey), as well as for patients with *pain increase* (n=8; dotted) and patients with *stable significant pain* (n=15; dashed) using the absolute decrease during the 2-year follow-up period
- (B) P progression scores for actual pain progressors (n=24; black) and non-progressors (n=107; grey), as well as for patients with *pain increase* (n=9; dotted) and patients with *stable significant pain* (n=15; dashed) using the regression over 2 years of each individual patient.

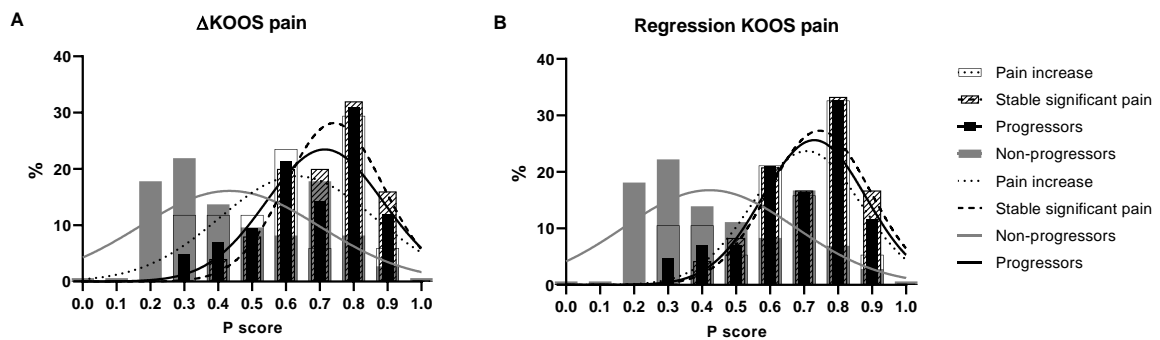
Figure S4d. P progression score of pain progressors and non-progressors excluding CHECK patients

Mean P progression scores

	Δ KOOS pain	Regression KOOS pain
Non-progressors	0.420±0.210	0.413±0.207
Progressors	0.629±0.160	0.636±0.155
<i>Pain increase</i>	0.569±0.192	0.594±0.182
<i>Stable significant pain</i>	0.670±0.121	0.670±0.124

Comparison of P progression scores between different pain progression groups.

	Δ KOOS pain	Regression KOOS pain
Progressors vs non-progressors	p<0.001	p<0.001
<i>Pain increase</i> vs non-progressors	p=0.009	p=0.001
<i>Stable significant pain</i> vs non-progressors	p<0.001	p<0.001

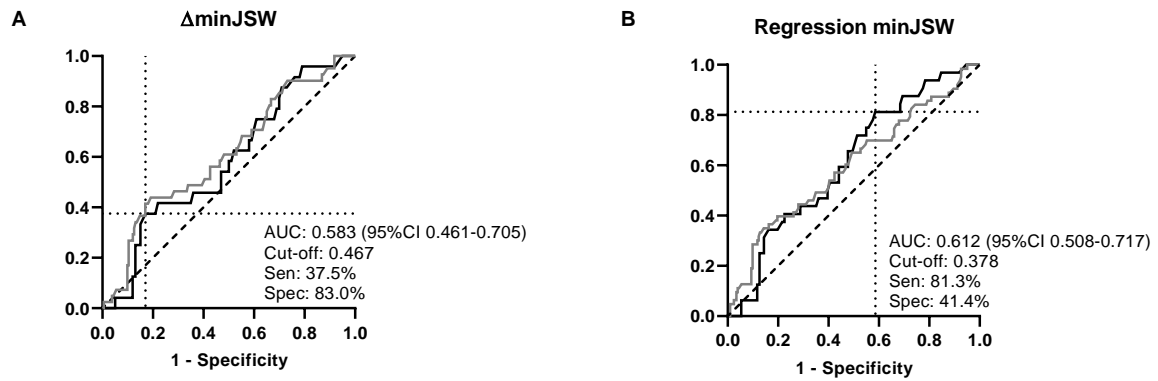


- (A) P progression scores for actual pain progressors (n=42; black) and non-progressors (n=73; grey), as well as for patients with *pain increase* (n=17; dotted) and patients with *stable significant pain* (n=25; dashed) using the absolute decrease during the 2-year follow-up period
- (B) P progression scores for actual pain progressors (n=43; black) and non-progressors (n=72; grey), as well as for patients with *pain increase* (n=19; dotted) and patients with *stable significant pain* (n=24; dashed) using the regression over 2 years of each individual patient.

Ability of S/P progression score to identify radiographic/pain progressors

Figure S5a. ROC-curves S progression score including only CHECK patients

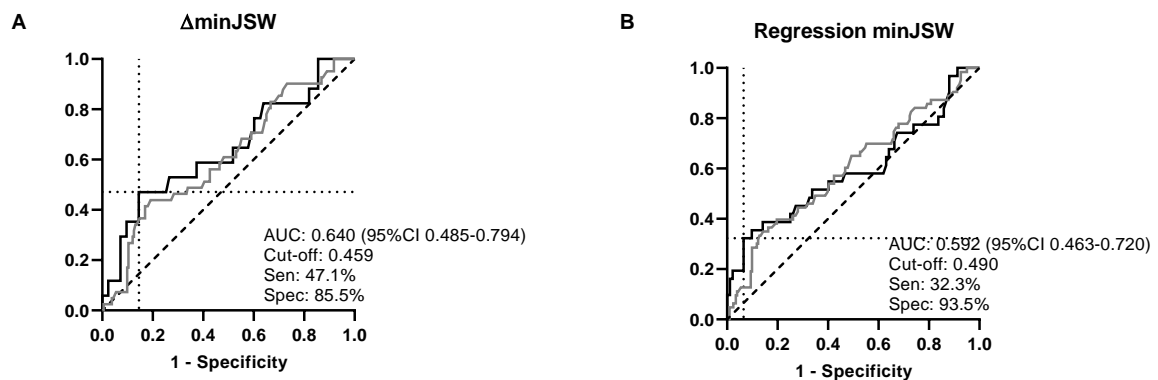
The black curves represent the ROC curves including only CHECK patients. The grey curves represent the ROC curves of all IMI-APPROACH patients, as presented in the main file.



ROC curves for Δ minJSW (A) and regression minJSW (B)
AUC: area under the curve, Sen: sensitivity, Spec: specificity

Figure S5b. ROC-curves S progression score excluding CHECK patients

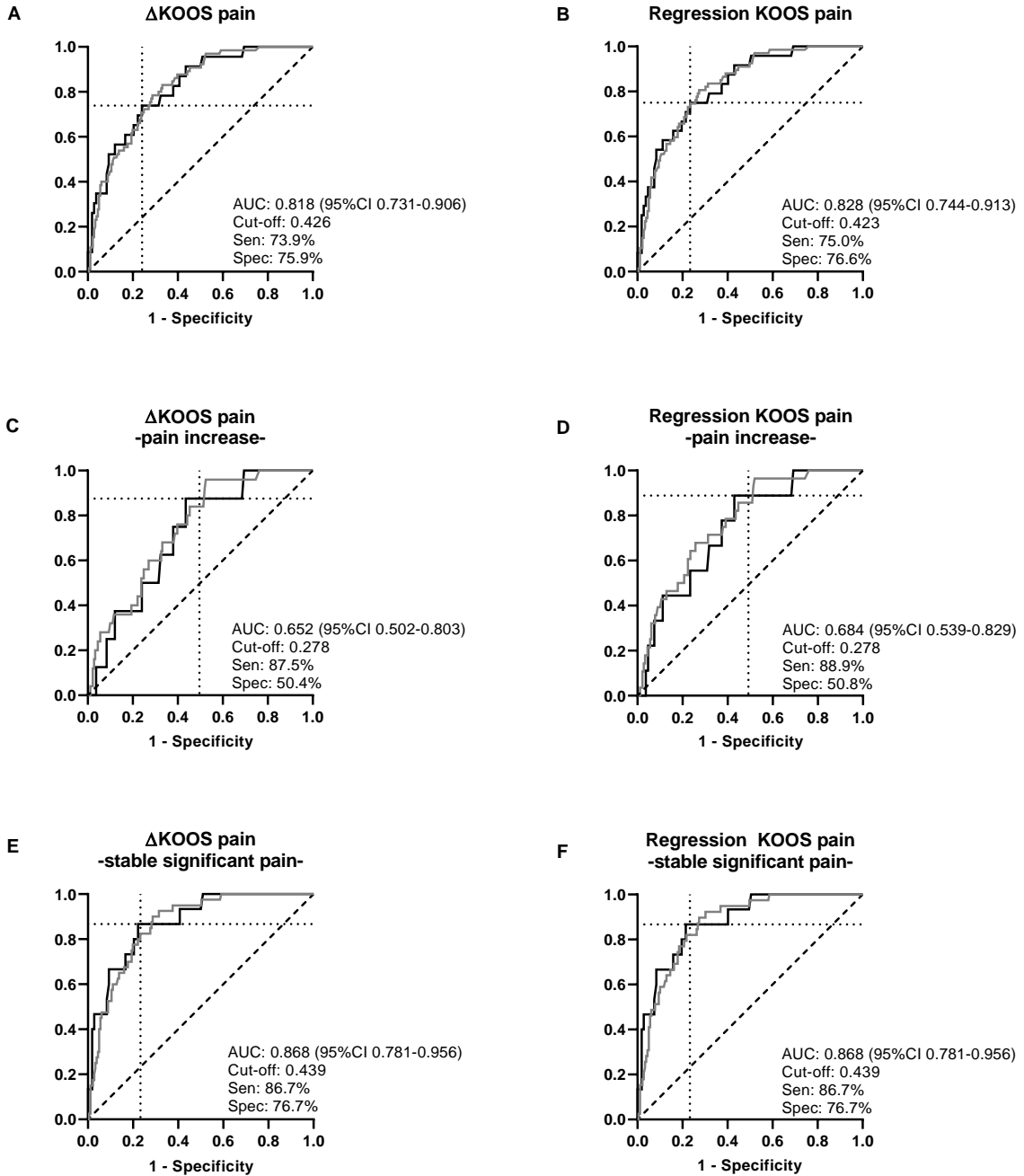
The black curves represent the ROC curves excluding CHECK patients. The grey curves represent the ROC curves of all IMI-APPROACH patients, as presented in the main file.



ROC curves for Δ minJSW (A) and regression minJSW (B)
AUC: area under the curve, Sen: sensitivity, Spec: specificity

Figure S6a. ROC-curves P progression score including only CHECK patients

The black curves represent the ROC curves including only CHECK patients. The grey curves represent the ROC curves of all IMI-APPROACH patients, as presented in the main file.

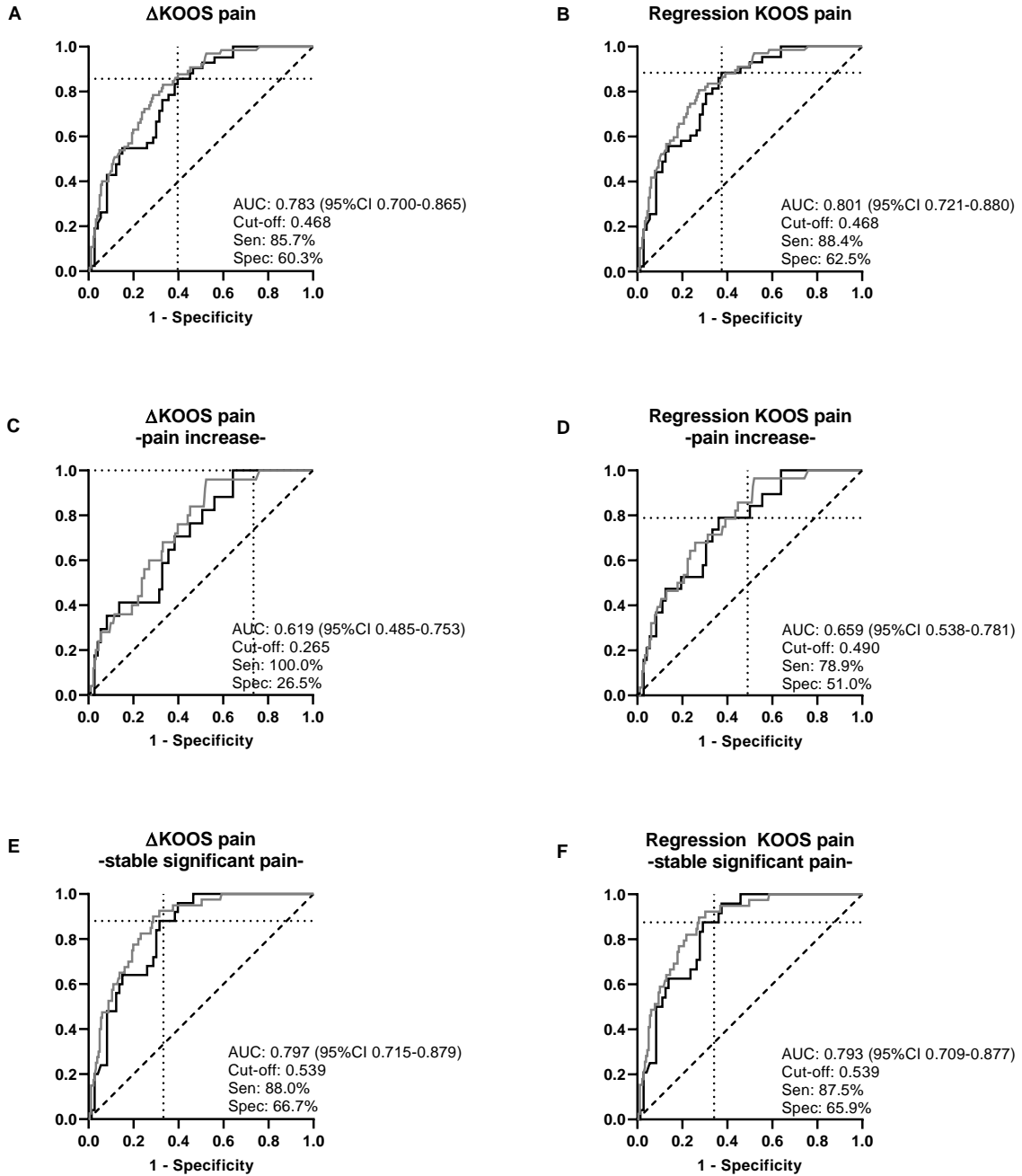


ROC curves for Δ KOOS pain and regression KOOS pain for total progressors (A+B), patients with *pain increase* (C+D), and patients with *stable significant pain* (E+F)

AUC: area under the curve, Sen: sensitivity, Spec: specificity

Figure S6b. ROC-curves P progression score excluding CHECK patients

The black curves represent the ROC curves excluding CHECK patients. The grey curves represent the ROC curves of all IMI-APPROACH patients, as presented in the main file.



ROC curves for Δ KOOS pain and regression KOOS pain for total progressors (A+B), patients with *pain increase* (C+D), and patients with *stable significant pain* (E+F)

AUC: area under the curve, Sen: sensitivity, Spec: specificity