MR imaging of the knee in primary care
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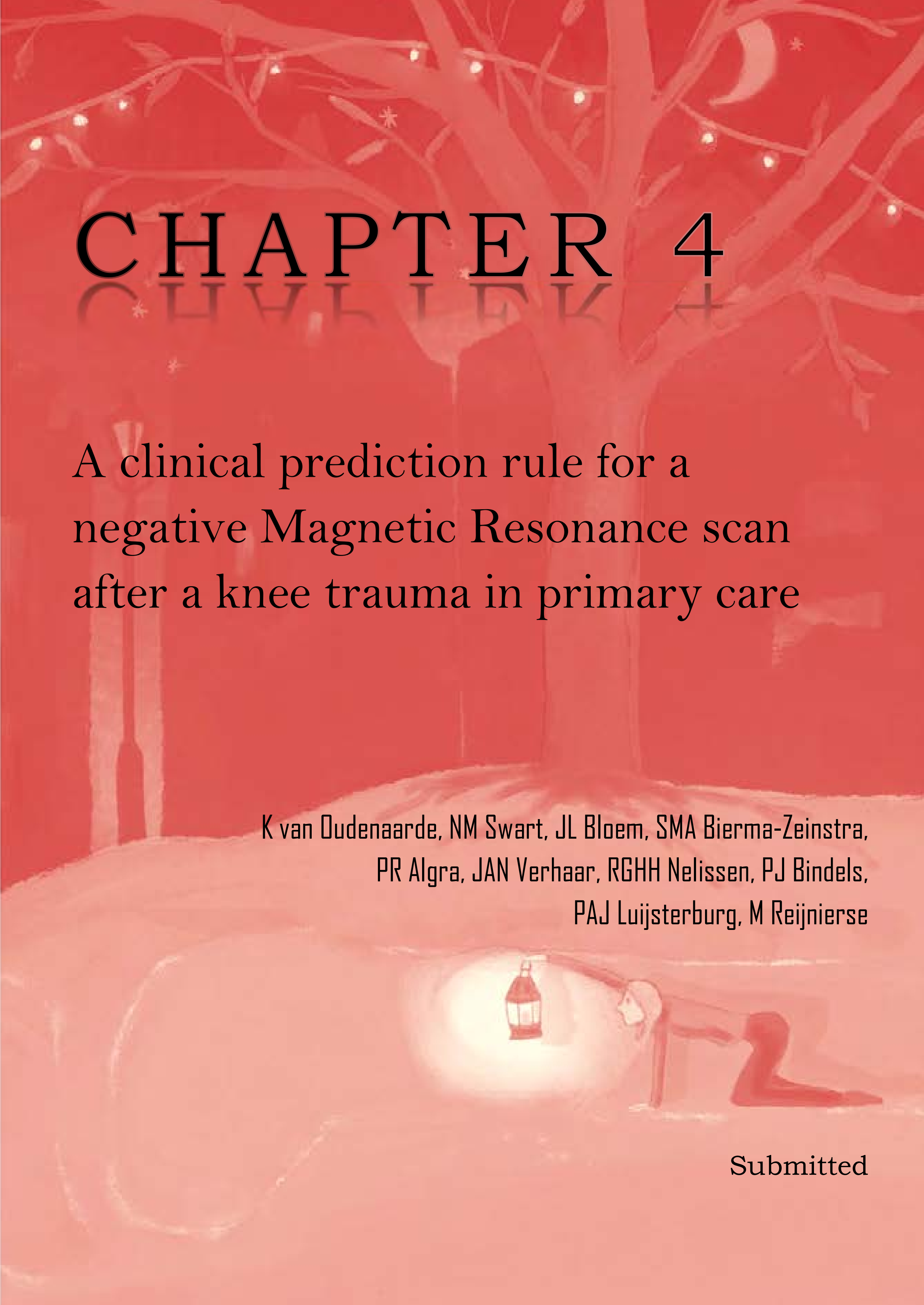

CHAPTER 4

A clinical prediction rule for a negative Magnetic Resonance scan after a knee trauma in primary care

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ABSTRACT

Background

The vast majority of patients present with self-limiting injuries in general practice after a knee trauma. Our aim was to develop a clinical prediction rule for a negative MR after a recent knee trauma in patients aged 18-45 years, supporting the initial treatment in primary care.

Questions

1. Which predictors are statistically significantly correlated with negative MR results?
2. Can we combine these predictors into a straightforward and non-time consuming prediction model to support GP's to maintain such patients in primary care?
3. What is the performance of this prediction model and does it result in an increased probability of a negative MR scan?
4. Is the prediction model externally valid using a comparable cohort in primary care?

Methods

We used self-reported data of patients with an available MR scan included in the MR imaging arm of a randomised controlled trial on the yield of MR imaging in primary care.
The outcome 'negative MR' was defined as all findings excluding fractures, complete ruptures of collateral ligaments, traumatic meniscal tears, cruciate ligament ruptures and full thickness cartilage defects. Candidate predictors were single questions extracted from validated knee questionnaires. A Lasso regression analysis selected the final independent predictors, for which a 0 (absent) or 1 (present) could be scored.

Results

1. Which predictors are statistically significantly correlated with negative MR results?
A non-sports related trauma, no severe pain during twisting/pivoting of the weightbearing knee, ability to squat below 90°, no morning joint stiffness, no direct pain after trauma, ≥3 months complaints and presence of a musculoskeletal comorbidity were selected for the final prediction model and showed highest association with a negative MR scan.

2. Can we combine these predictors into a straightforward and non-time consuming prediction model to support GP's to maintain such patients in primary care?

Presence of a predictor will score 1 point in the clinical prediction rule including these 7 predictors. With the presence of 3 or more predictors the post-test probability raised from 61% to 82%.

3. What is the performance of this prediction model and does it result in an increased probability of a negative MR scan?

We measured an area under the curve of 0.850 with a 81% sensitivity and 72% specificity. The median score in the group with a negative MR was 4 (interquartile (IQR) range 3 to 5), compared to a median score of 1 (IQR 1 to 2) in the group with a positive MR, $p<0.001$

4. Is the prediction model externally valid using a comparable cohort in primary care?

The prediction rule showed a similar performance in a comparable cohort of patients with traumatic knee complaints seen in general practice, with an AUC of 0.75 (95%CI 0.63 to 0.86).

Conclusions

The high discriminative ability enables the general practitioner to identify patients for a watchful waiting policy, without the use of MR imaging.

INTRODUCTION

Magnetic Resonance (MR) Imaging has a high diagnostic accuracy for the detection of menisci and cruciate ligaments injuries and is therefore the imaging modality of choice to diagnose traumatic injuries of the knee.[1] In primary care, the amount of ordered MR scans has increased substantially the past decades[2], and the need for guidelines on the appropriate use of MR imaging have emerged.[3] Several guidelines have been published, unfortunately with conflicting advices on indications for a radiograph prior to MR imaging and when to refer to MR imaging or to an orthopaedic surgeon.[4–6] It is known that MR imaging increases the general practitioner's (GP) diagnostic and therapeutic confidence.[7,8] However, GPs should also be confident without MR imaging and be able to make a shared decision with the patient regarding a watchful waiting policy, moreover since the vast majority present with self-limiting injuries.[9] Furthermore, a recent randomized controlled trial concluded that requesting an MR scan in primary care for young patients (<45 years) with a recent knee trauma is not cost-effective.[10]

In previous studies several signs and symptoms were identified being associated with either the presence of a meniscal tear or the presence of a cruciate ligament rupture.[11–14] To our knowledge, no data exists on factors associated with the overall yield of the MR scan, in which a positive MR scan often results from a combination of ligamentous injury, meniscal pathology and/or bone and cartilage injury and in which a negative MR scan results from the absence of such findings.

We included relatively young patients (<45 years) with knee symptoms after a recent trauma who received an MR scan as part of a randomized controlled trial in primary care (MR scans in half of the cohort) and sought answers to the following questions:

1. Which predictors are statistically significantly correlated with negative MR results?
2. Can we combine these predictors into a straightforward and non-time consuming prediction model to support GP's to maintain such patients in primary care?
3. What is the performance of this prediction model and does it result in an increased probability of a negative MR scan?
4. Is the prediction model externally valid using a comparable cohort in primary care?

MATERIAL AND METHODS

Study design

Data were used from the TraumAtic Complaints of the Knee – LUMC and Erasmus MC (TACKLE) Trial, a multicentre randomised controlled trial to determine the (cost-) efficacy of an MR scan requested by the GP for patients with a recent knee trauma. The complete study protocol was published previously.[15] Inclusion criteria were patients aged 18 to 45 years with knee complaints after a knee trauma in the preceding 6 months. Exclusion criteria were an indication for direct referral (e.g. fracture, locked knee), fulfilled referrals to MR or to secondary care, knee surgery in the past of the affected knee, knee osteoarthritis diagnosed by a physician and contra-indications for MR imaging. Eligible patients were selected during consultation by the GP or by an invitational letter from the GP when missed during consultation in the period of November 2012 to December 2015. For the present study, we used half of the randomised cohort's data, with patients being allocated to receive a 1.5 Tesla MR scan within 2 weeks after the baseline measurement, the other half of the cohort received no MR scan and were therefore not eligible to this study. We used data of the baseline questionnaires on knee function and trauma characteristics to associate with the MR findings. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center and by the Dutch national Central Committee on Research Involving Human Subjects (CCMO).

The outcome

The predicted outcome was a negative MR, hence positive MR findings were first determined that may need further, specialized assessment and treatment by an orthopaedic surgeon. Positive MR findings were a trabecular fracture, a complete rupture of a collateral ligament, a traumatic meniscal tear, a cruciate ligament rupture and a full thickness cartilage defect. All other findings (or absence of abnormalities) were regarded as 'negative' MR findings, being manageable conservatively by the GP, including presence of effusion-synovitis, a bone bruise, partial distortions of a collateral ligament, horizontal or degenerative meniscal tears and partial thickness cartilage defects.

MR imaging

The MR scans were acquired in six hospitals and MR centers. All protocols were executed on 1.5 Tesla MR system using dedicated knee coils. The scanning protocols included sequences in the sagittal, coronal and transversal planes, with at least one sequence with fat suppression and one gradient echo sequence targeted on cartilage damage. These protocols were all predefined in each center, tailored to the specific MR scanner and were familiar to the radiologists working in the particular center. Twelve musculoskeletal radiologists were involved in the study and were trained prior to the start of the study. We developed a standardized MR knee report online that was filled in by the radiologist, producing an automatic referral advice based on the presence of a positive MR findings. In such case, the advice was to refer the patient to an orthopaedic surgeon. This advice was then incorporated in the conclusion of the MR scan report to the GP.

Selection of candidate predictors

Potential predictors for the prediction model were predictors being easily obtainable in primary care, meaning that total scores of the knee specific questionnaires used in the TACKLE Trial were not suitable, although the single questions involved were. We subtracted items from validated knee specific questionnaires used in the TACKLE Trial: the Lysholm questionnaire on knee function[16] and 2 subscales ('symptoms' and 'pain') of the Knee injury and Osteoarthritis Outcome (KOOS) questionnaire.[17] These data were categorical in origin and were first dichotomized into simple and perceptible answer options (i.e. the candidate predictors). We eradicated double predictors since the Lysholm and KOOS questionnaires show multiple overlapping questions. In the TACKLE Trial no data were collected on physical examination findings by the GP, mainly since these tests were not standardized and therefore it was difficult to collect robust data on physical examination findings from the 150 GP's involved in this study. Furthermore we composed predictors using patient and trauma characteristics, including demographics (age, gender, BMI), musculoskeletal comorbidities (defined as pre-existing pain in the hips, ankles or spine), duration of complaints and trauma characteristics as summed in table 2.

Development of the prediction model

After the candidate predictors were composed, we assessed the univariate associations with the outcome 'MR negative', using Pearson's ρ. Statistically significant associations (p-value <0.05) were pre-selected for the final prediction model. With a Lasso (least absolute shrinkage and selection operator) regression analysis the final predictors were selected.[18] The Lasso technique shrinks regression coefficients of weak predictors, enabling an 'automatic' selection of the most relevant predictors. Predictors with a beta ≥0.10 were selected and included in the final prediction model. Then we created a simple clinical prediction rule in which predictors can be scored according to presence (1) or absence (0). This prediction rule is presented as a score chart, in which the sequence of predictors is according to highest beta, i.e. highest correlation with a negative MR scan. Increasing scores derived from this score chart represent increasing probabilities for the outcome of a negative MR.

Performance of the clinical prediction rule

We determined the discriminative ability of the clinical prediction rule with the area under the receiver operator curve (AUC) and the 95% confidence interval (95%CI). The receiver operator curve was also used to determine the optimum cut-off score by assessment of the corresponding sensitivity and specificity rates. We used a cross tabulation of the predicted outcomes and the observed outcomes to calculate the positive predictive value (PPV) of a negative MR scan. We calculated the difference in median prediction scores between the positive MR group and the negative MR group using the Mann Whitney U test. Percentage explained variation was expressed using Nagelkerke's r^2. The Hosmer-Lemeshow goodness of fit test was used to test for the calibration of the model, i.e. the agreement between observed outcomes and predictions. A P-value of <0.05 suggests that the model is not well calibrated. We tested the external validity of the clinical prediction rule using a similar primary care cohort, the HONEUR cohort, in which we selected patients aged 18 to 45 years with available MR information and baseline data who visited the GP with traumatic knee complaints.[9] We performed the statistical analyses in IBM SPSS version 22.0.

Description of study population

In total 177 patients were allocated to MR imaging in the trial. Three patients never received an MR scan because of pregnancy, no show and personal circumstances. Complete data were therefore available in 174 patients. Of the 174 patients, 107 patients (61%) had a negative MR scan. Table 1 shows baseline data on patient and trauma characteristics and the MR findings.

Table 1 Baseline patient and trauma characteristics with the MR findings in patients aged 18-45 with posttraumatic knee complaints, seen in primary care, n=174

Patient and trauma characteristics	
Age, median (IQR) years	34 (26 to 41)
Male gender, n (%)	110 (63)
BMI, mean (SD)	25.3 (3.9)
Duration of complaints, median (IQR) days	41 (17, 86)
Musculoskeletal comorbidities, n (%)	39 (22)
Sports related trauma, n (%)	105 (60)
Rotational trauma, n (%)	70 (40)
MR findings	**n (%)**
No abnormalities	30 (17)
Effusion-synovitis	71 (41)
Bone bruise	61 (35)
Trabecular fracture	12 (7)
MCL and/or LCL distortion	27 (16)
Traumatic meniscal tear	26 (15)
Horizontal (degenerative) meniscal tear	30 (17)
ACL and/or PCL rupture	40 (23)
Cartilage defect	39 (22)
Positive MR findings	67 (39)

IQR: interquartile range, SD: standard deviation, MCL: Medial Collateral Ligament, LCL: Lateral Collateral Ligament, ACL: Anterior Cruciate Ligament, PCL: Posterior Cruciate Ligament. Positive MR findings: trabecular fracture, traumatic meniscal tear, cruciate ligament rupture, complete rupture collateral ligament and/or a full thickness cartilage defect.

RESULTS

1. Which predictors are statistically significantly correlated with negative MR results?

Table 2 shows the selection procedure of candidate predictors for the final model. We composed 28 candidate predictors including 10 patient and trauma characteristics, 7 Lysholm items and 11 predictors from the subscales KOOS symptoms and KOOS pain. In the univariate analyses 9 predictors were dropped, due to the absence of a statistically significant correlation with the outcome 'MR negative'.

2. Can we combine these predictors into a straightforward and non-time consuming prediction model to support GP's to maintain such patients in primary care?

In the Lasso regression analysis, 7 predictors were selected for the final clinical prediction rule as shown in figure 1.

3. What is the performance of this prediction model and does it result in an increased probability of a negative MR scan?

The sensitivity of the clinical prediction rule was 81% with a specificity of 72% using a cut-off score of 3 or higher (table 3). With the presence of 3 or more predictors, the pre-test probability of 61% raised to a post-test probability of 82%. The median score in the group with a negative MR was 4 (interquartile (IQR) range 3 to 5), compared to a median score of 1 (IQR 1 to 2) in the group with a positive MR, p<0.001 (figure 2). The prediction rule was well calibrated with an AUC of 0.85 (95%CI 0.79 to 0.91; table 4). In an exploratory analysis we weighted the predictors in the model according to the Lasso's betas instead of assigning a 0 or 1, almost no impact was seen on the performance of the model, with the same PPV and AUC values.

Table 2 Selection procedure of predictors for a negative MR scan

Patient and trauma characteristics	N (%)	MRneg %	ρ	P-value	Lasso's B
Male gender	110 (63)	64	.009	0.909	
Age >35 year	86 (49)	61	-.050	0.513	
MSK comorbidity	**39 (22)**	**80**	**.199**	**0.009**	**.010**
≥3 months complaints	**68 (39)**	**81**	**.329**	**<0.001**	**.037**
Non-sports related trauma	**69 (40)**	**81**	**.328**	**<0.001**	**.164**
No rotational trauma	104 (60)	68	.170	0.025	.000
No popping sensation	110 (63)	68	.180	0.017	.006
No direct pain after trauma	**47 (27)**	**79**	**.215**	**0.004**	**.044**
No swelling after trauma	47 (27)	81	.242	0.001	.006
Able to continue activity	50 (29)	76	.189	0.012	.000
Lysholm					
Walking no problem	53 (31)	77	.216	0.004	.000
No use of stick or crutches	153 (88)	67	.287	<0.001	.000
Climbing stairs no problem	60 (35)	75	.201	0.008	.000
Squatting below 90° possible	**115 (66)**	**75**	**.381**	**<0.001**	**.144**
No or seldom instability	114 (66)	69	.221	0.003	.000
No pain or intermittent	72 (41)	61	-.007	0.931	
Never knee swelling	88 (51)	72	.210	0.005	.000
KOOS Symptoms					
No grinding/clicking/noise	52 (30)	64	.026	0.730	
Full extension often or always possible	110 (63)	72	.278	<0.001	.000
No joint stiffness in the morning	**73 (42)**	**80**	**.314**	**<0.001**	**.052**
No joint stiffness later in the day	28 (16)	86	.218	0.004	.000
KOOS Pain					
Pain less than weekly	49 (28)	69	.012	0.875	
No severe pain during twisting or pivoting the weightbearing knee	**93 (54)**	**79**	**.374**	**<0.001**	**.153**
No pain during full extension	91 (53)	70	.190	0.012	.000
No pain walking flat surface	50 (29)	82	.102	0.182	
No pain at night	62 (36)	69	.120	0.114	
No pain sitting or lying	56 (32)	68	.090	0.237	
No pain standing upright	55 (32)	69	.106	0.163	

MRneg: Negative MR findings, all findings excluding a trabecular fracture, traumatic meniscal tear, cruciate ligament rupture, complete rupture collateral ligament and/or a full thickness cartilage defect. Prevalence of negative MR findings was 61% in our study. ρ: univariate correlation coefficient, with the corresponding p-value. Lasso's B: the shrunk regression coefficient beta derived from a Lasso regression analysis. MSK comorbidity: musculoskeletal comorbidity, defined as pre-existing pain in the hips, ankles or spine.

Figure 1 Clinical prediction rule for a negative MR after a recent knee trauma in patients aged 18-45 years, seen in primary care.

Predictors negative MR	**Points if true**	
Non-sports related trauma	1	
No severe pain during twisting/pivoting of the weightbearing knee	1	
Squatting below 90° possible	1	
No joint stiffness in the morning	1	
No direct pain after trauma	1	
Three months or longer complaints	1	≥3 points? Negative MR:
Presence of musculoskeletal comorbidities	1	PPV = 82%
Total Score		

Negative MR findings: all findings with exclusion of a trabecular fracture, traumatic meniscal tear, cruciate ligament rupture, complete rupture collateral ligament and/or a full thickness cartilage defect.

Table 3 Performance of the clinical prediction rule for a negative MR in patients aged 18-45 with posttraumatic knee complaints, seen in primary care

Cut off scores	N	PPV %	Se %	Sp %
≥7	1	100	2	100
≥6	7	100	7	100
≥5	33	91	28	96
≥4	72	93	63	93
≥3	106	82	81	72
≥2	128	77	93	57
≥1	157	67	98	22
≥0	174	61	100	0

MRneg: negative MR findings, all findings with exclusion of a trabecular fracture, traumatic meniscal tear, cruciate ligament rupture, complete rupture collateral ligament and/or a full thickness cartilage defect. PPV: positive predictive value, Se: sensitivity, Sp: specificity. A cut-off score of ≥3 was chosen with a PPV of 82%.

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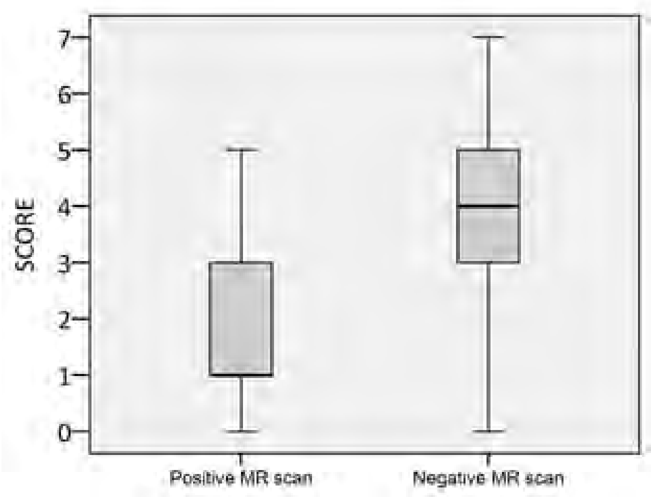
Figure 2 Boxplots of differences in median scores derived from the clinical prediction rule between patients with positive MR findings (n=67) and negative MR findings (n=107)



4. Is the prediction model externally valid using a comparable cohort in primary care?

In the HONEUR cohort, complete data and MR information of 81 patients were available. Patients had a mean age of the 33 years (standard deviation 7.4) with 56% males and a sports related trauma in 49 patients (61%). The median duration of complaints was 12 days (IQR 6 to 22), implying that the predictor '≥3 months complaints' was negative in all patients. The KOOS questionnaire was not available from which we subtracted the predictor 'no severe pain during twisting or pivoting of the weightbearing knee'. Instead we used the question on pain during squatting (5-point Likert scale) from the adapted knee-specific version of the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) questionnaire.(18) The prediction rule showed a similar performance in this cohort, with an AUC of 0.75 (95%CI 0.63 to 0.86; table 4).

Table 4 Performance of the clinical prediction rule (score ≥3) for a negative MR in patients aged 18-45 with posttraumatic knee complaints, with validation in another similar cohort

	Tackle cohort n=174	**Honeur cohort** n=81
Percentage observed outcome negative MR	61%	61%
Predicted number of outcomes per observed number of outcomes	106/107	43/49
Hosmer-Lemeshow goodness of fit test, p-value	0.169	0.416
AUC (95%CI)	0.85 (0.79 to 0.91)	0.75 (0.63 to 0.86)
Nagelkerke's R^2	46%	23%
Sensitivity	81%	71%
Specificity	72%	75%
Positive predictive value	82%	81%

Negative MR: all findings excluding a trabecular fracture, traumatic meniscal tear, cruciate ligament rupture, complete rupture collateral ligament and/or a full thickness cartilage defect. AUC: area under the receiver operator curve, 95%CI: 95% confidence interval, Nagelkerke's R2: percentage explained variance

DISCUSSION

Background and rationale

In general practice most patients present with self-limiting injuries after a knee trauma. Furthermore, recent evidence suggests that MR imaging in primary care for patients with traumatic knee complaints is not cost-effective. We aimed to construct a prediction model to guide the general practitioner to keep the majority of patients presenting with traumatic knee complaints in primary care without the use of MR imaging. We constructed a clinical prediction rule with statistically significant associated predictors for a negative MR scan.

Seven predictors were identified consisting of information being easily obtainable in only a few minutes during history taking. These were a 'non-sports related trauma', 'no severe pain during twisting or pivoting of the weightbearing knee', 'squatting below 90° possible', 'no direct pain after trauma', 'three months or longer complaints' and 'presence of a musculoskeletal comorbidity' (figure 1). The prediction rule showed a high discriminative ability and was also validated in a similar cohort in general practice, with comparable performance. With the presence of 3 or more predictors, the pre-test probability to have a negative MR raised from 61% to a post-test probability of 82%.

Limitations

Some limitations to this study can be noted. In this study we did not collect data on the physical examination findings by the GP, some important information could have been missed. However, two predictors are verifiable with physical examination: squatting below 90° and pain during twisting/pivoting of the weightbearing knee. We believe the exclusion of physical examination findings did not affect our results significantly, given earlier research on the low to absent additive value of physical examination in primary care for the detection of meniscal tears and ACL ruptures.[11,19,20] Furthermore, we used a relatively small number of patients to construct the model and to externally validate the study, further validation might be required, preferably in a prospective study.

Comparison with existing literature

Snoeker et al.[14] composed a clinical prediction rule for the detection of meniscal tears in primary care. Male gender, higher age, weightbearing during trauma, effusion and a positive deep squat test were associated with the presence of a meniscal tear in the univariate analyses. Combining predictors into a model raised the post-test probability for the presence of a meniscal tear from 44% to 55% with an optimism-corrected AUC of 0.76. The usefulness of the prediction model is however debatable, with low added probability and because the authors included degenerative tears which are known to lack clinical significance and therapeutic options.[21–23] Also, the authors presented a complex prediction model from which a score could be derived ranging from 0 to 252 points, indicating this model is more time-consuming to apply in general practice.

Two other studies identified predictors from history taking; for the presence of a meniscal tear these were, among others, swelling of the joint, not able to flex or extend the knee and pain with flexion or extension.[24] For the presence of an ACL rupture the predictors were hearing a plop or snap during trauma, effusion in the first 24 hours and giving way or instability.[25] All these predictors were also statistically significant correlated to the MR outcome in our study, although not selected for the final model.

An unexpected predictor in our model was 'absence of joint stiffness in the morning'. Morning stiffness is an acknowledged biomarker in osteoarthritis and rheumatoid arthritis[26,27], but is less known for its predictive value in traumatic knee complaints. One earlier study mentioned the predictive value of joint stiffness, being associated with ACL injury.[28] A possible explanation is the presence of effusion with or without synovitis causing the joint stiffness in these relatively young patients with a recent knee trauma.

In a systematic review on the accuracy of clinical examination for the detection of meniscal and ligamentous knee injuries, the authors concluded that a combination of specific knee tests combined with historical items is probably required for an adequate diagnosis.[29] These authors addressed the importance of the historical items 'duration of complaints' and the 'presence of musculoskeletal co-morbidities', also incorporated in our prediction model.

Conclusions

We presented a straightforward and simple, externally validated clinical prediction rule that can easily be implemented in primary care for patients with traumatic knee complaints. It is designed to be applied in only a few minutes and addresses important items to be discussed during history taking. The score derived by this model significantly alters the probability of a negative MR scan, supporting the GP to maintain the majority of patients in primary care for a watchful waiting policy, without using MR imaging.

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