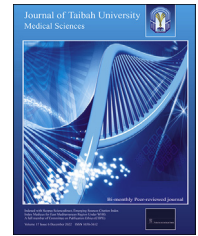




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Original Article

## Identifying female responders to proximal control exercises in patellofemoral pain syndrome: A clinical prediction rule

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### المخلص

**أهداف البحث:** نظرا لانتشار متلازمة آلام الفخذ الرضفي والدور الفعال لتمارين التحكم القريبة ونقص الدراسات التي تعالج تنبؤات هذا التأثير، أجريت هذه الدراسة لفحص تأثير العمر، مؤشر كتلة الجسم، مدة الأعراض، وانحراف الركبة الداخلي الديناميكي على استجابة المرضى (الألم والوظيفة) لتمارين التحكم القريبة عند الإناث المصابات بمتلازمة آلام الفخذ الرضفي.

**طرق البحث:** تم تجنيد خمسين أنثى مصابات بمتلازمة آلام الفخذ الرضفي من جامعة عين شمس بمتوسط عمر ٢٥ عاما، حصلوا على تمارين التحكم القريبة. تم عمل هذه التمارين مرتين أسبوعيا لمدة ٤ أسابيع. تم تقييم المرضى من أجل آلام الركبة عن طريق المقياس التناظري البصري، ووظيفة الركبة باستخدام استبانة كوجالا، وانحراف الركبة الداخلي الديناميكي باستخدام برنامج التحليل الحركي كينوفيا. تم حساب نسب الاحتمالية لتحديد عناصر الفحص التي كانت أكثر تنبؤا بنتائج العلاج. حدد تحليل الانحدار اللوجستي للعناصر المدرجة في تحديد المتغيرات السريرية التي تتنبأ بالنجاح مع النتائج التي تحسن صنع القرار وكفاءة العلاج.

**النتائج:** نجحت خمسة وثلاثون (٧٠٪) من الإناث المصابات بمتلازمة آلام الفخذ الرضفي ولقد تجاوز التحسن الحد الأدنى من الفرق المهم السريري (١,٨، سم للألم و٨ نقاط للوظيفة) مع تمارين التحكم القريبة.

من بين أربع تنبؤات تم اختبارها، يمكن أن تتنبأ مدة الأعراض (القيمة الاحتمالية = ٠,٣٢)، وانحراف الركبة الداخلي الديناميكي (القيمة الاحتمالية = ٠,٠٧)، فقط زاوية انحراف الركبة الداخلي الديناميكي التي مقدارها  $\geq 21,5$  درجة لها منطقة مقبولة تحت المنحنى من حيث الحساسية، والنوعية ٠,٧٢، و٠,٦ و٠,٦ على التوالي مع القيمة الاحتمالية = ٠,١٥. واطهرت النتائج انه لا توجد مؤشرات على تحسن وظيفة الركبة.

**الاستنتاجات:** مدة الأعراض وانحراف الركبة الداخلي الديناميكي من الممكن أن تتنبأ بالتحسن في متلازمة الألم الرضفي الفخذي بعد تمارين التحكم القريبة.

**الكلمات المفتاحية:** آلام الركبة الأمامية؛ إختلال وظيفة الركبة؛ تمارين التحكم القريبة؛ قاعدة التنبؤ السريري؛ إعادة التأهيل؛ متلازمة الألم الرضفي الفخذي

### Abstract

**Objectives:** Given the high prevalence of patellofemoral pain syndrome (PFPS) and the effectiveness of proximal control exercises, as well as the lack of studies addressing the predictors of this effect, we conducted this study to examine the effects of age, body mass index, symptom duration, and dynamic valgus of the knee on the pain and function responses to proximal control exercises in women with PFPS.

**Methods:** Fifty women with PFPS with a mean age of 25 years, recruited from Ain Shams University, performed proximal control exercises twice weekly for 4 weeks. Knee pain was assessed with the visual analogue scale; knee function was assessed with the Kujala questionnaire; and dynamic knee valgus (DKV) was assessed through Kinovea Computer programmer video analysis.

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Likelihood ratios were calculated to determine the examination items most predictive of treatment outcomes. Logistic regression analysis identified items in the clinical prediction rule (identification of clinical variables predicting successful outcomes to improve decision-making and treatment efficacy).

**Results:** Proximal control exercises resulted in successful improvement exceeding the minimal clinical important difference (1.8 cm for pain and 8 points for function) in 35 (70%) women with PFPS. Among the four tested predictors, symptom duration ( $P = 0.032$ ) and DKV ( $P = 0.007$ ) predicted amelioration of knee pain with proximal control exercises. However, the DKV angle  $\geq 21.5^\circ$  acceptable area under the curve, sensitivity, and specificity were 0.72, 0.6, and 0.6, respectively ( $P = 0.015$ ). No predictors of improvement in knee function were identified.

**Conclusions:** Symptom duration and DKV can predict amelioration of PFPS after proximal control exercises.

**Keywords:** Anterior knee pain; Clinical prediction rule; Knee dysfunction; PFPS; Proximal control exercises; Rehabilitation

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## Introduction

Patellofemoral pain syndrome (PFPS) is a non-traumatic musculoskeletal condition found in diverse populations, particularly among women.<sup>1,2</sup> The high incidence rate of PFPS in clinical settings has been extensively described. A high estimate of 22.7% in the general population and 28.9% in adolescents was reported in 2018.<sup>1</sup>

Strong evidence indicates that the hip muscles play a crucial role in controlling and managing femoral excursions in both the frontal and transverse planes.<sup>3,4</sup> Additionally, individuals with PFPS have poor isometric and dynamic hip abductor and extensor strength.<sup>5,6</sup> This weakness decreases their ability to control excessive femoral adduction and internal rotation that overloads the patellofemoral joint.<sup>6,7</sup>

In contrast, the muscles responsible for proximal control provide stable proximal attachment sites for hip muscles. Hip muscles are responsible for increasing the force production during functional activities and decreasing excessive frontal plane motions of the pelvis during single-limb stance activities.<sup>8</sup>

Clinical prediction rules (CPRs) are methods that help clinicians make better decisions in clinical practice, such as directing them toward a specific diagnosis, determining prognosis, or assigning patients to the best intervention methods according to selected predictor variables highlighted during the patient's interview and assessment.<sup>9</sup>

One of the major challenges faced by physical therapists is deciding when and which exercise should be recommended to patients with PFPS. Thus, decision-making in the treatment of PFPS according to patient outcomes is not clearly defined, and further research studies are required.

Proximal control exercises, taping, orthotics, and activity modification have been demonstrated to be effective for the management of PFPS, and the predictors of such effects have been reported.<sup>10–13</sup> However, to our knowledge, no published reports have identified variables predicting which PFPS patients will respond positively and successfully to proximal control exercises. Moreover, proximal control exercises are important for PFPS, owing to their effects on the pathomechanics that predominate in women.<sup>14</sup>

In addition, documentation of the predictors of success with these exercises would enable therapists to implement a clinical decision-making algorithm to improve treatment efficiency, thereby decreasing treatment duration and yielding optimal results.

Thus, this study investigated the effects of age, body mass index (BMI), symptom duration, and the dynamic knee valgus (DKV) angle on the pain and function responses to proximal control exercises in women with PFPS.

## Materials and Methods

### Participants

This study was designed as a prospective clinical trial to investigate predictors of the success of proximal control exercises in women with PFPS. It was conducted between May 2020 and October 2021. The convenience sample comprised 50 female participants recruited from the Ain Shams university hospital through written and oral announcements, who completed this study. Participants were referred by an orthopedic surgeon who confirmed the diagnosis of PFPS. All participants provided signed informed consent after the study's timeline and details were described. Privacy of all delivered information was ensured through patient de-identification with numerical identifiers for all participant information.

For greater accuracy, the inclusion criteria comprised women with 1) non traumatic retropatellar/anterior knee pain, for more than 6 weeks, exacerbated by at least two activities (stair climbing, prolonged sitting, kneeling, squatting, running, jumping, or hopping),<sup>15</sup> 2) tenderness on the patellar facets, or 3) pain elicited by stepping down from a height of 15 cm. To control for the effects of sex differences, only women were included in the study, given that women are more liable to develop PFPS and have been reported to respond well to proximal control exercises.<sup>14</sup>

Participants were excluded if they informed the researcher of any other associated injury or pathology at the knee level, including surgeries, joint instability, effusion, or Osgood–Schlatter disease. In addition, participants with hip or lumbar spine disorder or pain who had previously undergone physical therapy (less than 1 year), used foot orthoses, or had any intake of anti-inflammatory agents or steroids were excluded.

### Sample size

This sample was chosen according to the recommendation that 10–15 participants should be enrolled for each prospective predictor variable in clinical prediction rule studies for accurate statistical results.<sup>16–18</sup>

### Measures

The following outcome measures were recorded before and after the 4 weeks of intervention for each participant.

#### Knee pain

Pain intensity was measured with a visual analogue scale consisting of a 100 mm line labeled with word descriptors by “no pain”/“worst imaginable pain” at each end of the scale. This scale is widely used, and is considered reliable and valid for pain recording.<sup>19</sup> Participants were asked to report their pain perception before and after 4 weeks of intervention.

#### Knee function

The functional scale used in this study for knee assessment was the Kujala scale,<sup>20</sup> a 13 item self-reported form. This tool assesses pain and difficulty during six activities (walking, squatting, jumping, stairs climbing, running, and sitting for lengthy periods). This tool also documents other symptoms including limping, failure to assume a unilateral stance on the involved limb, swelling, abnormal patellar tracking, atrophy, and knee flexion limitation. The Kujala scale (Arabic form) has been found to be valid and reliable in functional knee pain assessment<sup>21,36</sup>. Similarly, Kujala scores were recorded before and after 4 weeks.

#### DKV

DKV was determined through Kinovea Computer programmer V.0.8.15 video analysis. This system has been found to be valid and reliable for calculating the range of motion in joints.<sup>22</sup> In contrast, a tape measure was used to assess the 2D frontal plane projection angle (FPPA). The axes of each hip, knee, and ankle joint were delineated, and markers were located midway between the malleoli of the ankle joint, at the midpoint of the femoral condyles for the axis of the knee joint, and at the central line from the anterior superior iliac spine to the knee joint axis. This technique has been reported to decrease intra- and inter-rater error, and to increase reliability, in comparison with manual calculations via video.<sup>23</sup>

With a video camera (ON EOS Rebel T3i/600D, fixed on a tripod at knee level, 3 m from the center of the landing floor, with video at 1080 p resolution at 30 fps), snapshots at the maximum knee valgus were taken. Participants were asked to flex the non-tested leg's knee from the floor and then to perform a squat with the tested leg.

Normative 2D FPPA or DKV values have been reported to usually be between 5° and 12° in women.<sup>24</sup> A knee valgus displacement greater than 10.6° suggests a PFP with sensitivity and specificity of .75 and .85, respectively. The associated positive probability ratio is 5.<sup>25</sup> For DKV, the reading used as a predictor was that of the pre-intervention measurement.

### Procedures

Participants enrolled in the study attended two physical therapy sessions per week for 1 month. The sessions consisted of proximal control exercises in the form of controlling pelvic motion through the execution of active lower-limb movement or alternative hip and knee flexion/extension motions. These exercises were performed in supine lying position with the pelvis stabilized by activation of deep trunk muscles through a drawing-in maneuver. The participants were asked to flex and extend one lower extremity while the other was kept flexed; change the motion to raise and lower the leg; repeat the steps on the other side; and finally perform alternating motions on both sides, 10 times each. Strengthening of the hip abductors was performed in the following position: patients were in side-lying position with both legs flexed 90° at the knees and neutral at the hips; they then externally rotated the uppermost one against 40% of 1RM by using sand-bag weights for ten repetitions and three sets. Patients progressed through increasing the lever arm by extending the highest knee, and the hip retained less than 25° external rotation and mild extension. Hip abductor and external rotator strengthening began from a quadruped starting position, and the external rotation/abduction/extension action of the lower extremity was performed against gravity.<sup>7</sup> Lateral core and posterior core muscle strengthening was performed with side and prone planks for ten repetitions, with the positions maintained for 30 s (in which patients were in side- and prone lying positions, bridged on the elbow and lateral foot, and on the elbow and toes, respectively).<sup>20</sup>

### Analysis

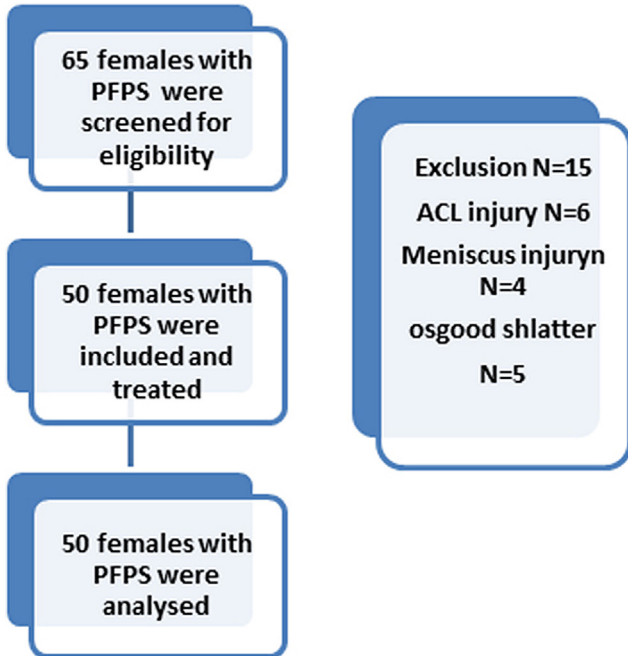
Statistical analysis was performed in statistical package for social studies version 24 for windows (SPSS Inc., Chicago, IL, USA). First, paired t-tests were used to assess the effects of proximal control exercises on PFPS (difference between pre- and posttest scores in pain and function). Then, to assess the ability to predict the outcomes of proximal control exercises by using the independent variables identified, we grouped all participants according to their outcomes (success or failure) for each dependent variable, on the basis of the minimally clinical important difference (MCID) (1.8 cm for pain and 8 points for function).<sup>14</sup> Because of the dichotomous nature of the outcome (success or failure), logistic regression was used for analysis. Univariate logistic regression analyses were performed between independent variables (pretest DKV, age, duration of symptoms, and BMI) and dependent variables (pain and function). Finally, all independent variables that were significantly ( $P < 0.25$ ) associated with each dependent variable were analyzed in a multivariate logistic regression model. This high P-value was chosen on the basis of recommendations by previous studies to avoid loss of any predictor in early stages that might be significant in subsequent analyses.<sup>26</sup> Sensitivity and specificity were calculated for all statistically significant independent variables measured on a continual scale. Receiver operating characteristic (ROC) curves were plotted to demonstrate the balance between sensitivity and specificity, and to determine the best cut-off points

distinguishing success from failure. The level of significance was set at  $P < 0.05$ .

**Results**

Sixty-five women with PFPS were initially screened according to the eligibility criteria, of whom 50 women with unilateral knees were found to be eligible and completed the sessions (Figure 1). The women with unilateral PFPS had a mean VAS score of  $5.8 \pm 2.4$  points. Basic participant demographics are summarized in Table 1.

The 50 included women with PFPS had age, BMI, symptom duration, and DKV values of 25 (3.75) years, 25.3



**Fig. 1:** Flowchart showing the flow of participants from screening to analysis.

**Table 1: Baseline characteristics of all participants (N = 50).**

Baseline characteristics	Mean (standard deviation)
Age (years)	25 (3.75)
BMI (kg/m <sup>2</sup> )	25.3 (4.5)
Symptom duration (years)	.56 (.32)
Dynamic knee valgus (degrees)	21.6 (1.24)

**Table 3: Descriptive statistics and differences between groups (successful and failed) in predictors of pain and function.**

Outcome	Age (years)	BMI (kg/m <sup>2</sup> )	Symptom duration (years)	DKV pre (degree)
<b>Pain</b>				
Success <sup>a</sup> (n = 35) mean (SD)	25 (3.8)	25.8 (5.2)	.5 (.25)	21.97 (1.01)
Failure (n = 15) mean (SD)	25 (3.8)	24 (1.2)	.68 (.42)	20.8 (1.37)
P-value	.94	.22	.071	.002*
<b>Function</b>				
Success (n = 33) mean (SD)	25.52 (3.67)	26.24 (3.5)	.52 (.34)	21.61 (1.4)
Failure (n = 17) mean (SD)	24 (3.8)	23.4 (5.6)	.64 (.27)	21.6 (.8)
P-value	.18	.03*	.21	.91

\*Significant at  $P < 0.05$ ; BMI, body mass index; DKV, dynamic knee valgus; SD, standard deviation.

<sup>a</sup> Success or failure was based on the minimally clinical important difference (MCID) (success if  $\geq 1.8$  cm for pain and  $\geq 8$  points for function).

**Table 4: Univariate regression analysis of each independent variable in predicting pain and function.**

	B	SE	Wald	df	Sig.	Odds ratio
<b>Pain</b>						
Age	-.007	.083	.007	1	.934	.993
Constant	1.020	2.104	.235	1	.628	2.773
BMI	.090	.079	1.294	1	.255	1.094
Constant	-1.398	1.993	.493	1	.483	.247
Symptom duration	-1.778	1.079	2.716	1	.099	.169
Constant	1.887	.715	6.959	1	.008	6.598
DKV pre	1.035	.407	6.466	1	.011	2.814
Constant	-21.323	8.688	6.024	1	.014	.000
<b>Function</b>						
Age	.112	.083	1.822	1	.177	1.118
Constant	-2.104	2.053	1.050	1	.306	.122
BMI	.258	.157	2.690	1	.101	1.294
Constant	-5.794	3.931	2.173	1	.140	.003
Symptom duration	-1.177	.976	1.452	1	.228	.308
Constant	1.341	.644	4.338	1	.037	3.821
DKV pre	-.027	.243	.012	1	.911	.973
Constant	1.250	5.270	.056	1	.813	3.490

B, unstandardized beta or slope of line; SE, standard error; BMI, body mass index; DKV, dynamic knee valgus; Wald test statistic = square (B/SE); OR, odds ratio.

**Table 2: Descriptive statistics and paired t-test for within group differences in pain and function.**

	Pre mean (SD)	Post mean (SD)	Paired differences (pre-post)				t	df	P-value	
			Mean	SD	SEM	95% CI				
						Upper	Lower			
Pain	6 (1.34)	4 (1.67)	2	.87	.1	1.8	2.3	16.4	49	.000*
Function	69.6 (15)	81.2 (9.24)	-11.7	12.1	1.7	-15	-8.2	-6.8	49	.000*

CI, confidence interval of difference; SD, standard deviation; SEM, standard error of the mean; (\*), significant at  $P < 0.05$ .

**Table 5: Multivariate logistic regression for independent variables in predicting pain and function.**

	B	SE	Wald	df	P-value	OR	95%CI for OR	
							Lower	Upper
<b>Pain</b>								
Symptom duration	-3.122	1.456	4.6	1	.032*	.044	.003	.765
DKV	1.388	.516	7.25	1	.007*	4.01	1.458	11.011
Constant	-27.03	10.69	6.4	1	.011	.000		
<b>Function</b>								
Symptom duration	-1.740	1.101	2.5	1	.114	.175	.020	1.519
Age	.094	.090	1.1	1	.294	1.1	.922	1.311
BMI	.304	.189	2.59	1	.108	1.36	.936	1.962
Constant	-8.217	5.138	2.56	1	.110	.000		

B, unstandardized beta or slope of line; SE, standard error; DKV, dynamic knee valgus. Wald test statistic = square (B/SE); OR, odds ratio; (\*), significant at P < 0.05.

**Table 6: Predictors of success of proximal control exercises in terms of symptom duration.**

Predictors of success	AUC	P-value	Std. error(a)	95% CI	
				Upper	Lower
Symptom duration	0.367	0.138	0.082	0.205	0.528

AUC, area under curve; CI, confidence interval of difference.

(4.5) kg/m<sup>2</sup>, .56 (.32) years, and 21.6 (1.24) degrees (mean and standard deviation), respectively.

*Effects of proximal control exercises on pain and function*

Paired t-tests for differences between posttest and pretest scores in the dependent variable (pain and function) revealed significant differences; a significant improvement in both variables (P < 0.001) was observed after proximal control exercise therapy, as shown in Table 2.

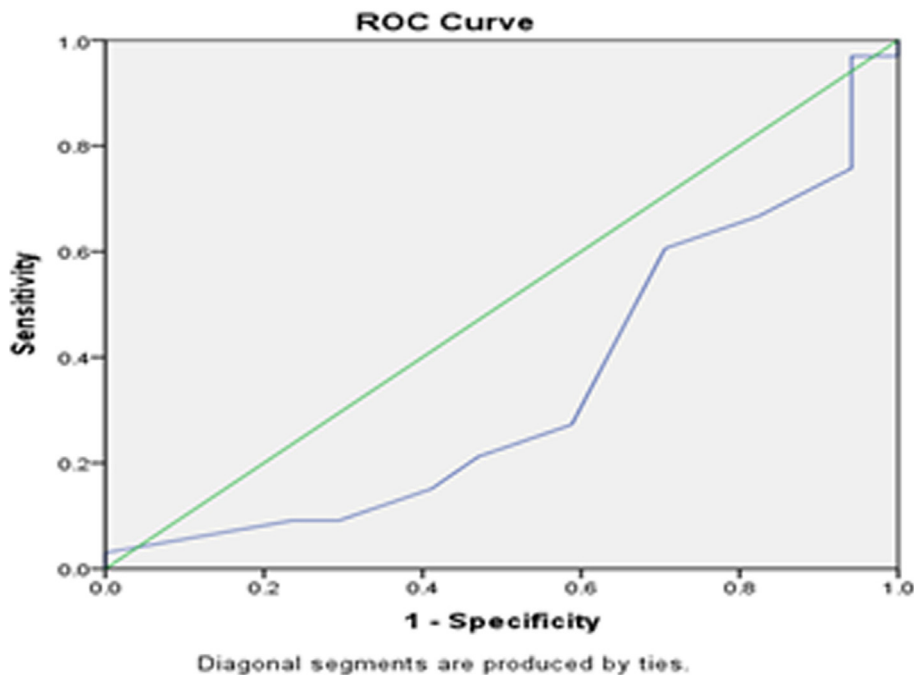
**Table 7: Predictors of success of proximal control exercises in terms of pain.**

Predictors of success	AUC	P-value	Sensitivity	1 – specificity	Cutoff score
DKV	0.72	0.015	0.6	0.4	≥21.50°

AUC, area under ROC curve; DKV, dynamic knee valgus.

*Predictors of success of proximal control exercises in terms of pain and function*

A total of 35 (70%) and 33 (66%) women with PFPS had successful outcomes of proximal control exercises in terms of pain and function, respectively. The descriptive statistics for patients in each group (success or failure) are presented in Table 3. Independent t-tests revealed significant differences in only DKV (P = 0.002) and BMI (P = 0.03) in terms of pain and function between groups.



**Fig. 2:** ROC curve of symptom duration.

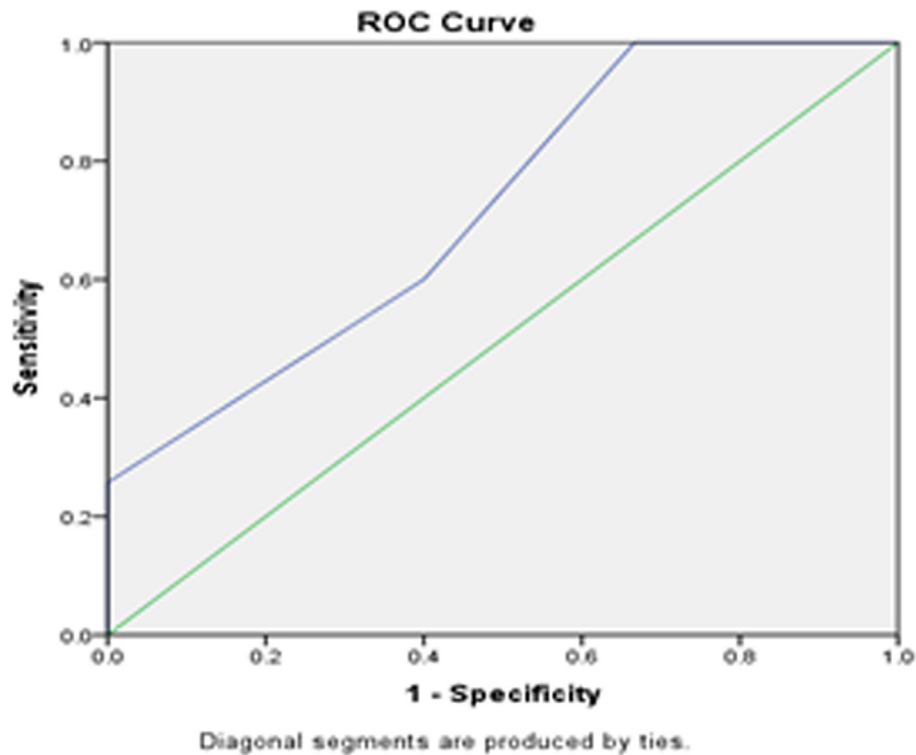


Fig. 3: ROC curve of DKV.

#### Univariate regression analysis

Each independent variable among the four independent variables identified was examined in a univariate logistic regression model. This analysis revealed that BMI, age, and symptom duration were statistically significant (at  $P < 0.25$ ) predictors of function, and DKV and symptom duration were predictors of pain, as shown in Table 4.

#### Multivariate logistic regression analysis

In the multivariate model, no single predictor was significant in predicting therapy success in terms of function, but two predictors (symptom duration and DKV) were significant in predicting therapy success in terms of pain, as shown in Table 5. This model explained 24% (Nagelkerke R squared) of the variance in success in terms of pain after proximal control exercises.

#### Receiver operating characteristic curves

ROC curves were generated for symptom duration and DKV to determine cut-off scores distinguishing between the success and failure of proximal control exercises in terms of pain. The area under the ROC curve of symptom duration was .367 ( $P = 0.138$ ) and was not a discriminate cutoff point (Table 6 and Fig. 2).

In addition, the results revealed that a cutoff point of  $\geq 21.5^\circ$  of DKV was a predictor of the success of proximal control exercises in terms of pain in women with PFPS. The true positive rate (i.e., sensitivity) was 60%, and the false

positive rate (i.e.,  $1 - \text{specificity}$ ) was 40%. The area under the ROC curve was .72 (Table 7 and Fig. 3).

#### Discussion

PFPS is a complicated and commonly encountered knee disorder. Although the origin of this condition is debated, most researchers agree on the need to classify people with PFPS according to distinct characteristics, thus potentially leading to development of disorders.<sup>27</sup> Similarly, subgroups of patients are likely to have unique traits causing them to respond well to specific interventions.<sup>10</sup>

The aim of the current study was to identify the characteristics of individuals with PFPS that are predictive of a positive response to proximal control exercises.

By definition, a clinical prediction rule incorporates the optimal number of clinical assessment items to predict a diagnosis or prognosis. Rehabilitation focusing on strengthening the hip and core musculature and improving neuromuscular control is expected to improve patient outcomes and decrease knee valgus, all of which are required for PFPS. This information may help health care providers make evidence-based judgments regarding which activities to include in PFPS rehabilitation programs.<sup>14</sup>

This study supports previous findings indicating that patients with PFPS show amelioration of pain and improvements in function after proximal control exercises.<sup>12,13</sup>

Our inability to detect a specific cutoff point for symptom duration that predicted the duration of success is supported by previous research indicating that proximal control exercises yield lower pain scores in women with PFPS with a long

symptom duration (>23 months).<sup>29,30</sup> Additionally, others have found that shorter symptom duration significantly predicts exercise intervention success in PFPS management.<sup>30</sup>

The results of this study regarding the importance of DKV for PFPS are concordant with the results of other studies<sup>28</sup> indicating that increased DKV is associated with PFP.<sup>4,31</sup> In addition, the hip muscles can control the DKV during activities.<sup>32</sup> Furthermore, proximal control exercises have been confirmed to be an efficient intervention to reduce pain and increase function in people with PFP.<sup>33</sup> These findings may explain why individuals with elevated DKV benefited from proximal control exercises.

In contrast, another study has found that the knee valgus angle does not predict pain relief.<sup>34</sup> These contradictory results might have been because the applied intervention addressed solely the quadriceps muscles, and no exercises addressed the hip or proximal muscles.

Proximal control exercises have been found to provide relief from pain and enhanced function in participants with PFPS.<sup>35</sup>

In contrast to the findings of the current study, a prior study has reported that age is the only variable significantly correlated with improvements in pain intensity.<sup>34</sup> However, more recently, another study<sup>30</sup> has concluded that younger individuals with PFPS show significantly greater success of interventions, owing to younger patients' greater neuromuscular and muscular adaptation abilities. The results of the current study contradict the results of these two studies, in that age did not predict pain. This difference in findings might have been due to the characteristics of the present sample, particularly that most of the participants were sedentary rather than athletic or involved in sport activities.

### Limitations

This study's inclusion of patients from one location and women only may limit the generalizability of the results. Improvement after proximal control exercise may be affected by an interaction of many factors (e.g., pretest hip strength, and internal rotation of femur deficit) beyond those examined in this study.

In addition, the small sample size is another limitation of this study, although the sample size is within the range used and/or recommended in research.

### Conclusions

We assessed the characteristics of participants with PFPS responding positively to definite proximal control exercises and developed CPRs integrating those findings.

Our results suggest that women with PFPS with DKV  $\geq 21.5^\circ$  respond favorably to proximal control exercises.

**Abbreviations:** PFPS, patellofemoral pain syndrome; VAS, visual analogue scale; BMI, body mass index; DKV, dynamic knee valgus; DS, duration symptoms; ROC, receiver operating characteristic; MCID, minimal clinical importance difference; CPRs, clinical prediction rules; FPPA, frontal plane projection angle.

### Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Conflict of interest

The authors have no conflict of interest to declare.

### Ethical approval

This study was approved by the Research Ethical Committee of Faculty of Physical Therapy, Cairo University, project **P.T.REC 012/002712** on 22 April 2020. The study is recorded at [ClinicalTrials.gov](https://clinicaltrials.gov) under identifier NCT04481022. The procedures followed were in accordance with the Declaration of Helsinki.

### Authors contributions

KS and AE conceived and designed the study, and wrote the initial and final drafts of the article. AC and AA conducted research, provided research materials, and collected and organized data. NM analyzed and interpreted data, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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