Male Sex, Revision Surgery, Low Volume of Anterior Cruciate Ligament Remnant, and Significant Instability Are Risk Factors for Posterior Root Tear of the Lateral Meniscus in Patients Undergoing Anterior Cruciate Ligament Reconstruction

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Purpose: To determine the incidence of lateral meniscus posterior root tears (LMPRTs) in patients undergoing anterior cruciate ligament (ACL) reconstruction and identify associated risk factors. **Methods:** We conducted a retrospective, multicenter study using data from the Francophone Arthroscopic Society's registry. The study included all the patients in the registry who underwent ACL reconstruction surgery between June 2020 and June 2023; we excluded incomplete data. We compared delay from injury to surgery between LMPRTs group and no-LMPRTs group. Variables investigated as potential risk factors for LMPRTs included age, sex, nature of surgery (primary or revision), pivot shift test result, side-to-side laxity under anesthesia, presence of ACL remnant, occurrence of medial meniscal tear, and presence of collateral ligament injury. Risk factors were analyzed using a logistic regression model. **Results:** Among the 5,359 patients analyzed, LMPRTs occurred in 7.0% (n = 375) of cases during ACL reconstruction. Mean age at surgery was 29.3 ± 10.3 years old [11-77]. Concerning delay to surgery, the mean time was 8.4 ± 23.1 weeks [0.0-347.2] in the no-LMPRTs group and 6.5 ± 10.2 weeks [0.2-61.6] in the LMPRTs group ($P = .109$). Univariate analysis revealed that male sex ($P < .001$), revision surgery ($P < .001$), medial meniscal injury ($P = .007$), ACL remnant (0% vs >70%, <10% vs >70%, 10%-30% vs >70%, >30%-50% vs >70%, >50%-70% vs >70%; $P < .001$), and greater pivot shift grade ($P = .011$) were significantly associated with a presence of LMPRTs. Age, side-to-side laxity, and collateral ligament injury were not found to be significant risk factors. In multivariate analysis, male sex, revision surgery, pivot shift test result, and a low volume of ACL remnant remained significant. Side-to-side laxity was also a significant factor in multivariate analysis. **Conclusions:** This study identified male sex, revision surgery, low volume of ACL remnant, side-to-side laxity, and greater grade of pivot shift as significant risk factors for LMPRTs during ACL reconstruction. **Level of Evidence:** Level III, retrospective comparative case series.

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Received November 10, 2023; accepted May 19, 2024.

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0749-8063/231531/$36.00
https://doi.org/10.1016/j.arthro.2024.05.028

Lateral meniscus posterior root tears (LMPRTs) frequently are associated with anterior cruciate ligament (ACL) injuries,[1] with registry data revealing that 11.3% to 42% of patients with ACL injuries also sustain lateral meniscal tears.[2] When it comes to lesions of the posterior root, series report a prevalence of between 6.6% and 17%.[3-6] The potential for these tears to cause persistent knee instability after ACL reconstruction, especially when left untreated, underlines their significance.[7] These tears can exacerbate rotatory and anteroposterior laxity, potentially affecting the outcome of the ACL reconstruction surgery.[8-12] These alterations in joint mechanics are associated with an increase in tibiofemoral contact pressure that could be at risk of knee joint arthritis.[13-15] On the contrary, LMPRT repair during ACL reconstruction shows good clinical outcomes.[16,17] The accurate identification and appropriate management of these root tears is therefore of particular importance. In addition, the diagnosis of LMPRTs may be difficult to establish using magnetic resonance imaging (MRI) alone, which relies heavily on indirect signs with a low concordance rate between MRI and arthroscopy, such as lateral meniscal extrusion.[18,19] Clinical examination is of little value.

Despite this, the literature remains underexplored concerning the epidemiology of LMPRTs and associated risk factors in ACL reconstruction. It is generally accepted that factors such as age, male sex, and a greater body mass index (BMI) are associated with an increased incidence of lateral meniscal injuries.[20] However, their specific implications in the context of root tears during ACL reconstruction have not been fully evaluated, although some risk factors have already been assessed and are reported in the meta-analysis by Wu et al.[21]

This multicenter study aimed to determine the incidence of LMPRTs in patients undergoing ACL reconstruction and identify associated risk factors. Our hypothesis was that the percentage of ACL remnant, revision surgery, and an increased pivot shift test would be independent risk factors for the presence of LMPRTs during ACL reconstruction.

Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of our institution (COS-RGDS-2023-10-003-THAUNAT-M). Informed consent was obtained when patients were added to the registry.

We conducted a retrospective, multicenter study using data sourced from the Francophone Arthroscopic Society's registry[22,23] between June 2020, and June 20203. At the time of the study, this registry included 43 surgeons specialized in arthroscopic knee surgery and affiliated to the Francophone Arthroscopic Society. Each member had to submit his or her application to the steering committee for approval. At the time of the consultation, the patient file was created on a secure database. Surgeons were asked to fill in the operative data on a standardized file. All patients included had a preoperative diagnosis of ACL lesion by clinical examination and MRI, and all underwent ACL reconstruction surgery. Patients were excluded if their medical records were incomplete, in regard to the variables under investigation in this study.

The primary outcome of the study was the presence of LMPRTs during ACL reconstruction, as identified intraoperatively. We only assessed isolated root lesions on the lateral meniscus. We investigated the following variables as potential risk factors for the presence of LMPRTs during ACL reconstruction: age at the time of surgery, sex, nature of the surgery (primary or revision), pivot shift test results under anesthesia (marked as absent, glide, clunk, gross), side-to-side anteroposterior laxity under anesthesia (evaluated in millimeters as <3 mm, 3 to 5 mm, >5 to 10 mm, >10 mm in the registry and compiled into 0-5 mm and >5 mm to limit the risk of interindividual variability), presence of an ACL remnant during arthroscopic assessment (evaluated by the surgeon as percentage of remnant according to the following criteria: absent (0%, <10%, 10%-30%, >30%-50%, >50%-70%, >70%-90%, >90%), occurrence of medial meniscal tear during arthroscopic evaluation, and presence of collateral ligament injury (evaluated preoperatively by MRI and physical examination). We also compared delay to surgery between the LMPRTs group and the no-LMPRTs group. All these variables were extracted from the registry.

A descriptive data analysis was conducted depending on the nature of the considered criteria. Characteristics of 5,572 patients included in the study were similar with 5,359 patients with available data for the final multivariate model. For qualitative data, this included the number of filled and missing data and, for each modality, the frequency and percentage (referring to filled data). Proportions was estimated with their exact 95% confidence intervals (CIs) when appropriate.

Comparisons of data were made using the χ^2 test or Fisher exact test, according to the expected values under the assumption of independence. For quantitative data, this included number of filled and missing data, arithmetic mean, standard deviation, median, first and third quartiles, minimum and maximum. Comparisons of data were made using the Student *t* test or Mann-Whitney-Wilcoxon test (nonparametric test comparing ranks) depending on the distribution of the variable of interest. Risk factors associated with different types of lesions were analyzed using a logistic regression model. The probability of having a LMPRT lesion was modeled with the following factors: sex, nature of the surgery (primary or revision), pivot shift test results under anesthesia, side-to-side laxity under anesthesia, presence of an ACL remnant, medial meniscal tear, and presence of collateral ligament injury. The multicollinearity between variables was tested before multivariate analysis (variance inflation factor criterion). Multicollinearity was present when the variance inflation factor was >5 to 10 or the condition indices were >10 to 30. Variance decomposition proportion obtained from the eigenvectors could identify the multicollinear variables by showing the extent of the inflation of the variance of the regression coefficients according to each condition index. When 2 or more variance decomposition proportions, which correspond to a common condition index >10 to 30, were >0.8 to 0.9, their associated explanatory variables were multicollinear. All comparisons were performed at the level of statistical significance set at $P < .05$. All calculations were made with SAS for Windows (version 9.4; SAS Institute Inc, Cary, NC).

Results

From the Francophone Arthroscopic Society Registry, we identified a total of 8,300 patients who underwent ACL reconstruction during the study period. We excluded patients with incomplete medical records concerning variables used in the risk factor analysis. The population analyzed was 5,359 patients (Fig 1). Among these, LMPRTs occurred in 7.0% (n = 375) of patients undergoing ACL reconstruction. Mean age was 29.4 ± 10.3 years [11-77], and mean BMI was 24.23 ± 3.93 [17-57.7]. Concerning delay to surgery the mean time was 8.4 ± 23.1 weeks [0.2-347.2] in the no-LMPRTs group and 6.5 ± 10.2 weeks [0.3-61.6] in the LMPRTs group ($P = .109$). Characteristics are presented in Table 1.

On univariate analysis, male sex ($P < .001$), revision surgery ($P < .001$), medial meniscal injury ($P = .007$), ACL remnant (0% vs >70%, <10% vs >70%, 10%-30% vs >70%, >30%-50% vs >70%, >50%-70% vs >70%; all $P < .001$) and pivot shift grade (0 vs 1, 0 vs 2, 0 vs 3; $P = .011$) were significantly associated with the presence of LMPRTs during ACL reconstruction. Age, side-to-side laxity, and collateral ligament injury were not associated with LMPRTs. Results are shown in Table 2.

On multivariate analysis, male sex (odds ratio [OR] 1.625, 95% CI 1.278-2.066, $P < .001$), revision surgery (OR 1.755, 95% CI 1.265-2.434, $P = .001$), ACL remnant (0% vs >70%, <10% vs >70%, 10%-30% vs >70%, >30%-50% vs >70%, >50%-70% vs >70%; $P = .003$), and pivot shift grade (0 vs 1, 0 vs 2, 0 vs 3; $P = .010$) remained significantly associated with the presence of LMPRTs. Although side-to-side laxity has become significant (OR 1.639, 95% CI 1.046- 2.568, $P = .031$) and other factors were not found to be significant. Results are shown in Table 3. A box plot is available (Fig 2).

Discussion

This study found that male sex, revision surgery, greater grade of pivot shift test, side-to-side anteroposterior laxity, and a smaller percentage of ACL remnant were significantly associated with the presence

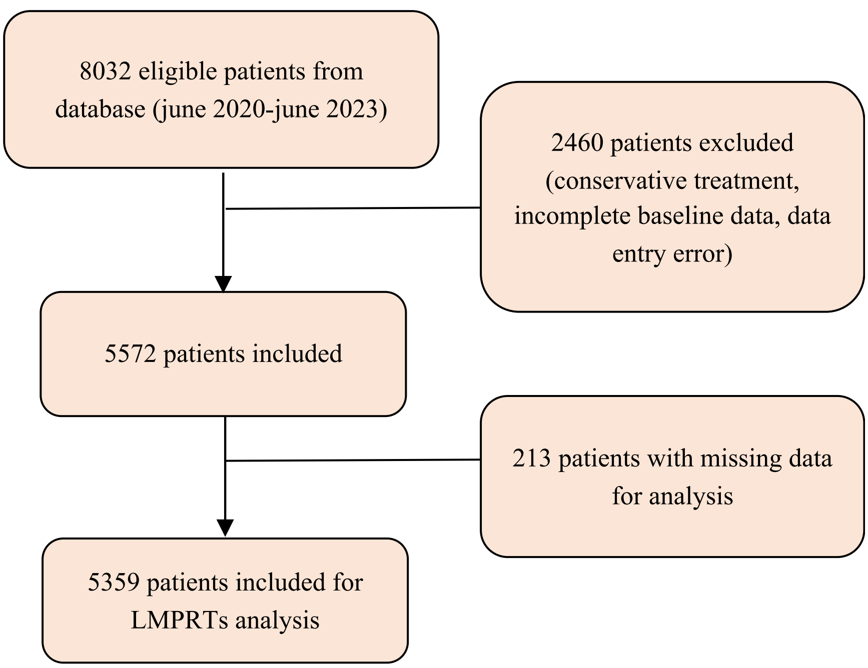

Fig 1. Consolidated Standards of Reporting Trials flowchart of the study. (LMPRT, lateral meniscus posterior root tear.).

Table 1. Descriptive Analysis of Factors Associated With LMPRTs: Population Analysis (N = 5,359)

	No LMPRTs (n = 4,984)	LMPRTs (n = 375)	Total (N = 5,359)
Sex			
Female	1,898 (95.0%)	99 (5.0%)	1,997 (100%)
Male	3,086 (91.8%)	276 (8.2%)	3,362 (100%)
Missing	0	0	0
Age, yr			
n	4,984	375	5,359
Mean (SD)	29.4 (10.3)	28.7 (10.5)	29.3 (10.3)
Median (Q1; Q3)	27.0 (22.0; 35.0)	26.0 (21.0; 34.0)	27.0 (22.0; 35.0)
Min; max	[12; 77]	[11; 68]	[11; 77]
Missing	0	0	0
Delay to surgery			
n	1,630	95	1,725
Mean (SD)	8.40 (23.07)	6.48 (10.21)	8.30 (22.56)
Median (Q1; Q3)	3.25 (2.00; 6.08)	3.15 (1.58; 5.88)	3.25 (1.97; 6.08)
Min; max	[0.0; 347.2]	[0.3; 61.6]	[0.0; 347.2]
Missing	3,561	286	3,847
Revision surgery			
No	4,621 (93.5%)	323 (6.5%)	4,944 (100%)
Yes	363 (87.5%)	52 (12.5%)	415 (100%)
Missing	0	0	0
Medial meniscal tear			
No	3,037 (93.8%)	202 (6.2%)	3,239 (100%)
Yes	1,947 (91.8%)	173 (8.2%)	2,120 (100%)
Missing	0	0	0
Collateral ligament injury			
No	4,523 (93.0%)	341 (7.0%)	4,864 (100%)
Yes	461 (93.1%)	34 (6.9%)	495 (100%)
Missing	0	0	0
ACL remnant			
0%	619 (88.7%)	79 (11.3%)	698 (100%)
<10%	655 (92.6%)	52 (7.4%)	707 (100%)
10%-30%	1,502 (93.6%)	103 (6.4%)	1,605 (100%)
>30%-50%	1,171 (93.2%)	85 (6.8%)	1,256 (100%)
>50%-70%	664 (94.1%)	42 (5.9%)	706 (100%)
>70%	373 (96.4%)	14 (3.6%)	387 (100%)
Missing	0	0	0
Side-to-side laxity			
0-5 mm	750 (94.0%)	48 (6.0%)	798 (100%)
>5 mm	4,234 (92.8%)	327 (7.2%)	4,561 (100%)
Pivot shift			
Missing	0	0	0
0 (absent)	135 (96.4%)	5 (3.6%)	140 (100%)
1 (+/glide)	934 (92.0%)	81 (8.0%)	1,015 (100%)
2 (++/clunk)	3,302 (93.6%)	226 (6.4%)	3,528 (100%)
3 (+++/gross)	613 (90.7%)	63 (9.3%)	676 (100%)
Missing	0	0	0

ACL, anterior cruciate ligament; LMPRT, lateral meniscus posterior root tear; SD, standard deviation.

of LMPRTs during ACL reconstruction. We have confirmed on a large scale the incidence of 7% already found by Praz et al.[3] in another article and by Wu et al.[21] in their meta-analysis. Interestingly, in the multivariate analysis, age, traditionally considered a critical risk factor for associated injuries,[20] was not found to be significantly associated with LMPRTs. Several studies, evaluating precisely LMPRTs,[3,5] such as that by Magosch et al.[6] did not find age to be a risk factor either.

The significant association between male sex and LMPRTs that we observed is consistent with previous studies.[5,21] Praz et al.[3] in their epidemiologic analysis of 3,956 patients reported a male trend in the incidence of LMPRTs, but it was not significant. We initially assumed that this was a sex-related difference in knee anatomy. However, although Kim et al.[24] and Bernholt et al.[25] reported an increased risk in the presence of a steeper lateral posterior tibial slope, Hosseinzadeh and Kiapour[26] reported in their study of 269 native knees an increase in the lateral posterior tibial slope in women compared with men. Thus, this could be explained by the generally greater level of physical activity and more traumatic athletic involvement among men which puts them at greater risk for knee injuries, including

Table 2. Univariate Analysis of Factors Associated With LMPRTs: Population Analysis (N = 5,359)

Variables		Univariate Analysis	
Factor	Comparison	Odds Ratio [95% CI]	Global *P* Value
Sex	Male vs female	1.71 [1.35-2.17]	**<.001**
Age, yr	<30 vs ≥30	1.22 [0.98-1.51]	.077
Revision surgery	Yes vs no	2.05 [1.50-2.80]	**<.001**
Medial meniscal tear	Yes vs no	1.34 [1.08-1.65]	**.007**
Collateral ligament injury	Yes vs no	0.98 [0.68-1.41]	.907
ACL remnant	0% vs >70%	3.40 [1.90-6.09]	**<.001**
	<10% vs >70%	2.11 [1.16-3.87]	
	10%-30% vs >70%	1.83 [1.03-3.23]	
	>30%-50% vs >70%	1.93 [1.09-3.44]	
	>50%-70% vs >70%	1.69 [0.91-3.13]	
Side-to-side laxity	>5 mm vs 0-5 mm	1.21 [0.88-1.65]	.239
Pivot shift	1 (+/glide) vs 0 (absent)	2.34 [0.93-5.88]	**.010**
	2 (++/clunk) vs 0 (absent)	1.85 [0.75-4.56]	
	3 (+++/gross) vs 0 (absent)	2.77 [1.10-7.03]	

NOTE. *P* value in bold are significant.
ACL, anterior cruciate ligament; LMPRT, lateral meniscus posterior root tear.

LMPRTs. However, with changing attitudes, this trend is disappearing nowadays, it would be interesting to evaluate this factor in the years to come.

We also found a significant association between the occurrence of LMPRTs and revision surgery. This could be attributed to the complexity and the extent of knee damage often seen in revision cases, increasing the likelihood of meniscal injuries. This is a very important information, as it has not been widely reported in the literature. In their series, Vial et al.[27] reported that LMPRTs were 5 times more frequent in the revision group than in the primary group, and involved 11 LMPRTs in 27 cases. Praz et al.[3] found no significant difference with only 14 LMPRTs in 324 revisions. In this study, we reported 52 LMPRTs in 415 revision surgeries. We cannot rule out the existence of sampling fluctuation between series, but this series is a multicenter series, which is more likely to be representative of reality. Furthermore, the proximity of the posterior root with the tunnel and the risk of LMPRTs in ACL reconstruction have already been reported in the literature with the use of double-bundle ACL reconstruction.[28,29] This leads us to recommend a precise arthroscopic examination of the posterior root of the lateral meniscus when revision surgery is performed. The presence of greater volume of ACL remnant was associated with a lower risk of LMPRTs, which can be attributed to the protective role of the remnant, possibly mitigating some of the abnormal joint biomechanics after ACL injury. In a recent series, Yoshihara et al.[30] reported a significantly greater number of complete ACL tears in the LMPRTs group than in the control group, without being able to establish a causality link. This confirmed other study on the subject.[31] This study also assessed the percentage of ACL remnants arthroscopically. A trend was found toward an increased risk of LMPRTs inversely proportional to remaining ACL remnant. This suggests a relationship between the

Table 3. Multivariate Analysis of Factors Associated With LMPRTs: Population Analysis (N = 5,359)

Variables		Multivariate Analysis (N = 5,359 Observations)		
Item	Comparison	Odds Ratio*	95% CI	Global *P* Value
Sex	Male vs female	1.622	[1.277- 2.062]	**<.001**
Age, yr	<30 vs ≥30	1.217	[0.975- 1.519]	.083
Revision surgery	Yes vs no	1.753	[1.264- 2.431]	**<.001**
Medial meniscal tear	Yes vs no	1.130	[0.906- 1.409]	.280
Collateral ligament injury	Yes vs no	0.994	[0.687- 1.438]	.974
ACL remnant	0% vs >70%	2.614	[1.436- 4.761]	**.029**
	<10% vs >70%	1.730	[0.975- 3.070]	
	10%-30% vs >70%	1.905	[1.066- 3.402]	
	>30%-50% vs >70%	1.733	[0.932- 3.224]	
	>50%-70% vs >70%	1.848	[1.002- 3.407]	
Side-to-side laxity	>5 mm vs 0-5 mm	1.640	[1.046- 2.570]	**.031**
Pivot shift	1 (+/glide) vs 0 (absent)	2.400	[0.937- 6.144]	**.010**
	2 (++/clunk) vs 0 (absent)	1.331	[0.533- 3.323]	
	3 (+++/gross) vs 0 (absent)	1.637	[0.634- 4.229]	

NOTE. *P* value in bold are significant.
ACL, anterior cruciate ligament; LMPRT, lateral meniscus posterior root tear.

Factors	LMPRTs N and % (N=375)	OR (95% CI)
Sex		
Female	99 (5.0%)	
Male	276 (8.2%)	1.622 [1.277;2.062]
Class of age		
>=30 years	135 (6.2%)	
<30 years	240 (7.5%)	1.217 [0.975;1.519]
Revision		
No	323 (6.5%)	
Yes	52 (12.5%)	1.753 [1.264;2.431]
Medial meniscal tear		
No	202 (6.2%)	
Yes	173 (8.2%)	1.130 [0.906;1.409]
Collateral ligament injury		
No	341(7.0%)	
Yes	34 (6.9%)	0.994 [0.687;1.438]
ACL Remnant		
>70%	14 (3.6%)	
0%	79 (11.3%)	2.614 [1.436;4.761]
<10%	52 (7.4%)	1.848 [1.002;3.407]
10 to 30%	103 (6.4%)	1.730 [0.975;3.070]
30 to 50%	85 (6.8%)	1.905 [1.066;3.402]
50 to 70%	42 (5.9%)	1.733 [0.932;3.224]
Side to side laxity (in mm)		
0-5 mm	48 (6.0%)	
>5 mm	327 (7.2%)	1.640 [1.046;2.570]
Pivot shift		
0 (Absent)	5 (3.6%)	
1 (+ / glide)	81 (8.0%)	2.400 [0.937;6.144]
2 (++ / clunk)	226 (6.4%)	1.331 [0.533;3.323]
3 (+++ / gross)	63 (9.3%)	1.637 [0.634;4.229]

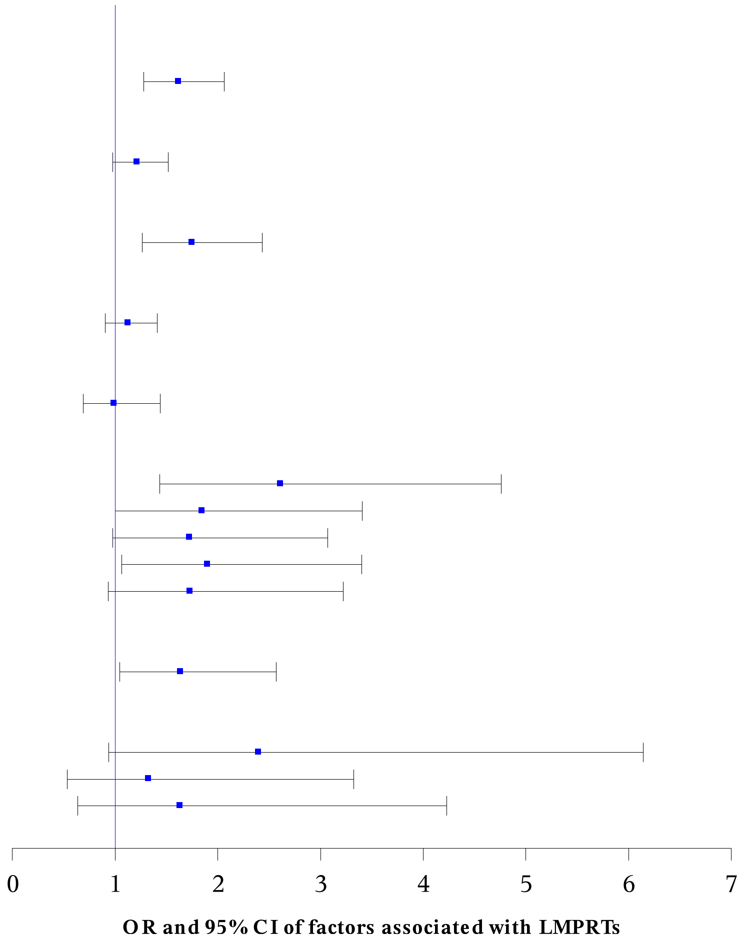

Fig 2. Forest plot of factors associated with lateral meniscus posterior root tears: population analysis (N = 5,361). (ACL, anterior cruciate ligament; CI, confidence interval; LMPRT, lateral meniscus posterior root tear; OR, odds ratio.).

severity of the initial trauma, the number of ACL fibers affected, subsequent rotational instability, and the presence of LMPRTs.

In this study, medial meniscal tears were found to be a risk factor in the univariate analyses possibly as the result of altered knee kinematics, importance of the initial injury, and increased strain on the lateral compartment. However, in the multivariate analysis, this association was no longer significant. Although Kim et al.[24] did not find medial meniscus lesions to be significant, Bernholt et al.[25] reported an increased incidence of ramp lesions concomitant with LMPRTs, but no association with other medial meniscal tears. Conversely, Praz et al.[3] found an OR of 1.532 (95% CI 1.266-2.285) for medial meniscal tears. Thus, there appears to be an association between the occurrence of a medial meniscal tear, most of the time a ramp lesion, and LMPRTs. This discrepancy may arise from confounding variables such as age, sex, or biomechanical factors like side-to-side laxity, and pivot shift test result.

A collateral ligament injury was not associated with a LMPRTs; to our knowledge only Kim et al.[24] reported an association between injury to the lateral meniscus and damage to the medial collateral ligament. In our view, the biomechanical forces causing a collateral ligament injury during an ACL rupture, which often result from a direct lateral or medial force, do not necessarily correspond to those that contribute to a root tear, which more often results from a rotational mechanism. This disparity in injury mechanisms may explain why the presence of a collateral ligament injury has not been found to be a significant risk factor for LMPRTs.

Concerning pivot shift and side-to-side laxity, they were found to be significant risk factors. As shown by several biomechanical studies,[12,32,33] the ACL primarily restricts anterior tibial translation and internal tibial rotation. When combined with a LMPRTs, the tibia's anterior translation and internal rotation can become even more pronounced, especially during pivot movements. This can be explained by the loss of hoop stress distribution after root tear enabling the meniscus to maintain its shape and function when the knee is loaded. Furthermore, Song et al.[36] had identified LMPRTs to be an independent risk factor of high-grade pivot-shift phenomenon in a population of 1,095 noncontact ACL injuries. Other clinical studies have also reported the presence of increased rotatory instability in the pivot shift test when ACL injury is associated with LMPRTs.[10,16,24,30]

Although some studies have found that lateral meniscal tears have no correlation with delay to surgery,[34,35] recent studies have founded the opposite.[36,37] These are small-scale studies, whose design was not intended to establish this causal link. Praz et al.[3] found an increased risk of LMPRTs in surgery <3 months. As the author points out in the article, there is probably a bias in this single-operator study related to the surgeon's desire to operate early in patients with meniscal lesions.[38,39] This study is not without bias, given the smaller number of data available on time to surgery we only compared LMPRTs group with no-LMPRTs group but, thus, even if the time to surgery did not seem to influence the presence of LMPRT, it is unfortunately impossible to provide a scientifically correct answer on the basis of these data.

Limitations

This study has some limitations. As a retrospective study, it may be subject to biases, such as selection bias and potential under-reporting of LMPRTs. In addition, we lacked some preoperative data, especially concerning time to surgery and BMI. In addition, the assessment of anterior laxity, pivot shift, ACL remnant was performed by each surgeon according to a careful clinical examination. The measurement of these variables cannot be free of interindividual variability bias. Standardized measurement of these values was impossible in this register, the discretization of variable was aimed at limiting the risk of bias. Finally, the data collected belonged to a registry that could be the cause of a data registration bias.

Conclusions

In conclusion, this study identified male sex, revision surgery, low volume of ACL remnant, side-to-side laxity, and greater grade of pivot shift as significant risk factors for LMPRTs during ACL reconstruction.

Disclosures

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.B. reports employment with Arthrex and consulting or advisory for Move Up and S.B.M. E.C. reports consulting or advisory for Arthrex, Amplitude SAS, and Orthonov. J-M.F. consulting or advisory for Arthrex and Newclip Technics. N.G. reports consulting or advisory for Newclip Technics; consulting or advisory for and speaking and lecture fees from S.B.M. and Arthrex; speaking and lecture fees from Stryker Orthopaedics and FH Ortho Olympus; and board of directors of Sport Clinic Merignac and Vivalto Santé Group. R.L. reports consulting or advisory for Arthrex and Amplitude SAS. M.T. reports consulting or advisory for Arthrex. C.T. reports consulting or advisory for FH Orthopedics SAS and Smith & Nephew. All other authors (N.B., P-J.L., T.N., The Francophone Arthroscopic Society ACL registry study) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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