Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

SCIENZE BIOMEDICHE E NEUROMOTORIE

Ciclo XXXIII

Settore Concorsuale: 06/F4

Settore Scientifico Disciplinare: MED33

BIOMECHANICAL MODELING FOR PREDICTION OF LAXITY AND FAILURE AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Esame finale anno 2020

SUMMARY

ABBREVIATIONS

ACL: Anterior Cruciate Ligament

PCL: Posterior Cruciate Ligament

MCL: Medial Collateral Ligament

LCL: Lateral Collateral Ligament

PLC: Postero Lateral Corner

LNS: Lateral Notch Sign

SB: Single-Bundle

SBLP: Single-Bundle + Lateral Plasty

IM: Intact Meniscus

MM: Medial Meniscectomy

LM: Lateral Meniscectomy

MR: Meniscus Repair

TPS: Tibial Plateau Slope

KOOS: Knee Injury and Osteoarthritis Outcome Score

PROMs: Patient-Reported Outcome Measures

PASS: Patient Acceptable Symptoms State

ADL: Activity of Daily Living

Qol: Quality of Life

INTRODUCTION

ACL ANATOMY

The anterior cruciate ligament (ACL) is located in intra-articular position but outside the synovial cavity. The ACL macro-anatomically resembles a band of dense connective tissue ranging in length between 22 and 41 mm, which originates from the femur and attaches to the tibia. The tibial insertion site has been described as a duck's foot" insertion pattern, while the femoral footprint has an oval shape, with a diameter of about 18 mm in length and 11 mm in width[1]. In particular, the ACL originates on the medial side of the lateral femoral condyle and runs antero-distally through the knee joint to its insertion site at the medial tibial eminence. In spite of it is described as a single ligament, ACL is composed of two separate bundles: the anteromedial (AM) bundle and the posterolateral (PL) bundle, terminology based on their respective insertion sites on the tibia. On the tibial side, the AM bundle inserts anteromedially, anterior and lateral to the medial tibial spine, while the PL bundle inserts slightly posterior and lateral to the AM bundle. On the femoral side the AM bundle originates on the posterior and proximal aspect of the medial wall of the lateral femoral condyle, while the PL bundle originates on the posterior and distal aspect of the wall[2]. The ACL receives most of its blood supply from the middle genicular artery, with the infrapatellar fat pad and the synovium being supportive with nutrients[3]. The ACL is innervated by a branch of the tibial nerve with important proprioceptive feedback via mechanoreceptors[4].

ACL BIOMECHANICS

The ACL is a key structure in the knee and allows, in combination with posterior cruciate ligament, the continuous contact between the femoral condyle and the tibial plateau during the range of motion of the knee. The two different bundles of the native ACL make varying contributions to knee stability at different knee flexion angles[5]. In extension the PL bundle is taut, while the AM bundle is more lax. With increasing flexion, the PL bundle becomes lax and tension increases in the AM bundle. Biomechanical studies showed that that the transection of the AM bundle leads to an increased anterior tibial translation (ATT) at 60° and 90° of knee flexion, while the transection of the PL bundle increases the ATT at 30° of flexion. Moreover, the transection of PL bundle increases combined rotation at 0° and 30° of flexion, compared with the intact status and with the isolated transection of the AM bundle[6]. The two bundles thus cooperate to restrict antero-posterior and rotatory knee laxity, dependent on the flexion angle of the knee.

ACL INJURY AND RECONSTRUCTION

ACL injuries represents more than 50% of knee injuries, with an incidence of approximately 85/100000 in patients aged between 16 years and 39 years[7]. ACL tears are associated with several modifiable and nonmodifiable risk factors including female sex, young age and earlier, more intense and more frequent participation in pivoting sports[8].

Moreover, variations in bone morphology, neuromuscular control, genetic profile, and hormonal pattern may play a role[9]. ACL injuries are often complicated by concomitant injury of others structures such as medial collateral ligament (19-38%) and lateral (20-45 %) or medial (0-28 %) meniscal lesions[10].

The majority of ACL ruptures happen in a non-contact trauma, which indicates that excessive loading leads to ACL injuries likely resulting from inappropriate movement patterns. Several studies showed that maximum ACL loading and strain occurs when the knee is near full extension, suggesting that a stiff landing with a small knee flexion angle significantly contributes to ACL injury[11,12].

ACL tears lead to loss of articular stability with subsequent functional impairment and potential long-term disability, in particular due to the development of knee osteoarthritis (OA)[13]. In clinical practice, the diagnosis is performed by clinical examination, magnetic resonance imaging and finally, in patient who underwent surgery, confirmed arthroscopically.

The treatment of ACL injury should be aimed to restore knee biomechanics avoiding short-term functional impairments, and to prevent further damage to the menisci and cartilage, which may contribute to the development of post-traumatic OA. ACL surgical reconstruction is indicated in patient with persistent knee instability, hindering physical activity and sports performance[14]. Furthermore, surgical treatment has traditionally been recommended to address the anteroposterior and rotatory knee laxity in high level athletes and in young patients engaged in pivoting sports[15]. However high-level evidence in support of surgical management is lacking. Patients with low physical demands or patients without feeling of instability during their daily lives (copers) could be considered for conservative treatment. About the capability of ACL reconstruction to reduce the risk of OA, conflicting evidence was reported in literature[16]. However, modern ACL reconstruction techniques have been developed and long-term follow-up studies of these procedures are warranted to evaluate their effect on the development of middle- and long-term OA.

ASSESSMENT OF KNEE LAXITY

By definition, laxity is the displacement, or the rotation, produced in response to an applied load or moment. Because the ACL represents the primary restraints to the tibiofemoral joint displacement and rotations, its tear lead to an increase of joint laxity[17].

An accurate joint laxity assessment represents a key tool during both the diagnosis of articular injury and the evaluation of post-operative treatment. Knee laxity is defined static (uniplanar) when only one degree of freedom is involved, and dynamic (multiplanar) when more than one degree of freedom is considered. Historically the first approach to evaluation of knee laxity consist in the measurement of joint antero-posterior tibial translation (ATT): Lachman and anterior drawer test are the most used tests to quantify the static antero-posterior laxity of the tibiofemoral joint[13]. In the anterior drawer test the examiner moves the tibia forward with respect to the femur, with the patient's knee at 90 degrees of flexion and the feet flat; excessive anterior translation indicates a positive test. The Lachman test is performed with the knee at 30° of flexion and is regarded as the most sensitive test for diagnosing an ACL rupture, with a sensitivity of 0.81 and 0.91 for awake and anesthetized patients respectively[18]. To enhance the quantification of anterior knee laxity and mitigate subjectivity, various devices have been developed. The KT-1000 arthrometer (MEDmetric Corp, San Diego, CA, USA) is one of the most used devices and allows to assess the ATT under a predefined torque or by the manual maximum test. The reliability of the KT-100 arthrometer varies with the examiner's experience and has been considered fair when performed by experienced professionals[19]. Another commonly used quantification tool of ATT is the Rolimeter (Aircast Europa, Neubeuern, Germany), a simple metallic device with two convex supports and a bar that connects them. Rolimeter has results comparable with those of KT-1000 arthrometer in terms of reliability[20].

The rotatory laxity can be measured both statically and dynamically, but both are associated with methodological difficulties. However, the dynamic rotatory laxity is more closely associated with the symptoms of instability and the development of OA than anteroposterior laxity[21].

In order to assess and better address the dynamic rotatory laxity, the pivot shift test was introduced in clinical and research practice. The pivot-shift test is a dynamic test of the rotatory laxity of the knee that produces subluxation and reduction (felt as a "clunk") of the lateral tibial plateau. Several different methods are used to quantify the pivot-shift test. Surgical navigation represents the gold standard of knee laxity assessment, but it is an extremely invasive procedure, performed mostly during the ACL reconstruction surgery (time-0)[22,23]. This triaxial sensor is fastened to the lateral aspect of the proximal tibia and quantifies the pivot-shift test by measuring the acceleration of the joint during the execution of the pivot shift maneuver. This device has been tested in terms of reliability, presenting an intraclass correlation coefficient of 0,79. The inertial sensor has a resolution of 0,03 m/s^2, and has been shown to have a strong correlation with surgical navigation systems[24].

FAILURES OF ACL RECONSTRUCTION

The risk of suffering from a subsequent anterior cruciate ligament (ACL) injury following ACL reconstruction is increased 10-fold in comparison to the first-incidence risk. A recurrence risk ACL injury of 10–25% is provided in the current literature[25].

Such re-injuries often occur in the first years following the surgery, in particular during, or shortly after, the successful return to sport (RTS)[26].

It is estimated that 200,000 ACL revision are performed annually in the United States, with reported revision rates ranging from 1% to 13%[27].

According to Johnson and Fu, failure can be attributed to 1 or more of 4 main categories: recurrent instability patholaxity, recurrent pain or arthritis, arthrofibrosis or loss of motion, or extensor mechanism dysfunction[28].

Several causes for recurrent instability, which could be classified as either early or late presentations, was highlighted. Early instability (< 6 months) may be attributed to technical error, failure of graft incorporation, premature return to high-demand activities, or overly aggressive rehabilitation. Late causes may include repeated trauma to the graft, poor graft placement, generalized ligamentous laxity, and concomitant abnormality not addressed at the time of the reconstruction[29].

Anterolateral rotary instability represents a potential cause of failure and should be considered in patients with ACL reconstruction failure[30]. After the recent anatomical definition of the antero-lateral ligament (ALL), attention has returned to the lateral extra-articular procedures, with the aim to better address knee laxity. In vivo studies, in which intra-operative evaluation was provided, reported that single bundle associated with lateral extra-articular tenodesis was superior in controlling internal rotation and anteroposterior tibial translation compared to isolated intra-articular single bundle or double bundle techniques[31].

MENISCI AND ACL RECONSTRUCTION

Given the complex nature of ACL failure, outside of graft rerupture, objective measures and subjective feelings of instability must be addressed on an individualized basis when revision surgery is being considered[32].

Meniscal tears are frequently associated with anterior cruciate ligament injuries and the correct management of concomitant meniscal lesion in ACL reconstruction surgery represents a challenging topic for orthopaedic surgeons[33]. The menisci have an important role in load bearing and shock absorption and their partial or complete loss and tears have been associated with an increased risk of osteoarthritis over time. Moreover, since the menisci also function as secondary stabilizers of the knee, the loss of meniscus in ACL-injured patients has been identified as a possible secondary cause of graft failure after ACL reconstruction[34]. In particular, the critical role of medial meniscus in restraining uniplanar anterior load in the ACL-deficient knee was underlined in previous cadaveric studies, with the most significant effect when the posterior horn was involved. Increase of antero-posterior laxity after medial meniscectomy was confirmed as well. The lateral meniscus, on the other side, is an important stabilizer of the knee under both isolated and combined rotatory loads and its tear or resection resulted in a significant increase of dynamic rotatory laxity in the ACL-deficient and ACL-reconstructed knee. From a clinical point of view, the menisci have been demonstrated to play a role in ACL reconstruction outcomes and failures, even if the long-term results and the role of meniscal repair has been studied marginally.

ANATOMY AND ACL RECONSTRUCTION

In the last years, great interest has been focused on the relationship between knee anatomy and the risk of anterior cruciate ligament (ACL) injury, knee laxity, and failure of ACL reconstruction (ACL-R). Original studies and meta-analyses have highlighted a narrow intercondylar notch and a steep posterior tibial slope as well recognized risk factors for ACL rupture. Several investigators have also established a correlation between preoperative laxity -especially pivot shift- and anatomical parameters such as lateral tibial slope[35], lateral tibial plateau diameter[36] and femoral condyle configuration[37]. However, there is a lack of an objective and comprehensive in vivo analysis, especially with accurate devices. of the correlation between bony morphological features of a joint and laxity values after an isolated ACL tear.

Recently, anatomical characteristics of the knee joint have been identified to predict failure of ACL-R as well. A mean anterior subluxation of 3.9 mm of the lateral compartment has been found in failed ACL-R with respect to normal knees and acute ACL tears[38]. Salmon et al.[39] reported a 3-fold hazard ratio of ACL graft rupture in patients with posterior tibial slope >12°. However, they performed the evaluation only on lateral radiographs and without discriminating between male and female patients. Moreover, the risk of contralateral ACL injury has been studied marginally, while the risk of multiple failures has never been studied.

Another aspect that is believed to correlate to ACL reconstruction outcomes is the lateral femoral notch sign (LNS), which is a bony impression on the lateral femoral condyle, that could be seen on conventional lateral radiograph or MRI in approximately 6% to 25% of the patients that sustained an anterior cruciate ligament (ACL) injury. Its presences have recently, the LNS has also been correlated with an increased incidence of lateral meniscus injury[40,41] and higher cartilage degradation on the lateral femoral condyle, even after an uneventful ACL-reconstruction[42]. However, its correlation with pre-operative laxity has never been explored.

It is also known that physiological bony morphologic variations, especially on the lateral side of the knee, have been associated with high grade-pivot shift and increased risk of ACL-revision[26, 30, 31, 39]. Considering this background, the present study aimed to investigate the effect and magnitude of LNS on rotatory laxity. The hypothesis of the study was that a positive LNS was correlated with higher rotatory laxity during the pivot shift maneuver quantified with the surgical navigation system.

BACKGROUND OF THE THESIS

At the beginning of this project, in November 2017, several questions related to knee laxity and risk factors for ACL failure were still unsolved; thus, the present and future trends in ACL research were clear.

In particular, the role of meniscal lesions and their removal or repair in combination with ACL reconstruction has been studied, but mostly in cadaveric setting; thus, the in-vivo role remains unexplored.

Another emerging topic is the role of anatomy -and in particular the role of posterior tibial slope- as risk factor for ACL failure. Moreover, the role of anatomy in the genesis of joint laxity had been studied only in cadaveric models or with static radiographic studies, and how anatomy can impact on the ACL reconstruction failure risk is still controversial; furthermore it has never been assessed in the cases of multiple failures or contralateral injuries in young adolescents.

Summarizing, based on the current available evidences, meniscus and joint anatomy have been suggested to play a relevant role on the amount of knee laxity before and after ACL reconstruction, and to affect short or long term outcomes; but these evidences are scarce or incomplete, and derives from basic clinical studies or from laboratory settings.

Thus, there is need of further clinical and in-vivo studies, especially using new technologies to allow accurate quantitative assessment of joint laxity.

AIMS OF THE THESIS

The present PhD thesis has 4 main aims developed within 11 original studies which investigate the role of meniscus and joint anatomy in the genesis of laxity before and after ACL reconstruction, and their role on the outcomes of ACL reconstruction. To answer the Aim 1 and Aim 2, a systematic review (**Study I**) and in-vivo experimental studies with surgical navigation (**Study II, III, IV and V**) were performed, while to answer the Aim 3 and Aim 4, prospective (**Study VI and VII**) and retrospective cohorts (**Study VIII, IX, X and XI**) of patients undergoing ACL reconstruction were investigated.

AIM 1: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF MENISCUS (STUDY I, II and III)

We investigated the role of meniscus in the genesis of knee laxity before and after ACL reconstruction under different point of views. First, we aimed to investigate the in vitro effects on static and dynamic laxity of total and partial meniscectomy and different types of meniscal tears of lateral and medial meniscus in the ACL-deficient knee through a systematic search of the literature (**Study I**). Second, we aimed to assess the in vivo role of partial medial and lateral meniscectomy on knee laxity before ACL reconstruction, with a navigation system (**Study II**). Third, we investigated the role of partial medial meniscus defect on antero-posterior laxity after ACL reconstruction with isolated anatomical single-bundle or over-the-top plus lateral plasty (**Study III**)

AIM 2: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IV and V)

We investigated the role of different knee anatomical parameters in the determination of laxity before ACL reconstruction. Specifically, morphological parameter such as tibial slope, tibio-femoral width, tibial subluxation and intercondylar notch were correlated with high or low dynamic laxity before ACL reconstruction (**Study IV**). Further, the magnitude of Lateral Notch Sign (LNS) was correlated to the amount of Pivot-Shift before ACL reconstruction (**Study V**).

AIM 3: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF MENISCUS (STUDY VI, VII and VIII)

We investigated role of concomitant meniscectomy (**Study VI**) and meniscal repair (**Study VII**) on short-term outcomes after ACL reconstruction. Further, the effects of meniscal injuries at time of ACL reconstruction in terms of PROMs and re-injuries were evaluated at long-term as well (**Study VIII**).

AIM 4: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IX, X and XI)

We aimed to investigate the correlation of knee anatomical parameters (in particular posterior tibial slope) with failures of ACL reconstruction or contralateral injuries. First, we compared patients with failed ACL-R with a control group of sex-matched patients with successful ACL-R (**Study IX**). Second, we compared the features of patients experiencing single ACL reconstruction failure or multiple ACL reconstruction failures (**Study X**). Third, we investigate the rate of second ACL injuries (ipsilateral or contralateral) according to the amount of posterior tibial slope in patients with less than 18 years of age (**Study XI**).

SUMMARY OF STUDIES

STUDY I: Medial and lateral meniscus have a different role in kinematics of the ACL-deficient knee: a systematic review *(Published: Journal of ISAKOS)*

STUDY II: The Contribution of Partial Meniscectomy to Preoperative Laxity and Laxity After Anatomic Single-Bundle Anterior Cruciate Ligament Reconstruction: In Vivo Kinematics With Navigation *(Published: AJSM)*

STUDY III: Anterior Cruciate Ligament (ACL) Reconstruction with Lateral Plasty Restores Anterior-Posterior Laxity in the Case of Concurrent Partial Medial Meniscectomy *(Submitted: Arthroscopy)*

STUDY IV: Anatomical features of tibia and femur: Influence on laxity in the anterior cruciate ligament deficient knee *(Published: The Knee)*

STUDY V: The Lateral Femoral Notch Sign could identify patients with increased rotatory instability after ACL-injury. Intraoperative evaluation using the surgical navigation system *(In Press: AJSM)*

STUDY VI: Influence of Surgical Techniques and Meniscus Status in Anterior Cruciate Ligament Reconstruction: Laxity Assessment and Subjective Outcomes at Minimum-Two-Years Follow-Up *(Submitted: Journal of Knee Surgery)*

STUDY VII: Clinical Outcomes, Healing Rate and Presence of Perimeniscal Cysts after All-Inside Meniscal Repair in Combination With Anterior Cruciate Ligament (ACL) Reconstruction: A Prospective Case-Control study with MRI Assessment *(Submitted: CJSM)*

STUDY VIII: Ten-year Survivorship, Patient-Reported Outcome Measures (PROMs) and Patient Acceptable Symptoms State (PASS) After Over-the Top Hamstring ACL Reconstruction with a Lateral Extra-articular Reconstruction: Analysis of 267 Consecutive Cases *(In Press: AJSM)*

STUDY IX: Patients With Failed Anterior Cruciate Ligament Reconstruction Have an Increased Posterior Lateral Tibial Plateau Slope: A Case-Controlled Study *(Published: Arthroscopy)*

STUDY X: Steep Posterior Tibial Slope, Anterior Tibial Subluxation, Deep Posterior Lateral Femoral Condyle, and Meniscal Deficiency Are Common Findings in Multiple Anterior Cruciate Ligament Failures: An MRI Case-Control Study *(Published: AJSM)*

STUDY XI: Posterior Tibial Slope is Associated to Higher Risk of Early Contralateral Anterior Cruciate Ligament (ACL) Injury in patients <18 Years Old *(Published: KSSTA)*

PATIENTS

To answer the 4 Aims of this PhD thesis, different patients' populations were analyzed, including patients operated of ACL reconstruction with different techniques, with different age and at various follow-ups; moreover, databases of failed ACL reconstruction was used. Finally, a systematic literature search was performed as well.

SYSTEMATIC REVIEW OF COMBINED MENISCUS AND ACL LESION (Study I):

It consists in a systematic search of all biomechanical cadaveric studies assessing the role of meniscal defect in the context of ACL lesion. Inclusion criteria for the systematic review were:

- biomechanical human cadaveric studies,
- meniscus cutting following ACL cutting,
- distinct kinematic evaluation of meniscus-intact status, single treated meniscus status and (if present) double resected meniscus status in ACL-deficient knee,
- quantification at least one of displacement or rotation under an external single or coupled load,
- articles with clear setting description or results.

Based on the aforementioned criteria, a total of 18 studies were included in the systematic review and analyzed.

Classification of meniscal lesion	Study	Description of meniscal lesion
Total/Subtotal meniscectomy	Levy *et al*[19]	Total meniscectomy
	Shoemaker and Markolf[20]	Total meniscectomy
	Bonnin *et al*[21]	Total meniscectomy
	Allen *et al*[22]	Total meniscectomy
	Seon *et al*[23]	Subtotal resection of the meniscus removing the inner 80% of the body and posterior horn
	Musahl *et al*[24]	Total meniscectomy
	Ahn *et al*[25]	Total meniscectomy
	McCulloch *et al*[26]	Resection of the 80% of the depth of the posterior horn to simulate a subtotal meniscectomy
Posterior horn lesion	Ahn *et al*[25]	Peripheral longitudinal tear from the posterior horn to the postero-medial corner at the menisco-capsular junction
	McCulloch *et al*[26]	Resection of the 50% of the depth of the posterior horn up to the midpoint of the body
	Lorbach *et al*[27]	Tear ranging from the pars intermedia to 5 mm away from the posterior root of the medial meniscus
Bucket handle tear	Shoemaker and Markolf[20]	Resection of a vertical bucket-handle tear 1.5–2 cm in length of the inner one-third of the medial meniscus
	Lorbach *et al*[28]	Standard vertical bucket-handle tear and resection of the bucket-handle tear
Posterior root lesion	Bonnin *et al*[21]	Posterior meniscal disinsertion
	McCulloch *et al*[26]	Release of meniscal root from its posterior tibial attachment
Posterior menisco-capsular lesion	Peltier *et al*[16]	Posterior menisco-capsular attachment lesion
	Stephen *et al*[11]	Menisco-capsular lesion was started laterally and taken medially to the junction of posterior one-third and anterior two-thirds of the meniscus
	DePhillipo *et al*[12]	Tear of posterior menisco-capsular junction

ACL NAVIGATED RETROSPECTIVE DATABASE (Study II, III, IV and V):

It consists in a retrospective database of all the kinematic data acquired from 2005 to 2017 during navigated ACL reconstruction in consecutive patients. Inclusion criteria for Navigated ACL reconstruction were:

- acute or chronic ACL deficiency with or without an irreparable medial or lateral meniscal tear,
- age between 16 and 65 years,
- no concomitant ligamentous other injuries,
- no previous knee surgery.

Based on the aforementioned criteria, 207 patients were included in this database.

Based on specific inclusion criteria for each specific study, subgroups of this databases were evaluated:

Study II: 164 patients (139 M, 25 F, mean age 29 ± 9 years). Meniscal repair excluded.

Study III: 101 patients (46 SB, 55 SB+LP). Other technique excluded.

Study IV: 42 patients (36 M, 6 F, mean age 26.3 ± 8.4 years). No MRI and Meniscal lesions excluded

Study V: 90 patients (78 M, 12 F, mean age 26 ± 8 years). No MRI excluded

“RICERCA FINALIZZATA” and “GIOVANI RICERCATORI” PROSPECTIVE PROJECTS (Study VI and VII):

It consists in a Randomized Controlled Study (RCT) of ACL reconstruction with different ACL reconstruction technique based on 2 imbricated projects funded by Italian Ministry of Health.

Inclusion criteria for this study were:

- acute or chronic ACL deficiency with or without a medial or lateral meniscal tear,
- age between 18 and 65 years,
- no concomitant other ligamentous injuries,
- no previous knee surgery.

Based on the aforementioned criteria, 60 patients (40 in the “Ricerca Finalizzata” project and 20 in the “Giovani Ricercatori” project).

Based on specific inclusion criteria for each specific study, subgroups of this databases were evaluated:

Study VI: 59 patients with 3 different surgical technique (SB, DB, SBLP)

Study VI Demographic data					
Gender (Male/Female)	**Age (years)**	**Injury-to-surgery (months)**	**Follow-up (months)**	**Surgical technique**	**Meniscus treatment**
48 / 11	25.8 ± 8.8	5.3 ± 4.5	26.1 ± 3.9	20 DB 15 SB 24 SBLP	24 IM 19 MR 11 MM 5 LM

Study VII: 40 patients with repaired meniscus (20) and a matched group (20) with intact meniscus

Study VII Demographics data	**ACL (n=20)**	**ACL + Suture (n=20)**	**p-value**
Demographics			
Age (years)	25.9 ± 8.1	25.8 ± 8.5	=0.9698
Sex (M/F)	17 (85%)/3 (15%)	18 (90%)/2 (10%)	=1.0000
Side (R/L)	11 (55%)/9 (45%)	13 (65%)/7 (35%)	=0.7469
Time from Injury to Surgery (months)	6.0 ± 5.0	4.9 ± 5.2	=0.4994
Surgical Technique			=0.5624
Single-Bundle	6 (30%)	4 (20%)	
Single-Bunble + Lateral Plasty	9 (45%)	8 (40%)	
Double-Bundle	5 (25%)	8 (40%)	

ACL 10-YEARS FOLLOW-UP RETROSPECTIVE SERIES (Study VIII):

It consists in a retrospective cohort of consecutive patients that underwent over-the-top and lateral plasty ACL reconstruction between 2007 and 2009, thus with a 10-year follow-up at time of evaluation in 2019. Inclusion criteria for this retrospective study were:

- Primary ACL reconstruction,
- No other concomitant procedures except of meniscal treatment,
- 10 years of follow-up.

Based on the aforementioned criteria, 325 patients were included in this retrospective study. Considering that 58 patients were not available at final examination, a total of 267 patients were included in the analysis

Study VII Demographic data

Variables	Patients
Follow-up	10.1 ± 0.6
Sex	
Males	205 (77%)
Females	62 (23%)
Age (years)	
Mean (SD)	30.7 ± 10.6
≥18 years	238 (89%)
<18 years	29 (11%)
Pre-operative Tegner	
Median (IQR)	7 (5 - 7)
≤5	76 (28%)
>5	191 (72%)
Reconstruction timing (months)	
Mean (SD)	29 ± 25
<3 months	69 (26%)
≥3 months	198 (74%)
BMI	
Mean (SD)	23.7 ± 3.5
<25	184 (69%)
≥25	83 (31%)
Smoke (Yes)	
No	187 (70%)
Yes	80 (30%)
Meniscus Injury	
Medial	118 (44%)
Lateral	56 (21%)
Medial and Lateral	15 (6%)
Chondropaty (≥2 grade Outerbridge)	
Medial	26 (10%)
Lateral	9 (3%)
Medial and Lateral	6 (2%)

FAILED ACL RETROSPECTIVE DATABASE (Study IX and X):

It consists in a retrospectively collected databases of failed ACL reconstructions that underwent first or second Revision ACL reconstruction between XX and XX. Inclusion criteria for this retrospective database were:

- Failed ACL reconstruction,
- Presence of pre-operative MRI,
- No other ligamentous procedures (PCL, MCL, PLC).

Based on the aforementioned criteria, 49 consecutive patients were included in this retrospective database; 14 further patients with multiple ACL failures were obtained within an International Collaboration with the "Hospital Italiano" of Buenos Aires (Argentina) and the "Casa di Cura Città di Parma" (Italy).

Based on specific inclusion criteria for each specific study, subgroups of this databases were evaluated:

Study IX: 43 failed ACL reconstructions (matched with a cohort of 43 non-failed ACL reconstr.)

	Control Group (n = 43)	Failed Group (n = 43)	*P* Value, Control vs Failed Group
Patient data:			
Sex, male/female	34/9	34/9	1.0000
Age, yr[†]	23.3 (19.6 − 23.2)	21.8 (18.6 − 26.7)	.4120
Side, right/left[‡]	22/21	24/19	.8290
Medial meniscus lesion, no/yes[‡]	35/8	31/12	.4444
Lateral meniscus lesion, no/yes[‡]	39/4	39/4	1.0000
Follow-up, yr[§]	3.0 ± 0.7	NA	NA

Study X: 25 multiple ACL failures and 25 single ACL failures (and 40 non-failed ACL reconstr.)

	Control (n = 40)	Failed ACL-R (n = 25)	Multiple Failures (n = 26)	*P* Value
Age at, y				
Primary	26.2 ± 8.6	25.2 ± 8.9	22.2 ± 3.6	.110
Revision	NA	32.2 ± 10.2	26.2 ± 6.1	.012[b]
Re-revision	NA	NA	31.0 ± 7.2	NA
Time to, y				
ACL failure	NA	7.0 ± 5.5	4.0 ± 5.3	.048[b]
Revision failure	NA	NA	4.8 ± 4.8	NA
Sex				.901
Male	34 (85)	22 (88)	23 (88)	
Female	6 (15)	3 (12)	3 (12)	
Graft at primary				.006[b]
Hamstring tendon	40 (100)	21 (84)	19 (73)	
BPTB	0 (0)	3 (12)	7 (27)	
Allograft	0 (0)	1 (4)	0 (0)	
Graft at revision				.131
Hamstrings	NA	3 (12)	6 (23)	
BPTB	NA	1 (4)	6 (23)	
Allograft	NA	18 (72)	13 (50)	
Others	NA	2 (8)	1 (4)	
Meniscectomy at primary				
MM	7 (17)	6 (24)	8 (31)	.365
LM	4 (10)	2 (12)	3 (11)	.405
Meniscectomy at revision				
MM	NA	10 (40)	17 (65)	.125
LM	NA	8 (32)	4 (19)	.285

[a]Values are presented as n (%) or mean ± SD. ACL, anterior cruciate ligament; ACL-R, anterior cruciate ligament reconstruction; BPTB, bone–patellar tendon–bone; LM, lateral meniscus; MM, medial meniscus; NA, not applicable.
[b]$P < .05$.

ACL UNDER-18 RETROSPECTIVE SERIES (Study XI):

It consists in a retrospective cohort of consecutive patients with less than 18 years of age that underwent over-the-top and lateral plasty ACL reconstruction between 2006 and 2017, thus with a 2-year minimum follow-up at time of evaluation in 2019. Inclusion criteria for this retrospective study were:

- primary ACL reconstruction,
- 2-years minimum follow-up,
- no other concomitant procedures except of meniscal treatment,
- intact contralateral knee,
- lateral knee radiograph available,
- non-contact ACL injury mechanism.

Based on the aforementioned criteria, 94 patients were included in this retrospective study (64 M, 30 F, mean age 15.7 ± 1.5 years).

METHODS

To achieve the purposes of each of the 11 studies, different methods were employed, including systematic search of the literature, in-vivo computer navigation, MRI and radiographic assessment of anatomical parameters, clinical and instrumental evaluation, patients surveys and PROMs.

OUTLINE OF STUDIES METHODS

AIM 1: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF MENISCUS

STUDY I: Systematic review

STUDY II: Intra-operative in-vivo navigation study (pre-operative)

STUDY III: Intra-operative in-vivo navigation study (pre-operative and post-operative)

AIM 2: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF ANATOMY

STUDY IV: Intra-operative in-vivo navigation study, MRI evaluation (pre-operative)

STUDY V: Intra-operative in-vivo navigation study, MRI evaluation (pre-operative)

AIM 3: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF MENISCUS

STUDY VI: Instrumental evaluation, PROMs (pre-operative and post-operative)

STUDY VII: MRI and instrumental evaluation, PROMs (pre-operative and post-operative)

STUDY VIII: Reoperations, Survivorship analysis, PROMs (post-operative)

AIM 4: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF ANATOMY

STUDY IX: Case-control MRI study

STUDY X: Case-control MRI study

STUDY XI: Survivorship analysis, contralateral injuries, radiographic evaluation (post-operative)

SURGICAL TECHNIQUES

Single-Bundle ACL Reconstruction: In the patients undergoing Single-Bundle ACL reconstruction, the hamstring was detached from their tibial insertion and looped on a suture button device in a quadrupled fashion. The ACL footprints were identified, and tibial and femoral tunnels were created in the central position after identifying the anteromedial (AM) and posterolateral bundles according to anatomic landmarks[43]. The graft, which was fixed with a suture button in the femoral side and interference screw in the tibial side at 20° of flexion (Figure 1).

Double-Bundle ACL Reconstruction: In the patients undergoing Double-Bundle ACL reconstruction, a non-anatomical technique with hamstrings was used.

Semitendinosus and gracilis tendons were harvested leaving the tibial insertion intact. The tibial tunnel was drilled with the knee flexed at 35° aiming at the postero-medial part of the ACL footprint. A 6 mm complete femoral tunnel was drilled through the anteromedial portal from the posterolateral part of the femoral footprint to the lateral femoral cortex. After a lateral incision proximal to the lateral epicondyle and dissection of the iliotibial band and inter-muscular septum, the over-the-top position was reached and the exit of the previously performed femoral tunnel. The graft was then passed in the tibial tunnel, intra-articularly and outside the joint, where it was fixed at the over-the-top position with two barbed metal staples flexed at 70°. Finally, the graft was retrieved from the femoral tunnel, introduced inside the joint and through the tibial tunnel, in order to allow fixation at the antero-medial tibial cortex with a barbed metal staple and the knee at 15° flexion (*Figure 1*).

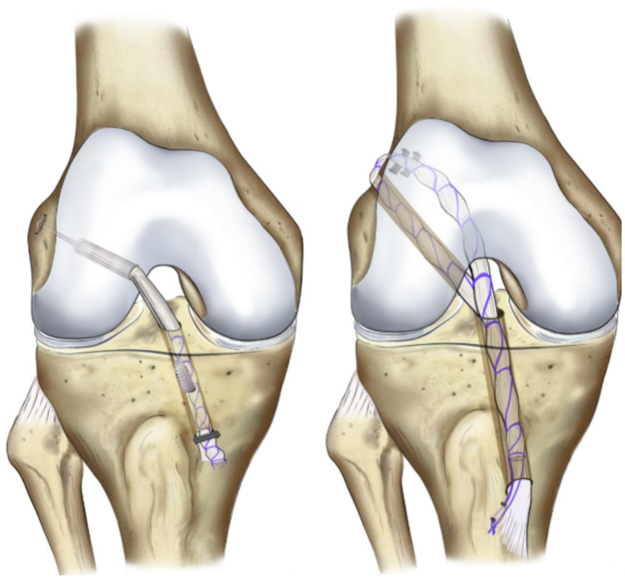

Figure 1: Single-Bundle (left) and Double-Bundle (right) ACL reconstruction technique

Single-Bundle and Lateral Plasty ACL Reconstruction: In the patients undergoing Single-Bundle Over-the-Top ACL reconstruction with the addition of a lateral plasty using both hamstring tendon[44], after tendons harvesting preserving the tibial attachment, graft was passed through the tibial tunnel and "over the top" of the femur. The knee was flexed to 75° with external tibial rotation, and a posterior drawer was applied. The tendons were then fixed to the cortical bone of the femur with 2 bone staples under manual maximum tension. The remaining part of the graft was then passed deep to the iliotibial band, superficial to the lateral collateral ligament, and fixed with a single staple onto Gerdy's tubercle as extra-articular plasty. All surgeries were performed by the senior surgeon (*Figure 2*).

Single-Bundle and Lateral Plasty ACL Reconstruction (open physis): A modified Single-Bundle and Lateral Plasty technique with hamstrings was used in the cases of children and adolescent patients with open physis[45]. After graft harvesting, under fluoroscopic control, the open epiphyseal plate of the tibia was visualized and a tunnel was drilled in the epiphysis entirely proximal to the growth plate, without damaging it. Then, the graft was passed through the tunnel, preserving its insertion on the pes anserinus and thus its neurovascular supply. The graft was then passed through the intercondylar notch and around the lateral femoral condyle through a lateral incision of the fascia and fixed in the over-the-top position with two staples; and finally, with the residual graft, a lateral tenodesis was performed, passing it between the fascia and the lateral collateral ligament and fixing it with a staple on the Gerdy's tubercle, under fluoroscopic control (*Figure 2*).

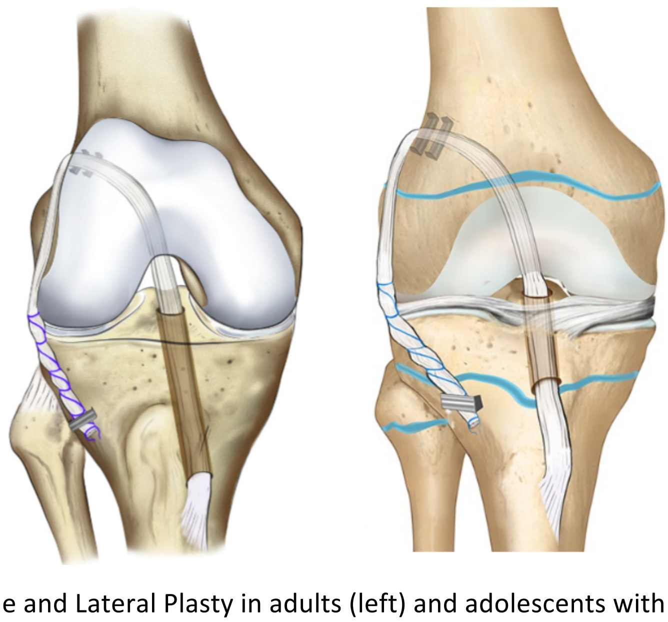

Figure 2: Single-Bundle and Lateral Plasty in adults (left) and adolescents with open physis (right).

All-inside meniscal repair: Indications for meniscal repair were unstable lesions larger than 5 mm in the red-red or white-white zone. Repair was performed in all cases with an all-inside device (Ultra FasT-Fix, Smith & Nephew, Andover, MA, USA) through the standard arthroscopic portals. Vertical or horizontal stitches were placed based on the lesion pattern. A stitch was placed every 5 mm, until a stable construct was obtained under probing. In the case of meniscal repair, an extension brace for 4 weeks was used with partial weightbearing, while passive range of motion exercises were initiated after 10 days.

INTRA-OPERATIVE NAVIGATION ASSESSMENT

In order to evaluate joint laxity, a surgical navigation system (BLU-IGS; Orthokey), equipped with software specifically dedicated to intraoperative kinematic acquisitions (KLEE; Orthokey) was adopted. The examination protocol was performed utilizing a previously validate method[47] in 2 possible stages: 1) before ACL reconstruction and treatment of any meniscal lesions, 2) after ACL reconstruction (*Figure 3*). The surgeon manually performed the following clinical kinematic tests at maximum force:

- **AP30**: Antero-Posterior displacement at 30° of flexion
- **AP90**: Antero-Posterior displacement at 90° of flexion
- **IE30**: Internal-External rotation at 30° of flexion
- **IE90**: Internal-External rotation at 90° of flexion
- **VV0**: Varus-Valgus rotation at 0° of flexion
- **VV30**: Varus-Valgus rotation at 30° of flexion
- Pivot-Shift Test, quantified through 3 different parameters: the anterior displacement of the lateral tibial compartment (**lateral AP**); the posterior acceleration of the lateral AP during tibial reduction (**PS ACC**); the area included by the lateral AP translation with respect to the flexion/extension angle (**area**), the internal-external tibial rotation during the maneuver (**PS IE**).

During the whole set of tests and reconstructions, the examiner was the same and was blinded to the test quantitative results in order to avoid bias in the acquisitions. Data were elaborated offline with a specifically developed MATLAB interface (The MathWorks Inc).

Figure 3: Setting of intra-operative knee kinematic assessment with navigation during ACL reconstruction

MAGNETIC RESONANCE IMAGING (MRI) EVALUTION

Pre-operative MRIs were measured by a single expert investigator using the DICOM viewer Osirix Lite 7.0.3 (Pixmeo, Switzerland). In particular, along the axial plane of the femur, the transepicondylar distance (TE) was evaluated. Along the coronal view the width of the lateral and medial femoral condyles (LFCw and MFCw) and tibial plateau (LTPw and MTPw), the notch width index (NWI) and the ratio of width and height of the femoral notch (N-ratio) were measured. Along the sagittal plane, the ratio between the height and depth of the lateral and medial femoral condyle (LFC-ratio and MFC-ratio), the lateral and medial posterior tibial slopes (LTPs and MTPs) and the anterior subluxation of the lateral and medial tibial plateau with respect to the femoral condyles (LTPsublx and MTPsublx) were measured.

This pool of anatomical parameters was measured as follows:

- TE: Was identified as the longest distance between the medial and lateral epicondyles of the distal femoral epiphysis.

- LFC-ratio and **MFC-ratio:** The femoral condyles were measured according to a modified method by Fridén et al.[37] using MRI images instead of radiography (*Figure 4*). First, the femoral axis was identified using the diaphysis as reference and reported in all the sagittal slices of the MRI. After identifying the most posterior portion of the femoral condyle using an axial reference, a tangent line parallel to the femoral axis was drawn (line A). The perpendicular line connecting line A with the femoral axis was defined as the depth of the femoral condyle (line C). After drawing a line tangent to the most distal portion of the femoral condyle and perpendicular to the femoral axis (line B), the distance between lines C and B was measured as the height of the femoral condyle. The LFC-ratio and MFC-ratio were obtained as height/depth. Values approaching one approximated a spherical shape, while values approaching 0 approximated a more elliptical shape.

- **LTPs** and **MTPs**: First, the tibial axis was drawn in the centre of the proximal tibial metaphysis of the sagittal slice just medial to the tibial tubercle and reported in all the sagittal slices, as described by Alici et al.[48]. Using the axial reference, the centre of the tibial plateau was identified and a line tangent to the articular surface was drawn (line A). The tibial slope was calculated by subtracting from 90° the angle obtained from line A and the tibial axis (*Figure 4*).

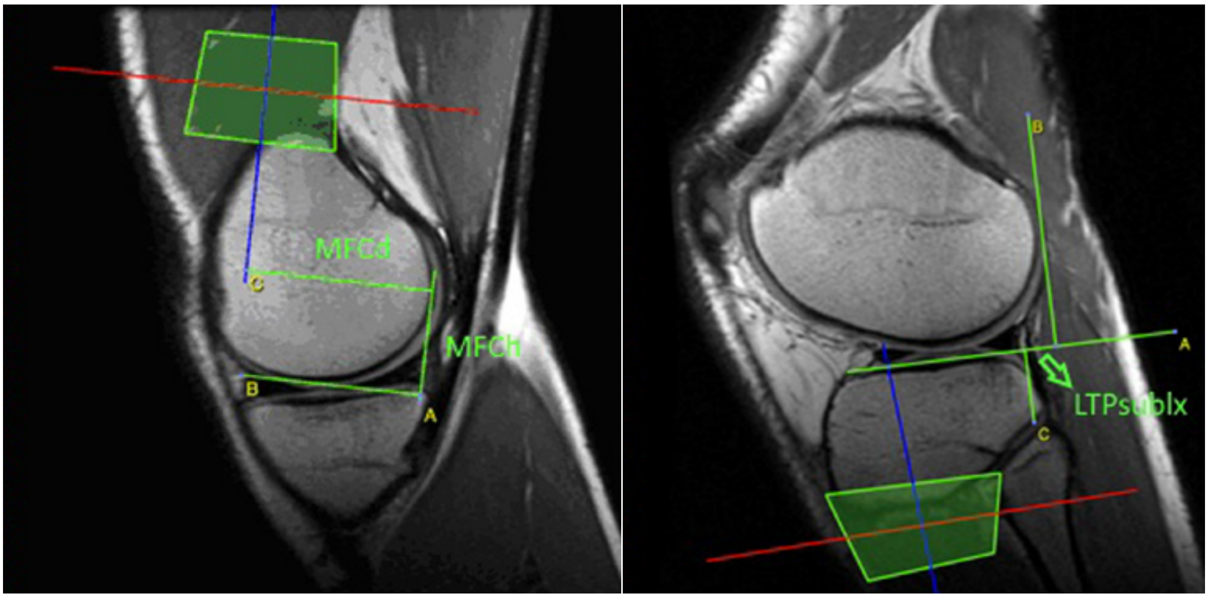

Figure 4: Measurement of LFC-ratio and MFC-ratio (left) and LTPs, MTPs, LTPsblx and MTPsblx (right)

- **LTPsublx** and **MTPsublx**: The tibial axis and the tangent to tibial plateau (line A) were used as for MTPs and LTPs. Two lines perpendicular to line A and tangent to the posterior condyle margin (line B) and posterior tibial plateau margin (line C) were drawn. The anterior tibial subluxation was defined as the distance between line B and line C (*Figure 4*)[49].

- **NWI**: Was measured as described by Souryal and Freeman[50], first identifying the bicondylar width at the level of the slice in which the popliteal groove is visible (line A) (*Figure 5*).

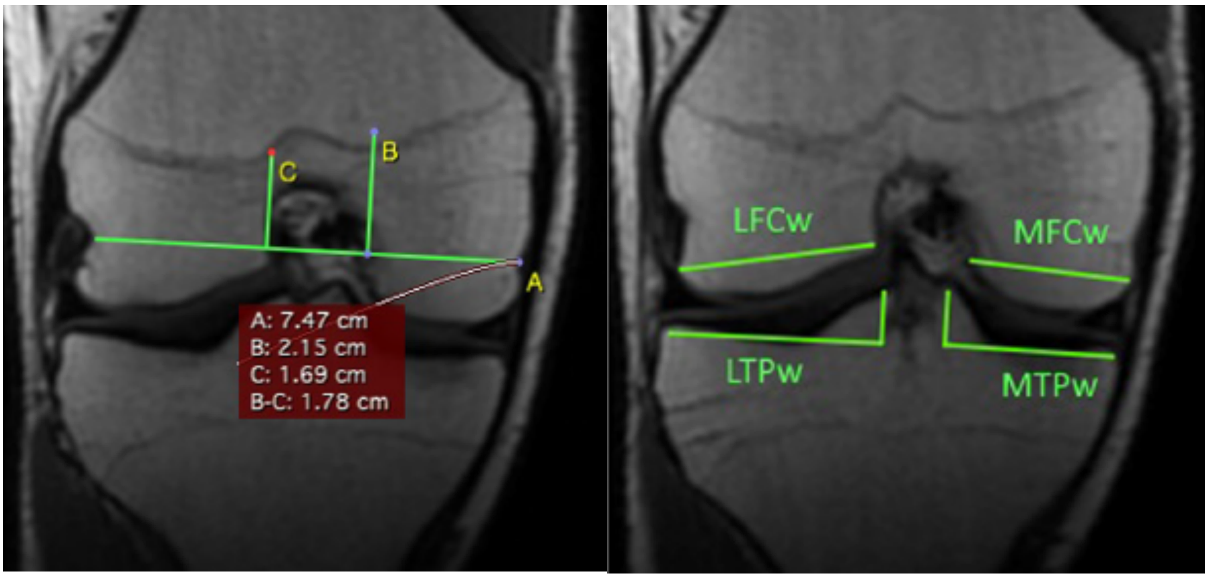

Figure 5: Measurement of NWI (left) and LFCw, MFCw, LTPw, MTPw (right)

- **N-ratio**: Was measured as the ratio between the width of the femoral notch obtained from the same coronal slice, and its height. A value approaching one indicated an almost squared notch, while lower values suggested a narrow and tall notch.
- **LFCw** and **MFCw**: Were measured on the coronal slice where both tibial intercondylar tubercles are identified, calculating the distance between the intercondylar notch and the subchondral bone margin of the LFCw and MFCw (*Figure 5*).
- **LTPw** and **MTPw**: Were measured on the same coronal slice, calculating the distance between the intercondylar tubercle and the subchondral bone margin of the LTPw or MTPw (*Figure 5*).
For 5 different patients, the observer performed the measurement twice to assess intra-observer repeatability, which resulted high and with a mean ICC of 0.75 ± 0.19 (*Table 1*)

Mean and standard deviation values for all the performed anatomical measurements.

Parameter	Abbreviation	Mean ± SD	ICC
Trans epicondylar distance (cm)	TE	8.47 ± 0.60	0.9926
Lateral femoral condyle ratio	LFC-ratio	0.54 ± 0.05	0.7935
Medial femoral condyle ratio	MFC-ratio	0.55 ± 0.04	0.8125
Lateral posterior tibial slope (°)	LTPs	4.50 ± 2.79	0.8975
Medial posterior tibial slope (°)	MTPs	4.28 ± 2.55	0.4276
Lateral subluxation (cm)	LTPsublx	0.75 ± 0.33	0.4448
Medial subluxation (cm)	MTPsublx	0.41 ± 0.21	0.9834
Notch width index	NWI	0.26 ± 0.03	0,5000
Notch ratio	N-ratio	0.72 ± 0.07	0.9081
Lateral femoral condyle width (cm)	LFCw	3.00 ± 0.28	0.6945
Medial femoral condyle width (cm)	MFCw	2.59 ± 0.30	0.6551
Lateral tibial plateau width (cm)	LTPw	3.12 ± 0.27	0.8531
Medial tibial plateau width (cm)	MTPw	3.01 ± 0.30	0.8878

ICC, interclass correlation coefficient; SD, standard deviation.

Table 1: Inter-Class Correlation for anatomical MRI measurements

- **LNS** (Lateral Notch Sign): Was identified on MRI sagittal images, and the slice with the deepest notch was used for the analysis[51]. Patients were firstly divided into two groups: patients without LNS, "no-LNS" group, and patients with a positive LNS (>1mm), "LNS" group. Further stratification was made within the LNS group based on the depth of LNS, and patients were divided in "LNS between 1 and 2mm" group and "LNS>2mm" group. To assess the inter-rater reliability, the same measurement was repeated on 25 MRI randomly chosen from the ones included in the study; ICC was =0.90, thus showing an excellent agreement.

RADIOGRAPHIC EVALUTION

Radiographic measurement of the Tibial Plateau Slope (TPS) was performed by a single investigator blinded to patients' outcomes. Radiographs were excluded in the case of inadequate lateral view such as presenting malrotation or tilting with more than 5 mm of distance between both the posterior and distal cortices of the medial and lateral femoral condyles and less than 10 cm of tibial length distal to the joint line. The posterior slope of medial tibial plateau was chosen for the radiographic measurement due to its better identification on lateral radiograph and for its wider use in the study of ACL re-injuries[52,53]. Three different measurements of TPS were calculated on the same 30° lateral knee radiographs according to previously established methods by a single trained examiner: Anterior TPS[52], Posterior TPS[52] and Central TPS[53]. A line tangent to the medial tibial plateau was drawn connecting the anterior and posterior apexes of the medial tibial plateau. Two lines tangent to the anterior and posterior cortex of the tibial shaft were drawn. Anterior and Posterior TPS were calculated subtracting from 90° the angle obtained from the intersection of medial tibial plateau tangent and the line of anterior and posterior cortex, respectively, according to Su et al.[52]. The Central TPS was instead measured according to Webb et al.[53] drawing three lines parallel to medial tibial plateau at 5 cm, 10 cm and 15 cm distal to the joint line. Then, the longitudinal axis was drawn intersecting the three lines having an equal distance from the anterior and posterior cortexes, which was defined as anatomical axis of the tibia.

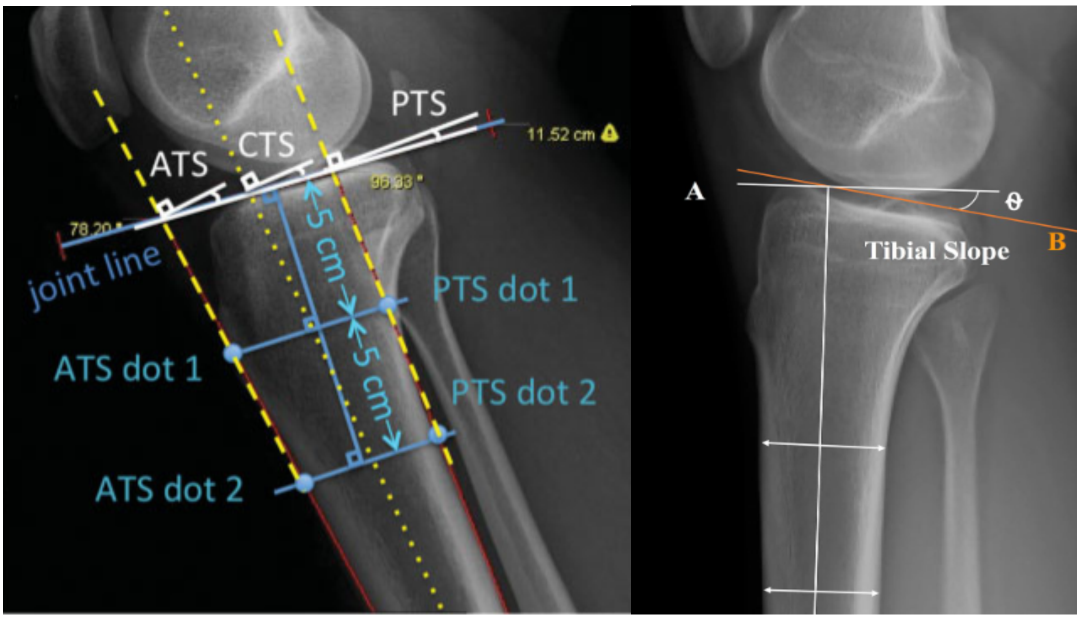

Figure XX: Measurement Anterior TPS and Posterior TPS (left) and Central TPS (right)

To establish the intra-rater reliability and repeatability of the radiographic measurements, the Anterior, Posterior and Central TPS of 15 randomly selected patients were measured two times by the same examiner, with at least 1 month apart for each patient. The Cronbach-alpha of the Anterior, Central and Posterior TPS were 0.81 (95%CI 0.54 -1.00), 0.84 (95%CI 0.61 – 1.00) and 0.80 (95%CI 0.51 – 1.00), respectively. Thus, intra-rater reliability was rated as “Good” for all the 3 TPS measurements.

INSTRUMENTAL EVALUTION

In order to evaluate pre and post-operative knee laxity in a non-invasive clinical setting (*Figure 6*), three evaluations were performed by a single examiner blinded to patients treatment and test quantitative results:

- **AP30**: Anterior/posterior displacement at 30° of knee flexion through KT-1000 at manual maximum (KT-MM) force;
- **AP90**: Anterior/posterior displacement at 90° of knee flexion through Rolimiter;
- **PS ACC:** Posterior acceleration of lateral tibial compartment during tibial reduction while performing the Pivot-Shift maneuver through KiRA device (Orthokey, Florence, Italy).

Figure 6: Instruments used to assess knee laxity: KT-1000 (left), Rolimeter (center), KiRa (right)

PATIENT-REPORTED OUTCOME MEASURES (PROMs)

One or more Patient-Reported Outcome Measures (PROMs) were administered to the patients via paper or during phone interview, in the context of prospective and retrospective clinical studies:
- **KOOS** (Knee Injury and Osteoarthritis Outcome Score): values were collected for each KOOS subscales. Moreover, the number of patients achieving the Patient Acceptable Symptoms State (PASS) for Pain (89.9 points), Symptoms (57.1 points), ADL (100.0 points), Sport (75.0 points), QoL (62.5 points) subscales were obtained[54].
- **Lysholm**: values were collected and stratified as “Excellent” (>94 points), “Good” (84-94 points), “Fair” (65-83 points) and “Poor” (<65 points).
- **Tegner Activity Scale**: values from 0 to 10 were collected. Considering the different age-related involvement in sport activity, a high level was considered in the case of values >5 points for general population cohorts and in the case of values >7 points for adolescents cohorts.
- **VAS for Pain**: pain was assessed both at rest and during activity in a scale from 0 to 10.
- **Marx Score**: level of activity in a scale from 0 (minimum) to 16 (maximum).
- **SF-36**: both the Physical Component Score (PCS) and Mental Component Score (MCS) were collected for a general non-specific assessment of outcomes.

REOPERATIONS AND SURVIVORSHIP ANALYSIS

Medical charts were reviewed in order to identify further ipsilateral reoperations or contralateral ACL reconstruction occurred within the considered follow-up. Also, to surgical procedures performed outside our institution all the patients were contacted to assess the occurrence of further knee surgeries. Kaplan Maier survival curves were prepared using the time to reoperation as endpoints. Survival rate with 95% Confidence Intervals (CIs) were calculated at annual time-point. A logistic regression analysis was performed using the demographic, surgical and radiographic variables such as sex, age, Outerbridge, meniscal lesions, BMI, pre-operative Tegner, timing of ACL, reconstruction smoke habits, Tibial Plaetau slope (TPS). For the variables that had a p-value <0.1 in the logistic regression analysis, the Log-rank test was used to compare the survival curves of the subgroups and the Hazard Ratios (HR) with 95% Confidence Intervals (CIs) were calculated.

DETAILED METHODS OF SINGLE STUDIES

AIM 1: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF MENISCUS (STUDY I, II and III)

STUDY I:

A Systematic Review of the existing literature was conducted to assess the biomechanical role of medial and lateral meniscus in the case of ACL rupture, regarding knee laxity.

Search strategy: A systematic search on MEDLINE (PubMed) and EMBASE was performed for the laboratory studies regarding role of medial and lateral meniscus in the kinematics of the ACL-deficient knee. Two reviewer independently conducted the search in June 2019 with the following keywords: ('ACL' OR 'anterior cruciate ligament') AND ('kinematic' OR 'kinematics' OR 'biomechanic' OR 'biomechanics' OR 'stabilising' OR 'stabilising') AND ('meniscus' OR 'meniscectomy' OR 'meniscal').

Inclusion criteria: All titles and abstracts were screened with the following inclusion criteria: biomechanical human cadaveric studies, meniscus cutting following ACL cutting, distinct kinematic evaluation of meniscus-intact status, single treated meniscus status and (if present) double resected meniscus status in ACL-deficient knee, quantification at least one of displacement or rotation under an external single or coupled load, English language, full text available. Exclusion criteria were as follows: articles that were off topic, clinical (in vivo) studies, articles with no clear setting description or results, other types of article such as systematic review, abstracts and technical notes.

Data extraction: Each study that met the inclusion criteria was abstracted for the following information: year of publications, number of humans cadaver knee specimens mean of age of human cadaver specimens, description of apparatus testing and instrumented kinematic evaluation, testing protocol and results. It was not possible to perform a quantitative analysis of the data abstracted because the results of the included studies were highly heterogeneous. Therefore, the results were qualitatively compared and summarized. The meniscal tears were distinguished in five typologies, based on what described in each study: total/subtotal meniscectomy, posterior horn tear, bucket handle tear, posterior root tear and posterior menisco-capsular tear. Performing the analysis of kinematics evaluation, we referred to two parameters: static laxity (anterior tibial translation and tibial rotation) at 0°, 30°, 60° and 90° of flexion and dynamic laxity (ATT with coupled rotation torque and valgus load or simulated pivot shift).

STUDY II:

A stratification of knee laxity obtained in ACL-deficient knees with surgical navigation was performed based on meniscal status.

Setting: Based on the intraoperative findings and concomitant meniscal treatment, the patients were assigned to 1 of 4 groups: IM group (both intact menisci); MM group (partial medial meniscectomy); LM group (partial lateral meniscectomy); MLM group (partial medial and lateral meniscectomy).

Kinematic evaluation: Kinematic parameters of static laxity (AP30, AP90) and dynamic laxity during Pivot-Shift (lateral AP, posterior acceleration, area) were obtained before ACL reconstruction.

Statistics: Normal distribution of the data was verified by the Kolmogorov-Smirnov test. Nonnormally distributed continuous variables were presented as median and interquartile range, while categorical variables were presented as percentage over the total. The Kruskal-Wallis test was performed to assess the between-group differences of continuous variables, while the Mann-Whitney U test was used to compare the groups with one another. Differences between the groups were considered statistically significant at $P<.05$. An a priori power analysis was performed based on the preliminary results of a similar study[55]: considering a value of AP laxity at 90° of 7 mm with intact meniscus and of 10.7 mm with partial meniscectomy and with a standard deviation of 2.5 mm, at least 13 patients in each group were required to have a power of 90% and a type 1 error of .05. P values were adjusted using the Sidak post hoc correction for multiple comparisons. All the statistical analyses were performed in MATLAB.

STUDY III:

The effect of partial medial meniscectomy in the post-operative antero-posterior laxity was investigated with a surgical navigation after SB or SBLP ACL reconstruction techniques.

Setting: Based on the intra-operative findings on the medial meniscus status, the patients were divided into four groups: SBLP Isolated ACL (isolated ACL reconstruction performed with SBLP technique with both medial and lateral intact meniscus); SBLP ACL+MM (concomitant ACL reconstruction performed with SBLP technique and partial medial meniscectomy); SB Isolated ACL (isolated ACL reconstruction performed with SB technique with both medial and lateral intact meniscus); SB ACL+MM (concomitant ACL reconstruction performed with SB technique and partial medial meniscectomy).

Kinematic evaluation: Kinematic parameters of static laxity (AP30, AP90) were obtained before (Pre-ACL) and after ACL reconstruction (Post-ACL) with SB or SBLP technique.

Statistics: The normal distribution of the data was verified by the Kolmogorov – Smirnov test. Normal-distributed continuous variables were presented as mean and standard deviation, while categorical variables were presented as a percentage over the total. The Two-Way ANOVA for repeated measures test was performed to assess the between-group differences of continuous variables, while the Student's t-test was used to compare each group with one another. Differences between the groups were considered statistically significant if $p<0.05$. For the multiple comparisons, p-values were adjusted using the Dunn-Sidak post-hoc correction. An a-priori power-analysis was performed based on the preliminary results of a similar study[55]: considering a value of antero-posterior laxity at 90° of 10.7 mm with intact meniscus and of 7.0 with partial meniscectomy and with a standard deviation of 2.5 mm, at least 13 patients in each group were required to have a power of 90% and a type I error of 0.05. All the statistical analyses were performed in MATLAB.

AIM 2: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IV and V)

STUDY IV:

Anatomical knee parameters, measured with MRI, were correlated with the amount of knee laxity before ACL reconstruction obtained with intraoperative navigation.

Setting: Patients with ACL injury and no meniscal lesion were enrolled in the study. Their anatomical features of their knees were assessed through MRI, and knee laxity measured with intra-operative navigation.

Kinematic evaluation: Kinematic parameters of static laxity (AP30, AP90, IE30, IE90, VV0, VV30) and dynamic laxity during Pivot-Shift were obtained before ACL reconstruction.

MRI evaluation: The TE, LFC-ratio, MFC-ratio, LTPs, MTPs, LTPsblx, MTPsblx, NWI, N-ratio, LFCw, MFCw, LTPw, MTPw were measured on pre-operative MRI.

Statistics: Normal distribution of the data was verified by the Kolmogorov–Smirnov test. Both the kinematics and the anatomical variables
were continuous data. All continuous data were expressed in terms of the mean and the standard deviation (SD). For each kinematics test, the univariate analysis with Pearson's method was used to identify those anatomical variables significantly correlated with the laxity values. The multivariate regression, with backward elimination, including only the previously identified anatomical variables, defined the independent predictors. Standardized regression coefficient (β) indicated the magnitude of the identified predictor. Finally, cut-off values able to discern high (above 75th percentile) from low (below 25th percentile) laxity cases were defined for each independent predictor. Comparison between continuous data was performed by applying the ANOVA test or the Mann–Whitney U-test with Monte Carlo Simulation according to the sample size. All statistical analysis was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA). Significance was set at P b 0.05.

STUDY V:

The presence and the magnitude of the Lateral Notch Sign (LNS), measured with MRI, was correlated with the amount of Pivot-Shift obtained with intraoperative navigation.

Setting: Patients with ACL injury were enrolled in the study. The presence and features of LNS was assessed through MRI, and knee laxity measured with intra-operative navigation.

Kinematic evaluation: Kinematic parameters of dynamic laxity during Pivot-Shift (PS ACC and PS IE) were obtained before ACL reconstruction.

MRI evaluation: The LNS was measured and dichotomized in “no-LNS” or “positive LNS” (>1mm); a further stratification was made within the LNS group based on the depth of LNS, dividing the patients in “LNS between 1 and 2mm” group and “LNS>2mm” group.

Statistics: The Normal distribution of the kinematic data was verified by Shapiro – Wilk test. Normal-distributed continuous variables were presented as mean and standard deviation, while categorical variables were presented as a percentage over the total. The One-way ANOVA was performed to assess the between-group differences of continuous variables, while the t-test with Dunn-Sidak post-hoc correction for multiple comparisons was used to compare each group with one another. Differences between the groups were considered statistically significant if $p<0.05$. A Receiver Operating Characteristic (ROC) curve analysis was performed to determine the most predictive LNS cutoff value. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Accuracy and Youden Index were computed for multiple LNS cutoff values (CIT 6 e 10) and used to determine the best one. Patients with values of PS ACC or PS IE above the 75th percentile were considered “high rotatory instability” patients. Moreover, the 75th percentile value of either the PS ACC or the PS IE parameters were used as cutoff input for the ROC analysis, aiming to identify patients with a “high grade rotatory laxity”. A further analysis was conducted to evaluate possible confounding variables in the group distribution. The parameters evaluated were sex, presence of medial meniscal tear, presence of lateral meniscal tear, presence of tibial slope greater than 9°, which was reported to influence the magnitude of pivot shift[31]. All the statistical analyses were performed in MATLAB.

AIM 3: OUTCOMES AND FAILURES OF ACL RECONSTRUCTIONS - THE ROLE OF MENISCUS (STUDY VI, VII and VIII)

STUDY VI:

The role of surgical technique of ACL reconstruction and the presence of meniscal injuries are evaluated in the relation of short-term outcomes.

Setting: Patients with ACL injury were randomized to receive SB, DB or SBPL ACL reconstruction. The 2-year clinical and instrumental outcomes were evaluated and stratified according to surgical technique. Meniscal injuries were stratified according to their treatment in IM (Intact Menisci), MR (Meniscal Repair), MM (Medial Meniscectomy) and LM (Lateral Meniscectomy)

Clinical evaluation: KOOS score was administered before surgery and at 2-year follow-up

Instrumental evaluation: AP30 with KT-1000, AP90 with Rolimter and PS with KiRa were measured before surgery and at 2-year follow-up

Statistics: The Kolmogorov–Smirnov test was used to verify the normal distribution of the data. Normal-distributed continuous variables were presented as mean and standard deviation (SD), while categorical variables were presented as a percentage over the total. The Repeated measure ANOVA test was performed to assess the between-group differences of continuous variables along with the two times assessment, while the two-tailed Student's t-test was used to compare each group with one another. A further analysis was conducted to evaluate the effect of meniscal treatment on laxity reduction and scores improvement. Differences between the groups were considered statistically significant if $p<0.05$. P-values were adjusted using the Dunn-Sidak post-hoc correction for multiple comparisons. An a-priori power analysis was performed based on the preliminary results of a similar study[56]. A number of 10 patients per group was required to have a power of 80% and a type I error of 0.05. All statistical analyses were performed in MATLAB.

STUDY VII:

The outcomes of meniscal repair performed with an all-inside device (Ultra FasT-Fix) in the setting of ACL reconstruction, the healing of the repair, and the presence of perimeniscal were investigated at short-term in comparison to ACL reconstruction with intact menisci.

Setting: Patients with ACL reconstruction and concomitant medial meniscus repair with all-inside sutures were matched 1:1 with patients with isolated ACL reconstruction.

Clinical evaluation: KOOS, MARX and SF-12 scores was administered before surgery and at 18-month follow-up

Instrumental evaluation: AP30 with KT-1000 and PS with KiRa were measured before surgery and at 18-month follow-up.

MRI evaluation: An MRI was performed before surgery and at 18-month follow-up. Meniscal lesions were graded according to Mink classification (Grade 0 to IIIb)[57,58], while meniscus healing was evaluated in the post-operative MRI according to the Henning's criteria[59,60] as "Full Healing" in the case of it was healed over the full thickness of the tear, "Incomplete Healing" in the case of healing over at least 50% of the tear and "No Healing" in the case of fluid-equivalent signal in the tear zone in more than 50% of tear size. The presence of perimeniscal cysts was defined as the presence of a round formation with high-intensity signal on T2 MRI sequences surrounding the suture anchors, with a diameter of at least 5 mm and co-localized with the position where the FasT-Fix was used.

Statistics: The statistical analysis was performed using the statistical software MedCalc. An a-priori sample size calculation identified a number of 18 patients per group to detect a 8±8 point difference in KOOS subscales between study and control group, which corresponds to the Minimally Clinical Important Difference (MCID), with a power of 90% and an alpha significance of 0.05[61]. Continuous variables were reported as mean ± standard deviation, while categorical variables were performed as raw number and percentage of the total. Differences between the two groups, and between different follow-ups were analyzed with the paired sample t-test. Regarding the KOOS score, the Patient Acceptable Symptom State (PASS) threshold values was used to dichotomize the KOOS subscales. When more than 2 groups were compared, ANOVA test was used. Categorical variables were compared using the chi-squared test or the 2x2 Fisher exact test based on the number of variables considered. The inter-rater agreement (kappa) of MRI parameters was calculated between the 2 investigators. Values were considered statistically significant with $p<0.05$.

STUDY VIII:

Predictors of ACL reconstruction failures, reoperations and PROMs were investigated at long-term, after a follow-up of 10 years.

Setting: Patients with ACL reconstruction and intact menisci or meniscal injuries were included and retrospectively evaluated in terms of reoperations and PROMs.

Clinical evaluation: KOOS, Lysholm, Tegner, VAS for Pain were administered at a follow-up of 10 years

Reoperations and survivorship analysis: ACL revision, meniscectomy, total reoperations were assessed along the follow-up.

Statistics: Statistical analysis was performed with MedCalc (MedCalc Software, Acacialaan, 22 Ostend, Belgium). Continuous variables were reported as mean ± standard deviation, while categorical variables were reported as absolute number and proportion of the total sample. Only the Tegner activity level was reported as median value with interquartile ranges. Independent sample t-test was used to compare the continuous variable between included patients and those lost to follow-up, Mann-Whitney to compare Tegner level and Fisher exact test to compare dichotomous categorical variables. Kaplan Maier survival curves were prepared using the time to reoperation, ACL revision, meniscectomy and ACL revision\meniscectomy as endpoint. A logistic regression analysis was performed using surgical and demographical variables. For the variables that had a p-value <0.1 in the logistic regression analysis, the Log-rank test was used to compare the survival curves of the subgroups. A multiple regression analysis for each PROMs was performed using the same variables, with the addition of bilateral ACL injury and reoperations during follow-up. Similarly, the probability of achieving the PASS of the KOOS subscales was investigated with a logistic-regression analysis using the same variables as before. Statistical significance was set with p<0.05.

AIM 4: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IX, X and XI)

STUDY IX:

The role of tibio-femoral joint anatomy was investigated as risk-factor for the failure of ACL reconstruction

Setting: All patients who experienced graft failure after primary ACL surgical reconstruction and underwent revision surgery (Revision Group) were matched 1:1 to a group of consecutive patients who had undergone primary successful ACL reconstruction (Control Group). MRI parameters were compared between Revision and Control Groups.

MRI evaluation: The TE, LFC-ratio, MFC-ratio, LTPs, MTPs, LTPsblx, MTPsblx, NWI, N-ratio, LFCw, MFCw, LTPw, MTPw were measured on pre-operative MRI.

Statistics: Statistical analyses were performed using MedCalc for Windows (MedCalc Software, Ostend, Belgium). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Variables with normal distribution were expressed in terms of mean and standard deviation (SD) and compared within groups using the independent sample Student's t-test. Variables without normal distribution were expressed as median and interquartile range (IQR) and compared within groups using the Mann-Whitney test. Dichotomous variables were analyzed using Fisher's exact test. A logistic regression with the enter method was performed including only the previously identified significant variables between the control and failed groups. These were defined as independent predictors for revision surgery and were controlled for confounding variables such as sex, age, and presence of medial or lateral meniscus injury at the time of primary reconstruction. A receiver operating characteristics (ROC) analysis was performed to find the optimal cutoff values for significant anatomical predictors of revision surgery. The Youden index was calculated to select the cutoff value corresponding to the highest sensitivity and specificity. The variable with the higher area under ROC curve (AUC) and Youden index was considered the best predictor of ACL failure. An a priori power analysis was performed to assess the sample size of the present study using the LTPs parameters. A sample size of 43 patients in each group was considered adequately powered to detect a significant difference of 2° with an SD of 3° between the 2 study groups and an alpha error of 0.05 and a power of at least 0.85.

STUDY X:

The role of tibio-femoral joint anatomy and meniscal defect were investigated as risk-factors for multiple failures of ACL reconstruction

Setting: A comparison of anatomical, demographical and surgical parameters was performed between patients that had multiple ACL reconstruction failures (Multiple Failure Group), patients that had single failure of ACL reconstruction (Failed ACL-R group) and patients without ACL failure (Control Group).

MRI evaluation: The LFC-ratio, MFC-ratio, LTPs, MTPs, LTPsblx, MTPsblx were measured on pre-operative MRI.

Statistics: Statistical evaluation was performed with MedCalc (v 18.11.3; MedCalc Software). The comparison of continuous variables among the 3 groups was performed via 1-way analysis of variance, while the chi-square test was used for categorical variables. When only 2 groups were compared, the independent-samples t test or the Fisher exact test was used for continuous or categorical measures, respectively. The Pearson test was used to evaluate correlation between continuous measures. The sample size was calculated per the values of the lateral posterior tibial slope reported by Christensen et al.[62]; these values were 8.4° among patients with failed ACL-R and 6.5° among patients without failure. Based on an SD of 2.4°, a sample size of 25 was required in each group to have a power of 80% and an alpha of .05.

STUDY XI:

The role of Tibial Plateau Slope (TPS) was investigated as risk factor for failure of ACL reconstruction and Contralateral ACL injury in adolescents with less than 18 years of age.

Setting: Patients under 18-year of age at time of ACL reconstruction were included and the incidence of a second ACL reconstruction (ipsilateral or contralateral) was analyzed based on the magnitude of tibial slope.

Radiographic evaluation: The Anterior, Central and Posterior medial Tibial Plateau Slope (TPS) were measured on lateral radiographs.

Reoperations and survivorship analysis: ACL revision and Contralateral ACL reconstruction occurred within the first 2 years of follow-up were considered ad primary outcome.

Statistics: Statistical analysis was performed with MedCalc (MedCalc Software, Acacialaan, 22 Ostend, Belgium). An a-priori sample size calculation was based on a study that demonstrated a

significant difference of TPS between failed and intact ACL graft (13.2° ± 2.5° vs 10.9° ± 3.1°)[63]. Considering ah hypothetical 25% rate of second injuries[64], a power of 80% and an alpha-value of 0.05, a total of 48 patients were required in the group with no reinjuries and 12 in the group of second injuries. Therefore at least 60 were needed to satisfy sample size calculation. The Kolmogorov-Smirnov test was used to assess the normal distribution of different TPS measurements. Continuous variables were reported as mean ± standard deviation, while categorical variables were reported as absolute number and proportion of the total sample. Only the Tegner activity level was reported as median value with interquartile ranges. Independent sample t-test was used to compare two continuous variables, while the one-way ANOVA was used form more than two variables and the Student-Newman-Kelus test for pairwise comparison. The Chi-squared test was used to compare dichotomous categorical variables. The Pearson r test was used to correlate the Anterior, Central and Posterior TPS. A forward logistic regression analysis was also performed to assess the contribution of TPS on risk of early revision, contralateral ACL reconstruction and 2nd ACL injury, after corrected for age, sex, and pre-injury Tegner activity level >7. Three different models were performed using Anterior, Central and Posterior TPS separately, if correlation was significant, in order to avoid multicollinearity bias due to correlated variables.
A Receiver Operating Characteristic (ROC) curve was produced to assess sensitivity and specificity of Anterior, Central and Posterior TPS in detecting early revision, contralateral ACL reconstruction and 2nd ACL injury. The Area Under Curve (AUC) was calculated, and the optimal cut-off with the highest Youden's index was selected. Patients were dichotomized according to the TPS above or below the cut-off values and a Kaplan-Meier curve was built, comparing the two subgroups with the log-rank test. Statistical significance was set with $p<0.05$.

RESULTS

The main results of each of the 4 aims of the thesis are briefly reported. The results of literature search (**Study I**) and in-vivo navigations studies (**Study II, III, IV and V**) highlighted the biomechanical importance of medial and lateral meniscus integrity in pre-and post-operative laxity, and a novel insight regarding the ability of Lateral Notch Sign -among all anatomical parameters- to detect "high grade" laxity is provided (**Study IV and V**). In the clinical setting, medial and lateral meniscal removal or repair demonstrated to affect outcomes and reoperations, either at short (**Study VI and VII**) and long-term follow-up (**Study VIII**). Finally, anatomical parameter -in particular Tibial Plateau Slope- were identified as possible risk-factors for failure of ACL reconstruction and contralateral ACL injuries (**Study IX, X and XI**). Following, the results of each of the 11 studies are reported and analyzed in detail.

AIM 1: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF MENISCUS (STUDY I, II and III)

Based on cadaveric in-vitro studies, medial meniscus -and in particular its posterior horn- is a critical secondary restraint to Anterior Tibial Translation (ATT) during static laxity evaluation in the ACL-deficient knee. Medial meniscus posterior menisco-capsular lesion increases both static and dynamic rotational laxity in ACL-deficient knee. The lateral meniscus is an important stabilizer of the knee under both isolated and combined rotatory loads and its tear or resection resulted in a significant increase of dynamic laxity in the ACL-deficient knee (**Study I**). Similarly, in-vivo evaluation of ACL deficient knees before ACL reconstruction showed that partial medial meniscectomy increased Antero-Posterior laxity at 30° and 90° up to 3 mm or 85% with respect to intact menisci, while partial lateral meniscectomy increased the Pivot-Shift magnitude up to 57% (**Study II**). A residual Antero-Posterior laxity of 1.3 mm is present at 90° of flexion after Single-Bundle ACL reconstruction in patients with partial medial meniscectomy respect to those with intact meniscus; differently, similar laxity between intact or resected meniscus are present in patients with over-the-top Single-Bundle and Lateral Plasty ACL reconstruction (**Study III**).

AIM 2: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IV and V)

Based on the evaluation with computer navigation of patients with isolated ACL injury and no meniscal lesion, a paradoxically higher antero-posterior laxity at 30° and 90° of flexion is identified in those with a lateral tibial slope <5.5°, while a minimal contribution of transepicondylar length is present in the pivot-shift magnitude; therefore, osseous anatomy in the ACL-deficient knee has a limited effect in determining static and dynamic laxities when both menisci are intact (**Study IV**). Regarding the Lateral Notch Sign (LNS), patients with LNS> 2 mm have an increased Pivot-Shift Acceleration and Internal-External respect to those with LNS absence; moreover, the cut-off of 2 mm have a sensitivity of 74.4% and specificity of 95.% to detect "high grade" laxity based on Pivot-Shift Acceleration, and a sensitivity of 77.8% and specificity of 93.9° to detect "high grade" laxity based on Pivos-Shift rotation (**Study V**).

AIM 3: OUTCOMES AND FAILURES OF ACL RECONSTRUCTIONS - THE ROLE OF MENISCUS (STUDY VI, VII and VIII)

Meniscus status and its surgical treatment influences both kinematics and subjective short-term outcomes in the setting of ACL reconstruction: patients with a medial meniscal tear subsequently treated with meniscectomy, have a 2.4 mm higher pre-operative AP laxity at 30° of flexion compared with isolated ACL patients, while patients with lateral meniscectomy have the lowest improvement of KOOS pain subscale (**Study VI**). Patients with meniscal lesions amenable for repair have inferior pre-operative PROMs (KOOS pain and ADL) respect to patients with intact menisci, while similar values are obtained at 18-month follow-up; full or partial healing of the repair at MRI is present in 84% of cases, while 1 patient out of 3 develops perimeniscal cysts which could compromise clinical outcomes only marginally (**Study VII**). At long-term, 10 years after ACL reconstruction, patients with concurrent medial meniscus injury have an increased risk (Hazard Ratio=2.6) to incur in a reoperation for ACL revision or meniscectomy (**Study VIII**).

AIM 4: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IX, X and XI)

Several anatomical parameters could be identified to differ significantly between patients with failed ACL reconstruction and those without a documented failure; the most accurate predictor of failure is a Lateral Tibial Plateau Slope >7.4° measured with MRI, with a sensitivity of 88% and specificity of 84% (**Study IX**). Moreover, a steep medial and lateral Tibial Plateau Slope, an increased depth of the lateral femoral condyle, an increased anterior tibial subluxation and medial or lateral meniscal defect have been identified as common findings among patients who experience multiple failures of ACL reconstruction, thus possibly identifying high-risk patients (**Study X**). Differently, the amount of Tibial Plateau Slope measured radiographically have no role in early failure of ACL reconstruction with lateral plasty in patients with less than 18 years of age, while a steep medial posterior tibial slope ≥12° is instead associated to a higher risk of contralateral ACL injury within 2 years, with an Odd Ratio=1.3 and a sensitivity and specificity of 63% and 75%, respectively (**Study XI**).

DETAILED RESULTS OF SINGLE STUDIES

STUDY I: SYSTEMATIC REVIEW OF ACL+MENISCUS LESION CADAVERIC MODELS

Medial Meniscus Posterior Horn Tear: Of the 3 studies that analysed the effect of posterior horn tear in ACL-deficient knee, 2 reported a significant increase in ATT maximal value at 15° and 30°. Only 1 reported a significant increase of dynamic laxity evaluation at 0° of flexion.

Medial Meniscus Bucket Handle Tear: both the two studies that evaluated bucket handle lesion of medial meniscus reported a significant increase in ATT after either tear or resection. One investigation provided data about dynamic laxity evaluation and reported not significant differences between tears status and meniscus-intact status.

Medial Meniscus Posterior Root Lesion: both the two studies that performed evaluation of ATT reported a significant increase after a posterior root lesion compared with ACL-deficient isolated status. No significant variation in rotational and dynamic laxity was described.

Medial Meniscus Posterior Menisco-Capsular Lesions: three studies investigated effect of menisco-capsular lesion in ACL-deficient knee. Two studies reported a significant increase of ATT in medial meniscus-lesioned status, with maximum between 30° and 90°.Three studies analyzed tibial rotation: two studies showed a significant increase in external tibial rotation at 20°, and in internal-external tibial rotation at all knee flexion angles. In two studies a kinematic evaluation of dynamic laxity was also performed: only one of these studies reported a significant increase of both ATT and internal rotation under a coupled valgus stress and internal rotation torque.

Lateral Meniscus Total Meniscectomy: in 2 studies the effect of total lateral meniscectomy on kinematics of ACL-deficient knee was investigated. Both studies reported lack of significant increase in ATT. In one study dynamic laxity evaluation was evaluated, reporting a significative increase of ATT of lateral compartment under a coupled internal rotation and valgus load.

Lateral Meniscus Posterior Root Lesions: four studies provided analysis of effect of a lateral meniscus root lesion in ACL-deficient knee on joint kinematic. In one study a significant increase of ATT was found only at 30° of flexion. Three studies investigated change in tibial rotation, and in two of them reported a significant increase between 60° and 90° degrees of flexion. Both the two studies in which the dynamic laxity evaluation was performed, showed a significant increase of ATT under coupled internal rotation torque and valgus load.

STUDY II: THE ROLE OF MENISCAL DEFECT BEFORE ACL RECONSTRUCTION

Anteroposterior Displacement. Concerning the AP30, a significant difference between the 4 groups of Intact Menisci (IM, n=84), Medial Meniscectomy (MM, n=52), Lateral Meniscectomy (LM, n=17) and Madial plus Lateral Meniscectomy (MLM, n=9) was found according to the Kruskal-Wallis test (P<.0001) (*Figure 7, Table 2*).

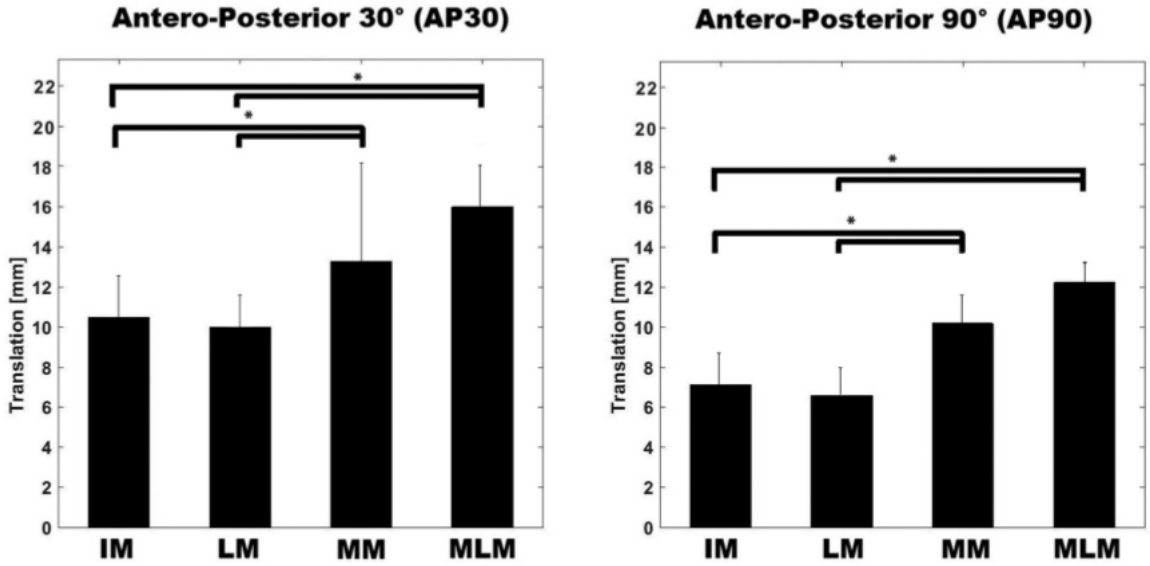

Figure 7: Graphic representation of anterior translation (mm) at 30° of knee flexion (AP30) and at 90° of knee flexion (AP90) for the 4 study groups. Bars with an asterisk represent the statistical differences (P<.05) between single groups. IM, both intact menisci group; LM, partial lateral meniscectomy group; MLM, partial medial and lateral meniscectomy group; MM, partial medial meniscectomy group

Laxity Values for the 4 Groups Before ACL Reconstruction[a]

Parameter	IM	LM	MM	MLM
AP30, mm	10.5 (9.2-12.7)	10.0 (8.2-11.7)	13.3 (10.9-18.7)[b]	16.0 (13.9-18.7)[b]
AP90, mm	7.1 (5.9-8.7)	6.6 (5.3-8.0)	10.5 (8.7-11.7)[b]	12.2 (10.2-13.0)[b]
PS–lateral AP, mm	24.2 (21.2-29.7)	29.0 (25.6-29.9)	25.7 (20.7-29.2)	28.4 (21.8-31.3)
PS–acc, mm/s^2	529 (403-649)	637 (481-737)	584 (387-873)	616 (449-786)
PS–area, mm·deg	385 (297-453)	606 (459-715)	422 (334-581)	499 (331-506)

Table 2: [a]Data are presented as median (25th-75th percentile interquartile range). All laxity tests were performed with the navigation system for the 4 groups before ACL reconstruction. acc, acceleration; ACL, anterior cruciate ligament; AP30, anteroposterior displacement at 30° of knee flexion; AP90, anteroposterior displacement at 90° of knee flexion; IM, both intact menisci group; lateral AP, lateral tibial compartment; LM, partial lateral meniscectomy group; MLM, partial medial and lateral meniscectomy group; MM, partial medial meniscectomy group; PS, pivot-shift test.
[b]Statistically significantly different from the IM and LM groups (P<.05); evaluated with the Kruskal-Wallis test.

Specifically, the MM group had a 27% significantly greater laxity compared with the IM group (P<.0001) and 33% greater laxity compared with the LM group (P=.002). Similar behavior was reported for the MLM group, with a 52% (P=.001) and 60% (P=.013) greater laxity compared with the IM and LM groups, respectively. No significant differences were reported between the IM and LM groups (P=.406) or between the MM and MLM groups (P=.109) (*Table 3*). Similarly, the AP90 was also significantly different among the 4 groups according to the Kruskal-Wallis test (P<.0001) (*Figure 7, Table 2*). Specifically, the MM group presented a 47% significantly greater laxity compared with the IM group (P<.0001) and 59% compared with the LM group (P<.0001). A similar behavior was reported for the MLM group, with a significant increase of 71% (P=.0007) and 85% (P=.003) compared with the IM and LM groups, respectively. No significant differences were reported between the IM and LM groups (P=.258) or between the MM and MLM groups (P=.084) (*Table 3*).

Laxity Differences Between Groups Before ACL Reconstruction[a]

Parameter	IM vs LM	IM vs MM	IM vs MLM	LM vs MM	LM vs MLM	MM vs MLM
AP30, mm	–0.5 (–5); .4062	+2.8 (+27); .0001[b]	+5.5 (+52); .0010[b]	+3.3 (+33); .0026[b]	+6.0 (+60); .0131[b]	+2.7 (+20); .1094
AP90, mm	–0.5 (–8); .2583	+3.4 (+47); .0001[b]	+5.1 (+71); .0007[b]	+3.9 (+59); <.0001[b]	+5.6 (+85); .0030[b]	+1.7 (+16); .0838
PS–lateral AP, mm	+5.6 (+21); .2394	+1.0 (+4); .8186	+4.1 (+17); .5316	–4.3 (–14); .1921	–1.2 (–3); .5328	+3 (+12); .4185
PS–acc, mm/s^2	+108 (+20); .2755	+55 (+10); .2768	+87 (+16); .3988	–53 (–8); .9274	–21 (–3); .9116	+32 (+5); .9112
PS–area, mm·deg	+221 (+57); .0175[b]	+37 (+10); .3531	+64 (+17); .2512	–184 (–30); .0616	–157 (–26); .2677	+27 (+6); .9114

Table 3: [a]Data are presented as difference (%); P value. acc, acceleration; ACL, anterior cruciate ligament; AP30, anteroposterior displacement at 30° of knee flexion; AP90, anteroposterior displacement at 90° of knee flexion; IM, both intact menisci group; lateral AP, lateral tibial compartment; LM, partial lateral meniscectomy group; MLM, partial medial and lateral meniscectomy group; MM, partial medial meniscectomy group; PS, pivot-shift test.
[b]Statistically significant difference between the groups (P<.05); evaluated with the Mann-Whitney U test.

Pivot-Shift Test. Concerning the anterior displacement of the lateral tibial compartment and the posterior acceleration of the lateral AP during tibial reduction, there were no statistical differences between the 4 study groups (*Figure 8*). A statistically significant between-group difference was found for the area parameter. In particular, the area of the LM group was 606 mm.deg (range, 459-715 mm.deg), and was 57% larger than the area of the IM group, 385 mm.deg (range, 297-453 mm.deg) (P=.0175). The area of the LM group was also larger (although not statistically significant) than the ones of the MM group (422 mm.deg) and MLM group (499 mm.deg), 30% and 26% more, respectively (*Table 3*).

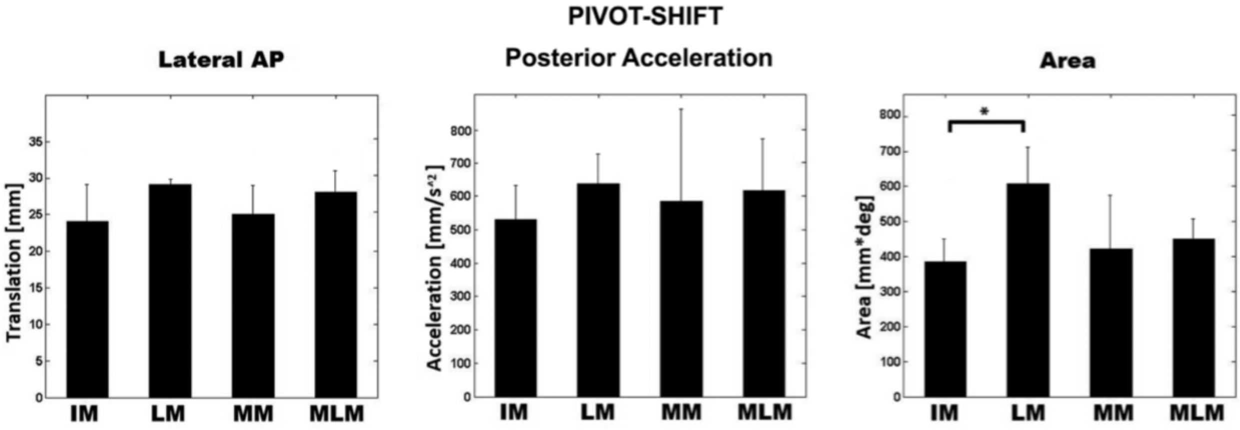

Figure 8: Graphic representation of pivot-shift test laxity parameters: lateral tibial compartment (lateral AP) translation (mm), posterior acceleration (mm/s2), and area (mm.deg) for the 4 study groups. Bars with an asterisk represent the statistical differences (P<.05) between single groups. IM, both intact menisci group; LM, partial lateral meniscectomy group; MLM, partial medial and lateral meniscectomy group; MM, partial medial meniscectomy group.

STUDY III: THE ROLE OF MENISCAL DEFECT AFTER ACL RECONSTRUCTION

Before ACL Reconstruction: The antero-posterior laxity at 30° (AP30) and at 90° (AP90) in the ACL-deficient status was significantly higher ($p>0.05$) in presence of a combined MM respect to isolate ACL injury, in both the SB (n=46) and SBLP (n=55) groups (*Table 4*). Differently, the AP30 and AP90 laxities laxities were comparable between the SB and SBLP groups, both in the case of intact menisci or combined MM (*Figure 9*).

Laxity Values Before and After ACL Reconstruction

	Before ACL Reconstruction			After ACL Reconstruction		
	Isolated ACL	ACL+MM	P-Value	Isolated ACL	ACL+MM	P-Value
AP30 transaltion						
SB	10.8 ± 2.2 mm	14.4 ± 3.2 mm	0.0035*	5.8 ± 2.3 mm	5.0 ± 1.0 mm	0.6941
SBLP	11.2 ± 2.9 mm	13.0 ± 2.7 mm	0.0220*	5.2 ± 2.3 mm	5.9 ± 3.0 mm	0.3400
AP90 transaltion						
SB	7.7 ± 2.5 mm	10.0 ± 2.6 mm	0.0002*	3.8 ± 1.2 mm	5.2 ± 1.8 mm	0.0473*
SBLP	7.7 ± 1.9 mm	10.2 ± 2.2 mm	0.0001*	3.4 ± 1.5 mm	3.6 ± 1.6 mm	0.6369

Table 4: AP30: Antero-posterior translation at 30° of flexion; AP90: antero-posterior translation at 90° of flexion; ACL: Anterior Cruciate Ligament; MM: partial medial meniscectomy. Asterisks represent the statistical differences ($p<0.05$) between single groups.

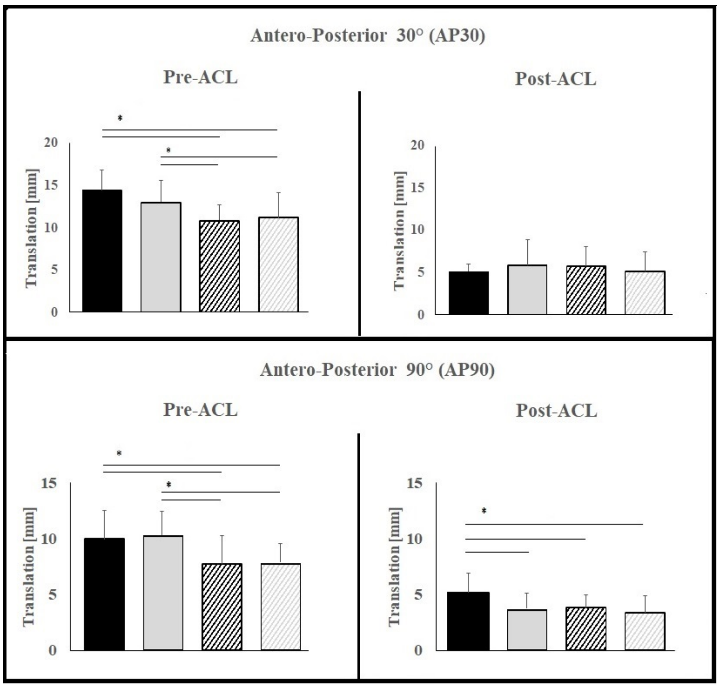

Table 9: AP30: Antero Comparison of preoperative (Pre-ACL) and postoperative (Post-ACL) laxity for the different meniscus condition (isolated ACL: hatched charts; ACL+MM: solid charts) within the surgical techniques (SB: black; SBLP: light grey). Bars with an asterisk represent the statistical differences ($p<0.05$) between single groups.

After ACL Reconstruction: AP30 and AP90 translations significantly decreased respect to the ACL-deficient status both with SBLP and SB techniques ($p<0.0001$), either in the case of intact menisci or with combined MM (*Table 5*).

Laxity Comparison Between Pre– and Post–ACL Reconstruction Status

	Isolated ACL		ACL+MM	
	Reduction (%)	P-Value	Reduction (%)	P-Value
AP30 translation				
SB	-5.0 mm (-47%)	<0.0001*	-9.4 mm (-65%)	<0.0001*
SBLP	-6.0 mm (-54%)	<0.0001*	-7.1 mm (-55%)	<0.0001*
AP90 transaltion				
SB	-4.0 mm (-51%)	<0.0001*	-4.8 mm (-48%)	<0.0001*
SBLP	-4.3 mm (-56%)	<0.0001*	-6.6 mm (-65%)	<0.0001*

Table 5: AP30: Antero-posterior translation at 30° of flexion; AP90: antero-posterior translation at 90° of flexion; ACL: Anterior Cruciate Ligament; MM: partial medial meniscectomy. Asterisks represent the statistical differences ($p<0.05$) between single groups.

In patients that underwent SBLP ACL reconstruction, no significant differences were found in postoperative AP30 and AP90 translations between patients with intact menisci ($n=31$) and concomitant MM ($n=24$). In patients that underwent SB ACL reconstruction, no significant differences were found in postoperative AP30 translation between patients with intact menisci ($n=33$) and concomitant MM ($n=13$), while a significantly higher value of AP90 translation was found in patients with concomitant MM ($p=0.0473$) (*Figure 10*). Moreover, the value of AP90 translation in the SB ACL+MM group was significantly higher than those of all the other three groups (SB with intact meniscus, SBLP with intact menisci, SBLP with concomitant MM), while no significant differences were found among the four groups for the postoperative AP30 translation (*Figure 9*).

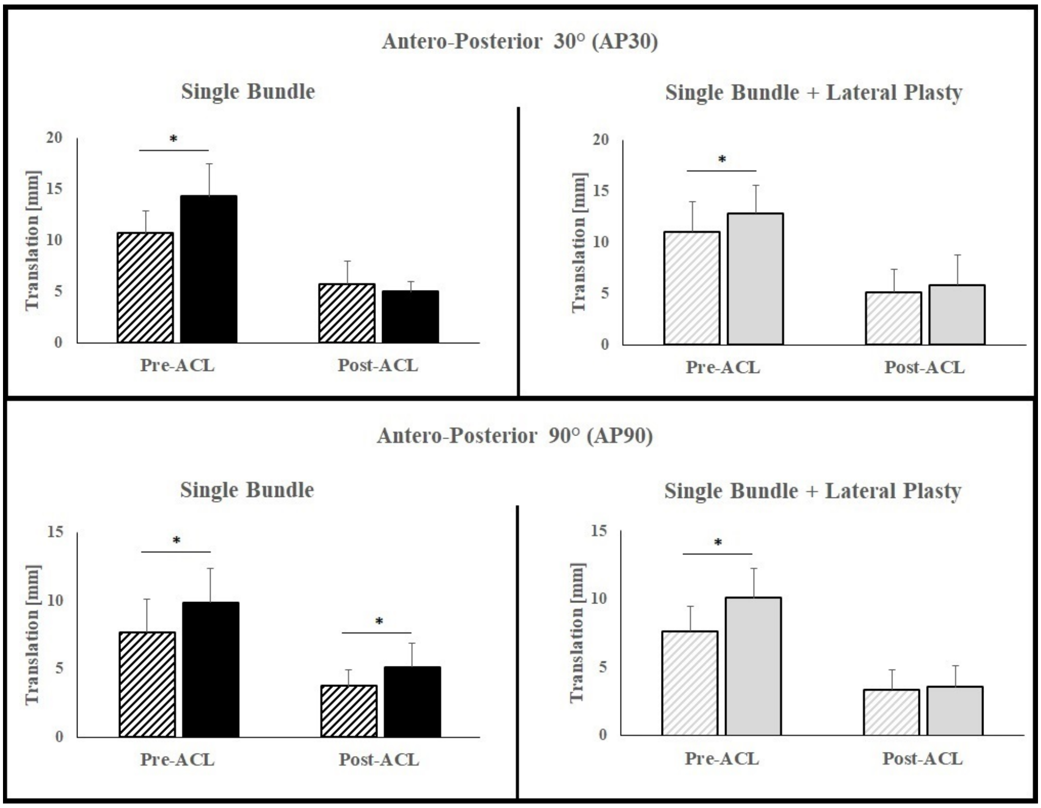

Figure 10: Comparison of AP30 and AP90 values before ACL reconstruction (Pre-ACL) and after ACL reconstruction (Post-ACL) between isolated ACL (hatched charts) and ACL+MM (solid charts) of either SB (black) or SBLP (light grey) reconstruction techniques. Bars with an asterisk represent the statistical differences ($p<0.05$) between single groups.

STUDY IV: THE ROLE OF ANATOMY IN LAXITY BEFORE ACL RECONSTRUCTION

Antero-Posterior Laxity at 30° (AP30): The multivariate regression with backward elimination identified the slope of the LTPs (P=0.047, β=−0.304) and the MTPsublx (P=0.039, β=0.316) as independent predictors. The identified cut-off value was 5.5° for LTPs. There is an inverse relationship between AP30 values and LTPs. In particular, those patients with LTPs ≥5.5° show a lower laxity compared to the remainder (6.5 ± 2.1 vs. 8.9 ± 3.1; P=0.018). The influence of the MTPsublx predictors on AP30 is continuous making it impossible to define a significant cut-off value.

Antero-Posterior Laxity at 90° (AP90): The multivariate regression with backward elimination identified the slope of the LTPs (P=0.049, β = −0.314) as independent predictors for AP90 laxity. The cut-off value was confirmed and, similarly to the AP30 analysis, those patients with LTPs ≥5.5° show a lower laxity compared to the remainder (4.9 ± 2.0 mm vs. 6.3 ± 2.0 mm; P = 0.028).

Internal-External Rotation at 30° (IE30): The multivariate regression with backward elimination was not able to identify any independent predictors for IE30 laxity (P = non-significant (n.s.)).

Internal-External Rotation at 90° (IE90): The multivariate regression with backward elimination identified the slope of the LTPs (P = 0.039, β = −0.327) as independent predictor for IE90 laxity. Concerning the preoperative IE90 laxity, the influence of the LTPs predictors is continuous making it impossible to define a significant cut-off value.

Varus-Valgus Rotation at 0° (VV0): The multivariate regression with backward elimination identified the width of the lateral femoral condyle (LFCw, P = 0.007, β = 0.417) as the only predictors for VV0 laxity. Cut-off value was set at 3.1 cm. In particular those cases with LFCw >3.1 cm have shown a higher laxity compared to the remainder (5.6 ± 2.2° vs. 4.0 ± 1.8°; P = 0.019).

Varus-Valgus Rotation at 30° (VV30): The multivariate regression with backward elimination was not able to identify any independent predictors for VV30 laxity (P = n.s.).

Pivot-Shift Test (PS): The multivariate regression with backward elimination identified the TE as a significant anatomical parameter (P = 0.004). The β = −0.445 underlined an inverse relationship between PS test values and TE values (i.e. as the TE increases, the PS test value gets lower). The cut-off value has been identified at TE = 8.7 cm. Those cases with TE >8.7 cm show a lower value of dynamic laxity compared to the remainder (23.2± 3.8 vs. 20.5 ±2.4; P = 0.034). Results of the previously reported regression analysis for AP30, AP90, IE90, VV0 and PS test are presented in *Table 6*.

Multivariate regression analysis results.

Coefficients										
Test		Non-standardized coefficients		Standardized coefficients	t	Sig.	95.0% confidence interval for B		Collinearity statistics	
		B	Standard deviation error	Beta			Lower limit	Upper limit	Tolerance	VIF
AP30	Cost.	7.855	1.220		6.438	0.000	5.382	10.327		
	LTPs	−0.331	0.161	−0.304	−2.057	0.047	−0.657	−0.005	1.000	1.000
	MTPsublx	4.528	2.116	0.316	2.140	0.039	0.240	8.816	1.000	1.000
AP90	Cost.	6.956	0.596		11.677	0.000	5.750	8.161		
	LTPs	−0.230	0.113	−0.314	−2.037	0.049	−0.459	−0.001	1.000	1.000
IE90	Cost.	31.416	1.360		23.107	0.000	280.664	34.169		
	LTPs	−0.550	0.258	−0.327	−2.135	0.039	−1.072	−0.028	1.000	1.000
VV0	Cost.	−4.618	3.281		−1.407	0.167	−11.261	2.025		
	LFCw	3.078	1.088	0.417	2.828	0.007	0.874	5.281	1.000	1.000
PS	Cost.	45.580	7.552		6.035	0.000	30.292	60.869		
	TE	−2.729	0.890	−0.445	−3.067	0.004	−4.531	−0.928	1.000	1.000

Table 6: AP30, anterior–posterior laxity at 30° of knee laxity; AP90, anterior–posterior laxity at 90° of knee laxity; IE90, internal–external rotation at 90° of knee laxity; LFCw, lateral femoral condyle width; LTPs, lateral posterior tibial slope; MTPsublx, medial subluxation; PS, pivot-shift test; Sig., significance; TE, trans-epicondylar distance; VIF, variance inflation factor; VV0, varus–valgus rotation at 0° of knee laxity.

STUDY V: THE ROLE OF LATERAL NOTCH SIGN IN PIVOT-SHIFT MAGNITUDE

The analysis of the confounding variables of the 90 patients included resulted in no statistically significant differences based on the sex, presence of medial/lateral meniscal tears, and presence of tibial slope greater than 9°. Patients with a positive LNS had higher PS ACC compared with patients without LNS, while PS IE was not significant (*Table 7, Figure 11*).

Dynamic laxity according to the presence of LNS

	no-LNS	LNS	p-value
PS ACC (mm/s^2)	543.4 ± 236.3	641.6 ± 236.5	0.0175*
PS IE (°)	21.6 ± 4.7	22.3 ± 4.3	0.1085

Table 7: Evaluation of the dynamic knee laxity through the Pivot-shift test performed with the surgical navigation system. Posterior acceleration of lateral tibial compartment during tibial reduction (PS ACC) and internal-external rotation (PS IE) were evaluated either in the presence (LNS) or absence (no-LNS) of the Lateral Notch Sign. "*" represent statistically significant differences (p<0.05).

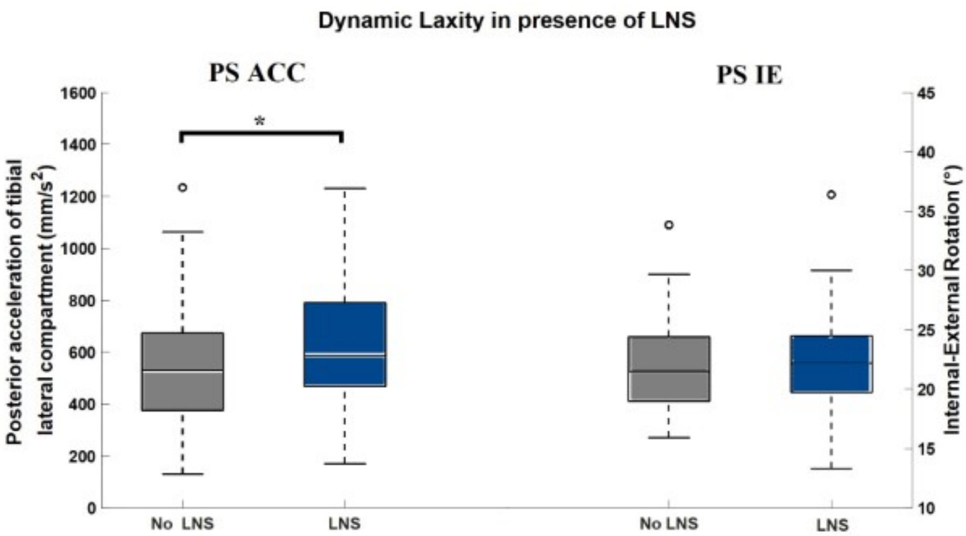

Figure 11: Graphic representation of posterior acceleration of the lateral compartment in mms^2 (PS ACC) and internal-external rotation in ° (PS IE) during the intraoperative evaluation of the Pivot-Shift. The groups represent patients without the Lateral Femoral Notch Sign (NO LNS) and patients with a positive Lateral Femoral Notch sign (LNS). Bars with * represent statistical differences between single groups (p<0.05).

When further stratifying the LNS according to its depth, patients with a notch deeper than 2 mm showed increase PS ACC and PS IE compared with the group without the LNS. However, no significative differences were present between the group with a notch between and 1 and 2mm and the patients without LNS in both the parameters analyzed (*Table 8, Figure 12*).

Dynamic laxity according to the LNS depths

		ANOVA	Multiple comparisons (Pairwise t-tests)			
PS ACC (mm/s^2)		*p-value*	*Group 1*	*Group 2*	*Mean diff*	*p-value*
no-LNS	543.4 ± 236.3		LNS>2mm	LNS 1-2mm	142.3	0.1425
LNS 1-2 mm	608.5 ± 222.2	0.0380*	LNS>2mm	no-LNS	207.4	0.0385*
LNS>2mm	750.8 ± 261.3		LNS 1-2mm	no-LNS	65.1	0.2131
PS IE (°)						
no-LNS	21.6 ± 4.7		LNS>2mm	LNS1-2 mm	4.3	0.0296*
LNS 1-2 mm	21.3 ± 3.4	0.0183*	LNS>2mm	no-LNS	4.0	0.0423*
LNS>2mm	25.6 ± 5.2		LNS 1-2mm	no-LNS	0.3	0.7304

Table 8: Evaluation of the dynamic knee laxity through the Pivot-shift test. Posterior acceleration of lateral tibial compartment during tibial reduction (PS ACC) and internal-external rotation (PS IE) were evaluated for either a Lateral Notch Sign higher than 2mm (LNS>2mm) and between 1 and 2mm (LNS 1-2mm) or without it (no-LNS). "*" represent statistically significant differences.

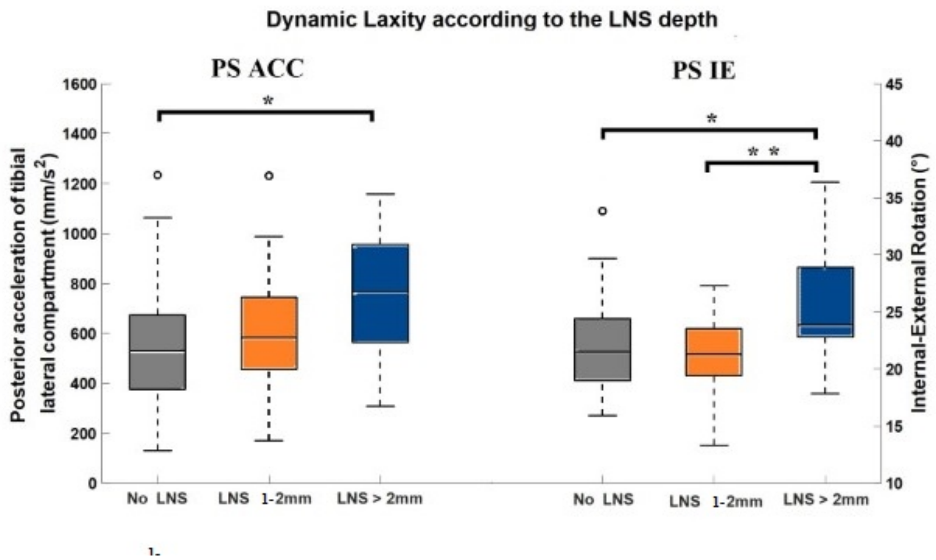

Figure 12: Graphic representation of posterior acceleration of the lateral compartment in mms^2 (PS ACC) and internal-external rotation in ° (PS IE) during the intraoperative evaluation of the Pivot-Shift. The groups represent patients without the Lateral Femoral Notch Sign (NO LNS), patients with a Lateral Femoral Notch sign between 1 and 2 mm (LNS 1-2mm), and patients with a notch deeper than 2 mm (LNS>2mm). Bars with "*" represent statistical differences between single groups (p<0.05).

The ROC curve analysis showed that 2 mm was the most predictive cutoff value for identify the "high grade rotatory instability" group, with an accuracy of 74.4% and 77.8% and a specificity of 95.5% and 93.9% referred to the PS ACC and PS IE (*Table 9*).

ROC curve analysis to determine the most predictive LNS cutoff value

PS ACC						
LNS Cutoff (mm)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy (%)*	*Youden index*
> 1	43.5	70.2	33.3	78.3	63.3	0.136
> 2	26.1	95.5	66.7	79.0	77.8	0.216
> 3	8.7	100.0	25.6	76.2	76.7	0.087

PS IE						
LNS Cutoff (mm)	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy*	*Youden index*
> 1	25.0	63.6	20	70	53.3	-0.114
> 2	20.8	93.9	55.6	76.5	74.4	0.148
> 3	4.2	98.5	50	73.9	73.3	0.027

Table 9: ROC curve analysis to determine the most predictive LNS cutoff value. The 75^{th} percentile of either the Posterior acceleration of lateral tibial compartment during tibial reduction (PS ACC, 748.0 mm/s^2) or internal-external rotation (PS IE, 24.4°) was used as cutoff input for the ROC analysis.

STUDY VI: THE ROLE OF MENISCECTOMY IN SHORT-TERM OUTCOMES OF ACL-R

Outcomes based on surgical technique: A total of 20 patients underwent ACL reconstruction with DB technique (DB Group), 15 patients underwent ACL reconstruction with SB technique (SB Group), 24 patients underwent ACL reconstruction with SBLP technique (SBLP Group). The side-to-side difference between injured and contralateral limb at KT-1000 (AP30), Rolimeter (AP30) and KiRa (PS) significantly decreased between baseline and final follow-up for each group ($p<0.0001$). All the KOOS subscales significantly improved as well ($p<.0001$) with no statistical differences between the three groups ($p>0.05$).

Outcomes based on meniscal status: A total of 19 patients received medial meniscus repair (MR), 11 patients received partial medial meniscectomy (MM), 5 patients received partial lateral meniscectomy (LM), 24 patients had an isolated ACL tear, so menisci were intact (IM). Since no statistical differences were found based on surgical technique, the role of meniscus was evaluated for both the clinical laxity and the KOOS regardless of the surgical technique adopted.

Regarding the clinical laxity, a significantly higher AP 30 ($p=0.0333$) was found at pre-operative status for the patients who undergone medial meniscectomy compared to the ones with the isolated ACL tear (mean difference IM vs MM: 2.37 mm). No statistical differences were found for the other laxity parameters (*Table 10*).

Clinical evaluation and subjective outcome (KOOS) evaluation before and at least 24 months after ACL reconstruction for different meniscus treatments

	IM		MR		MM		LM	
	BL	FU	BL	FU	BL	FU	BL	FU
KT-MM (mm)	4.2 ± 2.1	1.3 ± 2.3	4.5 ± 2.4	1.6 ± 2.5	6.5 ± 3.0	2.0 ± 1.4	5.0 ± 6.5	2.2 ± 3.0
ROLIMETER (mm)	2.6 ± 2.4	0.6 ± 0.9	3.1 ± 2.2	-0.1 ± 1.0	3.6 ± 1.7	0.4 ± 1.3	3.4 ± 1.3	0.2 ± 0.4
KiRA (m/s^2)	2.0 ± 1.3	0.2 ± 0.9	1.9 ± 1.2	0.1 ± 1.2	2.1 ± 1.0	0.1 ± 0.8	2.4 ± 1.4	0.7 ± 1.4
PAIN	80.0 ± 14.8	93.3 ± 9.3	71.3 ± 12.3	93.3 ± 7.6	79.4 ± 17.3	91.9 ± 15.9	87.8 ± 8.2	86.5 ± 4.7
SYMPTOMS	74.6 ± 14.7	87.3 ± 3.1	76.4 ± 11.8	86.9 ± 3.1	72.8 ± 14.9	89.0 ± 3.1	77.9 ± 12.7	87.3 ± 3.1
ADL	88.2 ± 14.0	98.6 ± 2.4	85.4 ± 12.8	99.0 ± 1.3	87.8 ± 13.9	96.5 ± 10.5	92.5 ± 4.6	96.9 ± 3.0
SPORT	48.1 ± 30.5	89.6 ± 13.9	43.9 ± 21.6	85.5 ± 18.3	45.1 ± 32.3	85.5 ± 23.7	48.0 ± 18.6	87.0 ± 4.5
QoL	40.8 ± 23.1	86.0 ± 14.1	38.3 ± 14.3	81.2 ± 19.2	41.9 ± 19.5	83.1 ± 18.7	47.6 ± 19.8	80.0 ± 19.5

Table 10: Values of laxity and KOOS according to the different meniscus status. (IM, Intact Menisci; MM, medial meniscectomy; LM, Lateral Meniscectomy; MR, Meniscal Repair).

Regarding the KOOS subscales, a significant difference in KOOS-Pain at final follow-up was found between patients who undergone lateral meniscectomy and either patients with meniscal repair or isolated ACL tear with intact menisci (*Table 11*).

Multiple comparisons among meniscus treatments

	Antero-posterior displacement at 30° (KT-MM)		**KOOS – PAIN**					
	BL		**BL**		**FU**		**Improvement**	
	mean difference (mm)	p-value	mean difference (mm)	p-value	mean difference (mm)	p-value	mean difference (mm)	p-value
IM vs MR	0.36	0.6110	8.66	0.0421*	0.09	0.9731	8.74	0.0752
IM vs MM	2.37	0.0333*	0.58	0.9246	1.38	0.7921	0.80	0.8516
IM vs LM	0.83	0.7896	7.86	0.1269	6.79	0.0331*	14.65	0.0087*
MR vs MM	2.02	0.0771	8.08	0.1921	1.47	0.7773	9.55	0.0385*
MR vs LM	0.47	0.8797	16.51	0.0055*	6.88	0.0290*	23.39	0.0003*
MM vs LM	1.54	0.6336	8.44	0.2068	5.41	0.3189	13.85	0.0111*

Table 11: Comparison of laxity and KOOS values at baseline (BL) and at final follow-up (FU) according to the meniscal status. (IM, Intact Menisci; MM, medial meniscectomy; LM, Lateral Meniscectomy; MR, Meniscal Repair).

STUDY VII: THE ROLE OF MENISCUS REPAIR IN SHORT-TERM OUTCOME OF ACL-R

Demographic characteristics: were similar between the 20 patients with isolate ACL reconstruction and the 20 patients with combined ACL reconstruction and meniscal repair. Overall, 21 menisci were repaired (17 medial and 4 lateral) in the 20 patients of the ACL reconstruction and suture group (*Table 12*).

Details of meniscal repairs and MRI assessment		
	Total Repair (n=21)	
Meniscus involved (Medial/Lateral)		
Medial	17 (81%)	
Lateral	4(9%)	
Teal Location		
Anterior Horn	1 (5%)	
Mid-Body	12 (57%)	
Posterior Horn	8 (38%)	
Tear Zone		
Red-Red	12 (57%)	
White-Red	9 (43%)	
White-White	0 (0%)	
Number of Stitches		
1 stitch	10 (47.5)	
2 stitches	10 (47.5)	
3 stitches	1 (5%)	
Mink Classification	**Pre-operative**	**18-month**
Grade I	0 (0%)	10 (48%)
Grade II	1 (5%)	8 (38%)
Grade IIIa	17 (81%)	0 (0%)
Grade IIIb	3 (14%)	3 (14%)
Repair Healing		
Complete Healing	10 (48%)	
Incomplete Healing	8 (38%)	
No Healing	3 (14%)	
Perimeniscal Cysts		
No	14 (67%)	
Yes	7 (33%)	

Table 12: Details of MRI characteristics of the included meniscal lesions.

MRI assessment of the repair: Overall, 10 lesions (48%) were classified as “Complete Healing” (*Figure 13 and 14*), 8 lesions (38%) as “Incomplete Healing”, while only 3 lesions (14%) were classified as “No Healing” (*Figure 15*) at the 18-MRI assessment (*Table 12*). Perimeniscal cysts with a diameter >5 mm were present in 7 cases (33%), either in the case of complete healing (3 cases) (*Figure 14*), incomplete healing (2 cases) and no healing (2 cases) (*Figure 15*). There were no significant differences in patients’ characteristics and lesion pattern based on the outcome of meniscal repair healing. Differently, patients with perimeniscal cysts were significantly older (p=0.0211) respect to those without cysts at the 18-month MRI evaluation (*Table 13*),

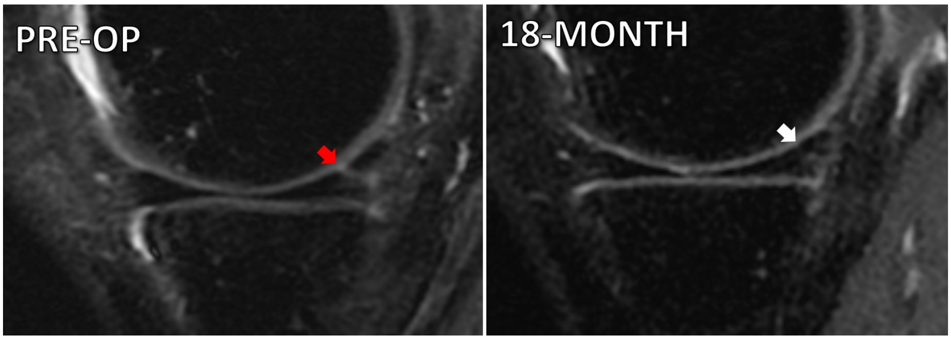

Figure 13: The horizontal tear of medial meniscus posterior horn at the pre-operative status (red arrow) is completely healed at the 18-months MRI evaluation (white arrow) without the development of perimeniscal cysts.

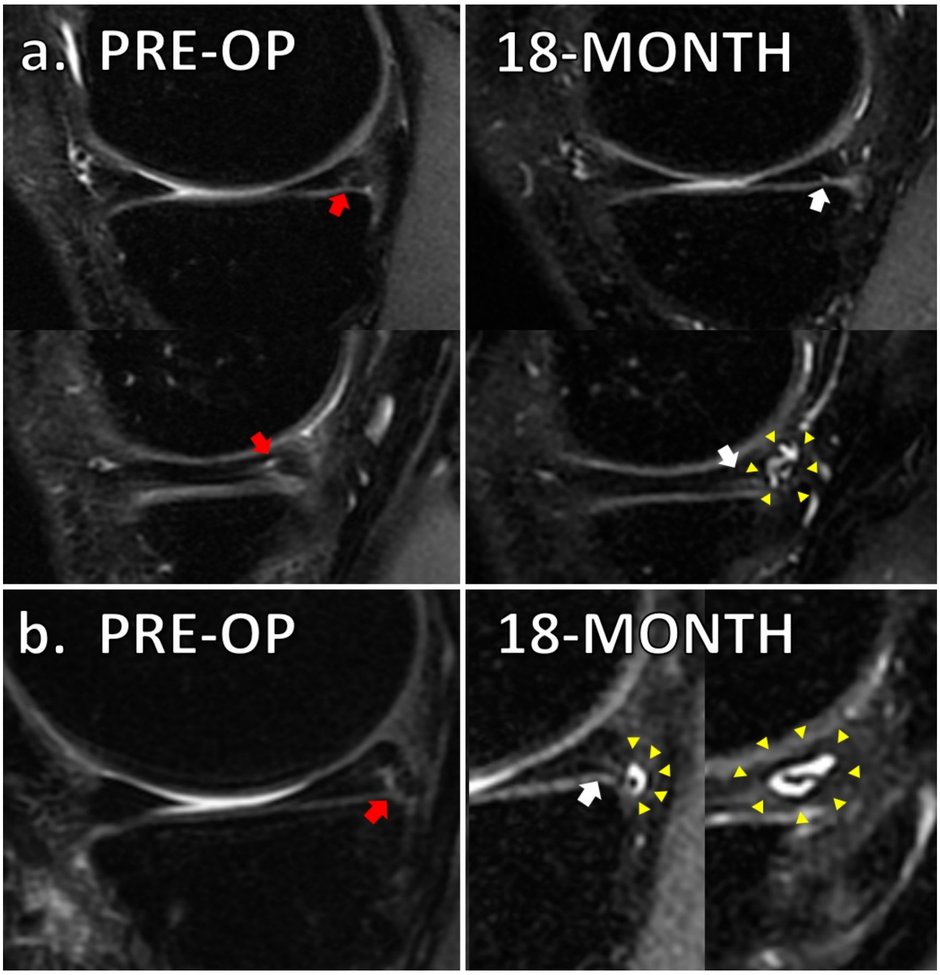

Figure 14: The vertical tear of medial meniscus posterior horn and mid-body at the pre-operative status (red arrow) is completely healed at the 18-months MRI evaluation (white arrow), but with the development of a perimeniscal cysts (yellow arrowheads) (a). Another medial meniscus posterior horn tear (red arrow) is completely healed after 18 months (white arrow) but with the development of two different cysts (yellow arrowheads) (b).

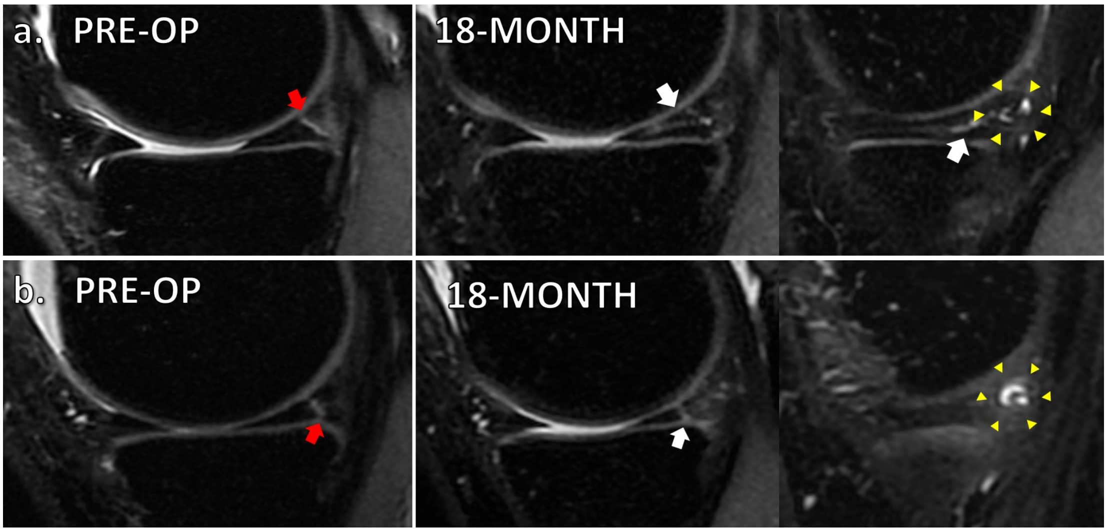

Figure 15: The oblique tear of medial meniscus posterior horn and mid-body at the pre-operative status (red arrow) is not completely healed at the 18-months MRI evaluation (white arrow) and a cyst is present (yellow arrowheads) (a). Another posterior horn tear (red arrow) is not healed at 18 months; hyperintense intrameniscal signal (white arrow) and perimeniscal cyst (yellow arrowheads) are present (b).

Comparison of patients characteristics and tear pattern based on MRI outcomes

	Repair Healing Assessment Complete (n=10)	Repair Healing Assessment Incomplete\No (n=11)	p-value	Perimeniscal Cysts Assessment No Cysts (n=14)	Perimeniscal Cysts Assessment Cysts (n=7)	p-value
Demographics						
Age (years)	25.2 ± 7.2	26.4 ± 10.1	=0.7596	23.4 ± 7.7	32.4 ± 7.8	**=0.0211***
Sex (M/F)	9 (90%)/ 1 (10%)	10 (91%)/ 1(9%)	=1.0000	12 (86%)/ 2(14%)	7 (100%)/ 0(0%)	=1.0000
Side (R/L)	6 (60%)/ 4(40%)	8 (72%)/ 3(28%)	=0.8772	8 (57%)/ 6(43%)	6 (86%)/ 1 (14%)	=0.3771
Inj to Surg (months)	4.7 ± 4.3	5.0 ± 6.2	=0.8999	3.4 ± 1.9	7.3 ± 8.2	=0.0988
Surgical Technique			=1.0000			=1.0000
Single-Bundle	2 (20%)	2 (19%)		3 (21%)	1 (14%)	
Single-Bunble + LP	4 (40%)	5 (45%)		6 (43%)	3 (43%)	
Double-Bundle	4 (40%)	4 (36%)		5 (46%)	3 (43%)	
Meniscus involved			=0.3107			=0.2549
Medial	7 (70%)	10 (91%)		10 (71%)	7 (100%)	
Lateral	3 (30%)	1 (9%)		4 (29%)	0 (0%)	
Teal Location			=0.5250			=0.1684
Anterior Horn	1 (10%)	0 (0%)		1 (7%)	0 (0%)	
Mid-Body	5 (50%)	7 (64%)		6 (43%)	6 (86%)	
Posterior Horn	4 (40%)	4 (36%)		7 (50%)	1 (14%)	
Tear Zone			=0.8499			=0.6400
Red-Red	5 (50%)	7 (64%)		9 (64%)	3 (43%)	
White-Red	5 (50%)	4 (36%)		5 (36%)	4 (57%)	
White-White	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Number of Stitches			=0.4155			=0.6873
1 stitch	4 (40%)	6 (55%)		7 (50%)	3 (43%)	
2 stitches	6 (60%)	4 (36%)		6 (43%)	4 (57%)	
3 stitches	0 (0%)	1 (9%)		1 (7%)	0 (0%)	
Mink Classification			=0.5098			=0.3669
Grade I	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Grade II	0 (0%)	1 (9%)		1 (7%)	0 (0%)	
Grade IIIa	9 (90%)	8 (73%)		12 (86%)	5 (71%)	
Grade IIIb	1 (10%)	2 (18%)		1 (7%)	2 (29%)	
Ortho one PROMT						
Median (IQR)	3 (2-4)	4 (2-4)	=0.5202	2 (1-4)	4 (3-5)	**=0.0171***
>4 points	1 (10%)	2 (18%)	=1.0000	0 (0%)	3 (43%)	**=0.0263***

Table 13: Comparison of patients characteristics based on the healing of meniscal lesion or cyst presence.

Clinical Outcomes: All the clinical scores improved from pre-operative status to the 4-months evaluation in the 2 groups, except of Marx score, MCS and KOOS Symptoms subscale (*Table 14, Figure 16*). However, the KOOS Symptoms subscale was significantly improved from the pre-operative status to the final 18-month follow-up only in patients with concomitant ACL and meniscal repair (p=0.0252), but not in those with isolate ACL reconstruction (p=0.1674) (*Table 15*).

Patients scores at different follow-ups

	Pre-operative Status			4-month follow-up			18-month follow-up		
	ACL	ACL + Suture	p-value	ACL	ACL + Suture	p-value	ACL	ACL + Suture	p-value
KT-1000 ssd (mm)	4.0 ± 2.2	4.5 ± 2.6	=0.6223	1.2 ± 2.9	1.6 ± 2.2	=0.5294	1.6 ± 2.3	1.5 ± 2.3	=0.8868
Kira	1.4 ± 1.8	1.2 ± 1.9	=0.7672	-0.1 ± 0.5	0.2 ± 0.9	=0.2460	0.2 ± 0.7	0.2 ± 1.0	=0.9789
KOOS Pain	81.7 ± 14.5	74.0 ± 11.6	=0.1718	89.6 ± 10.1	90.8 ± 7.6	=0.7197	93.2 ± 8.4	92.4 ± 8.5	=0.6878
KOOS Sym	76.5 ± 15.4	77.0 ± 12.3	=0.930	79.3 ± 15.5	84.1 ± 8.0	=0.2187	82.3 ± 16.5	86.2 ± 14.0	=0.3252
KOOS ADL	89.2 ± 15.2	87.0 ± 13.0	=0.5436	97.8 ± 13.2	94.5 ± 5.9	=0.6194	98.5 ± 1.9	98.4 ± 1.4	=0.2015
KOOS Sport	52.4 ± 33.4	45.7 ± 23.8	=0.4811	80.6 ± 16.5	85.3 ± 14.9	=0.4143	85.3 ± 18.4	86.8 ± 18.3	=0.6615
KOOS Qol	42.8 ± 22.6	41.5 ± 15.7	=0.8494	75.5 ± 15.4	76.1 ± 17.3	=0.9362	82.3 ± 16.0	80.9 ± 22.0	=0.8085
Marx	7.6 ± 7.0	8.9 ± 6.7	=0.5189	8.0 ± 7.0	9.3 ± 5.9	=0.4601	10.0 ± 4.6	10.2 ± 3.9	=0.8506
PCS	46.0 ± 7.9	41.6 ± 6.8	=0.0667	53.3 ± 3.8	51.5 ± 4.2	=0.5321	55.3 ± 3.7	52.8 ± 4.5	=0.0714
MCS	51.5 ± 8.4	53.0 ± 7.6	=0.4541	49.4 ± 8.6	53.0 ± 6.6	=0.3716	50.3 ± 9.3	52.7 ± 8.1	=0.4588

Table 14: Comparison of clinical scores between patients with isolate ACL and ACL plus suture groups, at the different time points (PCS, Physical Component Score; MCS, Mental Component Score; * p<0.05)

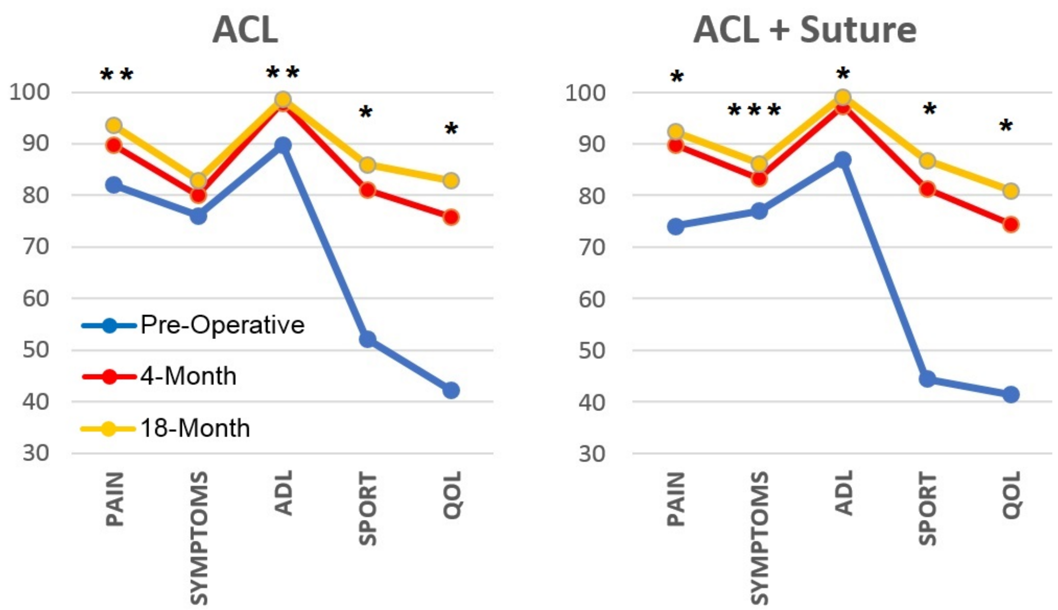

Figure 16: KOOS subscales of the Isolated ACL and ACL plus meniscal suture groups (*p<0.05 pre-op vs 4-month; ** p<0.001 pre-op vs 4-month; *** p<0.05 pre-op vs 18-months).

P-values of clinical score improvements				
	P-value pre-op vs 4-month		P-value 4-month vs 18-month	
Score	**ACL**	**ACL + Suture**	**ACL**	**ACL + Suture**
KT-1000 side-to-side (mm)	**=0.0001***	**=0.0010***	=0.3997	=1.0000
Kira	**=0.0023***	**=0.0070***	=0.7447	=0.8414
KOOS Pain	**=0.0304***	**=0.0001***	=0.1369	=0.5430
KOOS Symptoms	=0.2979	=0.0667	=0.4260	=0.4441
KOOS ADL	**=0.0219***	**=0.0014***	=0.4154	=0.3737
KOOS Sport	**=0.0026***	**=0.0001***	=0.4342	=0.6399
KOOS Qol	**=0.0001***	**=0.0001***	=0.1320	=0.3580
Marx	=0.8597	=0.3853	=0.6418	=0.3162
PCS	**=0.0012***	**=0.0001***	=0.1601	=0.7506
MCS	=0.3997	=0.9631	=0.5972	=0.9361

Table 15: P-values for the comparison of clinical scores at different time points, for both the two groups (PCS, Physical Component Score; MCS, Mental Component Score; * p<0.05)

At the pre-operative status, despite the similar mean values of all KOOS subscales, the group of ACL and meniscus lesion had a lower percentage of patients with KOOS values reaching the PASS threshold, respect to those with intact menisci, both for the Pain (5% vs 35%, p=0.0435) and ADL (0% vs 30%, p=0.0201) subscales (*Figure 17*).

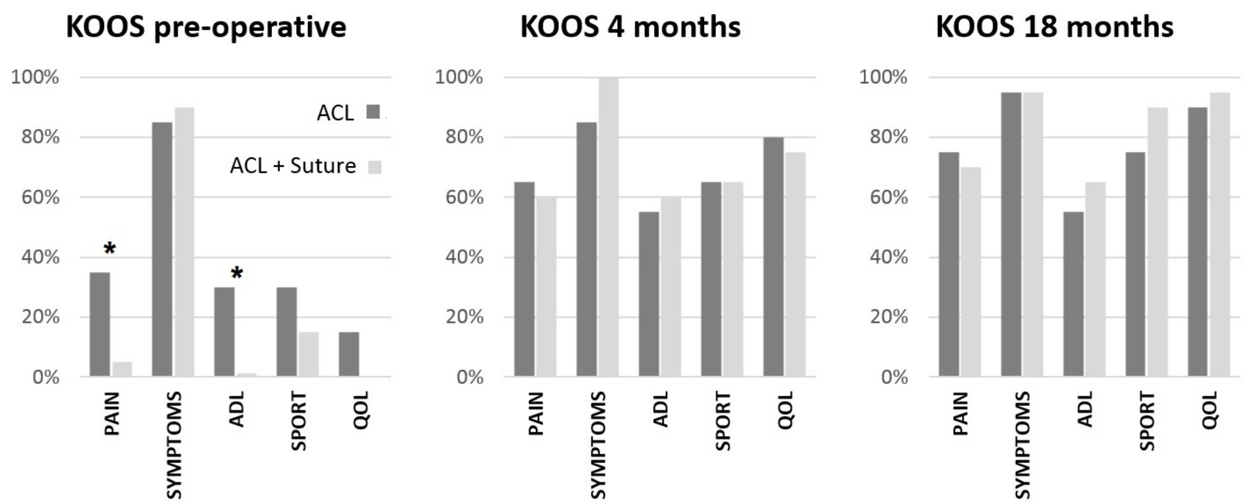

Figure 17: Percentage of patients achieving the Patients Acceptable Symptoms State (PASS) for the KOOS subscales at the different time points, for both Isolate ACL (dark gray) and ACL plus suture (pale gray) groups (* p<0.05).

Differently, no difference between the 2 groups in the percentage of patients reaching the PASS was found at the 4-month and 18-month follow-up.

No differences were noted at the 18-months between the control group of isolate ACL and the group of patients with “Complete Healing” or “Incomplete\No Healing” of meniscal repair (*Figure 18*). Differently, significantly lower values of the Qol KOOS subscale were registered in patients presenting perimeniscal cysts after all-inside repair (67.0 ± 30.4) respect to patients without cysts (89.1 ± 10.4) and with intact menisci (82.9 ± 15.8) (*Figure 18*).

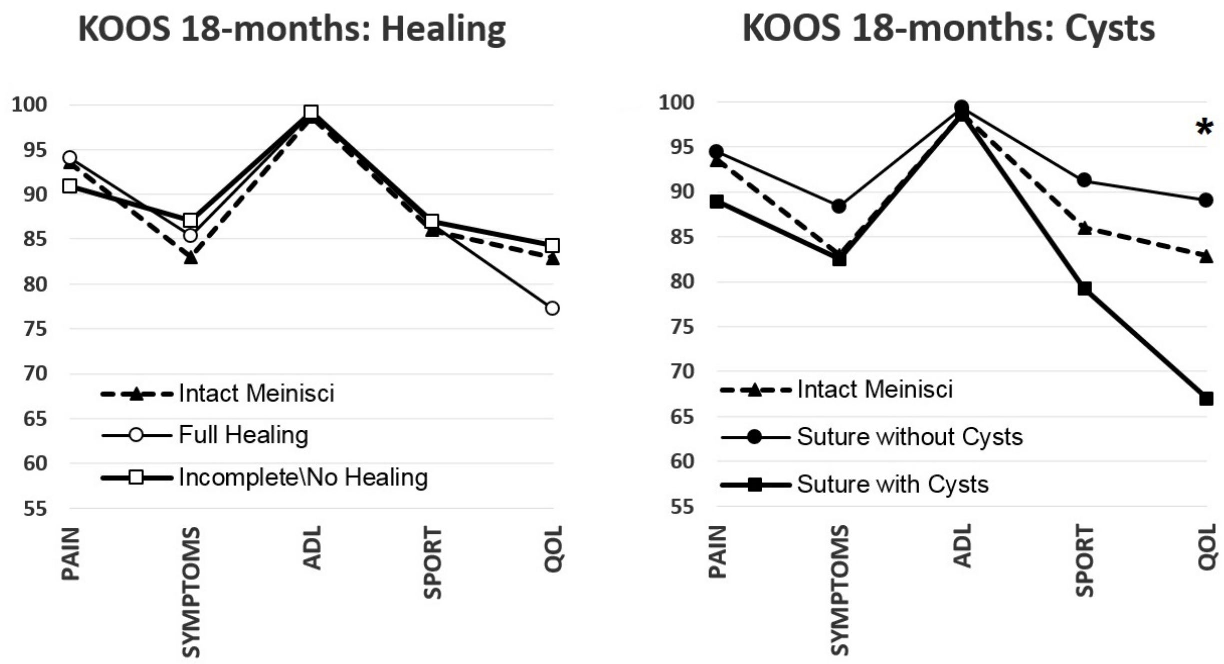

Figure 18: KOOS subscales at the final 18-month follow-up, stratified based on meniscal healing (left graph) or presence of perimeniscal cysts (right graph) (* $p<0.05$).

Complications and Reoperations

One patient (5%) in the ACL and meniscal repair group experienced a traumatic ACL re-rupture due to a knee sprain during a motocross race 22 months after surgery, while no patients (0%) with isolate ACL reconstruction experienced a re-rupture. One other patient (5%) that underwent meniscal repair and with “No Healing” of the repair at 18-months MRI, underwent partial medial meniscectomy due to increasing pain 42 months after initial surgery. Both surgeries were performed after the completion of the study, after the 18-month follow-up.

STUDY VIII: THE ROLE OF MENISCUS LESION IN LONG-TERM OUTCOMES OF ACL-R

Patients characteristics: In combination with ACL injury, 44% of the 267 patients included in the study had a medial meniscus lesion while only 21% had a lateral meniscus lesion. Chondropathy with Outerbridge ≥II involving medial compartment was present in 10% of cases, while in only 3% of cases involved the lateral compartment.

Reoperations: During the 10-year follow-up, 35 patients (13.1%) underwent a re-operation in the indexed knee: 8 (3.0%) Revision ACL reconstruction, 10 (3.7%) meniscectomies, 13 (4.9%) staples removal, 1 (0.04%) loose body removal, 1 (0.04%) arthroscopic lavage for post-operative septic arthritis, 1 (0.04%) Unicompartmental Knee Arthroplasty (UKA) and 1 (0.04%) Total Knee Arthroplasty (TKA). No significant predictors were found for all reoperations at the logistic regression analysis (p=0.8700). However, when considering the combined risk of Revision ACL or new meniscectomy, having a pre-operative Tegner Activity level >5 had and Hazard Ratio of 6.9 (95% CI 2.5 – 19.2; p=0.0.285), while having a medial meniscus lesion at time of ACL reconstruction had an Hazard Ratio of 2.6 (95% CI 1.0 – 6.6; p=0.0487) (*Figure 19*). Of the 18 patients that underwent ACL revision or new meniscectomy during the follow-up, 12 (67%) had a medial meniscus lesion at time of initial ACL reconstruction treated with either meniscectomy (n=7, 58%) or suture (n=5, 42%), respect to 106 out of 249 (43%) who did not experienced reinjuries (p=0.0468).

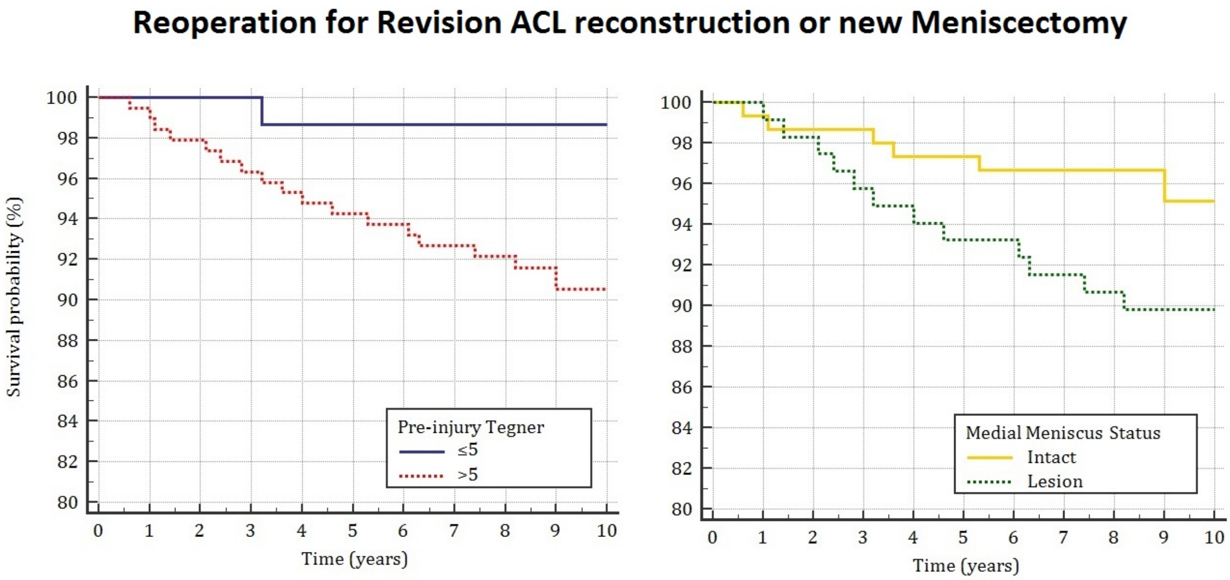

Figure 19: Survivorship from Revision ACL or new Meniscal surgery according to Tegner ≤5 (blue line), Tegner >5 (red dotted line), intact medial meniscus (yellow line) or medial meniscus lesion (green dotted line).

Patient-Reported Outcome Measures (PROMs): A total of 10 patients (3.7%) were excluded from PROMS analysis because underwent Revision ACL reconstruction (8) or total\partial knee replacement (2) during the follow-up. The mean Lysholm score was 94.1 ± 10.8, with 73%of patients rated as Excellent, 15% as Good, 9% as Fair and 3% as Poor. The mean VAS for pain was 0.2 ± 0.9 at rest and 2.1 ± 2.6 during activity. The mean values of the KOOS subscales were 95.7 ± 8.1 for Pain, 92.5 ± 0.10.5 for Symptoms, 98.4 ± 7.4 for ADL, 90.7 ± 17.2 for Sport and 91.2 ± 17.1 for Qol. Moreover, 88%, 99%, 81%, 89% and 91% of patients passed the PASS threshold for Pain, Symptoms, ADL, Sport and ADL subscales. According to the multiple regression analysis, meniscal lesions did not showed any effect on final PROMs, differently, the presence of chondropaty ≥II was a significant predictor of lower values of Lysholm score (-8.2 points), lower KOOS subscales (-3.5 to -15.5 points) and higher values of VAS for pain at rest (+0.8 points) and during activities (+2.1 points) (*Figure 20*). Chondropaty ≥II was also a significant risk factor of not achieving the PASS thresholds for Pain, ADL, Sport and Qol subscales. Female sex was a significant predictor of lower Sport (-6.1 points) and Qol (-6.2 points) subscales, and a risk factor for not achieving the PASS threshold for Qol subscale. Finally, early reconstructing was predictor of higher KOOS Sport subscale (+5.1 points).

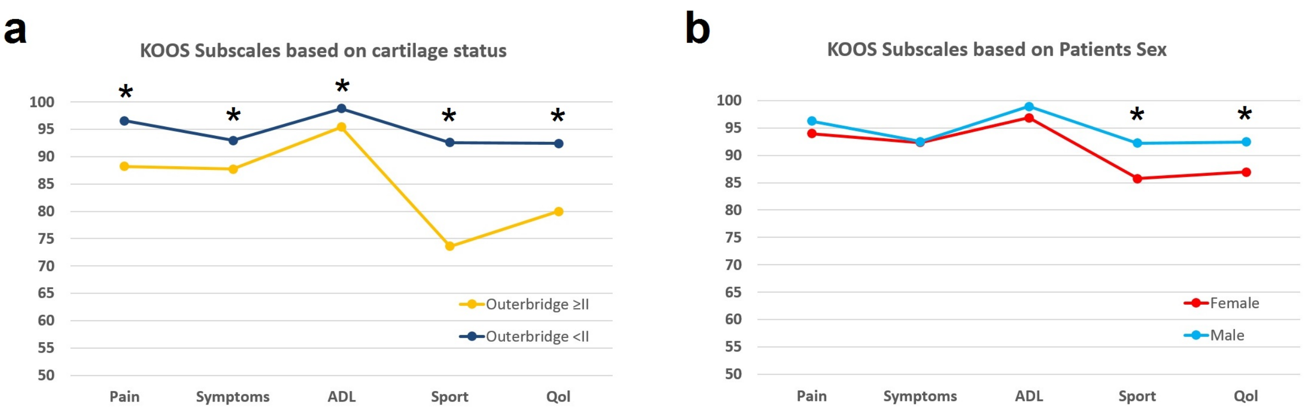

Figure 20: KOOS subscales stratified for cartilage status with Outebridge ≥II (yellow line) or <II (dark blue line) (a) or stratified according to male sex (light blue line) or female sex (red line) (b). P-values <0.05 are marked with *.

STUDY IX: THE ROLE OF ANATOMY IN ACL RECONSTRUCTION FAILURE

Patient Characteristics: The 43 patients in the Failed Group and the 43 patients in the Control Group had similar baseline characteristics (P>0.05). At the time of the MRI evaluation, the mean follow-up for the control group was 3.0 ± 0.7 years.

MRI Evaluation: The anatomical variables that were significantly different between the 2 study groups were both posterior tibial slopes (LTPs and MTPs), both subluxations (LTPsublx and MTPsublx), both tibial plateau widths (MTPw and LTPw), the MCFw, and the TE (*Table 16*).

	Control Group (n = 43)	Failed Group (n = 43)	*P* Value, Control vs Failed Group
Magnetic resonance imaging parameters:			
TE, cm§	8.4 ± 0.6	8.7 ± 0.7	.0417*
LFC-ratio†	0.53 (0.51 − 0.58)	0.52 (0.50 − 0.56)	.1816
MFC-ratio†	0.55 (0.52-0.57)	0.55 (0.52-0.56)	.4443
LTPs, degrees§	4.8 ± 3.0	11.4 ± 4.2	<.0001*
MTPs, degrees†	4.4 ± 2.7	9.4 (6.6-13.1)	<.0001*
LTPsublx, cm§	0.7 ± 0.3	1.1 ± 0.4	.0003*
MTPsublx, cm§	0.4 ± 0.2	0.6 ± 0.2	.0001*
NWI†	0.28 (0.25-0.28)	0.27 (0.25-0.30)	.2880
N-ratio§	0.72 ± 0.78	0.71 ± 0.07	.3780
LFCw, cm†	3.0 (2.8-3.1)	3.1 (2.8-3.4)	.0710
MFCw, cm§	2.6 ± 0.3	2.8 ± 0.3	.0001*
LTPw, cm§	3.1 ± 0.3	3.3 ± 0.4	.0148*
MTPw, cm§	3.0 ± 0.3	3.1 ± 0.3	.0403*

Table 16. Variables with normal distribution are expressed in terms of mean and standard deviation while variables without normal distribution are expressed with median and interquartile range. LFC/MFC-ratio, lateral/medial femoral condyles height and depth ratio; LFCw/MFCw, width of the lateral/medial femoral condyles; LTPs/ MTPs, lateral/medial posterior tibial slope; LTP/MTPsublx, lateral/medial tibial plateau subluxation; LTPw/MTPw, width of the lateral/medial tibial plateau; N-ratio, notch ratio; NWI, notch width index; TE, transepicondylar distance.
*Statistically significant (P < .05).

The multivariate regression analysis including only the previously identified anatomical variables and controlling for confounding variables identified the LTPs (P=.0010), the MTPsublx (P= .0364), and the MFCw (P= .0161) as significant independent predictors, with LTPs being the one with the highest coefficient and the lowest P value. According to the ROC analysis performed for the 3 variables (*Figure 21*), the highest AUC and Youden index were obtained for the LTPs, which exhibited a sensitivity of 88% and a specificity of 84% considering the optimal cutoff value of 7.4°.

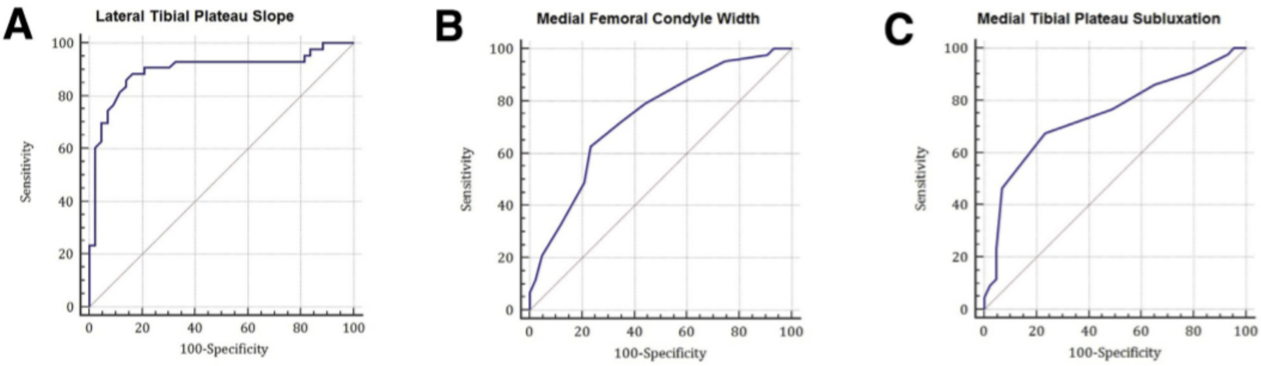

Figure 21: Receiver operating characteristic analysis with LTPs (A), MTPsublx (B), and MFCw (C) as independent predictors.

MRI Comparison of Male and Female Patients: The demographical and surgical characteristics were similar between the control group and failed group both for male and female patients. The LTPs and MTPs, MTPsublx, and MFCw were significantly different between the control and failed groups for both male and female patients. When the failed and control groups were compared considering only male patients or only female patients, no differences were found regarding demographic and surgical characteristics (*Table 17*). However, several anatomical variables were significantly different between male and female patients. The TE, MFCw, LFCw, MTPw, and LTPw were higher in male patients, while the NWI was higher in female patients.

	Male Sex (n = 68)			Female Sex (n = 18)		
	Control Group (n = 34)	Failed Group (n = 34)	*P* Value, Control vs Failed Group	Control Group (n = 9)	Failed Group (n = 9)	*P* Value, Control vs Failed Group
Patient data:						
Age, yr[†]	23.2 (20.3-29.4)	21.7 (18.3-27.2)	.3205	23.3 (18.5-27.5)	23.3 (21.0-25.0)	.9296
Side, right/left[‡]	20/14	19/15	1.0000	2/7	5/4	.3336
Medial meniscus lesion, no/yes[‡]	27/7	25/9	.7750	8/1	6/3	.5708
Lateral meniscus lesion, no/yes[‡]	30/4	30/4	.7076	9/0	9/0	.8137
Follow-up, yr[§]	3.1 ± 0.6	NA	NA	2.4 ± 0.4	NA	NA
Magnetic resonance imaging parameters:						
TE, cm[§]	8.4 ± 0.4	9.0 ± 0.6	.0085*	7.5 ± 0.5	7.8 ± 0.5	.3484
LFC-ratio[†]	0.54 (0.51-0.58)	0.52 (0.50-0.58)	.3195	0.52 (0.50-0.56)	0.51 (0.48-0.53)	.3306
MFC-ratio[†]	0.55 (0.51-0.58)	0.54 (0.52-0.59)	.7401	0.52 (0.51-0.55)	0.56 (0.55-0.64)	.0149*
LTPs, degrees[§]	4.3 ± 2.7	11.7 ± 4.3	<.0001*	6.7 ± 3.4	10.4 ± 4.1	.0497*
MTPs, degrees[†]	3.4 (2.0-5.9)	9.2 (6.6-13.1)	<.0001*	5.0 (3.6-5.6)	11.1 (7.0-12.7)	.0193*
LTPsublx, cm[§]	0.7 ± 0.3	1.1 ± 0.4	.0011*	0.7 ± 0.2	1.0 ± 0.4	.1219
MTPsublx, cm[§]	0.4 ± 0.2	0.6 ± 0.2	.0013*	0.4 ± 0.1	0.6 ± 0.2	.0279*
NWI[†]	0.26 (0.24-0.28)	0.27 (0.25-0.29)	.2867	0.28 (0.28-0.30)	0.30 (0.27-0.31)	.6261
N-ratio[§]	0.72 ± 0.07	0.70 ± 0.07	.3273	0.73 ± 0.10	0.72 ± 0.08	.7470
LFCw, cm[†]	3.0 (3.0-3.2)	3.2 (3.1-3.5)	.0070*	2.5 (2.5-2.6)	2.4 (2.4-2.7)	.4268
MFCw, cm[§]	2.7 ± 0.2	2.9 ± 0.3	.0002*	2.2 ± 0.1	2.5 ± 0.2	.0023*
LTPw, cm[§]	3.2 ± 0.2	3.4 ± 0.3	.0069*	2.7 ± 0.2	2.9 ± 0.3	.1480
MTPw, cm[§]	3.0 ± 0.3	3.2 ± 0.3	.0494*	2.7 ± 0.2	2.8 ± 0.3	.2315

Table 17: LFC/MFC-ratio, lateral/medial femoral condyles height and depth ratio; LFCw/MFCw, width of the lateral/medial femoral condyles; LTPs/ MTPs, lateral/medial posterior tibial slope; LTP/MTPsublx, lateral/medial tibial plateau subluxation; LTPw/MTPw, width of the lateral/medial tibial plateau; NA, none; N-ratio, notch ratio; NWI, notch width index; TE, transepicondylar distance. *Statistically significant (P<.05).

STUDY X: THE ROLE OF ANATOMY IN MULTIPLE ACL RECONSTRUCTION FAILURES

Patient Characteristics: There was a prevalence of male sex (85% in the control group, 88% in the failed ACL-R group, and 88% in the multiple-failure group) with no significant differences among the 3 groups (P = .901), likewise for the age at primary ACL-R (P = .110). The number of meniscectomies performed at the time of primary ACL-R was not different among the 3 groups for medial (P = .365) and lateral (P = .405) meniscus. When the patients of the 2 groups that had a failed ACL-R were compared, those in the multiple-failure group had an early failure (P = .048) and younger age at revision (P = .012) with respect to those of the failed ACL-R group. However, the graft used for the primary or revision ACL-R and the number of meniscectomies performed at the primary or revision ACL-R were not significantly different.

Anatomic Parameters: The patients in the multiple-failure group had significantly higher values of lateral tibial plateau slope (P<.001) and medial tibial plateau slope (P<.001) when compared with the control group and the failed ACL-R group (*Table 18, Figure 22*).

Magnetic Resonance Imaging Anatomic Parameters[a]

	Control (n = 40)	Failed ACL-R (n = 25)	Multiple Failures (n = 26)	*P* Value
LFC-H/D	0.54 ± 0.04	0.54 ± 0.04	0.51 ± 0.06	.038[b]
LTPs, deg	4.5 ± 2.8	10.6 ± 3.6	13.0 ± 4.7	<.001[b]
LTPsublx, mm	0.75 ± 0.33	0.95 ± 0.4	1.21 ± 0.4	<.001[b]
MFC-H/D	0.55 ± 0.04	0.56 ± 0.05	0.55 ± 0.06	.734
MTPs, deg	4.3 ± 2.5	8.3 ± 4.6	11.7 ± 4.3	<.001[b]
MTPsublx, mm	0.41 ± 0.21	0.55 ± 0.20	0.74 ± 0.27	<.001[b]

Table 18: [a]Values are presented as mean 6 SD. ACL-R, anterior cruciate ligament reconstruction; LFC-H/D, lateral femoral condyle height/depth ratio; LTPs, lateral tibial plateau slope; LTPsublx, lateral tibial plateau subluxation; MFC-H/D, medial femoral condyle height/depth ratio; MTPs, medial tibial plateau slope; MTPsublx, medial tibial plateau subluxation. [b]P < .05.

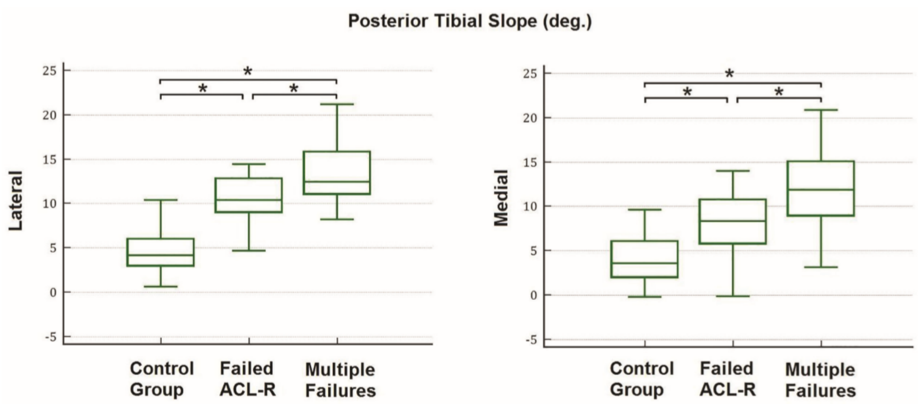

Figure 22: The multiple-failure group had significantly higher values of lateral (P<.001) and medial (P<.001) posterior tibial slope with respect to the control group and the failed ACL-R group. ACL-R, anterior cruciate ligament reconstruction. Values are presented as median, interquartile range, and 95% CI. *P < .05.

A similar finding was reported for the lateral femoral condyle height/depth ratio (P = .038) but not for the medial femoral condyle height/depth ratio (P = .734) (*Figure 23*). No significant correlation was found between tibial slope and condyle height/depth ratio for the medial and lateral compartments. The lateral tibial plateau slope and medial tibial plateau slope were similar between the patients who underwent meniscectomy at the time of primary ACL-R (n = 91) and revision ACL-R (n = 51). The same finding was reported for the lateral and medial femoral condyle height/depth ratios.

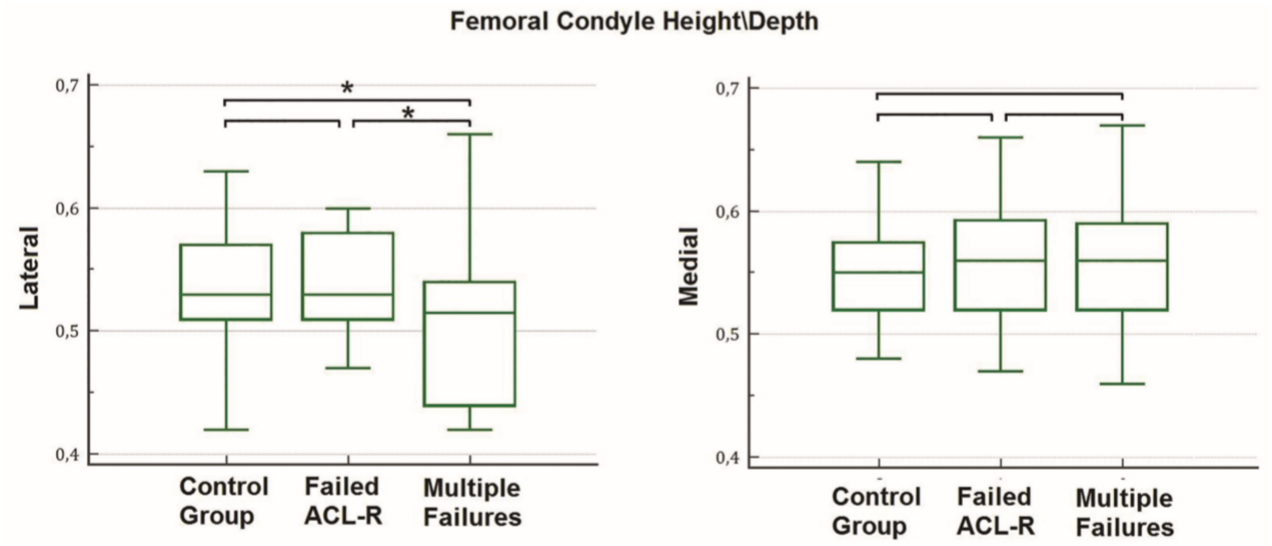

Table 23: The multiple-failure group had significantly higher values of lateral height and depth ratios (P = .038) but not medial (P = .734). ACL-R, anterior cruciate ligament reconstruction. Values are presented as median, interquartile range, and 95% CI. *P < .05.

Tibial Plateau Subluxation: The patients in the multiple-failure group had significantly higher values of lateral tibial plateau subluxation (P < .001) and medial tibial plateau subluxation (P< .001) with respect to the control group and the failed ACL-R group (*Figure 24*). Also, a significant direct correlation was found between posterior tibial slope and anterior tibial subluxation for the lateral (r = 0.325,P = .017) and medial (r = 0.421, P< .001) compartments (*Figure 25*). No correlation was present between subluxation and femoral anatomy. For the lateral and medial compartments, higher values of anterior subluxation were found among patients with a meniscal defect at the time of the MRI as compared with patients with an intact meniscus (*Table 19*). No differences were reported for all measurements between male and female patients or between patients aged <18 or >18 years at the time of primary ACL-R.

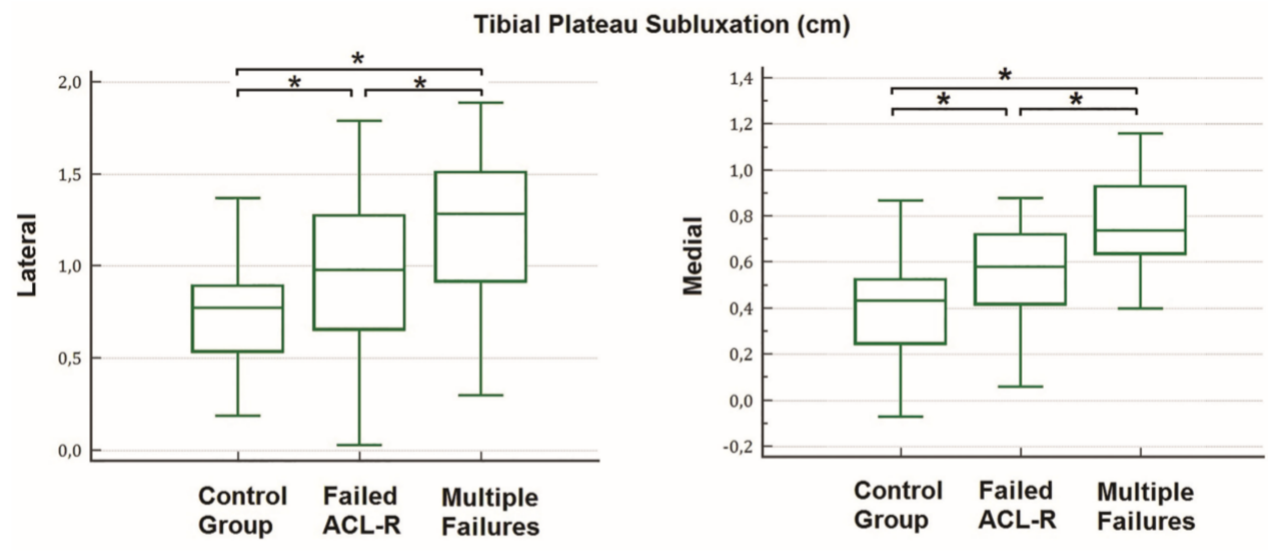

Figure 24: The multiple-failure group had significantly higher values of lateral (P\.001) and medial (P\.001) tibial plateau subluxation with respect to the control group and the failed ACL-R group. ACL-R, anterior cruciate ligament reconstruction. Values are presented as median, interquartile range, and 95% CI. *P \ .05.

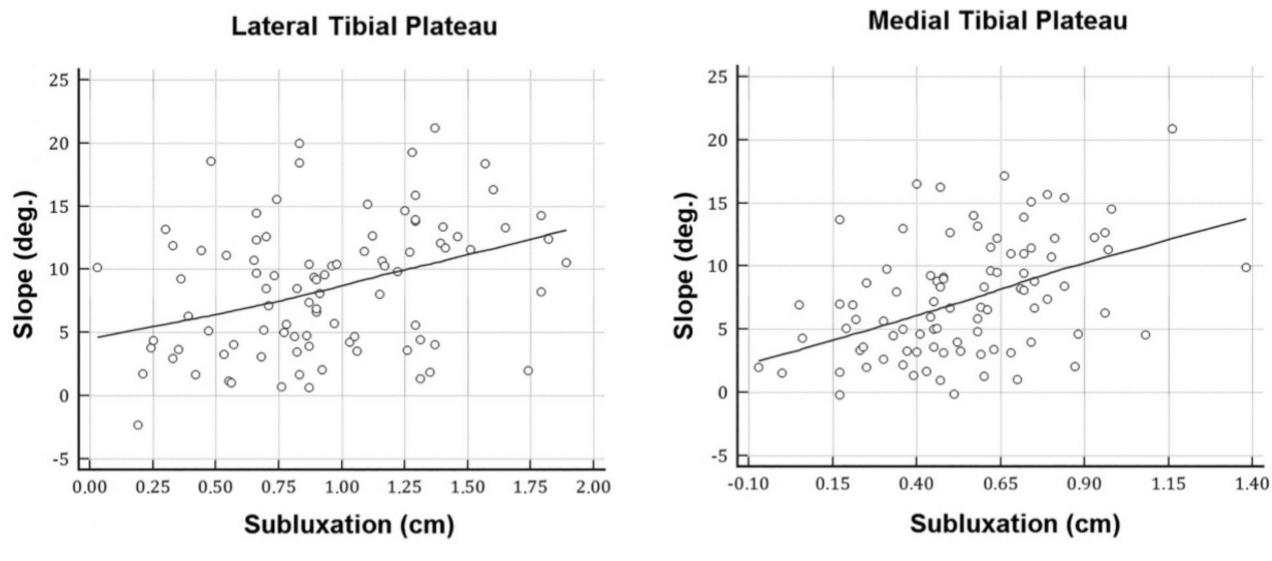

Figure 25: A significant direct correlation exists between posterior tibial slope and anterior tibial subluxation for the lateral (r = 0.325, P = .017) and medial (r = 0.421, P < .001) compartments

Tibial Subluxation Based on Meniscal Status at Time of Magnetic Resonance Imaging[a]

	Intact	Defect	P Value
Medial meniscus			<.001[b]
Control	40 (100)	0 (0)	
Failed ACL-R	19 (76)	6 (24)	
Multiple failure	9 (35)	17 (65)	
Total	68	23	
MTPsublx, mm	0.48 ± 0.23	0.74 ± 0.27	<.001[b]
Lateral meniscus			.001[b]
Control	40 (100)	0 (0)	
Failed ACL-R	17 (68)	8 (32)	
Multiple failure	22 (81)	4 (19)	
Total	79	12	
LTPsublx, mm	0.89 ± 0.40	1.23 ± 0.42	.008[b]

Table 19: [a]Values are presented as n (%) or mean 6 SD. ACL-R, anterior cruciate ligament reconstruction; LTPsublx, lateral tibial plateau subluxation; MTPsublx, medial tibial plateau subluxation. bP \ .05.

STUDY XI: THE ROLE OF TIBIAL SLOPE IN IPSI\CONTRALATERAL ACL INJURY

Patient Characteristics: Of the 90 patients included, 8 (9%) had Ipsilateral ACL Revision and 8 patients (9%) had Contralateral ACL Reconstruction within the first 2 years after indexed ACL Reconstruction. Considering that 1 patient (1%) underwent both Ipsilateral ACL Revision and Contralateral ACL reconstruction, a total of 15 patients (16%) had a 2nd ACL Reconstruction.

Radiographic measurements: All the Anterior, Central and Posterior TPS had normal distribution, and their mean values were 15.1°±9.9°, 9.4°±6.3° and 6.6°±3.3° respectively. There were no significant differences between males and females for the 3 slopes measures. A positive significant correlation was present between Anterior and Central TPS (r=0.7404, 95%CI 0.6340-0.8258; p<0.0001), Anterior and Posterior TPS (r=0.5031, 95%CI 0.3346-0.6405; p<0.0001) and Central and Posterior TPS (r=0.4553, 95%CI 0.2784-0.6024; p<0.0001). The Central TPS was significantly higher in patients with Contralateral ACL Reconstruction respect to those with no reinjuries (p=0.042) (*Figure 26, Table 20*).

Tibial Plateau Slope (TPS) values according to 2nd ACL Reconstructions

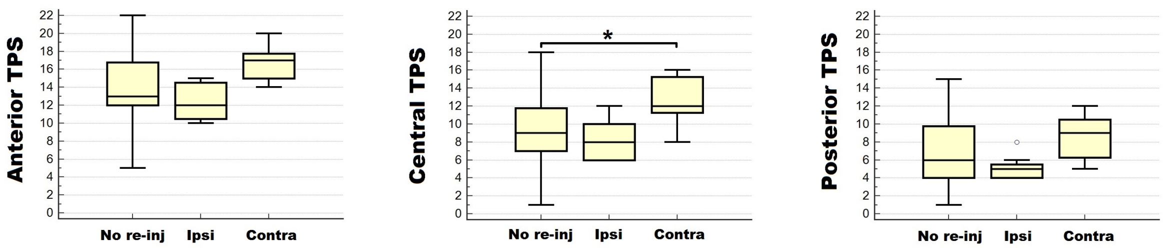

Figure 26: Comparison of the mean values of Anterior, Central and Posterior Tibial Plateau Slope according to the presence of no reinjuries, Ipsilateral ACL Revision or Contralateral ACL Reconstruction. TPS, Tibial Plateau Slope.

Comparison on Tibial Plateau Slope (TPS) mean values				
	No Reinjuries	**2nd ACL Reconstruction**		**p-value**
Anterior TPS	14.1 ± 3.5	14.3 ± 3.0		=0.7716
Central TPS	9.3 ± 3.7	10.3 ± 3.2		=0.3306
Posterior TPS	6.6 ± 3.4	6.7 ± 2.6		=0.9178
	No Reinjuries	**Ipsilateral ACL Revision**	**Contralateral ACL Reconstruction**	**p-value**
Anterior TPS	14.1 ± 3.5	12.6 ± 2.5	16.6 ± 2.1	=0.077
Central TPS	9.3 ± 3.7	8.3 ± 2.3	12.6 ± 2.8	=0.042*
Posterior TPS	6.6 ± 3.4	5.5 ± 1.7	8.4 ± 2.6	=0.223

Table 20: Comparison of the mean values of Anterior, Central and Posterior Tibial Plateau Slope according to the presence of no reinjuries, Ipsilateral ACL Revision, Contralateral ACL Reconstruction or both. TPS, Tibial Plateau Slope.

Receiving Operator Characteristic (ROC) curves for TPS measurements: No cut-off values of Anterior, Central and Posterior TPS were found for Ipsilateral ACL Revision and 2nd ACL Reconstruction, since all the AUC were not significant (>0.05). A significant AUC was found for the Anterior TPS (AUC=0.716, 95%CI 0.614-0.804; p=0.0009) regarding Contralateral ACL Reconstruction. The optimal cut-off for Anterior TPS was ≥14° (Youden's Index 0.5233), with a Sensitivity of 100% and Specificity of 52%. A significant AUC regarding Contralateral ACL Reconstruction was found for the Central TPS (AUC=0.758, 95%CI 0.659-0.840; p=0.0092) as well. The optimal cut-off for Central TPS was ≥12° (Youden's Index 0.3880), with a Sensitivity of 63% and Specificity of 75% (*Figure 27*).

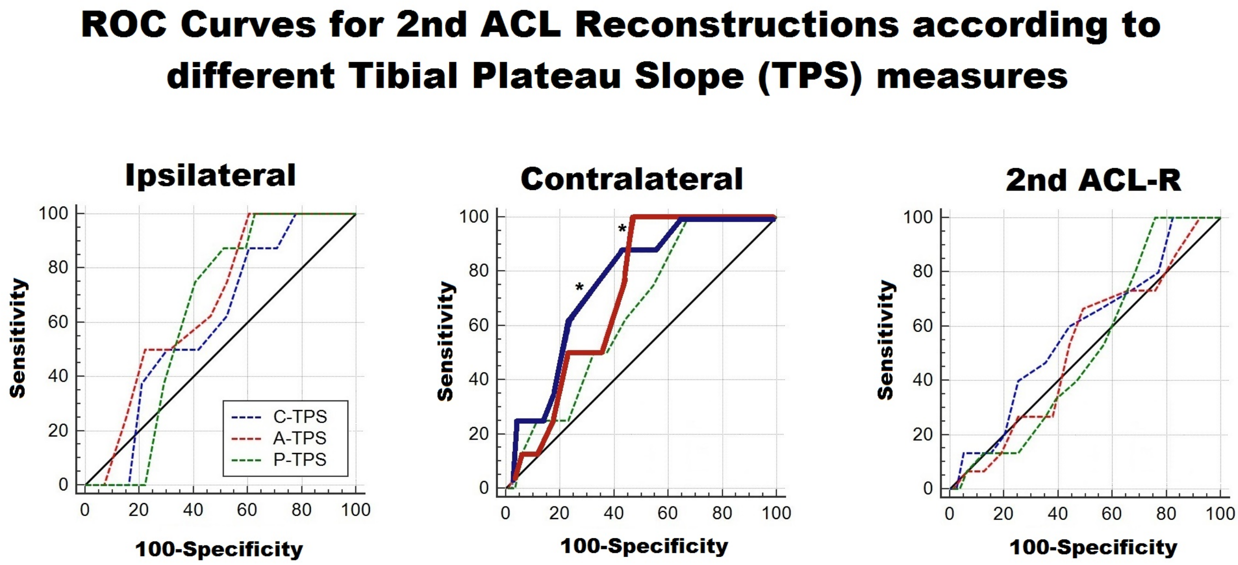

Figure 27: Receiving Operator Characteristic (ROC) curves for Ipsilateral ACL Revision, Contralateral ACL Reconstruction or 2nd ACL Reconstruction according to Anterior TPS (red line), Central TPS (blue line) and Posterior TPS (green line). Dotted lines have non-significant AUC. Asterisk and bold lines have significant AUC (TPS, Tibial Plateau Slope; AUC, Area Under Curve).

Analysis of 2nd ACL Reconstruction based on TPS cut-offs

A significantly higher rate of Contralateral ACL Reconstruction was present in patients with Anterior TPS ≥14° (16%) respect to those with values <14° (0%) (p=0.0151). A similar result was found for those with Central TPS ≥12° (19%) respect to those with values <12° (4%) (p=0.0420) (*Table 21*). The Kaplan-Meier curve for Contralateral ACL Reconstruction was significantly different between patients with Anterior TPS ≥12° and <12° (p=0.0049) and between patients with Central

TPS ≥12° and <12° (p=0.0189) (*Figure 28*). Logistic regression analysis identified preoperative Tegner Activity Level >7 as a risk factor for both Contralateral ACL Reconstruction and a 2nd ACL Reconstruction in all models. Moreover, Anterior TPS had an OR=1.3 (95%CI 1.1–1.7) of Contralateral ACL Reconstruction for every degree >14° (p=0.0354). Central TPS had a similar OR=1.3 (95%CI 1.1-1.7) for every degree >12° as well (*Table 22*).

Rates of 2nd ACL Reconstructions							
		Anterior TPS			Central TPS		
	Total (n=94)	<14° (n=45)	≥14° (n=49)	p-value	<12° (n=68)	≥12° (n=26)	p-value
Ipsilateral ACL Revision	8/94 (9%)	5/45 (11%)	3/49 (6%)	=0.6164	7/68 (10%)	1/26 (4%)	=0.6002
Contralateral ACL Reconstruction	8/94 (9%)	0/45 (0%)	8/49 (16%)	=0.0151*	3/68 (4%)	5/26 (19%)	=0.0420*
2nd ACL Reconstruction	15/94 (16%)	5/45 (11%)	10/49 (20%)	=0.3604	9/68 (13%)	6/26 (23%)	=0.3823

Table 21: Rates of Ipsilateral ACL Revision, Contralateral ACL Reconstruction or 2nd ACL Reconstruction according to the Tibial Plateau Slope (TPS) values.

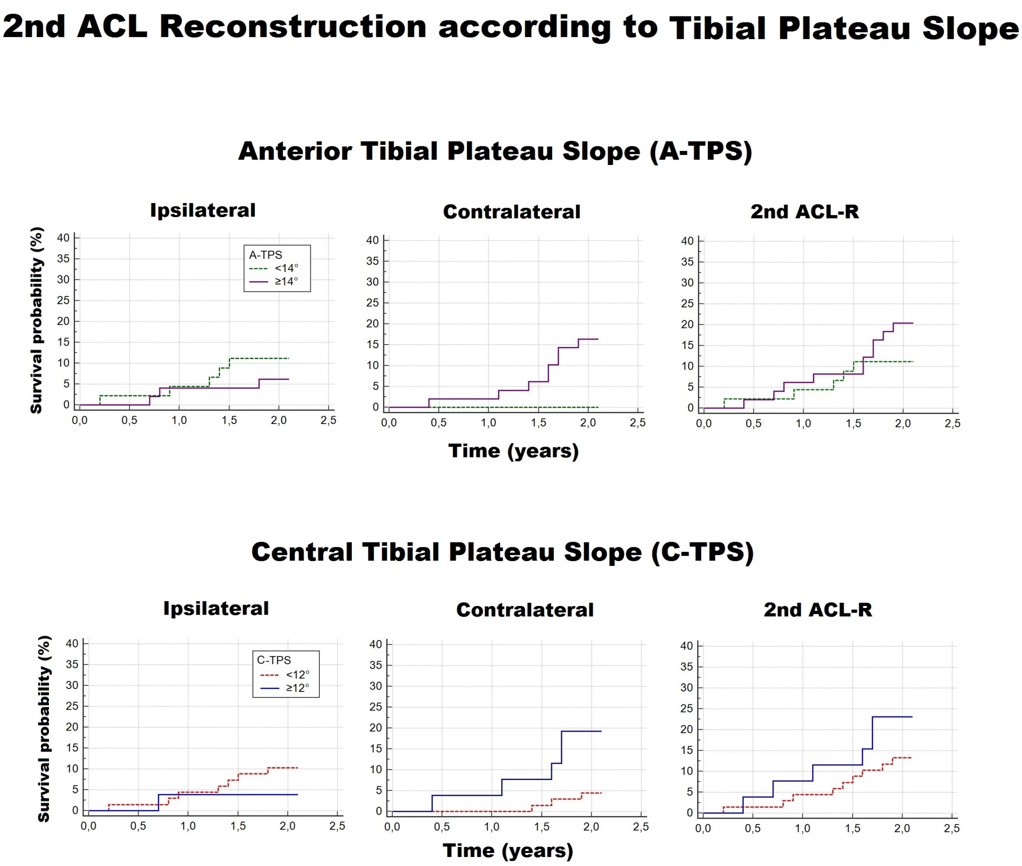

Figure 28: Kaplan-Meier curves for Ipsilateral ACL Revision, Contralateral ACL Reconstruction or 2nd ACL Reconstruction according to the Tibial Plateau Slope (TPS) values.

Logistic Regression Analysis for 2nd ACL Reconstructions							
		Ipsilateral ACL Revision		Contralateral ACL Reconstruction		2nd ACL Reconstruction	
	Variables	Odd Ratio (95%CI)	p-value	Odd Ratio (95%CI)	p-value	Odd Ratio (95%CI)	p-value
Anterior TPS	Slope	-	-	1.3 (1.1 - 1.7)	=0.0354	-	-
	Tegner	-	-	23.9 (2.7 - 222.7)	=0.0053	7.6 (2.2 - 26.5)	=0.0015
	Age	-	-	-	-	-	-
	Sex	-	-	-	-	-	-
	Overall model		n.s.		=0.0003		=0.0006
Central TPS	Slope	-	-	1.3 (1.1 - 1.7)	=0.0299	-	-
	Tegner	-	-	19.4 (2.1 - 177.6)	=0.0086	7.6 (2.2 - 26.5)	=0.0015
	Age	-	-	-	-	-	-
	Sex	-	-	-	-	-	-
	Overall model		n.s.		=0.0003		=0.0006
Posterior TPS	Slope	-	-	-	-	-	-
	Tegner	-	-	17.1 (2.0 - 146.1)	=0.0096	7.6 (2.2 - 26.5)	=0.0015
	Age	-	-	-	-	-	-
	Sex	-	-	-	-	-	-
	Overall model		n.s.		=0.0010		=0.0006

Table 22: Logistic regression analysis for Ipsilateral ACL Revision, Contralateral ACL Reconstruction or 2nd ACL Reconstruction. (TPS, Tibial Plateau Slope; 95%CI, 95% Confidence Intervals).

DISCUSSION

AIM 1: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF MENISCUS (STUDY I, II and III)

From the analysis of the literature on cadaveric models of laxity of combined meniscal and ACL injury, it emerges that the medial and lateral meniscus acts differently in providing secondary stability in ACL-deficient knee. The results indeed supported that the medial meniscus was more important than the lateral meniscus in restraining uniplanar anterior loads on the tibia. On the other hand, the results suggested that the lateral meniscus was a critical secondary stabilizer of the knee under combined rotatory load. All kinds of medial meniscal tear analyzed were associated with an increase of ATT. One important observation was the increase of ATT after progressive meniscal resection, with most significant effect when posterior horn was involved. Furthermore, the internal-external rotation in ACL-deficient knee was not influenced by medial meniscus resection with the interesting exception of the menisco-capsular lesion. The tears of the menisco-capsular junction of the medial meniscus (termed 'ramp' lesions), associated in 16%–24% of all anterior cruciate ligament lesions, represent a challenging topic for the orthopaedic surgeons and their role in ACL-deficient knee laxity is still unclear. In two different studies Stephen et al.[65] and DePhillipo et al.[66] reported a significant increase of internal and external tibial rotation after a simulated ramp lesion in ACL-deficient knee from 15° to 90° degrees of flexion. Moreover, in both these two studies a significant decrease of static rotatory laxity was reported after repair the simulated tear. Regarding the dynamic laxity evaluation after medial meniscus tear in only one study a significant increase was reported12: DePhillipo[66] and colleagues provided a significant increase in both ATT and tibial rotation under a coupled internal torque and valgus load after a simulated ramp lesion. Moreover, after performing a suture of the tear, the authors described a significant decrease in the meniscus-repaired status compared with meniscus sectioned status, suggesting that the suture of this kind of lesions associated with ACL-reconstruction would better restore the knee biomechanics compared with ACL reconstruction
alone.

In the studies that analyzed biomechanical role of lateral meniscus in ACL-deficient knee only a total meniscectomy or a posterior root tear was investigated. Posterior root tears of lateral meniscus are present in 8%–14% of patients with an ACL tear, and this type of lesion has been reported to have a similar effect on knee joint loading as a meniscectomy. Lateral meniscus posterior root tear and meniscectomy analyzed in this review resulted in a not significant increase of ATT in ACL-deficient knee specimen. On the other hand, lateral meniscus played a role of critical stabilizer in the ACL-deficient knee in both static and dynamic rotational laxity evaluation. In particular lateral meniscus root lesions are associated with an increase of internal tibial rotation, especially at high degrees of flexion (≥60°). One important observation is that in all studies which performed a dynamic laxity evaluation lateral meniscus root lesion or meniscectomy resulted in a significant increase of ATT under a simulated pivot-shift test. Therefore, the data provided in this systematic review suggested that lateral meniscus was a critical secondary stabilizer, and its root tear or resection increased dynamic laxity evaluated under a combined axial and rotatory load. Previous studies reported a significant correlation of the lateral meniscus and lateral compartment to the grading of the pivot shift[67-70]. Pivot shift test is accepted to be more closely correlated with the clinical symptoms of dynamic instability than static tests. The clinical relevance of these findings is that lateral meniscus, in association with ACL reconstruction, should be repaired and preserved whenever possible. The different effect of lateral meniscectomy and medial meniscectomy in the kinematics of ACL-deficient knee was confirmed when a coupled medial and lateral meniscectomy was performed. Static ATT increase in ACL-deficient knee with double meniscectomy was significant compared with single-meniscectomy status only when lateral meniscus was resected first. On the other hand, a significant increase of ATT under a complex rotatory and axial load of a pivoting maneuver was reported only when medial meniscus was resected first.

Therefore, medial meniscus -and in particular its posterior horn- is a critical secondary restraint to ATT during static laxity evaluation in the ACL-deficient knee, while the lateral meniscus is an important stabilizer of the knee under both isolated and combined rotatory loads and its tear or resection resulted in a significant increase of dynamic laxity in the ACL-deficient knee.

These results from cadaveric studies have been confirmed in-vivo for the first time using a navigation system in patients. In fact, we reported that AP translation before ACL reconstruction increased significantly in presence of partial medial meniscectomy and that dynamic laxity evaluated through the PS test, significantly increased in presence of lateral meniscectomy in terms of area included by the lateral tibial translation with respect to the flexion/extension angle. Surgical navigation is considered the standard for intraoperative in vivo kinematic assessment. Moreover, the strict inclusion criteria with patient selection among a pool of more than 200 navigated ACL reconstructions allowed determination of homogeneous groups of patients regarding pattern of meniscal lesions. These characteristics, which resemble one of the most frequent clinical scenarios of ACL injury and management, make the finding of the present study generalizable to everyday clinical practice and of value for clinicians involved in sports medicine. Regarding the effect of medial meniscus removal on AP laxity, several cadaveric studies have reported results that are consistent with those of the present study. Lorbach et al.[71], in an experimental setting of 18 human knee specimens with transected ACL, showed a significant increase of anterior tibial translation after partial medial meniscectomy with respect to the isolated ACL injury using a robotic testing system. Despite different settings and instruments, the values of 13.6 mm for isolated ACL sectioning and 15.4 mm for ACL and medial meniscectomy during the Lachman maneuver at 30° are consistent with the values of 11.1 and 15.8 mm, respectively, reported in the 2 groups of the present study. The present study confirms the relevant role of medial meniscal defect at higher degrees of flexion at 90° during the anterior drawer test as well, reporting consistent with previous cadaveric findings. Moreover, the value of 10.9 mm in the MM-ACL group can be considered consistent with the laxities of 11.7 and 11.4 mm reported in 2 different studies[71,72]. Based on the laxity assessment at different degrees of flexion, the anterior tibial displacement appeared greater at 30° during the Lachman test, while the difference between intact menisci and partial medial meniscectomy was similar at 30° and 90°. This can be explained considering the more relevant laxity produced by ACL transection at 30°[71] while the effect of meniscus removal could be considered consistent at both 30° and 90° and estimated between 3.8 and 4.7 mm. Few studies have investigated the combined effect of lateral meniscectomy and ACL deficiency in terms of knee laxity. Our findings are in line with the current knowledge that lateral meniscectomy influences dynamic instability, which is not however affected by the addition of medial meniscectomy. However, differently from our in-vivo work, cadaveric studies included an old specimen age and artificial meniscal lesion, making their setting quite far from daily clinical practice, where patients are usually young and present with different types of meniscal lesions and the meniscectomy performed aims to spare as much tissue as possible.

Despite the amount of research on the stabilizing role of the medial meniscus, only few cadaveric studies have investigated the effect of meniscal removal on the kinematics after ACL reconstruction. Bedi et al.[73] did not report significant differences in anterior tibial translation between the intact ACL and menisci condition with respect to both anatomic single-bundle ACL reconstruction and double-bundle ACL reconstruction plus bilateral meniscectomy. However, since the authors tested only the translation at 30° during the Lachman test, the results are consistent with those of the present study. Similar findings were also reported in a cadaveric model of the anatomic AM single-bundle technique and with different graft diameters, thus minimizing the role of tunnel placement and graft size. In contrast, Seon et al.[74] tested the effect of medial meniscectomy at different degrees of flexion, from 0° to 90°, reporting an increased anterior translation at all degrees of flexion after single-bundle ACL reconstruction and meniscus removal, with respect to the native intact knee. This slightly differs from the in vivo results of our study, where a significant difference was found only at 90° but not at 30°. This can be explained by the different setting, since Seon et al.[74], in their protocol, did not test the condition of ACL reconstruction with intact meniscus. Moreover, the subtotal meniscectomy performed in these models could be considered more extended than the partial meniscectomy performed in the patients enrolled in our study. Despite the amount of meniscectomy, Seon et al.[26] concluded that the effect of medial meniscectomy ‘‘was larger at higher flexion angle than lower flexion angle’’ after ACL reconstruction. This insight from their cadaveric study is confirmed by the data of the present in vivo evaluation, where in fact a significantly greater laxity was found only at 90° of flexion and, conversely, a greater laxity reduction after ACL reconstruction was found at 30°. Based on these findings, it could be concluded that partial medial meniscectomy increases preoperative laxity at low and high degrees of flexion, and single-bundle ACL reconstruction is effective in controlling anterior translation ‘‘overlooking’’ this increased laxity only at 30°. The long-term effect of the residual laxity derived from medial meniscectomy on the ACL and the overall knee joint remains unknown, even if an elegant dynamic stereoradiographic study by Akpinar et al.[75] showed an increased anterior tibial translation during downhill running even 24 months after ACL reconstruction in patients with medial meniscal lesion with respect to contralateral knee and isolated ACL reconstruction.

Differently, when ACL reconstruction was performed with a Single-Bundle and Lateral Plasty technique the postoperative AP laxity in patients with concomitant medial meniscectomy was comparable both at 30° and 90° of flexion to the one of patients with an intact medial meniscus.

Therefore, the addition of the lateral plasty compensated the negative effect of the medial meniscectomy on AP laxity at high degrees of knee flexion. The indication for the addition of a lateral plasty to ACL reconstruction has been recently drafted in a specific expert consensus statement[76]. The major criteria for this surgery are a high grade of knee laxity, patients' involvement in pivoting sports, and ACL revision surgery. In such situations, the lateral plasty is believed to provide better rotational control, thus reducing the strain on the neo-ACL graft. The present data demonstrated for the first time the effectiveness of a lateral plasty addition in reducing AP laxity in the context of a medial meniscectomy. Only one previous study[77] demonstrated that the addition of lateral plasty to a Single-Bundle reconstruction decreased the anterior translation or lateral tibial compartment; however, in the latter study the authors focused only on isolated ACL reconstructions. Given its indication in high-laxity scenarios, the addition of a lateral plasty could be an opportune treatment when a medial meniscectomy needs to be performed.

AIM 2: KNEE LAXITY BEFORE AND AFTER ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IV and V)

One of the most controversial and investigated anatomical features in relation to ACL injury and knee laxity is the posterior tibial slope. Through a multivariate analysis we found an inverse correlation between lateral posterior tibial slope and anteroposterior laxity both at 30° and 90° of flexion. Moreover, we were able to find 5.5° as a cut-off value to discern high or low laxity. Our finding that antero-posterior laxity decreases with a lateral posterior tibial slope >5.5° seems counterintuitive with respect to evidences reported in the literature. In fact, a correlation between increased antero-posterior tibial laxity and a steep posterior slope has been reported. The effect of posterior tibial slope in knee kinematics has been investigated in several cadaveric studies. Giffin et al.[78] reported a relative anterior shift of the tibial resting position of 3.6 mm when the posterior tibial slope was increased by almost five degrees with an anterior high tibial osteotomy (HTO). However, they did not report significant changes of anterior tibial displacement under an antero-posterior load of 134 N. The authors thus hypothesized an anterior shift of the entire "envelope". We believe that the decreased antero-posterior laxity of 2.4 mm in knees with higher lateral tibial slope found in our study could be due to this anterior shift. A more anterior resting position could have reduced the effective translation of the tibia from the starting position to the final endpoint when secondary restrains, such as menisci, play their role. Since our method of anteroposterior laxity quantification detected the tibial position relative to the centre of the femur before and after the application of a postero-anterior stress, it is possible that a pre-existing anterior displacement could have underestimated the overall laxity. Moreover, since Giffin et al.[78] measured the antero-posterior translation only in ACL-intact knees, it is not possible to know whether such an anterior shift of the tibial resting position will result in a decreased laxity when ACL is insufficient. Similarly, Agneskirchner et al.[79] reported an increased anterior shift of the resting tibial position of 4.43 mm after a posterior tibial slope increase of 10° with an anterior HTO also in an ACL-deficient model. However, the authors failed to evaluate the anterior translation under the application of an anteriorly directed stress. Voos et al.[80], who instead evaluated the antero-posterior displacement, did not report a significant correlation with the lateral posterior tibial slope when ACL was transected. However, they limited the anterior stress to 10 kg and evaluated the specimen with a mean lateral posterior tibial slope higher (9.0° ± 3.9°) than that of the present study (4.5 ± 2.79°). The same senior researcher[81] did not reported a significant difference in the Lachman test after increasing or decreasing the posterior tibial slope by five degrees through a navigation-controlled HTO; but they did not provide information regarding the magnitude of the initial and corrected slopes. Despite our speculations, we were not able to find a correlation between antero-posterior laxity and anterior translation of lateral compartment, probably because of the less evident anterior shift of the extended knee[79] in which the MRI measurement was performed. In another milestone paper of 1994, Dejour and Bonnin[82] reported a six-millimeter increase in antero-posterior laxity for every 10° of increased slope. However, these authors evaluated only the radiographic medial tibial slope and measured the anterior tibial translation with respect to the posterior femoral condyle during the axial load of the single-leg stance. Therefore, the different setting, the lack of lateral posterior tibial slope measurement, the simple measurement of anterior tibial translation with respect to a reference line without the evaluation of the "delta" difference between basal and anteriorly shifted position and the inclusion of meniscal-deficient patients could account for the different findings compared to our study. Finally, due to the inability of our method to detect how the anteriorly or posteriorly directed shift contributed to the whole antero-posterior laxity, it could also be possible that a steep posterior tibial slope would restrict posterior tibial translation, thus resulting in an overall laxity reduction. Despite these findings, decreasing-slope osteotomies for multiple-ACL failures suggested by some authors should not discouraged, since the strain on ACL (especially in meniscal-deficient patients) during loading activities and axial compression, rather than the mere antero-posterior laxity, could be responsible for the repeated failures. Based these data, solid indications for additional procedures to ACL reconstruction based exclusively on posterior tibial slope could not be formulated.

Regarding the PS test, it was found that only the TE influences its magnitude. Our hypothesis is that larger condyles could increase iliotibial band tension, altering the biomechanics of the PS maneuver and resulting in a decreased magnitude. However, because the difference in laxity between those higher or lower values with respect to the cut-off value of 8.7 cm was minimal (23.2 ± 3.8 vs. 20.5 ± 2.4), a real clinical implication could be questioned. Interestingly, the lateral posterior tibial slope did not seem to affect PS magnitude, similar to what was reported by Galano et al.[81] in a cadaveric model. Conversely, the lateral tibial slope has been demonstrated to affect PS magnitude in vivo. Both Song et al.[83] and Rahnemai-Azar[84], who evaluated the PS through manual examination and with an image analysis technique, respectively, however included higher percentages of patients with meniscal injury, which has been reported to increase the rotatory laxity, thus possibly biasing the evaluation. Moreover, since a correlation between a steep posterior tibial slope and meniscal lesions has been reported[83], it is possible that the inclusion of only patients with intact menisci in our study could have inadvertently selected a specific slope pattern.

When evaluating the PS based on an inconsistent anatomical characteristic such as the Lateral Notch Sign (LNS), a strong correlation with rotatory laxity in ACL injured patients is present. In fact, patients with a LNS >2 mm had a more accentuated Pivot-Shift respect to those with LNS <2 mm or without LNS. These findings are in contrast with the ones reported by Kanakamedala et al.[85], who also investigated the effect of the LNS on pivot-shift with inconsistent results. There are several differences between the two studies that could explain the different conclusions. Firstly, the number of cases analysed with MRI was 64 cases with 6 notches deeper than 2 mm, while in our study, we included 90 cases, and 10 of them had a deep LNS. It is, therefore, possible that we were able to identify significant differences thank to a larger cohort of patients and a higher number of deep notches. Besides, the PS was quantified with different tools: Kanakamedala et al.[85] used the triaxial accelerometer and tablet-based image analysis software, while in this study, the biomechanical analysis was carried out with the surgical navigation system. The latter tolls are considered the gold standard for intraoperative biomechanical quantification because it can overcome the buffering effect of the skin. Finally, they choose a different analysis setting performing a direct correlation between the notch depth and the amount of laxity. As already pointed out, only the patients with a notch deeper than 2mm present increased laxity; therefore, an analysis without this data stratification could not have given the same results. Furthermore, The ROC curve analysis identified 2 mm as the most predictive cutoff value for identify the “high grade rotatory instability” patients. In the specific, this cut-off value showed a very high specificity suggesting that, if a deep LNS is present, a high laxity is very probable. However, the low sensibility highlights that this test could not be used as a “screening” during the workup of ACL injured patients, probably because other factors needs to be taken into account and can be responsible for increased instability even if the LNS is absent.

The pivot shift is a multifactorial phenomenon and different bony morphological variations, as well as soft-tissue lesions, like lateral meniscal tears (see previous results), influence its magnitude. Many studies were focused on physiological osseous variations while little is known about pathological and incontinent bony lesions that, such as the Segond fracture, may entail a complex pattern of instability. The association between LNS and increased rotatory instability is not easy to interpret and could be explained by different hypotheses. First of all, since it is known that ligaments fail by a progressive and sequential mechanism of collagen fibril failure, it is conceivable that there could be some differences in the ACL injury patterns, such as during multiligament injuries. A low-grade injury could result in somewhat isolated ACL tears, while a high-grade energy injury may involve ACL tears, a consequent bony impression on the lateral femoral condyle, and involvement of secondary rotatory stabilizers. Moreover, the injury mechanism responsible for the LNS could be directly associated with tears of the anterolateral capsule. Finally, it is also likely, that the LNS could directly impair the knee kinematics with a mechanism of bone engagement as already hypothesized by Galway and MacIntosh[86].

It is essential to point out that these findings could be easily translated into the clinical setting because the assessment of the LNS was performed using MRI images, which are mandatory when managing patients with an ACL injury, and the possibility to identify at least some of the patients that are at high risk of increased laxity would be useful in order to set patients expectation and possibly modify the surgical planning in order to reduce the risk of failure. In fact, in a recent consensus paper, the role of the LNS on anterolateral instability has been reconsidered, and it was included as a secondary criterion for the decision to perform an additional lateral extra-articular tenodesis (LET)[76]. To this regard, Getgood et al.[87] demonstrated that the addition of a LET to the intra-articular ACL-reconstruction reduce from 40% to 25% the incidence of persistent rotatory instability and from 11% to 4% the graft failure in high-risk patients with high Pivot-Shift. In a similar cohort, Sonnery-Cottet et al. reported a failure reduction with LET procedure of 2.5 times compared to B-PT-B grafts and 3.1 times concerning quadrupled hamstring graft[88].

Thus, osseous anatomy in the ACL-deficient knee has a limited effect in determining static and dynamic laxities when both menisci are intact, while the LNS could be considered a reliable radiological sign that could be used to identify patients with a high risk of increased rotatory instability and to better define the surgical planning.

AIM 3: OUTCOMES AND FAILURES OF ACL RECONSTRUCTIONS - THE ROLE OF MENISCUS (STUDY VI, VII and VIII)

Despite outcomes of ACL reconstruction have been reported to be influenced by the surgical technique, no group differences were found in terms of laxity reduction or PRO according to our data. Differently, patients who underwent medial meniscectomy presented a significantly higher AP 30 compared to isolated ACL group. This finding is in line with the literature: the critical role of medial meniscus in restraining uniplanar anterior load in the ACL-deficient knee was underlined in previous cadaveric studies, with the most significant effect when the posterior horn was involved. Dejour et al. analysed a clinical series of ACL-injured knee and reported a significantly higher AP at 20° of flexion measured on stress radiographs in patients with medial meniscal lesion[89]. Furthermore, a significantly lower pain score was found in patients who underwent lateral meniscectomy compared with patients who underwent isolated ACL reconstruction or associated meniscal repair.

Differently, medial meniscus repair with all-inside sutures exhibited a significant increase of subjective scores since the 4th month after surgery, and the profile of scores improvement was similar to isolate ACL reconstruction with intact menisci. This is relevant because, at the pre-operative status, patient with meniscal lesion amenable for repair presented significantly higher pain and lower performances in daily life activities according to the PASS thresholds. Therefore, it could be affirmed that meniscal repair was able to minimize the clinical consequences of meniscal injury in the setting of ACL reconstruction. This was further confirmed by the presence of a significant improvement of KOOS Symptoms subscale at 18-month follow-up, which was not instead detected after isolated ACL reconstruction. The KOOS mean values in the present series can be considered comparable to the KOOS reference values after ACL reconstruction and to similar series of ACL reconstructions.

Another important aspect emerged from the current data is the healing rate of meniscal repair with the all-inside Ultra FasT-Fix device; in fact, the rates of complete (48%), incomplete (38%) or no healing (14%) were is similar to the distribution reported by Willinger et al.[60] (56%, 35% and 9%, respectively). These data further confirm the healing capacity of meniscal repair with the all-inside suture, which exhibit a complete lack of healing at MRI only in a limited number of cases. Interestingly, comparing clinical scores stratified for MRI healing did not produced significant findings, suggesting that the main method to assess the success of meniscal repair remains the clinical evaluation, with MRI reserved only for possible complications. However, it should be acknowledged that, due to the small sample size and an exiguous number of not-healed repair (3), it was possible to compare only patients with complete healing to patients with incomplete or no healing, thus possibly missing the real clinical effect of MRI complete lack of healing. In fact, 1 of the 3 patients with no healing worsened his symptoms after the completion of the study and required a partial meniscectomy 42 months after the repair. Considering this single case, the effective short-term failure of meniscal repair with the all-inside suture was 5%, thus lower respect to the 17-19% reported with other techniques and devices[90]. Without minimizing this promising data, it should be acknowledged that all patients evaluated underwent also concomitant ACL reconstruction -which is a known positive prognostic factor for ACL repair-, all repairs were performed less than 12 months after trauma except of 2 cases, and that complex or bucket handle tears were excluded because of the original study protocol. All those reasons could be responsible of the brilliant results obtained in terms of reoperations. A special mention should be reserved for the presence of perimeniscal cysts, that were noted in 33% of cases. This value is surprisingly similar to the nearly one third reported in other studies. However, the clinical relevance of cyst presence could be questioned, since no meaningful differences between patients with or without cysts were found, except of the KOOS Qol subscale. Despite significant from a statistical and clinical point of view, the lower KOOS Qol subscale could be considered marginal in young patients with ACL reconstruction and meniscal injury, compared to other subscales such as Sport or Pain. These data explore for the first time the clinical effect of perimeniscal cysts in comparison of intact meniscus, despite the results could be underpowered due to the small sample size. Therefore, meniscal repair with the all-inside sutures have been proved being able to produce good short-term results when performed in combination to ACL reconstruction, similar isolate ACL reconstruction with intact menisci, and to reach full or partial healing at MRI was present in 84% of cases while requiring partial meniscectomy for a re-tear in 5% of cases.

The long-term role of meniscal injuries (treated with repair or removal) was investigated as well as a follow-up of 10 years. Due to the small number of failures of ACL reconstruction, it was not possible to detect any significant predictor of ACL revision. However, when we considered both revisions (3.0%) and new meniscectomies (3.7%), a higher risk was found, apart from patients with a high level of sport activity, also in patients who had a medial meniscus injury at time of the originary ACL reconstruction. This finding supports what reported by Parkinson et al.[91] which found a higher risk of ACL failure in patients with medial meniscus deficiency. From a biomechanical point of view, medial meniscus removal generates a post-operative laxity during static and dynamic tasks, which could be deleterious for the ACL graft survival. Of note, a similar effect was suggested after meniscal repair as well[75]. Another method to assess the success of ACL reconstruction is the analysis of PROMs. However, meniscal injury was not found to be a significant predictor of worst PROMs, differently from female sex and chondropaty ≥II, which affected the Lysholm and the KOOS scores.

Summarizing, meniscal lesions represent important concomitant injury to the ACL rupture, which could affect both short-term results in the case of lateral lesion, and long-term results in the case of medial lesion. Repair is considered an effective treatment with excellent short-term results, good healing rate and minimal complications, even the results at long-term should be confirmed.

AIM 4: OUTCOMES AND FAILURES OF ACL RECONSTRUCTION - THE ROLE OF ANATOMY (STUDY IX, X and XI)

The study of osseous anatomy and risk of ACL failure or contralateral ACL injury completes what previously suggested in previous studies. In fact, Christensen et al.[62] in an MRI study with a design and protocol similar to the one employed in this thesis, were able to report a significant difference in the LTPs values between failed ACL and the control group only for female patients but not for male patients. In contrast, our results demonstrated a significant difference of LPTs in females as well as males, thus extending the deleterious effect of tibial slope to both sexes.

According to the ROC analysis, LPTs, a cutoff value of 7.4° for the Lateral Tibial Plateau Slope was identified as having a sensitivity of 88% and specificity of 84%. The high value of sensitivity indicates a low chance of a false negative and thus a limited number of patients with LPTs <7.4° experiencing ACL failure. This finding highlights the detrimental effect of a steep posterior tibial slope in the outcomes of ACL-R and graft failure. However, that the sensitivity value does not reach 100% leaves room for graft failure even in cases of more physiological slope values. In fact, other conditions such as varus malalignment, meniscal deficiency, anterolateral ligament or capsule injury or hyperlaxity have been suggested to potentially have a role in the failure of primary ACL-R. Similarly, the slightly lower value of specificity indicates the possibility of a false positive and thus the presence of patients with a Lateral Tibial Plateau Slope >7.4° and no ACL failure. This result highlights the LPTs as a nonperfect predictor of failure, underlining the complexity of failure mechanisms.

Moreover it further strengthens what has been reported in several biomechanical and clinical studies. In fact, a steep tibial slope has been associated with a risk of native ACL injury due to increased force and strain in the ligament during axial compression. Cadaveric and computational studies demonstrated that axial-loading tasks such as walking, squatting, and jump landing produced a vertical shear force through the tibiofemoral joint, which is converted to a slope-related anteriorly directed tibial translational force that overloads the ACL, possibly increasing the risk of injury. Despite extensive literature on the role of posterior tibial slope in ACL injury, only a few prospective series from the same Australian group[92-94] investigated its role in ACL-R failure. Webb et al.,[94] in a series of 200 ACL-Rs, reported that 59% of patients with a radiographic posterior tibial slope >12° experienced a rupture of ACL graft or an injury of the contralateral ligament, with an odds ratio of 5.2. The same authors[93] reported a 20-year ACL-R survival rate of 62% in patients with a posterior tibial slope >12° compared with 84% for patients with a value <12° and identified a further steeper posterior tibial slope in those with more than 3 ACL injuries[92]. Considering this background, it is relevant how 2 recent studies were able to demonstrate good results when combining a closing-wedge anterior high tibial osteotomy with ACL revision to treat multiple ACL-R failures in the absence of technical errors and with a radiographic slope >12°[95,96]. Sonnery-Cottet et al.[96] reported 5 cases of rerevisions, where a slope correction from 13.6° to 9.2° combined with ACL revision allowed sport activity resumption, even at a competitive level at 3 years of follow-up without further failures. Similarly, Dejour et al.[95] reported good results and no failure at 4 years of follow-up in 9 cases after combined posterior slope correction from 13.2° to 4.4° and ACL rerevision. Another important finding of the present study was the significantly higher anterior subluxation of the tibial plateau in cases of failed ACL-R with respect to the control group of primary ACL injuries. The 3-mm difference was similar to that reported by Tanaka et al.,[17] which compared the MRI of 16 patients undergoing revision ACL-R with those of 63 patients with primary injury. They imputed a mechanical explanation to the fixed anterior subluxation of the lateral compartment based on the suboptimal clinical results after revision ACL-R. Since we were not able to compare MRIs of the same patients at the time of primary and revision reconstruction, we can not affirm whether the subluxation is stable over time or whether it is related to the patient's inherent anatomy or to repeated ligament injuries. However, our findings confirm in a larger sample what was previously reported, thus delineating a possible area for further studies. The impact of medial femoral condylar width (MFCw) should be confirmed as well, since this feature has never been associated with a higher risk of ACL failure or increased laxity. However, a difference lower than 2 mm considering an average MFCw between 25 and 30 mm could be considered clinically and biomechanically irrelevant, as are the TE, LTPw, and MTPw. Other parameters such as notch width and shape of femoral condyles were similar between the failed and control group and thus did not confirm what has been reported for knee laxity and risk of primary ACL injury.

Differently, when comparing patients with a single failure of ACL reconstruction to patients with multiple failures, significant differences were found regarding the shape of lateral femoral condyle. In fact, a significantly lower ratio between height and depth has been reported for patients with multiple failures as compared with all other patients. In practical terms, a lateral femoral condyle with an increased depth with respect to its height could be associated with recurrence of ACL failure. This seems to support what was recently reported by Pfeiffer et al.[98], who measured a similar ratio on lateral radiographs. The authors found a higher depth of the femoral condyle among patients with bilateral ACL injury as compared to patients having unilateral ACL-R. As in the present study, the authors failed to demonstrate a difference between patients with primary and revision ACL-R; therefore, we could argue that lateral condyle anatomy could be a secondary risk factor for ACL-R failure, especially for multiple episodes. As suggested by Pfeiffer et al.[98], the detrimental effect could be due to an altered tibiofemoral interaction responsible for altered gait and loading mechanics and also to increased length and anisometry of anterolateral structures.

Regarding posterior tibial slope, a progressive increase is instead reported from patients with no ACL failure, single ACL failure and multiple ACL failures, thus suggests a sort of ‘‘gradient’’ of the slope effect. A possible clinical implication could be represented by extending the indication of slope-correcting high tibial osteotomy for those patients with multiple failures of ACL-R and an increased posterior tibial slope, as suggested by Sonnery-Cottet et al and Dejour et al.[95,96], although the slope cutoff and the amount of correction should be addressed in further studies. A similar “gradient-like” behavior was noted also for the anterior tibial subluxation. This aspect requires an important clarification: its measurement is not supposed to be static over time (ie, different from bony anatomy). Therefore, it exclusively represents the situation at the time of MRI execution, possibly resulting from the influence of the number of ACL injuries or meniscal status, as suggested by McDonald et al.[99] Those authors, with the same MRI measurement protocol of the present study, demonstrated a 2-mm increase of medial and lateral tibial plateau anterior subluxation among patients with ACL failure as compared with first-episode ACL injury, which is surprisingly consistent with the 1.4- to 2.0-mm increase of our data. Moreover, we were able to demonstrate a further 1.9- to 2.4-mm increase among patients with multiple failures, thus suggesting tibial subluxation as an indirect measure of injury severity or even timing of ACL injury. In fact, since McDonald et al.[99] reported greater subluxation in knees with chronic versus acute ACL ruptures, we are not able to discern if the exaggerated anterior subluxation reported in patients with multiple failures represents an inherent anatomic characteristic, if it is caused by multiple injuries, or if it is caused by a longer time since initial ACL injury. To elucidate this, further studies should be performed with repeated MRI measurements at different time points and possibly in weightbearing status.

Finally, the role of meniscal injuries in ACL reconstruction failure represents a controversial issue. Although medial or lateral meniscal deficiency during primary ACL-R was suggested as a risk factor for failure, no difference in meniscal removal at the time of primary reconstruction was present among the 3 groups of this study. No differences of slope or condyle anatomy were noted per meniscal status, either. However, a higher anterior tibial subluxation was present among patients with a meniscal defect, independent from the number of ACL reconstructions.

When trying to understand the anatomy of knees with multiple ACL failures, all these findings should not be considered singularly. In fact, a direct correlation was found between posterior tibial slope and anterior subluxation, as well as greater subluxation among patients with a lack of medial or lateral meniscus. Therefore, we believe that inherent knee anatomy could have a role in the failure, especially multiple failures, of ACL-R. Also, since the rate of meniscal injuries was not different among the 3 groups at the time of primary ACL-R, these data can be interpreted to suggest that patients suffering from multiple ACL injuries are incurring further meniscal damage. This would result in an anterior tibial subluxation and in increased risk of ACL failure. In fact, cadaveric and in vivo studies demonstrated an increased tibial anterior displacement and an increased ACL strain in the case of medial meniscal loss. On the basis of these findings, we could suggest the worst-case scenario for ACL-R, as represented by steep posterior tibial slope, increased anterior tibial subluxation, high depth of lateral femoral condyle, and meniscal deficiency. For these reasons, it is possible that surgical procedures aimed at correcting tibiofemoral anatomy or replacement of the meniscal defect could play a role in the management of knees with multiple ACL failures.

When investigating the role of Posterior Tibial Slope on ACL reconstruction plus lateral plasty in adolescents with less than 18 years of age, the amount of the posterior tibial slope measured radiographically was not able to predict the risk of failure. The latter finding seem to contradict the multitude of studies that highlighted Posterior Tibial slope as risk factor for ACL reconstruction failure in adults and with what reported by Salmon et al.[99], which reported the highest incidence of ACL graft re-ruptures in young patients with steep Tibial Plateau Slops. However, several important aspects should be considered. The present study evaluated only patients that underwent combined ACL reconstruction and lateral plasty. This technical detail could be responsible of the 9% failure rate at 2-year follow-up, which is lower respect to the 15-18% reported at the same follow-up in similar populations where isolated ACL reconstruction was performed[100]. Considering the similar rates of failures independently from the magnitude of PTS reported in this study, it is possible that lateral plasty could mitigate the negative biomechanical and clinical effects of PTS. However, further studies comparing ACL and lateral plasty to isolated ACL in patients with steep posterior slope should be performed to confirm this finding.

The posterior tibial slope has been investigated on the context of contralateral ACL injury as well. The present data show a higher risk of contralateral ACL injuries in patients with steep posterior tibial slope during the first two years after surgery. First of all, the overall 9% rate of contralateral injuries at 2-year follow-up was similar to the 8-8.7% reported in other studies evaluating adolescent populations[93,101], thus confirming the dimension of the problem. However, according to the cut-offs of PTS identified through the ROC analysis, a contralateral injury rate of 19% was found in patients with Central TPS ≥12°, respect to a rate of 4% reported in those with a lower TPS. This represents an important aspect from a methodological point of view as well, because the optimal cut-off was identified through an accurate statistical analysis which confirmed the value of 12° already suggested empirically by several authors[94]. Differently, while using the anterior tibial cortex as reference, a 2-degree higher value was found, which is consistent with studies performed comparing different PTS measurement methods. The high risk of contralateral injuries found also with Anterior TPS ≥14° confirms that the detrimental role of TPS is independent from the measurement technique. In fact, the survivorship evaluation and the multivariate analysis corrected for variables such as sex, age and sport level -well known risk factor for ACL re-injuries. The ROC analysis, beside from identifying an optimal cut-off for high- and low-risk patients, provided a sensitivity and specificity to predict contralateral ACL injury. Specifically, Anterior TPS ≥14° presented the highest performance (Youden's Index 0.5233) in identifying the event, with a Sensitivity of 100% and a specificity of 52%. From a practical and theoretical point of view, this result would indicate that applying an adequate preventive measure in patients with Anterior TPS ≥14°, such as preventing return to sport, all contralateral ACL injuries would be avoided, since none occurred in patients with values <14°. However, due to the low specificity, near half of patients would abandon sport career despite having a low risk of reinjury. Similarly, Central TPS had a significant but sub-optimal sensitivity of 63% and specificity of 75%. Therefore, further studies should be performed to confirm the validity of TPS measurements, and the cost-effectiveness of preventive approaches based on the identified cut-offs.

LIMITATIONS AND FUTURE PERSPECTIVES

The main limitations of this thesis are related to the patient populations and the methodologies used. In the systematic review of cadaveric works with combined ACL injury and meniscal defects, heterogeneous loads were applied, and different degrees of flexion were used during the tests for laxity evaluation. Moreover, not homogeneous cutting sequence and surgical procedure on the knee specimen was performed in distinct studies. Finally, some of the studies included used a low number of knee cadaveric specimens. Thus, further studies with standardized load and flexion angle are needed, especially evaluating the more complex and recent types of meniscal lesions, in order to better understand the biomechanical consequences of their presence.

The main limitation of the clinical and experimental studies was the limited sample sizes and the super-selection of patient with an incomplete spectrum of kinematic or laxity variables, caused by the application of strict inclusion criteria aimed to identify homogeneous patient populations. However, each study had a specific purpose and thus the maximal efforts were put to exclude most of the confounding factors applying highly selective criteria.

Regarding the analysis of intraoperative kinematic data obtained with the surgical navigation, there are several limitations that depend from both the technology used and the surgical setting. In fact, the complex setting and inclusion criteria allowed to include a limited number of patients, especially for ACL reconstruction plus lateral meniscectomy, or with deep Lateral Notch Sign. Therefore, it was not possible to confirm post-operatively the detrimental biomechanical effect of these conditions. Further studies should be focused on the postoperative PS kinematic assessment in the presence of partial lateral meniscectomy and deep Lateral Notch Sign. A further limitation is represented by the lack of standardization of partial meniscectomy. However, on one hand, it is impossible and unethical to standardize meniscetomies in actual patients for study purposes; therefore, disparities in the amount of meniscal tissue removed could be present within patients. On the other hand, after applying gross exclusion criteria, the partial meniscectomies performed in the present study represent a quite homogeneous group, resembling the real clinical scenario, which should be considered even more realistic than cadaveric in vitro studies.

Regarding the use of intraoperative navigation, with respect to cadaveric studies, it was not possible to assess the lack of contralateral knee laxity evaluation due to ethical reasons, and laxity evaluation was performed manually rather than with mechanical devices and standardized forces.

In the future, non-invasive devices with the application of standardized loads could help extend the biomechanical knowledge on laxity genesis.

When assessing the joint anatomy with MRI and radiographs, specific anatomical patterns could have been inadvertently selected based on inclusion\exclusion criteria, such as in the case of meniscal injuries. Moreover, the technical execution of radiologic exams, despite accurately selected based on their quality, could vary among patients, thus possibly biasing the parameters measured. Also, parameters were measured on 2-dimensions and this could not give the perfect estimations of their amount, while some other aspects, such as meniscal healing, were assessed "qualitatively" by an examiner. In this cases, future studies should be directed to utilize reliable parameters or 3D computerized measurements to confirm these findings.

In the case of follow-up MRI evaluation, as for meniscal repair, the short-term follow-up of 18-month does not allow to investigate the stepwise healing course nor the long-term effects, which should be analyzed in further studies with longer follow-up.

CONCLUSIONS

Based on the findings reported in the 11 studies according to the initial 4 aims of the thesis, the following statements and recommendations could be formulated, summarizing the main findings:

- High antero-posterior laxity after ACL injury could indicate a medial meniscus lesion or defect;
- 1-2 mm of residual antero-posterior laxity at 90° could be present after Anatomic Single-Bundle ACL reconstruction and concurrent partial medial meniscectomy;
- Lateral plasty with ACL reconstruction could better control antero-posterior laxity in the case of concurrent partial medial meniscectomy, and could be indicated in such cases;
- In the injured ACL, partial defects of the lateral meniscus are associated with increased Pivot-Shift, thus lateral plasty could be indicated in the case of partial lateral meniscectomy with the aim to better control rotatory laxity;
- In the injured ACL, the Lateral Notch Sign is associated with an increased Pivot-Shift, thus lateral plasty could be indicated in the case of Lateral Notch Sign, especially if >2 mm, trying to better control rotatory laxity;
- Lateral meniscectomy could have detrimental short-term clinical outcomes after ACL reconstruction, thus lateral meniscus should be preserved as much as possible;
- Medial meniscectomy does not have a relevant influence on short-term outcomes after ACL reconstruction, while at long term it could increase the risk of reoperation for new ACL or meniscal injuries;
- Medial meniscus repair with ACL reconstruction could provide comparable outcomes with ACL reconstruction and intact menisci, and presents an high healing rate;
- Osseous anatomy does not have a relevant role in pre-operative laxity of knees with injured ACL;
- Patients with high posterior tibial slope (>7.4° at MRI or >12° at radiographs) could be at high risk of repeated ACL injury, either ACL reconstruction failure or contralateral ACL injury.

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DISCUSSION

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LIST OF PAPERS

STUDY I:
<u>Grassi A</u>, Dal Fabbro G, Di Paolo S,Stefanelli F, Macchiarola L, Lucidi GA, Zaffagnini S
"Medial and lateral meniscus have a different role in kinematics of the ACL-deficient knee: a systematic review".
Journal of ISAKOS: Joint Disorders & Orthopaedic Sports Medicine 2019;4:233-241.

STUDY II:
<u>Grassi A</u>, Di Paolo S, Lucidi GA, Macchiarola L, Raggi F, Zaffagnini S.
"The Contribution of Partial Meniscectomy to Preoperative Laxity and Laxity After Anatomic Single-Bundle Anterior Cruciate Ligament Reconstruction: In Vivo Kinematics With Navigation."
Am J Sports Med. 2019;47(13):3203-3211. doi:10.1177/0363546519876648

STUDY III:
Di Paolo S, **<u>Grassi A</u>**, Pizza N, Lucidi GA, Zaffagnini S. et al.
"Anterior Cruciate Ligament (ACL) Reconstruction with Lateral Plasty Restores Anterior-Posterior Laxity in the Case of Concurrent Partial Medial Meniscectomy"
Submitted to Arthroscopy

STUDY IV:
<u>Grassi A</u>, Signorelli C, Urrizola F, Raggi F, Macchiarola L, Bonanzinga T, Zaffagnini S.
"*Anatomical features of tibia and femur: Influence on laxity in the anterior cruciate ligament deficient knee.*"
Knee. 2018 Aug;25(4):577-587. doi: 10.1016/j.knee.2018.03.017.

STUDY V:
Lucidi GA**, <u>Grassi A</u>**, Di Paolo S, Zaffagnini S, et al.
"The Lateral Femoral Notch Sign could identify patients with increased rotatory instability after ACL-injury. Intraoperative evaluation using the surgical navigation system"
Am J Sports Med (in printing)

STUDY VI:
<u>Grassi A</u>, Di Paolo S, Dal Fabbro G, Eroglu ON, Macchiarola L, Lucidi GA, Zaffagnini S
"Influence of Surgical Techniques and Meniscus Status in Anterior Cruciate Ligament Reconstruction: Laxity Assessment and Subjective Outcomes at Minimum-Two-Years Follow-Up"
Submitted to Journal of Knee Surgery

STUDY VII:

<u>Grassi A</u>, Macchiarola L, Lucidi GA, Dal Fabbro G, Cucurnia I, Lopomo N, Filardo G, Zaffagnini S.
"Clinical Outcomes, Healing Rate and Presence of Perimeniscal Cysts after All-Inside Meniscal Repair in Combination With Anterior Cruciate Ligament (ACL) Reconstruction: A Prospective Case-Control study with MRI Assessment"
Submitted to Eureopean Journal of Radiology

STUDY VIII:

<u>Grassi A</u>, Macchiarola L, Lucidi GA, Silvestri A, Dal Fabbro G, Marcacci M, Zaffagnini S.
"Ten-year Survivorship, Patient-Reported Outcome Measures (PROMs) and Patient Acceptable Symptoms State (PASS) After Over-the Top Hamstring ACL Reconstruction with a Lateral Extra-articular Reconstruction: Analysis of 267 Consecutive Cases."
Am J Sports Med (in printing)

STUDY IX:

<u>Grassi A</u>, Signorelli C, Urrizola F, Macchiarola L, Raggi F, Mosca M, Samuelsson K, Zaffagnini S.
"*Patients With Failed Anterior Cruciate Ligament Reconstruction Have an Increased Posterior Lateral Tibial Plateau Slope: A Case-Controlled Study".* Arthroscopy. 2019 Apr;35(4):1172-1182. doi: 10.1016/j.arthro.2018.11.049. Epub 2019 Mar 14.

STUDY X:

<u>Grassi A</u>, Macchiarola L, Urrizola Barrientos F, Zicaro JP, Costa Paz M, Adravanti P, Dini F, Zaffagnini S.
"*Steep Posterior Tibial Slope, Anterior Tibial Subluxation, Deep Posterior Lateral Femoral Condyle, and Meniscal Deficiency Are Common Findings in Multiple Anterior Cruciate Ligament Failures: An MRI Case-Control Study".* Am J Sports Med. 2019 Feb;47(2):285-295. doi: 10.1177/0363546518823544. Epub 2019 Jan 18.

STUDY XI:

<u>Grassi A</u>, Pizza N, Zambon Bertoja J, Macchiarola L, Lucidi GA, Dal Fabbro G, Zaffagnini S
"Posterior Tibial Slope is Associated to Higher Risk of Early Contralateral Anterior Cruciate Ligament (ACL) Injury in patients <18 Years Old."
Knee Surg Sports Traumatol Arthrosc (in printing)