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**“PREDICTORS OF FAILURE AND CLINICAL OUTCOMES IN PATIENTS
UNDERGOING MENISCAL SUBSTITUTION WITH MENISCUS
SCAFFOLD or MENISCUS ALLOGRAFT TRANSPLANTATION”**

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1. Abstract

The meniscus is a fibrocartilaginous structure essential for knee biomechanics, contributing to load distribution, shock absorption, joint stability, and cartilage protection. Meniscal injuries are frequent and, when not amenable to repair, often require partial or total meniscectomy. Although meniscectomy can provide short-term symptom relief, it is well established that even partial resections may accelerate cartilage degeneration and predispose to early osteoarthritis. Consequently, considerable research has focused on developing strategies for meniscal substitution in order to preserve joint function and delay degenerative progression.

Two main approaches currently exist for the replacement of meniscus: meniscal scaffolds and meniscal allograft transplantation (MAT).

- *Scaffolds* are bioengineered implants designed for partial meniscal replacement after segmental resection. They provide a porous structure to support cell ingrowth and tissue remodeling, aiming to restore some biomechanical function and reduce symptoms. However, compared with allografts, the body of literature on scaffolds is smaller, with fewer long-term studies and limited evidence regarding surgical and demographical predictors of outcome. For this reason, the first work of the present thesis specifically investigates demographic and surgical risk factors that may influence scaffold survival and clinical results.
- *Meniscus allograft transplantation (MAT)*: is indicated in cases of subtotal or total meniscus loss. Unlike scaffolds, MAT has been widely studied, with numerous publications identifying predictors of success and failure such as age, cartilage status, limb alignment, and associated procedures. Yet, despite this substantial literature, little attention has been given to the role of donor–recipient mismatch in MAT. This aspect has been shown to

influence survival and outcomes in osteochondral allografts, but its effect on meniscus allografts remains poorly defined.

Aims of the Thesis

The overarching goal of this thesis is to expand current knowledge on biologic meniscus substitution by addressing these gaps:

1. **Meniscal scaffolds:** to evaluate the long-term clinical outcomes and predictors of failure after scaffold implantation, with particular focus on patient demographic and surgical factors.
2. **Meniscal allograft transplantation:** to investigate the influence of donor–recipient mismatch on survival and functional outcomes after MAT.

By integrating these two lines of investigation, the thesis aims to provide a more comprehensive understanding of the determinants of success in meniscal substitution and to contribute to improved patient selection and surgical decision making.

2. Background and Literature Review

2.1 Anatomy and biomechanics of the meniscus

2.1.1 Macroscopic Anatomy

The medial and lateral menisci are semilunar fibrocartilaginous structures interposed between the femoral condyles and the tibial plateau. Together, they cover approximately two-thirds of the tibial surface, increase articular congruence, and play an essential role in load transmission¹.

The medial meniscus is larger, more C-shaped, and covers 50–60% of the medial tibial plateau². It has firm capsular and ligamentous attachments, particularly to the deep layer of the medial collateral ligament, which reduce its mobility but increase its susceptibility to injury during rotational forces. Śmigielski et al. proposed a detailed five-zone division of the medial meniscus, ranging from the anterior root (zone 1) to the posterior root (zone 5), each with specific anatomical and surgical considerations³. For instance, the posterior horn (zone 4) is frequently injured and technically challenging for repair, while the posterior root (zone 5) plays a crucial role in hoop stress transmission and is fundamental for joint biomechanics⁴.

The lateral meniscus is more circular, covering a greater portion (up to 70–80%) of the lateral tibial plateau [4]. It is more mobile, due to looser capsular attachments and the presence of the popliteal hiatus, a unique region that allows passage of the popliteus tendon⁵. The hiatus is reinforced by the popliteomeniscal fascicles, the meniscofibular ligament, and the posterior capsule, which together stabilize the lateral meniscus while maintaining its mobility⁶. The lateral meniscus is further connected to the femur by the anterior and posterior menisiofemoral ligaments (Humphrey and Wrisberg), which function as secondary stabilizers against posterior tibial translation and contribute to distributing loads across the lateral compartment⁶.

Both menisci are anchored to the tibial plateau by anterior and posterior roots, which are crucial for their mechanical function. The anterior root of the medial meniscus inserts near the medial tibial eminence, whereas the anterior root of the lateral meniscus overlaps with the footprint of the anterior cruciate ligament (ACL)⁷. This overlap explains the risk of iatrogenic injury to the lateral meniscal root during ACL reconstruction. Posterior root tears or avulsions are biomechanically equivalent to total meniscectomy, as they cause loss of hoop stresses and meniscal extrusion⁸.

2.1.2 Microstructure and Composition

The meniscus consists of approximately 65–75% water, 22% collagen, 0.8% glycosaminoglycans, and 0.12% DNA⁹. The predominant collagen type is type I (90%), arranged in a circumferential orientation to resist hoop stresses, interspersed with radially oriented “tie fibers” that prevent longitudinal splitting¹⁰. The proteoglycans and glycoproteins within the extracellular matrix retain water, giving the tissue its viscoelastic properties¹¹.

Cellularity differs by region. The superficial layers are populated by fibroblast-like cells, while deeper zones contain fibrochondrocytes embedded in the extracellular matrix¹². This arrangement reflects the adaptation of the meniscus to heterogeneous mechanical loading conditions: the peripheral rim resists tensile stress, whereas the inner portion withstands compressive forces.

2.1.3 Vascularisation and Innervation

In early development, the meniscus is fully vascularized, but this decreases with age and weight-bearing. In adults, vascularization is restricted to the peripheral 10–30% (the “red zone”), supplied by branches of the superior and inferior geniculate arteries that form a perimeniscal capillary network. The central two-thirds remain avascular (the “white zone”), nourished only by diffusion from synovial fluid, which severely limits healing potential¹³.

Innervation parallels vascularization, with nerve fibers particularly concentrated in the anterior and posterior horns. These neural elements provide proprioceptive input, reflex control of quadriceps function, and nociception, contributing to both stability and pain perception in meniscal pathology¹⁴.

2.1.4 Biomechanical Role

The menisci are critical for knee biomechanics. They increase tibiofemoral contact area by up to 200% and reduce peak contact pressures by 50–70%¹⁵. They function as shock absorbers, joint lubricators, and secondary stabilizers.

The medial meniscus provides greater stability due to its firm attachments to the tibia and capsule. However, this stability makes it more vulnerable to tears, especially in the posterior horn, which is commonly injured during combined rotational and axial loading¹⁶. In ACL-deficient knees, the medial meniscus becomes a primary secondary stabilizer, often leading to higher injury risk in this structure¹⁷.

The lateral meniscus is more mobile and adapts to femoral rollback and tibial rotation during knee flexion. Its complex network of stabilizing structures (popliteomeniscal fascicles, meniscomfibular ligament, meniscomfemoral ligaments) permits this mobility while maintaining load distribution¹⁸. Nevertheless, disruption of these structures can lead to hypermobility syndromes and predispose to secondary tears. The integrity of meniscal roots is particularly critical. Root tears or avulsions cause loss of hoop stresses, extrusion, and biomechanical conditions equivalent to total meniscectomy, which significantly accelerates cartilage degeneration and the development of osteoarthritis⁸.

Table 1. Differences between the medial and lateral meniscus

Feature	Medial Meniscus	Lateral Meniscus
Shape	C-shaped, larger	More circular, smaller
Coverage of tibial plateau	50–60% of medial plateau	70–80% of lateral plateau
Mobility	Less mobile due to firm capsular and MCL attachments	More mobile due to looser attachments and popliteal hiatus
Attachments	Firmly attached to capsule and deep MCL	Popliteomeniscal fascicles, menisofibular ligament, menisofemoral ligaments
Injury risk	More prone to injury, especially posterior horn	Less commonly injured but at risk in ACL reconstructions
Biomechanical role	Stability, secondary stabilizer in ACL-deficient knees	Mobility, adaptation to femoral rollback and tibial rotation

2.2 Meniscal injuries and management

2.2 Meniscal Injuries

Meniscal injuries represent one of the most common causes of knee pain and disability, with a substantial burden on both sports medicine and general orthopaedic practice. Their incidence is high in athletic populations but also in the general public, making meniscal tears a leading indication for knee arthroscopy worldwide. Large-scale studies report an annual incidence of approximately 60 to 70 per 100,000 individuals, although true prevalence is likely underestimated given the frequency of asymptomatic lesions. Meniscal pathology occurs across the lifespan: acute traumatic tears are characteristic of adolescents and young adults engaged in pivoting or contact sports, whereas degenerative meniscus lesions are more typical of middle-aged and elderly patients, often in the context of early osteoarthritis.

From a pathophysiological perspective, meniscal injuries can be broadly divided into two categories: traumatic tears and degenerative lesions. This distinction, now widely accepted and endorsed by the ESSKA consensus documents^{19 20}, is fundamental, as the two entities differ not only in etiology but also in natural history, healing potential, and management strategies.

Traumatic tears occur in otherwise normal meniscal tissue following a sufficient injury, typically involving a twisting or pivoting movement on a flexed, weight-bearing knee. They are often associated with sports such as soccer, basketball, or skiing. Patients present with sudden pain, effusion, and in many cases mechanical symptoms such as catching or locking, especially when a displaced fragment is present. Common tear patterns include vertical longitudinal lesions, bucket-handle tears, radial tears, flap tears, and posterior root avulsions. Their biomechanical consequences are significant: for example, radial tears interrupt the circumferential collagen network and abolish hoop stress transmission, while root avulsions are biomechanically equivalent to a total

meniscectomy, leading to early cartilage degeneration. The ESSKA 2019 consensus stresses that meniscus preservation through repair should be the primary objective in traumatic tears. Repairs, even of lesions previously considered complex or irreparable, are associated with better long-term clinical and radiological outcomes compared to partial meniscectomy. Early repair is generally favored, as healing rates decline with chronicity of the lesion¹⁹.

Degenerative meniscus lesions, in contrast, occur gradually without a clear traumatic event, reflecting the progressive weakening of meniscal tissue associated with aging, cumulative microtrauma, and biochemical alterations of the extracellular matrix. They are particularly common in the medial meniscus, especially in the posterior horn, where repetitive compressive and shear forces are concentrated. These lesions are frequently associated with early osteoarthritis and may coexist with cartilage defects or subchondral bone changes. Clinical presentation is often less dramatic than in traumatic tears, consisting of intermittent pain, swelling, and reduced function, but mechanical symptoms are less consistent. Importantly, many degenerative lesions are incidental findings on magnetic resonance imaging and may be present in asymptomatic knees. The 2016 ESSKA consensus emphasizes that arthroscopic partial meniscectomy should not be used as a first-line treatment in degenerative lesions. Instead, non-operative strategies—including exercise-based physiotherapy, weight reduction, analgesia, and activity modification—are recommended as initial management. Arthroscopy may be considered only in selected patients with persistent mechanical symptoms that do not respond to structured conservative therapy. Radiographs are recommended before MRI to evaluate osteoarthritis, as many symptomatic presentations are multifactorial rather than isolated meniscal disease²⁰ (figure 1).

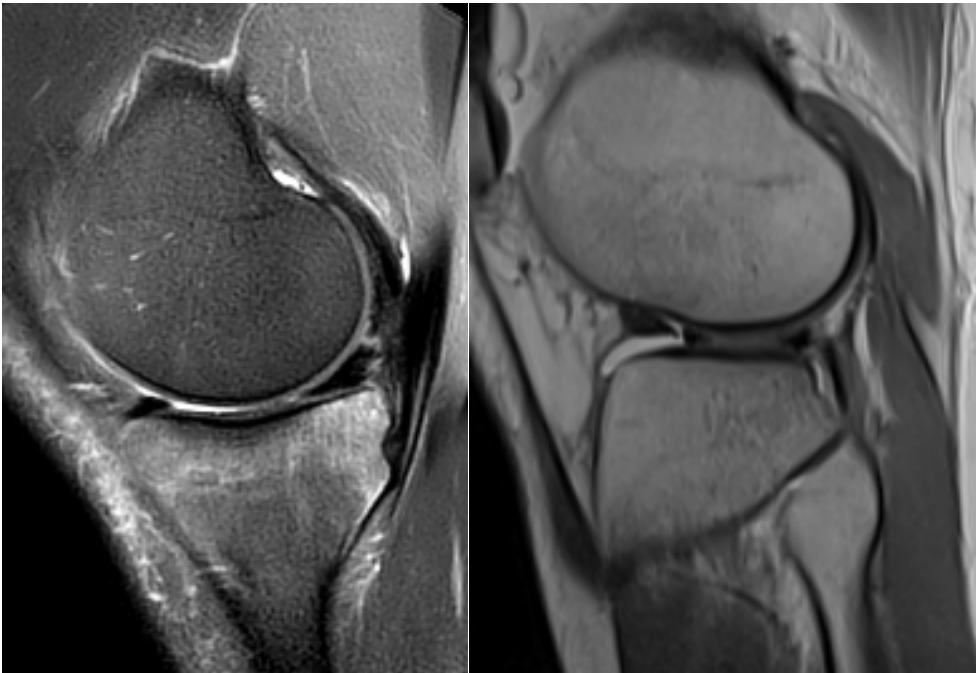


Figure 1: MRI images of a medial meniscus ramp lesion (left) and an anteriorly-displaced lateral meniscus bucket handle tear.

The distinction between traumatic and degenerative tears is summarized in Table 2. This division guides the clinician toward an individualized management pathway, reflecting the paradigm shift from routine meniscectomy to a preservation-first approach.

Table 2. Distinction between traumatic and degenerative meniscal tears

Feature	Traumatic tears	Degenerative tears
Etiology	Acute injury, usually sports-related	Progressive tissue degeneration, age-related
Patient profile	Younger, active individuals	Middle-aged to elderly, often with OA changes
Onset	Sudden, acute symptoms	Gradual, chronic or insidious
Tissue quality	Healthy, vascularized meniscus	Degenerated, avascular central tissue
Symptoms	Pain, swelling, catching, locking	Chronic pain, swelling, less frequent true locking

Preferred management	Meniscus repair when feasible	Conservative treatment first, APM only in selected cases
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Beyond the traumatic versus degenerative classification, meniscal tears can also be categorized by location and morphology, which influence both symptoms and treatment options. Vertical longitudinal tears follow the circumferential collagen fibers and are often repairable, but when displaced centrally into the intercondylar notch, they form bucket-handle tears that cause true locking and frequently require urgent surgical reduction and repair. Radial tears, oriented perpendicular to the collagen bundles, compromise load distribution and may be more challenging to repair, though techniques continue to evolve. Horizontal cleavage tears divide the meniscus into superior and inferior leaflets, are often degenerative, and may lead to unstable flap formation. Complex tears combine different patterns and are common in chronic or osteoarthritic knees. Posterior root tears, increasingly recognized in recent years, disrupt the anchoring function of the meniscus and dramatically alter tibiofemoral mechanics; their repair is now considered essential to prevent early joint degeneration. A summary of the main tear patterns and their clinical implications is provided in Table 3.

Table 3. Common meniscal tear patterns and clinical relevance

Tear pattern	Description	Clinical relevance
Vertical longitudinal	Tear along circumferential fibers, may evolve into bucket-handle	Repairable, often associated with locking when displaced
Bucket-handle	Displaced longitudinal fragment into notch	Causes true locking, urgent repair indicated
Radial	Perpendicular to circumferential fibers	Disrupts hoop stresses, challenging to repair
Horizontal	Splits meniscus into upper and lower parts	Often degenerative, may form flaps, controversial treatment

Flap/complex	Irregular tears with unstable fragments	Can cause mechanical symptoms, often partial resection
Root tear	Avulsion of meniscus from tibial insertion	Biomechanical equivalent to total meniscectomy, repair indicated when possible

Although classification systems are diverse, ranging from morphological to biomechanical and from radiological to arthroscopic, they all underscore the heterogeneity of meniscal pathology. Clinicians must integrate history, imaging, and intraoperative findings to define the lesion type and guide treatment. Ultimately, the overarching principle remains consistent: in traumatic tears, every effort should be made to preserve meniscal tissue, while in degenerative lesions, surgery is reserved for carefully selected refractory cases. This patient-specific approach reflects the current gold standard of meniscal management and highlights the meniscus as a key determinant of long-term joint preservation.

2.3 Meniscal scaffolds

Regenerative tissue engineering strategies have been extensively researched to develop a new generation of meniscal implants for both partial and total replacements. The primary goal is to create biomaterials—whether acellular or cell-seeded constructs—that not only mimic the biomechanical properties of native meniscal tissue but also provide the necessary biological functions for tissue regeneration. These innovative approaches hold promise for developing patient-specific implants, ensuring correct size and shape while incorporating advanced techniques such as the combination of cells, bioactive agents, hydrogels, or gene therapy.

Scaffolds serve as essential carriers for cytokines and cells, guiding the regeneration process. Natural materials, including collagen, offer several advantages over synthetic alternatives due to their superior

biocompatibility, biodegradability, and biological activity, which are critical for effective tissue integration and repair. Specifically, biocompatibility is crucial to avoid inflammatory responses; structural similarity and biological inductive activity facilitate the integration of repair tissue with surrounding healthy tissue; biodegradability allows the material to degrade while new tissue grows in. In fact, scaffolds serve as essential carriers for cytokines and cells, guiding the regeneration process.²¹

Collagen, the most abundant extracellular matrix (ECM) protein, is an ideal candidate for meniscal scaffolds due to its biodegradability, low immunogenicity, and wide availability. Collagen self-assembles into cross-striated fibers that support cell growth and provide mechanical elasticity, essential for the load-bearing function of the meniscus.

For a successful scaffold implantation, specific patient criteria must be met. The patient must have a healthy meniscal rim with intact anterior and posterior roots to properly anchor the implant. Additionally, the meniscal defect should extend into the red-red or red-white zones (or be surgically resected and prepared to expose these zones) to ensure adequate vascularization and cellular repopulation of the scaffold.

Table 4. Indications and contraindications for meniscus scaffold surgery.

Indications	Contraindications
Irreparable Meniscal Tears: Suitable for patients with acute meniscal tears requiring partial meniscectomy due to trauma, or those with chronic degenerative loss of more than 25% of the meniscus circumference.	Severe Ligament Instability: Grade III ligament instability, including posterior cruciate ligament (PCL) or medial/lateral collateral ligament (MCL/LCL) insufficiency.
Meniscus Horns: The anterior and posterior meniscus horns must remain intact and well-preserved.	Severe Cartilage Damage: Outerbridge grade IV cartilage degeneration in any knee compartment.
Meniscus Rim Integrity: The meniscal rim must be intact, with a width of more than 1 mm around the entire circumference.	Untreated Axial Malalignment: Axial malalignment greater than 5° that has not been corrected.
Cartilage Condition: Outerbridge grade I to III cartilage lesions. Note: If focal cartilage defects are present, they may be treated with concurrent cartilage repair techniques.	Allergies: Known allergy to collagen or chondroitin sulfate products.

ACL Laxity: If there is anterior cruciate ligament (ACL) laxity, an ACL reconstruction or revision should be performed in conjunction with the meniscus substitution procedure.	Infection: Presence of systemic or local infection.
Axial Malalignment: Axial malalignment must be less than 5°. If greater, high tibial osteotomy (HTO) or distal femoral osteotomy (DFO) should be performed either concurrently or staged.	Corticosteroid Use: Recent administration of local or systemic corticosteroids within 30 days prior to surgery.
	Osteonecrosis: Evidence of osteonecrosis in the affected knee.
	Autoimmune Conditions: History of rheumatoid arthritis, inflammatory arthritis, or other autoimmune diseases.
	Pregnancy: Meniscus substitution is contraindicated during pregnancy.
	Obesity: A BMI over 30 may be a relative contraindication, particularly for lateral meniscus scaffolds.

The **Collagen Meniscus Implant (CMI)** was the first scaffold introduced into clinical practice. It is composed of type I collagen fibers, glycosaminoglycans, and other extracellular matrix components derived from bovine Achilles tendon. The implant acts as a resorbable biological matrix that supports cell infiltration and neotissue formation. Over time, CMI undergoes progressive resorption and is replaced by vascularized fibrocartilaginous tissue^{22 23}.

The **Actifit scaffold** (Orteq Bioengineering, UK) represents a second-generation synthetic alternative. It is made of a highly porous polyurethane–polyester copolymer, specifically designed for meniscal application. The polyester segments degrade progressively, while the polyurethane segments provide mechanical stability and resistance. This composition ensures flexibility, cell migration, and gradual resorption into non-toxic by-products. Indications largely overlap with CMI: painful post-meniscectomy syndrome in young and active patients, intact horns and peripheral rim, and absence of advanced osteoarthritis²⁴.

Both scaffolds have demonstrated safety and short- to mid-term clinical improvements, with reduction of pain and functional gains²⁵. However, current evidence highlights that outcomes are

not equivalent to those of an intact meniscus, and long-term protective effects against osteoarthritis remain uncertain (*Table 5*). Limitations include risk of extrusion, incomplete remodeling, and the need for strict patient selection.

Table 5. Comparison between Collagen Meniscus Implant (CMI) and Actifit scaffold

Feature	Material	Indications	Contraindications	Surgical technique & remarks
CMI (Collagen Meniscus Implant)	Type I collagen (bovine Achilles tendon), glycosaminoglycans	Painful partial meniscectomy; intact horns and rim; young patients; no advanced OA	Severe cartilage damage (Outerbridge IV); instability; malalignment >5° not corrected; systemic disease	Arthroscopic implantation; press-fit; sutures to rim and capsule; gradual resorption and replacement by fibrocartilage
Actifit (Polyurethane scaffold)	Polyurethane-polyester copolymer (porous, biodegradable)	Symptomatic segmental defects after partial meniscectomy; intact horns and rim; young patients; no advanced OA	Root tears; advanced OA; instability; uncorrected malalignment; systemic disease	Arthroscopic implantation; scaffold cut oversized; fixation with sutures; synthetic, predictable degradation

Surgical Technique:

Once the patient has been positioned correctly, standard “high and tight” anterolateral (AL) and anteromedial (AM) portals are created, followed by diagnostic arthroscopy to confirm the surgical indications. During this step, it is essential to assess the presence and integrity of the meniscal roots. If the meniscectomy involves these parts, a meniscus allograft transplantation (MAT) may be more appropriate than a scaffold procedure. Additionally, the stability of the anterior cruciate ligament (ACL) should be evaluated using a probe and the anterior drawer test. The cartilage surfaces must also be inspected for focal lesions, which should be documented and treated after meniscus substitution surgery, if necessary.

Next, attention turns to the meniscus. The area of the previous meniscectomy should be debrided, and any degenerated or unstable meniscal tissue should be removed using a shaver or basket. It is crucial to ensure that the anterior and posterior meniscus horns are intact and biomechanically stable. The area designated for scaffold implantation must be trimmed squarely to allow for an initial “press-fit” fixation of the scaffold into the native meniscal defect. To further improve blood supply and scaffold integration, the capsule can be debrided with a shaver or an arthroscopic awl. At this stage, the defect size is measured using an arthroscopic ruler, and the scaffold is trimmed on the operating table using a scalpel. Oversizing the scaffold by approximately 10% is recommended to ensure primary stability during the initial fixation phase. The scaffold is inserted into the knee through an enlarged portal using a delivery clamp, and a blunt probe is used to position it correctly (figure2). Once a press-fit stability is achieved, the scaffold is sutured to the meniscal remnant using an "all-inside" suture technique. It is advisable to begin suturing the posterior portion of the scaffold to the host meniscus to prevent intraoperative dislocation,. The anterior and posterior sections of the scaffold should be secured to the meniscal remnant with horizontal sutures, while vertical mattress sutures (spaced 5-7 mm apart) should be used to fix the body of the scaffold to the capsule. Care must be taken to avoid overtightening the sutures, as this could damage the scaffold due to “cheese-wiring” effect, leading to instability or dislocation (figure 3).

Figure 2: The meniscus scaffold is introduced into the knee using a delivery clamp. Achieving an initial press-fit fixation at this stage is crucial.

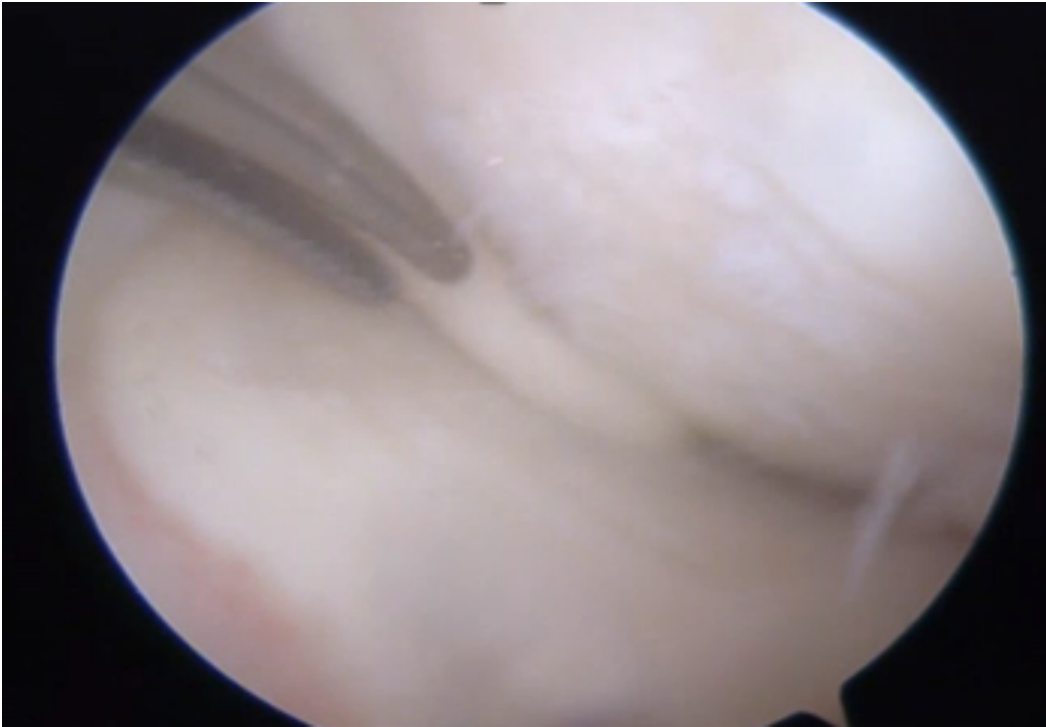
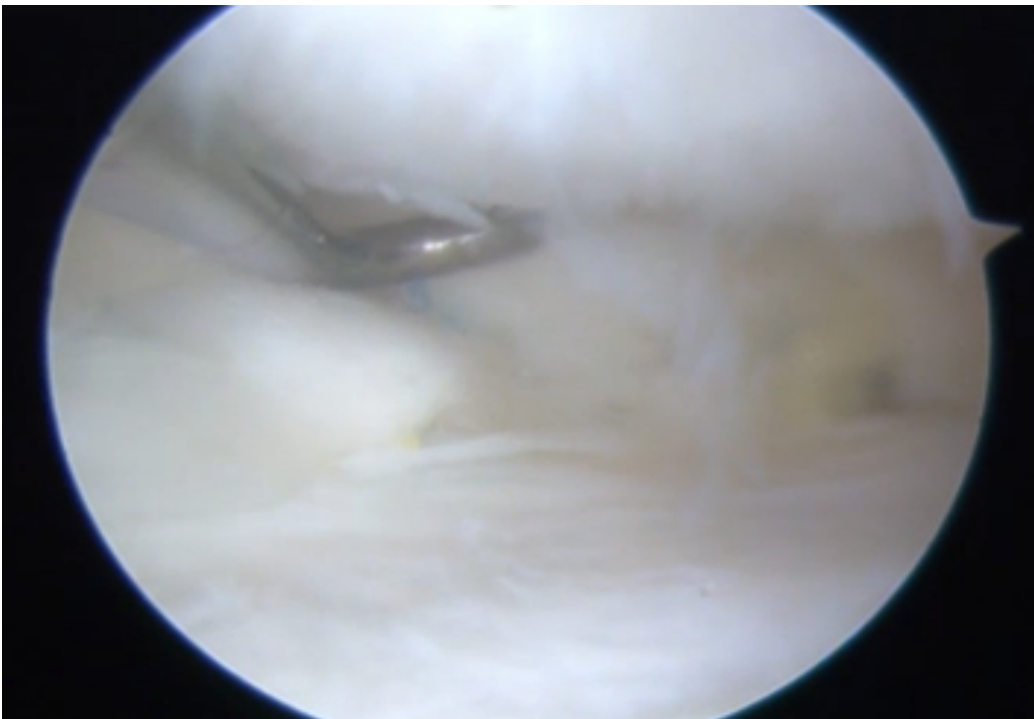


Figure 3: Final stability check of the meniscus scaffold using a probe.



2.4 Meniscal Allograft Transplantation

Rationale and Historical Background

Meniscal allograft transplantation (MAT) has emerged as the most validated biological treatment for patients suffering from post-menisectomy syndrome after subtotal or total meniscectomy. The goal is to restore the biomechanical function of the meniscus, redistribute joint loads, and reduce contact pressures, thereby slowing the progression toward osteoarthritis. Since the initial experimental procedures in the 1980s, MAT has evolved considerably thanks to improvements in graft preservation, sizing techniques, and surgical fixation methods²⁶. While originally considered an experimental salvage technique, MAT is now recognized as a reliable joint-preserving option for young and active patients with disabling pain and swelling following meniscal loss.

Indications and Contraindications

MAT is typically indicated in patients younger than 50 years presenting with pain, swelling, or mechanical symptoms after total or subtotal meniscectomy. Ideal candidates have neutral alignment, stable ligaments, and no or minimal cartilage degeneration (Outerbridge grades I–II)²⁷.

The main indications include:

- Symptomatic subtotal or total meniscectomy with persistent pain and swelling.
- Neutral or corrected limb alignment ($<5^\circ$ varus or valgus).
- Stable or stabilized knee, with or without concurrent ACL reconstruction.
- Cartilage surfaces preserved or with mild focal lesions amenable to simultaneous repair.

Contraindications are similar compared to the scaffolds and include:

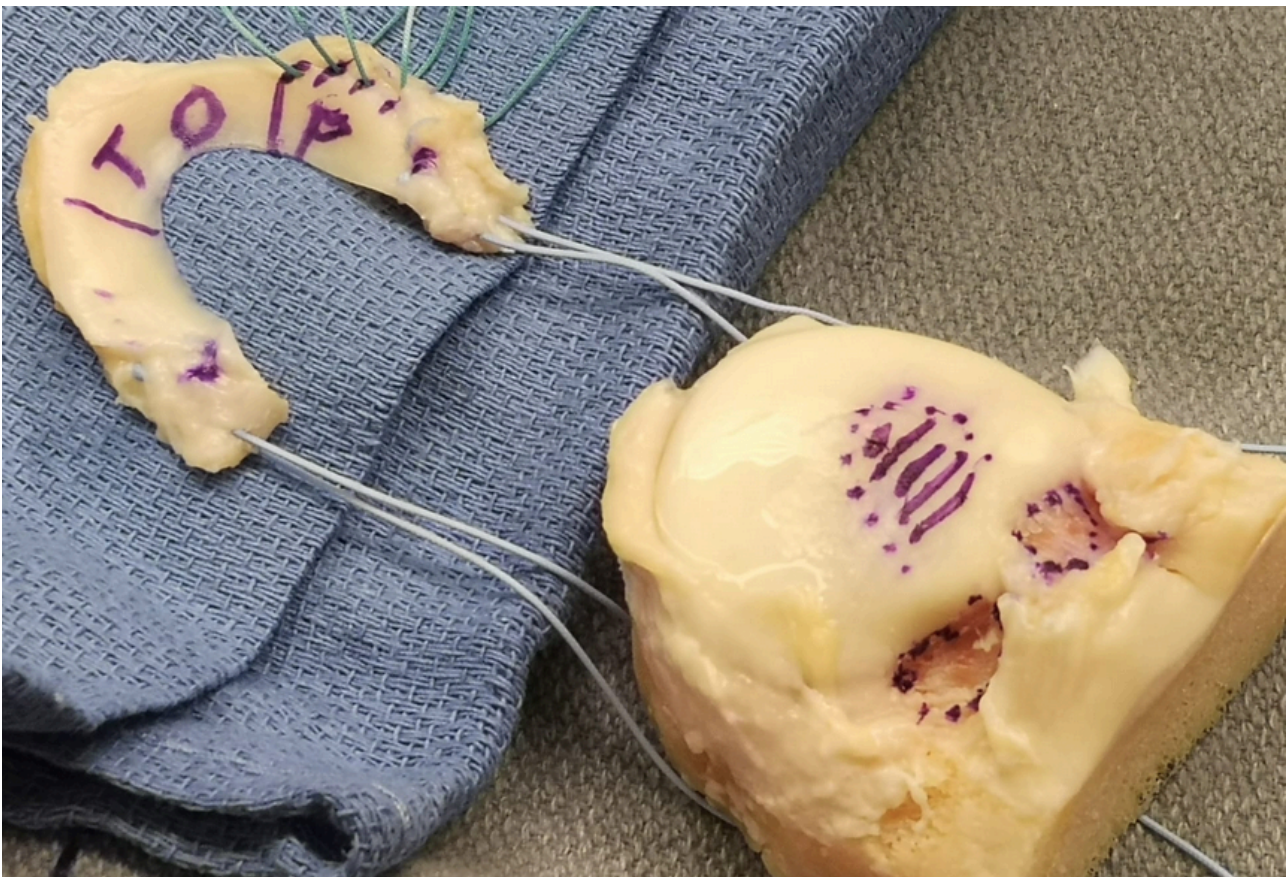
- Advanced osteoarthritis (Outerbridge grade III–IV).
- Untreated axial malalignment $>5^\circ$.
- Severe ligamentous instability not addressed during surgery.
- Systemic inflammatory or autoimmune diseases.

- Obesity (BMI >30), which negatively affects outcomes.
- Active or previous joint infection.

Graft Processing and Sizing

Accurate graft sizing is crucial for successful outcomes, as undersizing or oversizing can compromise biomechanics and lead to extrusion or early graft failure. Preoperative measurements are commonly obtained using plain radiographs (Pollard method) or MRI, and computer-based templating has improved reproducibility. Regarding preservation methods, fresh-frozen and cryopreserved grafts are widely used, whereas fresh viable grafts are less common due to logistical and immunological concerns.

Figure 4: Meniscus allograft harvested in the operating room for soft-tissue technique.



Surgical Technique (Soft Tissue Fixation)

Several fixation methods have been described, including bone plug, bone bridge, and soft tissue fixation. In our practice, the soft tissue technique is the technique of choice while it provides reliable fixation while allowing for an easy sizing.

The procedure begins with a diagnostic arthroscopy to confirm indications and exclude contraindications. After debridement of any unstable remnants, a thin vascularized rim is preserved to facilitate healing. The thawed graft is introduced arthroscopically through an enlarged anteromedial portal (Figure 4). Sutures from the anterior and posterior horns are passed through tibial tunnels and secured over the tibial cortex, ensuring root fixation. The graft is then circumferentially sutured to the capsule using a combination of all-inside and, eventually outside-in techniques, restoring hoop stresses. Oversizing of the graft by 5–10% is recommended to improve stability and compensate for shrinkage. Careful fixation is mandatory to minimize graft extrusion, one of the most common postoperative findings²⁸.

Rehabilitation after MAT is structured and protective. Patients are kept non-weight bearing or partial weight bearing for 4–6 weeks, with the knee immobilized in a hinged brace limiting flexion to 90°. Progressive loading and range of motion are allowed after the first month. By 3 months, patients may resume cycling and swimming, whereas pivoting or high-impact sports are typically restricted for at least 9–12 months. The primary objective is to balance graft integration with gradual functional recovery, minimizing the risk of graft failure.

Clinical Outcomes

MAT has shown consistent improvements in pain relief, knee function, and quality of life. Short- to mid-term outcomes are favorable, with most patients reporting significant reduction of symptoms. Survival rates of 70–80% at 10 years and up to 60% at 15 years have been reported, although results decline with longer follow-up²⁹. Younger age, minimal cartilage degeneration, correct alignment,

and intact or reconstructed ligamentous structures are associated with better outcomes.

Despite these encouraging results, MAT does not fully restore normal knee function, nor does it prevent osteoarthritis progression in all cases. Complications include graft tear, resorption, extrusion, or persistent pain. Revision procedures and conversion to arthroplasty occur in a minority of patients but increase with longer follow-up.

While MAT remains the gold standard for meniscal replacement in extensive meniscectomy, it is not without limitations. Long-term graft survival decreases over time, and outcomes are heavily dependent on patient selection. Technical demands are high, and postoperative rehabilitation is lengthy. Furthermore, graft availability and regulatory issues may limit its widespread use.

Future directions include the combination of MAT with biologic adjuncts such as growth factors, stem cells, or scaffolds, aiming to enhance graft integration and cartilage preservation.

Meniscal allograft transplantation is the most established option for restoring meniscal function in cases of subtotal or total meniscectomy. The soft tissue fixation technique provides reliable outcomes and avoids tunnel-related complications, with good mid- to long-term survivorship in carefully selected patients. Although not curative, MAT serves as a valuable joint-preserving strategy to delay the progression of osteoarthritis. Compared with meniscal scaffolds, MAT addresses larger and more complex defects, representing a complementary option within the spectrum of biological meniscal restoration.

3. Thesis Aims

The general aim of this thesis is to investigate clinical outcomes and predictors of failure in patients undergoing meniscal substitution procedures. By focusing on two different strategies—biological scaffolds and meniscal allograft transplantation (MAT)—this work intends to clarify the role of patient-related and surgical variables in determining both short- and long-term outcomes.

Ultimately, the purpose is to provide clinically relevant evidence to optimize patient selection and surgical planning.

3.2 Specific Objectives – Meniscal Scaffolds

Although collagen and polyurethane scaffolds have been introduced into clinical practice for more than two decades, current evidence is still limited, with most studies reporting small series and short- to mid-term follow-up. While safety and feasibility are well established, there is a lack of data regarding prognostic factors that may influence failure and clinical results.

The first specific objective of this thesis is therefore:

- To evaluate demographic, clinical, and surgical predictors of outcomes and failure in patients treated with meniscal scaffolds.

This analysis aims to identify which variables (e.g., age, body mass index, concomitant procedures, cartilage status) most strongly correlate with functional improvement or risk of revision.

3.3 Specific Objectives – Meniscal Allograft Transplantation (MAT)

In contrast to scaffolds, MAT has been more widely studied and validated, with clear evidence supporting its indications and expected outcomes. Nevertheless, some aspects remain poorly defined. In particular, the role of graft-host mismatch has not been thoroughly investigated, despite

evidence from osteochondral transplantation suggesting its influence on joint biomechanics and long-term survival.

The second specific objective of this thesis is therefore:

- To investigate the impact of meniscal graft mismatch on clinical outcomes and failure rates following MAT.

This evaluation may provide important insights into the relevance of accurate sizing and improve surgical planning for allograft transplantation.

3.4 Overall Purpose

By addressing these two complementary areas, this thesis aims to expand current knowledge on meniscal substitution strategies. The ultimate purpose is to provide new evidence for clinical practice, allowing surgeons to refine indications, improve surgical decision-making, and optimize long-term outcomes for patients suffering from symptomatic meniscal loss.

4. Materials and Methods

4.1 Study 1 – Meniscus Scaffold

Patients selection and evaluation

All the consecutive patients who underwent CMI scaffold implantation at Orthopaedic Rizzoli Institute between 2005 and 2010 were screened.

Demographics and surgical details such as patient sex, CMI side (medial or lateral), BMI, time from first meniscectomy, concurrent procedures and cartilage status were obtained by chart review. Patients with acute irreparable tears who underwent meniscectomy and immediate CMI implantation were considered to have a time from meniscectomy to CMI of 0 years. For the purpose of the analysis, the chondropathy was stratified as “low grade” in the case of Outerbridge 0 to 2, and “high grade” in the case of Outerbridge 3 and 4.

All patients were contacted via phone and the KOOS, Lysholm and Tegner questionnaires were administered. Patients were also asked to rate the knee pain at rest or during activity on a 10-point VAS scale. Data on sport activity and participation were investigated as well. Patients were also questioned whether they had undergone any additional surgeries on the operated knee during the follow-up period and if they were satisfied with the results of the CMI. Finally, medical record from the hospital database were screened for possible complications or further surgeries.

Surgical failures were defined as any reoperations that required a partial or total scaffold removal, including (1) infection, (2) scaffold-related complications such as CMI fragmentation or dislocation, (3) conversion to meniscus allograft transplantation (MAT), (4) unicompartmental knee arthroplasty (UKA), (5) total knee arthroplasty (TKA).

Statistical Analysis

Statistical analysis was performed with MedCalc (MedCalc software, Acacialaan 22, Ostend, Belgium). The continuous variables were expressed as mean $\pm$ SD, while the categorical variables were expressed as number and percentage. A comparison among various follow-up points and

between the Isolated and Combined Group was performed with unpaired-samples t test in case of continuous variables, and differences in categorical variables were analyzed with the chi-square test. The patients were also stratified according to the Patients Acceptable Symptoms State (PASS) threshold for the Lysholm score (66.5 points), KOOS Symptoms (73.0 points), KOOS Pain (43.0 points), KOOS ADL (74.5 points), KOOS Sport (22.5 points) and KOOS QoL (53.0 points) as defined by Liu et al. for Meniscal transplantation³⁰. In the case of missing values for clinical scores owing to surgical failure, the preoperative values were used to avoid overestimation of the clinical status when calculating the post-operative average values. Moreover, patients with surgical failure were considered as not achieving the PASS for all the scores and subscales. The total of patients with Surgical Failure and those not reaching the PASS for the Lysholm score were defined as Clinical Failure.

Multiple regression analysis models with a stepwise approach were performed using clinical scores as endpoints and Sex (Male vs Female), CMI side (Medial vs Lateral), Age (<45 years vs $\geq$ 45 years), Chondropathy (Outerbridge 0-II vs III-IV), associated procedures (Isolated vs Combined), BMI (<25 vs $\geq$ 25) time from meniscectomy (<5 years vs $\geq$ 5 years) as independent variables. The same variables were used in logistic regression analysis models when assessing patients not achieving the PASS for the various scores; the results were reported as Odd Ratios with 95% confidence intervals. Multiple and Logistic regression analyses were normalized for the pre-operative value of each score. Differences were considered significant with $P < .05$.

4.2 Study 2 – Meniscus Allograft Transplantation

Patients selection:

The present study consists in a retrospective analysis of 375 consecutive meniscal allograft transplantation (MAT) with soft-tissue fixation. All surgical procedure were performed between July 2006 and February 2021 in a single institution.

Inclusion criteria were complete demographic and pre-operative clinical data and at least 2 years follow-up time. Demographics data of our interest were sex, age at surgery/explant, BMI and blood group of both recipient and donor; freezing time of the graft was also noted.

The indications for MAT were unicompartmental knee pain due to a previous total or subtotal meniscectomy, grade I to III OA according to the Kellgren-Lawrence radiographic evaluation, no signs of contralateral-compartment and patellofemoral-compartment damage. Depending on the surgical demands of the patients, concomitant ACL reconstruction/revision, osteotomy, or cartilage procedures may have been performed.

Exclusion criteria were incomplete demographics or pre-operative clinical evaluation and follow-up time of less than 2 years.

Patient Evaluation

Pre- and post-operative evaluations were performed by clinical evaluation and data collection with phone interview or written questionnaire; moreover, any surgical procedures performed during the FU time were recorded.

Surgical failure was defined as revision procedure related to the initial MAT, such as total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), MAT revision or meniscectomy due to graft tears.

Demographic details from the allograft donor (including sex, age at surgery, blood group and BMI), explant and freezing date were extracted from the institutional Tissue-Bank database.

Sex mismatch was evaluated creating 4 different groups: in the first (1) both donor and recipient were male, in the second (2) the donor was male, while the recipient was a woman, in the third (3) the donor was a woman, while the recipient was a man and, finally, in the fourth (4) both donor and recipient were women.

Blood group mismatch was evaluated creating 3 different groups: in the first (1) both donor and recipient had the same group, in the second (2) the two groups were concordant, while in the third (3) the two groups were non concordant.

Meniscus Allograft Harvesting and Processing

The menisci implanted in the present cohort study were harvested in Italy within the Emilia-Romagna and Tuscany regions. Each donor was selected following the criteria established in the Italian guidelines as defined by the National Transplant Centre (CNT). Regarding tissue-specific selection criteria for meniscus donation, donors were excluded if they met at least one of the following conditions: Osteoporosis, Diseases affecting the structural properties of the bone extracellular matrix, Age below 15 years or above 55 years.

The harvesting procedure was conducted in an operating room located in the hospital where the donor's death occurred, within 24 hours of the donor's passing. During the procurement, the tibia with the attached menisci was sterilely wrapped and stored in a freezer at -80°C.

At a later stage, the frozen tibia underwent processing inside a cleanroom facility. The procedure included the following steps: the tibia was thawed, the tibial plateau was cut approximately 1 cm from the cartilage, the plateau was further divided along the sagittal plane to separate the two menisci and finally the menisci were measured for length and width to ensure proper donor-recipient matching.

After processing, the menisci were stored at -80°C until their use. The distributed menisci remained attached to approximately 1 cm of subchondral bone from the tibial plateau, enabling the surgeon to shape the bone plug according to the specific surgical procedure.

Statistical Analysis

Normal data distribution was verified through the Shapiro-Wilk test. Continuous variables were presented as mean $\pm$ standard deviation, while categorical variables were presented as median and interquartile range (IQR) or number and percentage. Differences between single groups were inspected through student's t-test or chi-squared test according to variable type. Differences were considered statistically significant for $p < 0.05$.

Survival analyses were performed using the Kaplan–Meier method. Survival proportions at 5, 10, and 15 years and mean estimated survival time with 95% confidence intervals (CI) were calculated. When present, the Surgical failure time was retrieved to not overestimate the survival time.

Univariate logistic regression analyses were performed using Surgical failure as endpoint and the group of sex accordance or blood group accordance as independent variable.

Multivariate analysis was performed using as endpoint Surgical failure and graft freezing time, BMI and age at surgery/explant of both donor and recipient, and the respective (ΔBMI and Δage) as independent variables. All statistical analyses were performed in MedCalc (MedCalc Software, Oostende, Belgium).

5. Results

5.1 Study 1 – Meniscus Scaffold

Patients characteristics

A total of 111 patients met the inclusion criteria; of them, 92 (83%) completed the long-term assessment at a mean follow-up of 11.8 ± 1.8 years (Figure 5). In the study population, there were 70 males (76%) and 22 females (24%) female with an average age at surgery of 42.2 ± 10.8 . A total of 68 patients received Medial CMI (74%) while 24 recieved Lateral CMI (26%) after an average of 9.7 ± 8.9 years from the meniscectomy (Table 2). A total of 36 patients (39%) were “Isolated” while 56 patients (61%) were “Combined”. In the study population, 19 patients (21%) underwent acute CMI implantation and, among them, 14 underwent CMI as isolate procedure. There were 24 patients (26%) who underwent an associated cartilage treatment (for details of the surgical procedure see table 5), of them, 12 were located on the medial femoral condyle, 3 on the medial tibial plateau, 6 on the lateral femoral condyle, 1 on the lateral tibial plateau and 1 on the throclea. The cartilage lesion were 1-2cm² in 6 patients, 2-3cm² in 10 patients and >3cm² in 8 patients.

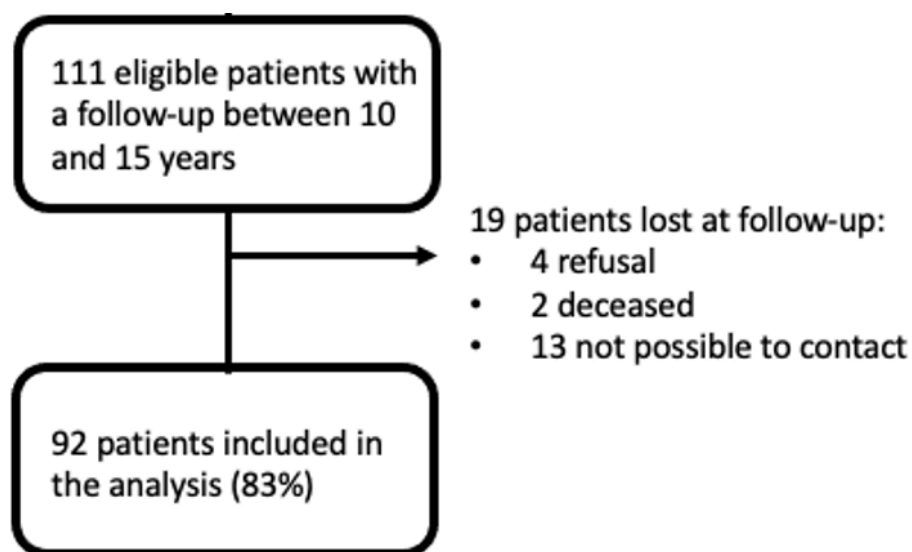


Figure 5. CONSORT diagram. CMI, collagen meniscus implant.

Table 5: Patients Demographic and Surgical Characteristics		
Variables		Values
Follow-up		11.8 ± 1.8
Sex	Males	70 (76%)
	Females	22 (24%)
Age at surgery (years)	Mean (SD)	42.2 ± 10.8
	<45 years	58 (63%)
	≥45 years	34 (37%)
Body Mass Index	Mean (SD)	25.4 ± 3.4
	<25	44 (48%)
	≥25	48 (52%)
CMI Side	Medial	68 (74%)
	Lateral	24 (26%)
Combined Procedure	Total	56 (61%)
	ACL Reconstruction	25 (27%)
	Primary	17
	Revision	8
	Knee Osteotomy	21 (23%)
	HTO	18
	DFO	3
	Cartilage Treatment	24 (26%)
	Microfractures	16
	Osteochondral Scaffold	6
	Mosaicoplasty	1
	ACI	1
Outerbridge Grade	Median (IQR)	3 (0-3)
	0-2	40 (43%)
	3-4	52 (57%)
Time from Meniscectomy (years)	Mean (SD)	9.7 ± 8.9
	<5 years	40 (43%)
	≥5 years	52 (57%)

Table 5: ACL, anterior cruciate ligament; HTO, high tibial osteotomy; DFO, distal femoral osteotomy; ACI, autologous chondrocyte implantation.

Clinical outcomes

A total of 25 patients (27%) underwent a surgical procedure during the considered follow-up, after an average of 4.3 ± 4.0 years from the CMI. Of these, only 12 (13%) were considered surgical failures (Table 6). Moreover, 19% of patients did not achieve the PASS for the KOOS Pain subscale, 40% for the KOOS Symptoms subscale, 23% for the KOOS ADL subscale, 24% for the KOOS Sport subscale and 36% for the KOOS Qol subscale.

Table 6: Reoperations	
Variables	Patients
Total Reoperations	25 (27%)
Average time to Reoperation	4.3 ± 4.0 years
Failures	12 (13%)
Average time to failure	4.3 ± 4.0 years
MAT	4 (4%)
UKA	3 (3%)
TKA	3 (3%)
CMI Removal (infection)	1 (1%)
CMI Removal (HTO)	1 (1%)
Other Reoperations	13 (14%)
Average time to Other Reoperation	4.2 ± 4.1 years
Hardware removal	7 (8%)
ACL Reconstruction	3 (3%)
ACL tunnel cyst removal	1 (1%)
Arthroscopic Debridement	1 (1%)
Stem Cell Injection	1 (1%)

A significant improvement of the Lyholm score was reported from 55.6 ± 17.2 at pre-operative status to 76.3 ± 19.6 at final follow-up ($p=0.0001$); overall, 25% of patients did not achieved the PASS for Lysholm. Considering either Surgical Failures and patients with not reaching the PASS for Lysholm score, a total of 28 patients (30%) were considered Clinical Failures.

The Tegner score improved from 4 (IQR 3-5) pre-operatively to 5 (IQR 4-5) at final follow-up ($p=0.002$), however, without reaching the pre-injury level of 7 (IQR 6-8). The VAS for pain

significantly decreased over time for both pain at rest ($p=0.0029$) and during activity ($p=0.0001$) (Figure 7) and the KOOS score improved for all its subscales as well (Figure 7).

Figure 6: VAS for pain during the preoperative period (blue bar) and at the last follow-up (orange bar); (indicates $p < 0.05$).*

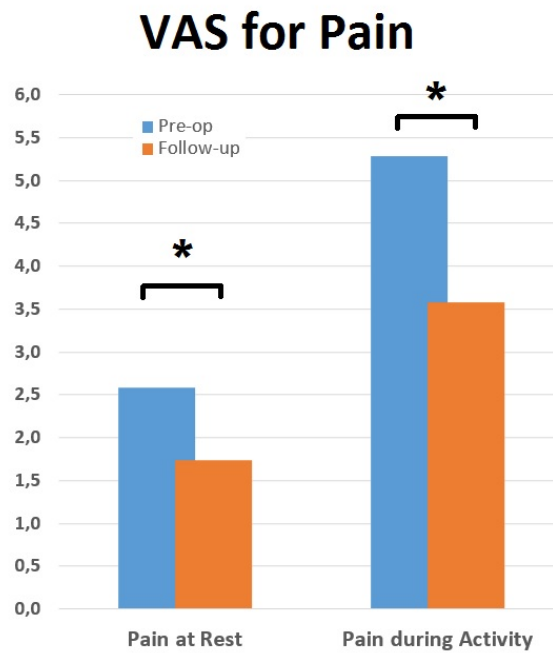
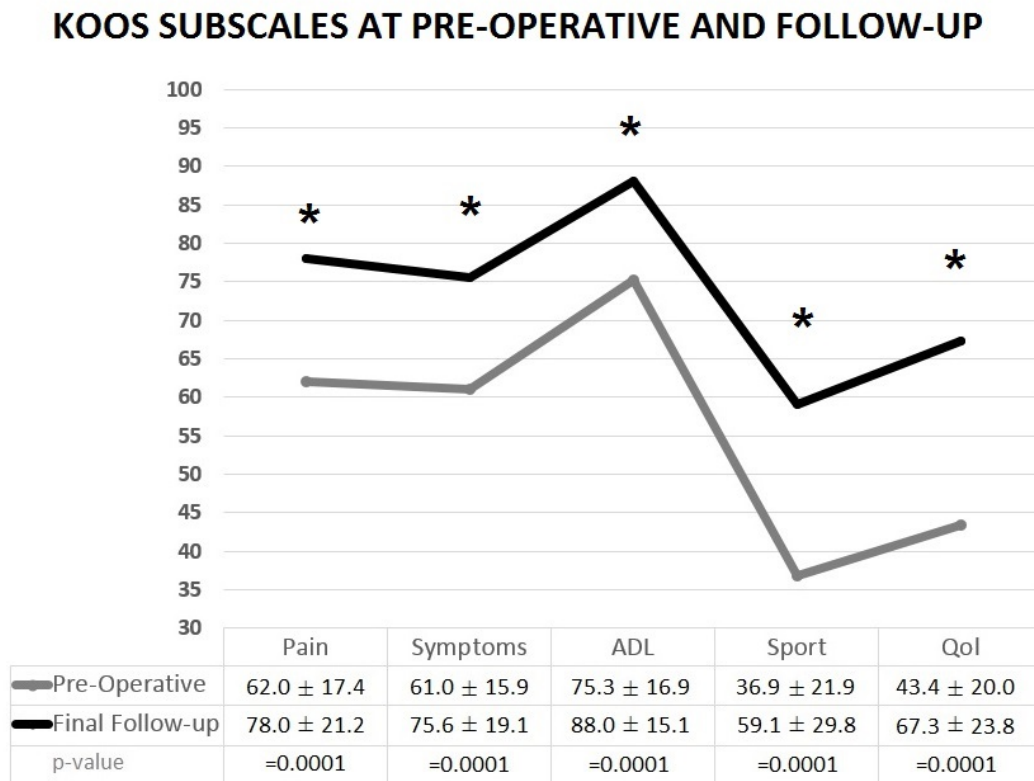


Figure 7: Comparison of the KOOS score during the preoperative period and at the last follow-up (* indicates $p < 0.05$).



In total, 63% of patients returned to sport practice after CMI, with 41% at the same or higher level. Finally, the overall average satisfaction was 4.0 out of 5.0 and 80% of patients were satisfied by the procedure.

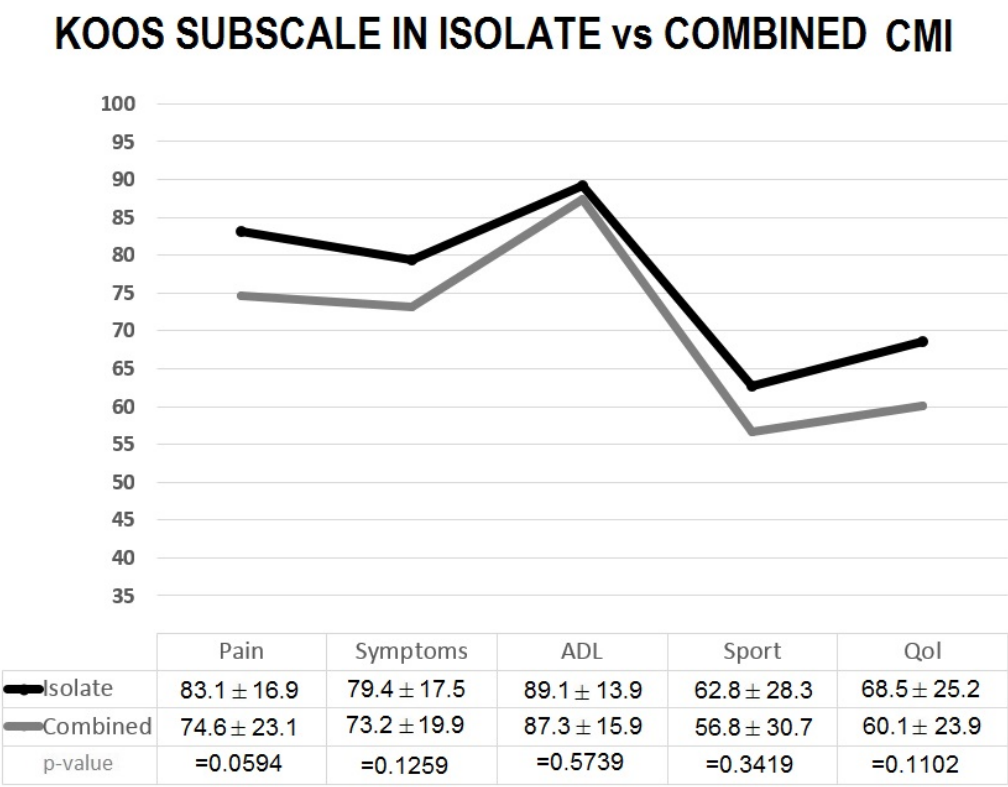
Isolated vs Combined CMI

Demographics and surgical characteristics were similar between the patient with Isolated CMI (36 patients) and those with a combined procedure (56 patients), except of the degree of chondropathy and the time since meniscectomy which were significantly higher in the cases of combined procedures (Table 8).

Table 8: Demographics of Patients with Isolated CMI vs. CMI with Combined Procedures			
	<u>Isolated (n=36)</u>	<u>Combined (n=56)</u>	<u>p-value</u>
Demographic			
Sex (Male/Female)	28 (78%)/8 (22%)	42 (75%)/14 (25%)	=0.8074
Age at surgery (years)	44.3 ± 11.7	40.8 ± 10.1	=0.1455
Follow-up (years)	12.5 ± 2.0	11.3 ± 1.8	=0.6198
BMI (kg/m ²)	25.1 ± 2.5	25.6 ± 3.7	=0.4781
CMI side (Medial/Lateral)	27 (75%)/9 (25%)	41 (73%)/15 (27%)	=1.0000
Outerbridge Grade			
Median (IQR)	0 (0-3)	3 (2-4)	=0.0231
0-2	22 (61%)	18 (32%)	
3-4	14 (39%)	38 (68%)	=0.0094
Time from Meniscectomy (years)			
Mean (SD)	6.2 ± 7.6	12.1 ± 9.1	=0.0017
<5 years	21 (58%)	19 (34%)	
≥5 years	15 (42%)	37 (66%)	=0.0308

Regarding clinical outcomes, significant improvements of all PROMs were reported in both “Isolated” and “Combined” Groups (Table 5). No relevant differences were reported in PROMs assessment between the two group, except slightly worst pre-operative Lysholm and KOOS Symptoms subscale in the “Combined” group, and a higher post-operative proportion of patients achieving PASS for the KOOS Pain subscale in the “Isolated” group (Figure 8).

Figure 8: Comparison of the KOOS score at the last follow-up between patients who underwent isolated scaffold surgery and those who underwent combined procedures (* indicates $p < 0.05$).



A significantly higher proportion of reoperations was reported in “Combined” group (36%) respect to “Isolated” group (14%); however, no difference between the two groups was reported for Clinical and Surgical Failure despite higher rates were reported in the case of a combined procedure (Table 9).

Table 9: Details of the outcomes of patients who underwent isolated and combined procedures.

CMI, collagen meniscus implant; PASS, patient acceptable symptomatic state; VAS, visual analogue scale;

KOOS, knee injury and osteoarthritis outcome score; ADL, activity of daily living; Qol, quality of life

Table 9: Outcomes of Patients with Isolated CMI vs. CMI with Combined Procedures			
	Isolated (n=36)	Combined (n=56)	p-value
Outcomes			
Lysholm			
Pre-operative	60.7 ± 17.6	52.3 ± 16.2	=0.0207
Follow-up	78.8 ± 17.4	74.6 ± 20.9	=0.3233
Improvement	18.1 ± 19.0	22.4 ± 23.8	=0.3212
Achieving PASS (>66.0)	26 (72%)	41 (73%)	=1.0000
VAS for Pain (rest)			
Pre-operative	2.1 ± 1.8	2.9 ± 1.7	=0.0340
Follow-up	1.2 ± 1.9	2.1 ± 2.3	=0.0525
Improvement	0.8 ± 2.5	0.6 ± 1.8	=0.6568
VAS for Pain (activity)			
Pre-operative	4.9 ± 2.4	5.5 ± 1.9	=0.1862
Follow-up	3.0 ± 2.6	4.0 ± 2.9	=0.0965
Improvement	1.5 ± 3.4	1.3 ± 2.3	=0.7371
KOOS Pain			
Pre-operative	65.3 ± 17.5	60.0 ± 17.1	=0.1614
Follow-up	83.1 ± 16.9	74.6 ± 23.1	=0.0594
Improvement	17.9 ± 21.4	14.6 ± 22.7	=0.5560
Achieving PASS (>43.0)	30 (94%)	41 (73%)	=0.0124
KOOS Symptoms			
Pre-operative	66.1 ± 12.3	57.8 ± 16.7	=0.0153
Follow-up	79.4 ± 17.5	67.8 ± 19.9	=0.1259
Improvement	13.3 ± 16.5	20.0 ± 20.8	=0.5272
Achieving PASS (>73.0)	25 (69%)	31 (55%)	=0.1963
KOOS ADL			
Pre-operative	74.7 ± 13.7	75.6 ± 17.1	=0.7965
Follow-up	89.1 ± 16.9	87.3 ± 15.9	=0.5793
Improvement	14.4 ± 15.0	11.7 ± 20.8	=0.5181
Achieving PASS (>74.5)	30 (83%)	41 (73%)	=0.3150
KOOS Sport			
Pre-operative	40.1 ± 23.0	34.8 ± 21.1	=0.2616
Follow-up	62.8 ± 28.3	56.7 ± 30.7	=0.3419
Improvement	22.6 ± 26.2	21.9 ± 30.9	=0.9745
Achieving PASS (>22.5)	31 (86%)	39 (70%)	=0.0838
KOOS Qol			
Pre-operative	48.5 ± 22.1	40.2 ± 18.0	=0.0523
Follow-up	68.6 ± 25.2	60.1 ± 23.9	=0.1102
Improvement	20.0 ± 28.7	19.9 ± 23.4	=0.8126
Achieving PASS (>53.0)	27 (75%)	32 (57%)	=0.1185
Reoperations	5 (14%)	20 (36%)	=0.0300
Surgical Failures	2 (6%)	10 (18%)	=0.1171
Clinical Failures	10 (28%)	18 (32%)	=0.8168

Assessment of Outcomes Predictors

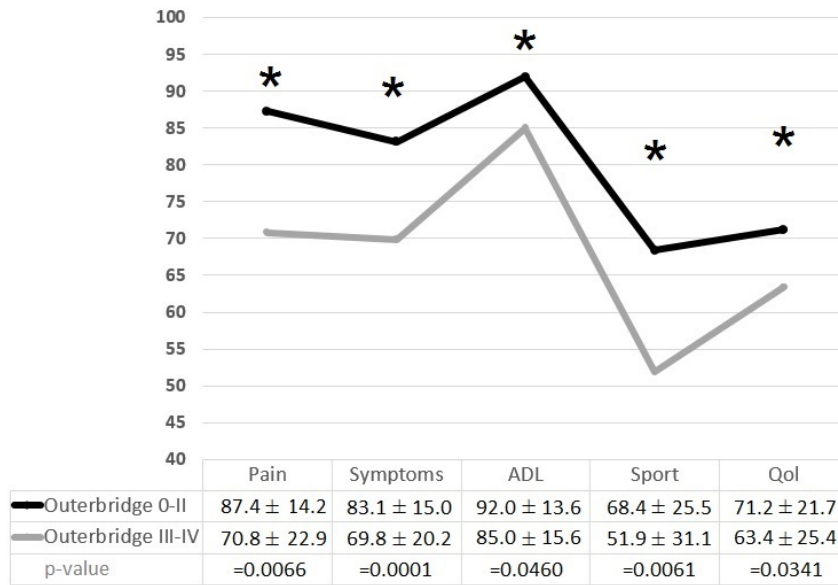
According to the multiple regression analysis performed on the whole series, having a chondropathy of III-IV Outerbridge grade resulted in -16.5 points in KOOS Pain subscale, -11.3 points in KOOS Symptoms subscale, -7.0 points in KOOS ADL subscale, -15.6 points in KOOS Sport subscale, -8.4 points in Lysholm score, +1.4 points in Pain at rest and +2.6 points in Pain during activity (Table 10); moreover, significantly lower values were reported in patients with chondropathy III-IV respect to those with chondropathy 0-II (Figure 9). Another outcomes predictor was the Timing of CMI ≥ 5 years after the meniscectomy, which resulted in +0.9 points in Pain at rest and -12.3 points in KOOS QoL subscale.

Table 10: Multivariate analysis of the effect on patient-reported outcomes of patients and surgical characteristics. CMI, collagen meniscus implant; VAS, visual analogue scale; KOOS, knee injury and osteoarthritis outcome score; ADL, activity of daily living; QoL, quality of life.

	<u>Lysholm</u>	<u>Tegner</u>	<u>VAS rest</u>	<u>VAS activity</u>	<u>KOOS Pain</u>	<u>KOOS Symptoms</u>	<u>KOOS ADL</u>	<u>KOOS Sport</u>	<u>KOOS QoI</u>
Sex (Female)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Age (≥ 45 years)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Overweight (BMI ≥ 25)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
CMI Side (Lateral)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Associated Procedure (Yes)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Chondropathy (Outerbridge III-IV)	-8.4 ($p=0.0402$)	N.S.	+1.4 ($p=0.0008$)	+2.6 ($p=0.0001$)	-16.5 ($p=0.0001$)	-11.3 ($p=0.0020$)	-7.0 ($p=0.0202$)	-15.6 ($p=0.0066$)	N.S.
Timing of CMI (≥ 5 years)	N.S.	N.S.	+0.9 ($p=0.0441$)	N.S.	N.S.	N.S.	N.S.	N.S.	-12.3 ($p=0.0075$)

Figure 9: Clinical scores according to the cartilage status. KOOS, knee injury and osteoarthritis outcome score. Asterisks represent statistically significant differences between the groups ($p < 0.05$).

KOOS SUBSCALES ACCORDING TO CARTILAGE STATUS



According to the logistic regression analysis, having a chondropathy of III-IV Outerbridge resulted in a higher Risk of not achieving the PASS for all the KOOS subscales and Lysholm, while an age at surgery ≥ 45 years resulted in a lower risk of not achieving PASS for the KOOS Pain subscale (Table 11).

Table 11: Analysis of Patients Acceptable Symptoms for KOOS and Lysholm Scores.

CMI, collagen meniscus implant; PASS, patient acceptable symptomatic state; VAS, visual analogue scale;

KOOS, knee injury and osteoarthritis outcome score; ADL, activity of daily living; Qol, quality of life

Table 11: Analysis of Patient Acceptable Symptoms State for KOOS and Lysholm Scores												
	KOOS Pain		KOOS Symptoms		KOOS ADL		KOOS Sport		KOOS QoI		Lysholm	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Patients Achieving PASS threshold												
Yes	74	(81%)	55	(60%)	70	(77%)	69	(76%)	58	(64%)	67	(75%)
No	17	(19%)	36	(40%)	21	(23%)	22	(24%)	33	(36%)	22	(25%)
Logistic Regression for Not Achieving PASS	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (Female)		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.
Age (≥45 years)	0.2 (0.1-0.8)	=0.0288		N.S.		N.S.		N.S.		N.S.		N.S.
Overweight (BMI ≥25)		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.
CMI Side (Lateral)		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.
Associated Procedure (Yes)		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.
Chondropathy (Outerbridge III-IV)	29.2 (3.1 - 270.2)	=0.0029	4.5 (1.7 - 12.1)	=0.0031	4.6 (1.4 - 15.6)	=0.0138	8.8 (2.2 - 35.7)	=0.0022	5.0 (1.8 - 14.0)	=0.0024	3.7 (1.2 - 11.2)	=0.0200
Timing of CMI (≥5 years)		N.S.		N.S.		N.S.		N.S.		N.S.		N.S.

5.2 Study 2 – Meniscus Allograft Transplantation

A total of 360 patients fulfilled the inclusion criteria (Figure 10). Mean follow-up time was 8.8 ± 3.6 years, mean age at surgery was 39.6 ± 11.4 years (*Table 12*).

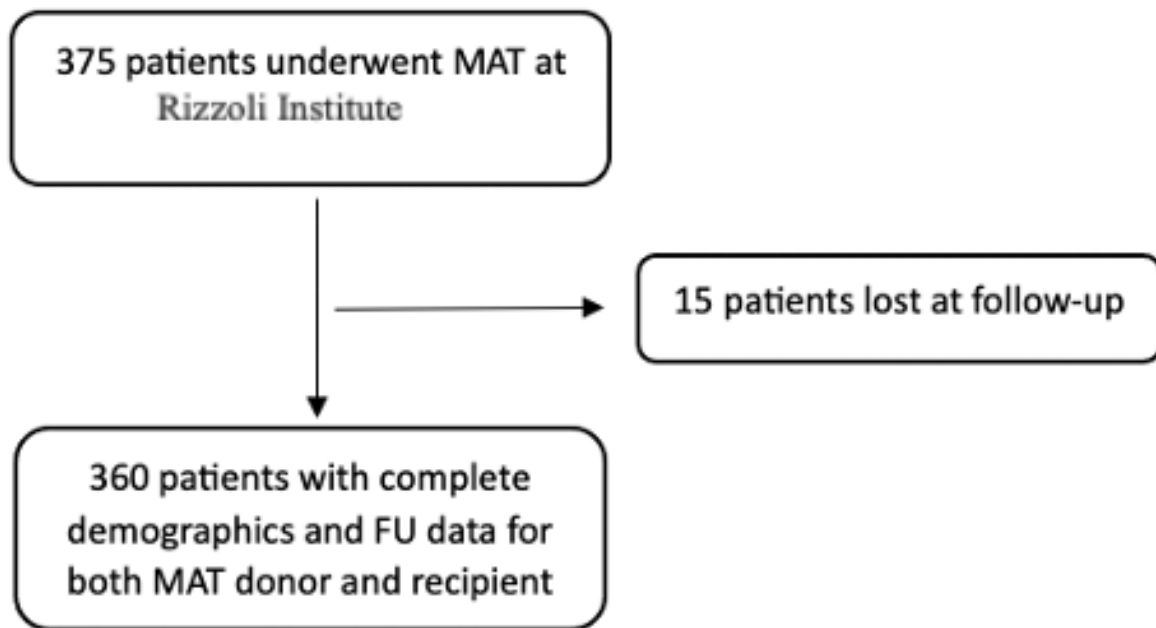


Figure 10: Consolidated Standards of Reporting Trials (CONSORT) diagram. Flowchart of patients included in the present study and reason for their exclusion. MAT (Meniscus Allograft Transplantation).

A total of 34 (9.44%) surgical failures were recorded, mean survival time was 15.3 ± 0.2 years. The most frequent cause of surgical failure was the necessity of allograft resection (22/34 failures); other type of reoperations were linked to infection, MAT revision, total knee arthroplasty and unicompartmental knee arthroplasty (*Table 13*, *Figure 12*).

A total of 170 concomitant procedures were performed during MAT: the most frequent ones were HTO (high tibial osteotomy), primary ACL (anterior cruciate ligament) reconstruction and ACL revision (*Table 14*).

	Recipient Population	Donor population
Number of patients (N)	360	360
Age at Surgery (y)	39.6±11.4	43.1±12.1
BMI	24.6±4.5	25.2
SEX	M = 247 (68.6%) F = 113 (31.4%)	M = 252 (70.0%) F= 108 (30.0%)
Mean FU (y)	8.8±3.6	

Table 12 Patient characteristics - BMI, body mass index

Type of reoperation	N. of failures
Surgical Failure (N)	34 / 360 (9.44%)
Total knee arthroplasty	5
Unicompartmental knee arthroplaty	2
MAT revision	2
Infection	3
Allograft resection	22

Table 13 Causes of reoperation. MAT: meniscus allograft transplantation.

Associated procedures	N. of surgery performed
HTO	46
DFO	14
Primary ACL reconstruction	34
ACL revision	31
HTO+ACL reconstruction	16
Cartilage procedure	26
Controlateral meniscal suture	3
Overall	170

Table 14 Associated procedures during meniscus allograft (MAT) transplantation; HTO: high tibial osteotomy; DFO: distal tibial osteotomy; ACL: anterior cruciate ligament

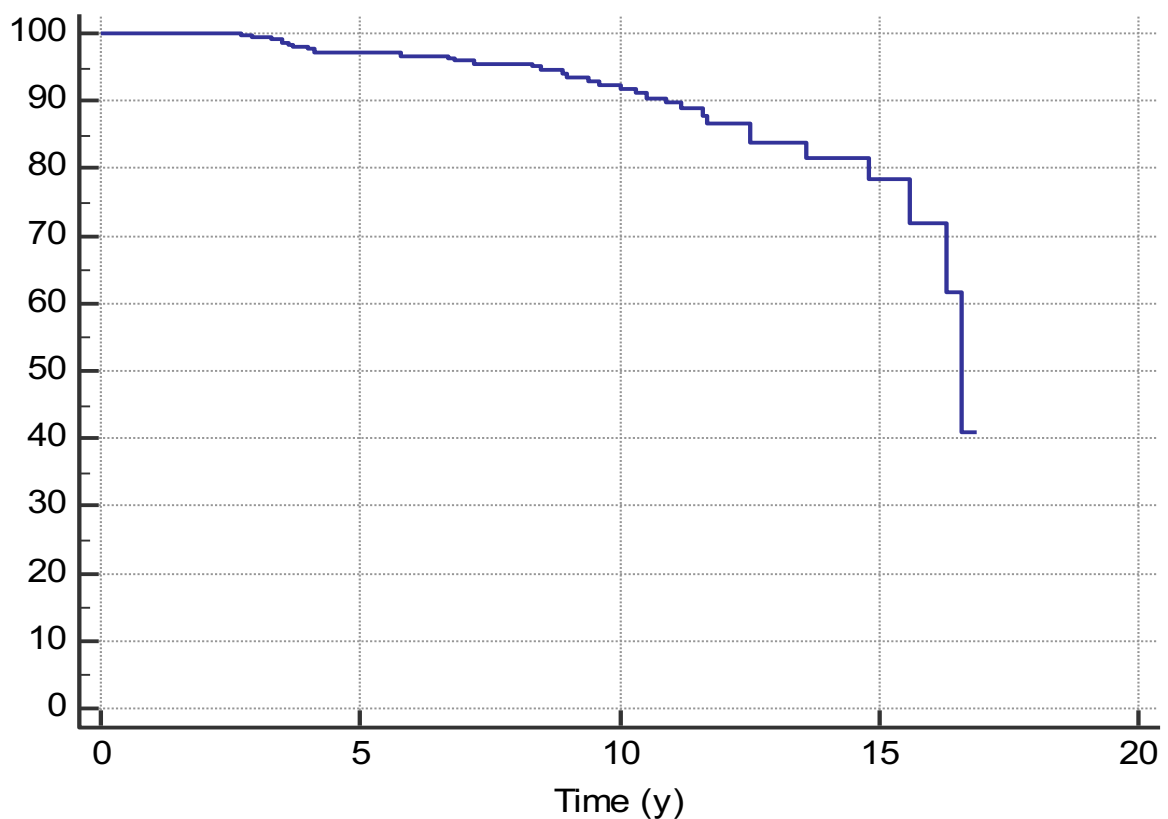


Figure 12: Kaplan-Meier mean survival rate.

Multivariate logistic regression did not show any significant correlation between surgical failure and the various factors mentioned below ($p=0.892$ - $r^2=0.010$). (table 15

	Coefficients		
	Estimate	Odds Ratio	P value
deltaBMI	-0.078	0.925	0.598
deltaWEIGHT	0.004	1.004	0.911
deltaAGE	0.004	1.004	0.838
Donor time harvesting to surgery (months)	-0.020	0.980	0.232
Recievent age at surgery	-0.010	0.990	0.696
Recievent weight at surgery (kg)	-0.003	0.997	0.929
Recievent BMI at surgery	-0.067	0.935	0.681
Donor age (years)	-0.013	0.987	0.600
Donor weight (kg)	-0.015	0.985	0.676
Donor BMI	-0.003	0.997	0.985

Table 15 Multivariate logistic regression.

Survivorship from Sex Mismatch

The only factors that resulted statistically significant in relation to surgical failure was sex mismatch between donor and recipient ($p < 0.001$). Sex concordance found 8/31 (25.81%) surgical failures in the non-concordant group, while only 26/329 (7.9%) failures were registered in the concordant group. Hazard ratios with 95% confidence interval (IC 95%) was calculated as 20.5 (5.0-83.5), with respect of non-concordant vs concordant group. (*table 16, figure 13*)

Subgroup analysis based on donor-recipient specific sex concordance found out statistically significant results. In particular, group 2 (male donor, female recipient) showed much higher failure rate (7/18 - 38.9%) than the other groups. Hazard ratios with 95% confidence interval (IC 95%) was calculated as 9.7 (1.3-71.1) in relation to group 2 vs group 1. (*table 16 and figure 14*)

	Failures (%)	Survival probability			P value
		5 y	10 y	15 y	
Overall	34/360 (9.4)	97.1	91.8	78.3	<0.0001
Concordant	26/329 (7.9)	98.7	93.5	79.7	
Non concordant	8/31 (25.8)	79.0	71.8	62.8	<0.0001
Male to Male	17/234 (7.2)	99.5	94.8	77.4	
Male to Female	7/18 (38.8)	67.6	54.1	36.0	
Female to Male	1/13 (7.6)	92.3	92.3	92.3	
Female to Female	9/95 (9.1)	96.8	90.2	85.4	<0.0001

Table 16 Kaplan Meier survivorship analysis in relation to sex mismatch between donor and recipient; concordant= donor and recipient share the same sex

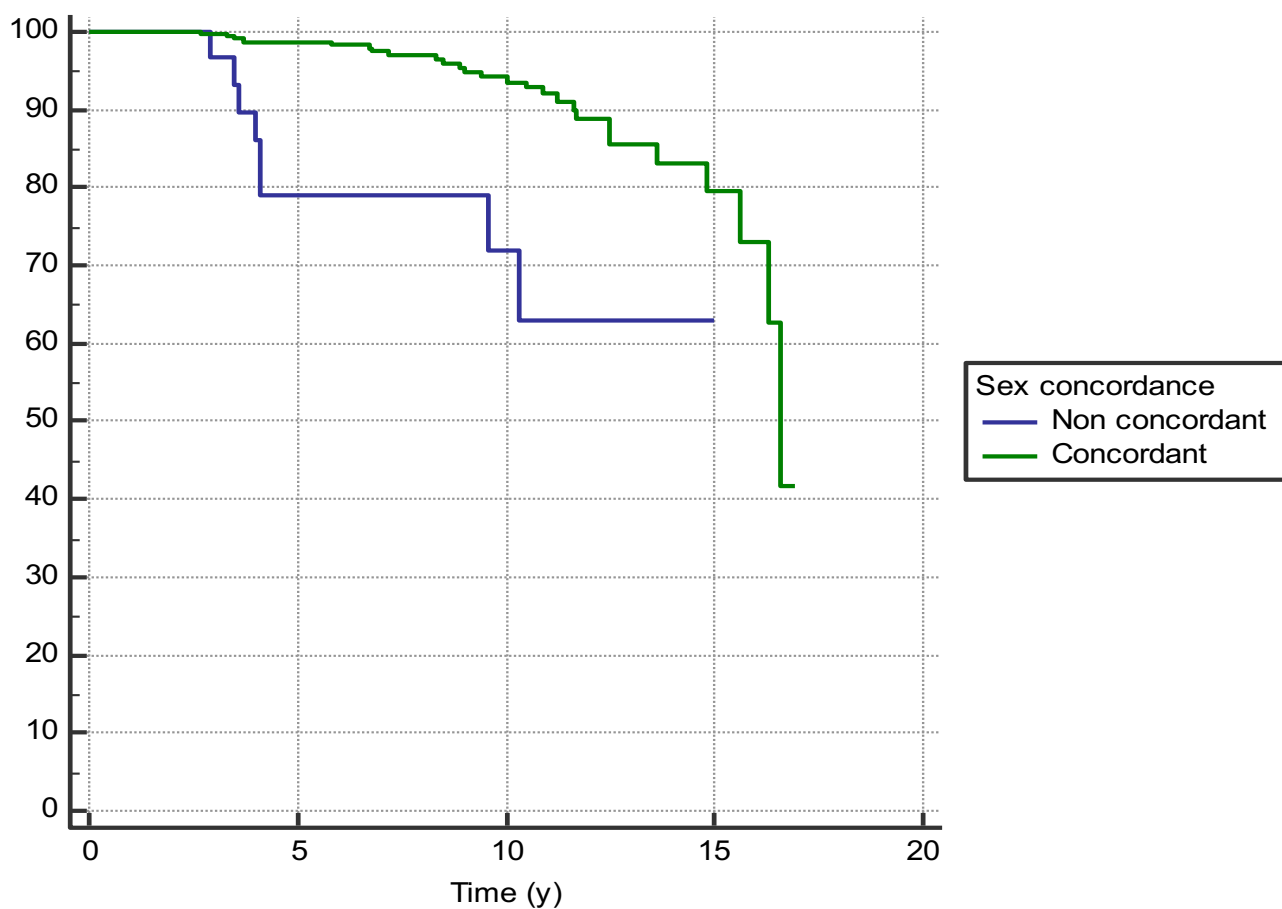


Figure 13 Kaplan Meier curves describing survivorship from surgical failure in relation to concordant/non concordant sex between donor and recipient.

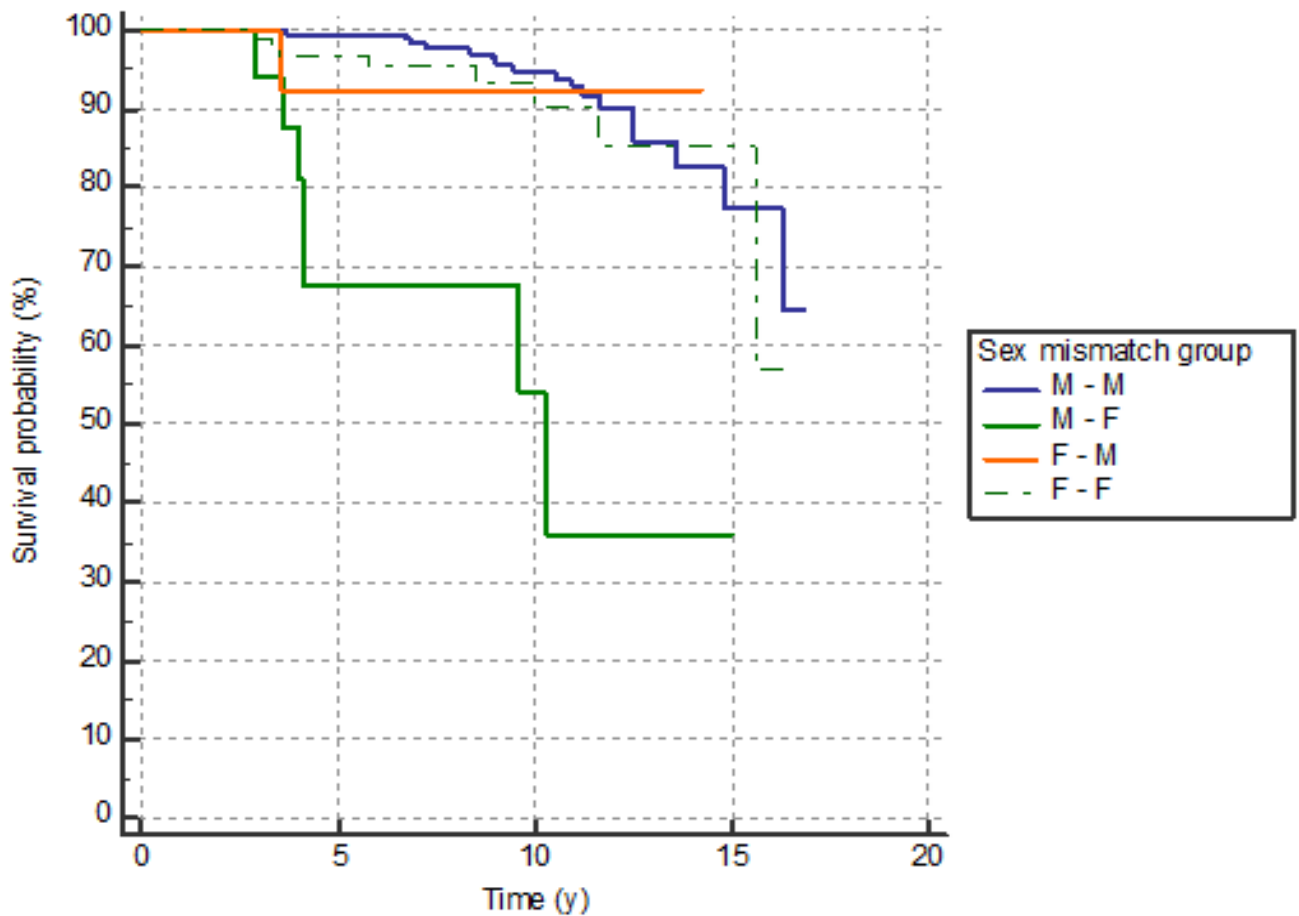


Figure 14 Kaplan Meier curves describing survivorship from surgical failure in relation to concordant/non concordant sex between donor and recipient (on the left) and survivorship from surgical failure in relation to specific group mismatch sex between donor and recipient (on the right)

Survivorship from Blood Group Mismatch

In relation to blood group analysis only a subgroup of 247 patients fulfilled the inclusion criteria, due to missing data from medical chart or patients lost at follow-up.

Among the donor population were registered 98 “A”, 25 “B”, 17 “AB” and 107 “O” blood groups.

Among the recipient population were registered 104 “A”, 29 “B”, 3 “AB” and 111 “O” blood groups. This subgroup presented no demographics statistically significant characteristics with respect to the general population. A total of 14/247 (5.67%) surgical failure was recorded.

Univariate blood group analysis did not show any significant correlation to surgical failure (p=0.915). (table 17, figure 15)

	Failures (%)	Survival probability			P value
		5 y	10 y	15 y	
Identical	5/94 (5.3)	98.8	93.4	81.9	0.915
Concordant	3/59 (5.0)	98.0	95.4	84.8	
Non concordant	6/94 (6.3)	100	93.9	85.4	
Overall	14/247 (5.6)	99.1	94.2	83.8	

Table 17 Kaplan Meier survivorship analysis in relation to blood group concordance; concordant: compatibility between donor and recipient blood group

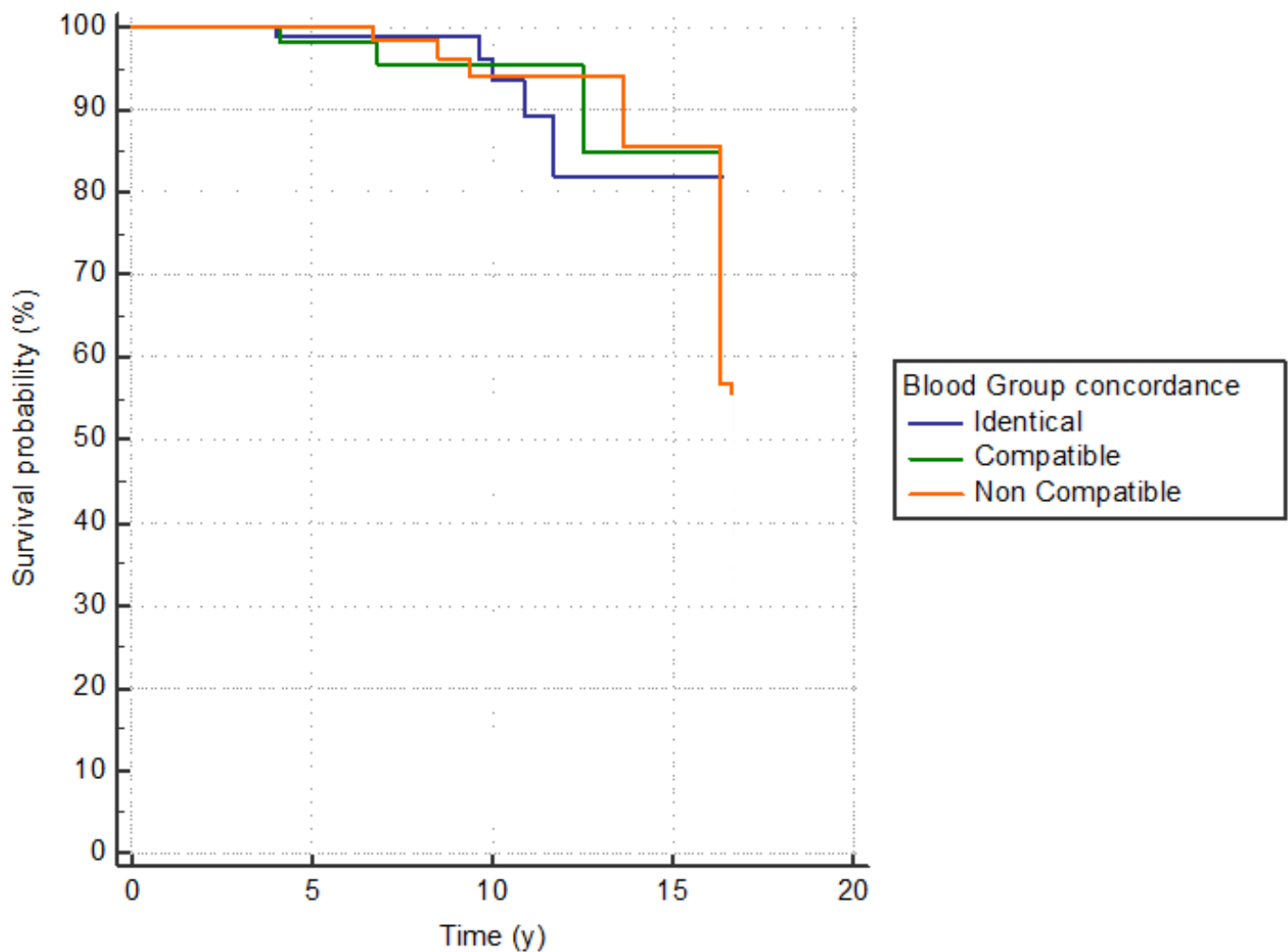


Figure 15 Kaplan Meier curves describing survivorship from surgical failure in relation to blood group concordance between donor and recipient.

6. Discussion

6.1 Study 1 – Scaffold

The most important findings of the present study are that the CMI provides satisfactory and long-lasting clinical results with only 13% of surgical failures and more than 70% of patients achieving the PASS for Lysholm at 12 years of follow-up. The sports activity level steadily improved compared to the preoperative status, and almost two-thirds of the patients were still active at the long-term evaluation. Furthermore, several factors were associated with lower clinical scores, including an increasing time from meniscectomy to scaffold, age, and the Outerbridge grade. Satisfactory clinical outcomes of the meniscus scaffold have been previously reported, with an improvement in symptoms and function compared to the pre-operative status at short to mid-term follow-up³¹. However, only three case series investigated the long-term outcomes of the CMI, and none of them evaluated the PASS and the predictive factors affecting the clinical outcomes after meniscus scaffold substitution.

Two separated long-term case-series with overall less than 40 patients reported significant and stable clinical outcomes at 10 years of follow-up after medial meniscus scaffold implantation with only two overall failures^{32,33}. On the other hand, results from a long-term multicenter study on the lateral CMI reported a significantly higher failure rate, more pain, and a lower activity level when compared with the existing literature on the medial scaffold³⁴. Similarly, a recent long-term survival analysis identified the lateral scaffold as a risk factor for surgical failure, with a 10-year survival rate of 77% versus 90% of the medial CMI³⁵.

Conversely, in the present study, the multivariate analysis found no significant difference in PROMs concerning the medial versus lateral scaffold. Those results align with a recent CMI and polyurethane meniscus scaffold meta-analysis that found no differences in clinical outcomes or

survival rates between medial and lateral meniscal scaffolds at short or mid-term follow-up³⁶.

Moreover, 75% of the patients achieved the PASS for the Lysholm score, and this satisfactory results are in line with studies investigating the clinical outcomes of different meniscus substitution techniques³⁷.

The return to sport rate, the reduced pain during activity, and the Tegner level at the final follow-up should be considered satisfactory considering the mean age of the patients and the multiple knee comorbidities of the study population. Similarly to studies investigating the outcomes of MAT, return to sports activity appears to be a reasonable expectation after meniscus scaffold substitution, especially for low-impact sports³⁸.

However, because there are few studies and limited evidence about the impact of sports activity and cartilage degeneration after meniscus substitution, high-impact activities must be considered with caution keeping in mind that the general ambition should be to preserve the knee function for daily living activities and work^{31 39 40 41}.

An interesting finding of the present study is that patients who underwent isolated CMI showed similar overall outcomes but less knee pain when compared with patients who underwent combined surgeries. These results contrast with Gelber et al.⁴², which reported inferior clinical results in patients with varus knee and meniscus deficiency when the HTO was associated with the implant of a polyurethane meniscus scaffold.

Our findings further underline the effect of the CMI as a standalone procedure and contest the conclusion of a recent systematic review that hypothesized that the presence of concomitant surgeries may have a significant influence on the positive results after scaffold substitution⁴³.

However, considering that 14 out of 36 patients (38%) included in the “Isolated” group underwent acute CMI implantation, it could also be hypothesized that the clinical benefit could be related to the meniscectomy itself rather than the scaffold. For this reason and due to the heterogeneity of the study population, it remains challenging to draw a definitive conclusion regarding the effect of the isolated CMI.

In the present study, sex and BMI did not show any impact on the clinical outcomes. However, while the effect of sex has been less investigated in the meniscus scaffold literature, two separate reports showed a higher incidence of revision and surgical failures in female patients requiring MAT^{44 45}. Moreover, conversely to our results, in a multicentric study of 43 patients who underwent lateral CMI, a higher BMI was correlated with inferior clinical results⁴⁶. Thus, the effect of these two parameters on the clinical outcomes should be further investigated due to inconclusive evidence.

One of the most debated topics in the meniscus substitution literature is the ideal time elapse between meniscectomy and meniscus transplant or scaffold implant⁴⁷. In the present study, we found that patients that waited more than 5 years for meniscus scaffold substitution reported significantly higher pain scores and reduced quality of life at the final follow-up. Although historically, the CMI has been advocated to be more effective in the chronic setting, there is now growing evidence of a potential superior benefit in more acute cases^{48 49}.

In a large case series of CMI, the authors reported that waiting more than 10 years after meniscectomy was correlated with a significantly higher risk of surgical or clinical failure regardless of the cartilage status³⁵. Interestingly another study reported that waiting for as little as 6 months after a meniscectomy may reduce clinical outcomes and sports level at short-term follow-up⁴⁸. Finally, an interesting study on the effect of meniscus transplant found that, compared to the conventional delayed MAT, an acute MAT achieved better cartilage and meniscus protection in the long-term. However, the impact on the clinical outcomes was minimal⁵⁰.

Another interesting result of the present study was that patients aged more than 45 years or older not only showed similar outcomes when compared with younger patients but were also more likely to achieve the PASS in the pain subscale. A previous study showed that age was not correlated with surgical failure. The present study's clinical results further confirm that age does not represent a contraindication for meniscus scaffold. This data appears promising, considering that one of the most common patient profiles of the candidates for meniscus scaffold is represented by a middle-

aged man with a previous partial meniscectomy or with meniscus tears on degenerated tissue.

Similarly to the MAT, during scaffold substitution, the patient should be carefully evaluated, and clinical outcomes and survivorship are predominantly affected by age-related factors, including time from meniscectomy and chondropathy, rather than age itself⁵¹.

Despite the strength of a long-term minimum follow-up of 10 years and the large number of patients and the a satisfactory follow-up rate, the present study presents several limitations. Firstly, this is a retrospective study, and there is a lack of a control group of patients who underwent isolated meniscectomy. One of the main limitations of the present study is related to the heterogeneity of follow-up assessment. Clinical outcomes were collected through a combination of in-person evaluations and telephone-based interviews, particularly in patients with long-term follow-up. Although this approach may introduce a potential source of bias, it reflects the real-world conditions of large retrospective cohorts and allowed the inclusion of patients who would otherwise have been lost to follow-up. Importantly, validated patient-reported outcome measures were consistently used in both assessment modalities, partially mitigating this limitation.

Another relevant aspect that may influence the interpretation of clinical outcomes is the role of lower limb alignment and associated capsulo-ligamentous conditions. Varus or valgus deformities, quantified by the hip–knee–ankle (HKA) angle, as well as the presence or progressive degeneration of the ACL over time, are known to significantly affect knee biomechanics and load distribution. Although alignment correction and ligament stabilization were performed when clinically indicated, residual or progressive alterations may still act as confounding factors during long-term follow-up, potentially influencing symptom recurrence, graft overload, or progression toward osteoarthritis. Therefore, multiple sub-analysis were performed to evaluate each parameter individually. Additionally, the PASS used in the present analysis was validated for patients requiring MAT³⁰. Nevertheless, it is to be considered that there are no PASS scores validated for meniscus scaffold and that the demographic characteristics and knee pathology of patients requiring one of these two procedures are similar.

Lastly, since no MRI was performed at the last follow-up, it is not possible to evaluate parameters such as cartilage degeneration over time, scaffold extrusion or reabsorption. However, this study was specifically designed to evaluate predictors of clinical outcomes and the radiological classification system and features of meniscus implant have been shown to be poorly correlated with patient's symptoms, especially at a long-term follow-up^{52 53}.

6.2 Study 2 – Meniscus Allograft Transplantation

The present study indicated that gender match between meniscus donor and recipient is an important graft survival determinant. Specifically, sex mismatch was found to have a negative impact on the outcome of MAT, with a four times increase of failure rate when a meniscus from a male donor was transplanted in female patient compared to the other groups.

When dealing with solid organs transplantation, the presence of sex mismatch between the donor and the recipient has been correlated with worse clinical results and increased complication rate [16] [34] [32].

On the other hands, while the immunogenicity of the meniscus and other musculoskeletal tissues like cartilage and bone has been generally considered to be very low after freezing, there is still the possibility that some immunologic mechanism may affect the outcome of MAT in the presence of sex mismatch [11] [31].

A recent mid-term study of a large series of more than 300 MAT found that female patients were much more likely to report poor Lysholm scores (i.e., a 100-point scoring system for examining a patient's knee-specific symptoms) when compared with male patients, with a percentage of 49% and 69%, respectively 9. Similarly, Frank et al. showed that female patients may be more likely to undergo MAT revision at 5 years of follow-up when compared with males [5].

Differently from the previously reported studies, the present research was designed to evaluate the

effect of sex mismatch and other parameters on the outcomes after MAT. Therefore, the increased failure rates reported in the present study only in female patients who received a mismatched meniscus could also represent one of the possible explanations for the inferior clinical outcomes experienced in female patients after MAT.

Similarly to our findings, a recent analysis of 154 osteochondral allograft transplantation (OCA) showed that the failure rate in the presence of sex mismatch between the donor and recipient was 3 times higher at 5 years of follow-up, with an estimate survival rate of 63% compared to more than 90% when donor and recipient had the same sex [22]. Furthermore, when the authors further divided the patients into four different groups, they found that an increased failure rate was not observed when female graft was transplanted into male patients but only when a male graft was implanted into female recipients [22].

Compared with OCA, in MAT procedures the biological interaction between the donor and the host appears to be even more crucial because of the lack of press-fit fixation of the MAT. After the initial meniscus fixation, the biological healing and integration of the graft with the capsule is crucial to allow the physiological meniscus movement without the risk of tears or meniscus-capsular separation of the allograft [17]. Furthermore, in literature there have been anecdotal reports of acute meniscus allograft rejection and histological studies describing intense synovitis, leukocyte infiltration and elevated antibodies after MAT, however post-transplantation immune response has not yet been thoroughly studied and the influence of sex has yet to be defined [10] [17] [23] [12]. Nevertheless, the negative impact of sex mismatch on the outcomes of MAT could not be necessarily related to host immune system and additional characteristics such as bony morphology, hormonal profile and general inflammatory response could be relevant factor influencing the inferior results observed in the female patients receiving a graft from male donors.

An additional relevant finding of the present study is that an increased age of the donor or an age mismatch between the donor and the patients were not associated with increased failure rate at mid-term follow-up. This finding is particularly interesting, considering that the age threshold for

meniscus donation in the present study was 55 years and this extended age range could raise concern on meniscus graft biomechanical properties and risk of degeneration with a potential clinical impact.

To best of our knowledge, this is the first clinical study investigating the impact of donor age on the outcomes after MAT and, therefore, the present's study results could only be compared to in-vitro studies. A biomechanical study performed on 58 fresh-frozen human meniscal allograft investigated the biomechanical and chemical graft properties as a function of age. The authors did not find any correlations between donor age and static or dynamic tensile stiffness for either the medial and the lateral meniscus. Moreover, increased age was not affecting collagens and proteoglycan content [2]. Notably, the authors included meniscus graft up to 45 years and for this reason their results should not be generalized to an older population. On the other hand, a similar study investigating biomechanical properties of meniscus graft of patients younger than 45 years or older than 65 years, found that menisci from the older group had 30% less tensile strain and absorbed 60% less energy before failure when compared with graft from younger donors [25]. Moreover, an increased age of the graft donor may also have an impact on the maturation, integration of the graft with the host capsule and with the meniscus long-term functions although it was not found to be clinically relevant in the present study.

In the past years, several investigations on the effect of graft processing and conservation have been performed to evaluate the impact of graft preparation on the MAT survival rate [30] [29]. Some of them have shown that the graft conservation modalities could have an impact on clinical outcomes with fresh-frozen allografts showing better clinical scores and low failure rate when compared with cryopreserved MAT [4]. Moreover, studies on human musculoskeletal tissue have found that prolonged freezing decreased load to failure, ultimate stress, ultimate strain and is responsible for histological alterations in human allograft [7]. However, these potential biomechanical alterations were not found to have any clinical impact in the present study.

The present study has several limitations. First, it is a retrospective analysis. Moreover, the main endpoint of the study was represented by surgical failure and, therefore, it was not possible to evaluate if the analyzed risk factors could have an impact on patient's reported outcomes. Similarly, since no MRI follow-up was performed, it was not possible to evaluate tears or extrusion of the transplanted meniscus and the cartilage wear over time in the different subgroups of patients. However, there is still no consensus on the clinical relevance of several imaging findings after meniscus transplantation procedures and the graft removal still represents the most commonly accepted failure criteria after MAT procedure [3] [28] [9] [20] [13].

Another limitation is that most of the patients included in the present study underwent several previous knee surgeries and a considerable amount of them underwent an associated surgical procedure to MAT surgery. However, this heterogeneous population is common when dealing with patients suffering from "post-meniscectomy syndrome" and complex patients with multiple knee comorbidities are more often referred to a high-level knee surgery centers in which MAT is performed routinely.

Another main limitation of the present study is represented by the reduced patient number in the female-to male (13 patients, 3.6% of total) and in the male-to-female patients (18 patients, 5.0% of the total) groups when compared with groups without sex mismatch. This aspect increases the fragility of our statistical analysis, however an imbalance between groups was expected because the sex was considered one of the criteria for MAT matching.

Finally, in the present study a surgical procedure with soft tissue fixation of fresh-frozen, non-irradiated MAT was performed. Therefore, the results of the present study could not be generalized, and different results could be possible with an allograft bony fixation or if the graft is stored and treated differently, or even sterilized. The distinction between medial and lateral meniscal substitution represents another important element to consider when interpreting clinical outcomes. Medial and lateral compartments are characterized by different biomechanical environments, loading patterns, and degenerative trajectories, which may influence both symptom evolution and

the progression toward osteoarthritis. While differences between medial and lateral collagen meniscus implants have been partially explored in the literature, the present study was not primarily designed to perform a dedicated comparison between medial and lateral MAT outcomes.

Nevertheless, compartment-specific differences should be taken into account when counseling patients and interpreting long-term survivorship, and they warrant further investigation in future studies with larger and more balanced cohorts.

7. Integrated Discussion and Conclusion

Integrated Discussion and Conclusions

This doctoral thesis focused on two complementary strategies for meniscal substitution: collagen-based scaffolds for partial defects and meniscal allograft transplantation (MAT) for total or subtotal meniscal loss. Although the clinical indications differ, both procedures aim to restore meniscal function and to delay the degenerative cascade that typically follows meniscectomy.

Main findings of Study 1 – Meniscus scaffold

Long-term follow-up of collagen scaffold implantation demonstrated overall improvement in patient-reported outcomes, particularly in pain and function scores. However, failure rates were not negligible, and certain demographic and surgical factors emerged as predictors of poor outcomes. In particular, advanced cartilage damage and previous meniscectomy at more than five years from scaffold implantation surgery were associated with inferior results, underlining the critical importance of careful patient selection. These findings confirm that scaffolds represent a viable option for symptomatic patients with segmental meniscal loss and preserved meniscal roots, but they are not a definitive substitute for the native meniscus.

Main findings of Study 2 – Meniscal allograft transplantation

The analysis of MAT outcomes highlighted the prognostic role of donor–recipient characteristics. While previous literature has mostly focused on graft sizing and preservation techniques, this study identified donor–recipient sex mismatch as a negative predictor of survival. Patients receiving a graft from a donor of the opposite sex showed lower survival rates compared to sex-matched transplantations. This novel observation may reflect biological differences in tissue composition, hormonal influences on meniscal cells and matrix, or subtle anatomical discrepancies between male

and female menisci. Importantly, other demographic factors such as age or BMI mismatch were not as strongly associated with outcomes, suggesting that sex mismatch should be specifically considered in donor allocation.

Integrated interpretation

Taken together, the two studies reinforce the concept that meniscal substitution should not be regarded as a single universal solution but as a set of tailored strategies. For partial defects, scaffolds provide a biological environment that may alleviate symptoms and slow degeneration, though with limitations in durability. For total loss, MAT remains the gold standard, but results can be optimized by refining selection criteria—not only on the recipient side (age, cartilage status, alignment, stability) but also on the donor side, with particular attention to sex matching.

These findings contribute to the ongoing refinement of treatment algorithms for post-meniscectomy syndrome. Scaffolds may be best reserved for focal, painful defects in young patients with low-grade chondropathy and preserved stability. MAT, on the other hand, can be indicated for subtotal or total loss, but donor–recipient sex matching should be prioritized whenever possible to improve survivorship. This suggests the need for updated allocation protocols in tissue banks.

Further research is required to confirm these results in larger multicenter cohorts and to clarify the biological mechanisms underlying sex mismatch in MAT. Moreover, emerging strategies such as cell-seeded scaffolds, 3D-printed implants, and biologically augmented grafts hold promise for the future. Integration of these technologies with refined patient selection criteria may pave the way toward more durable and personalized meniscal restoration.

Future research should aim to further clarify the impact of limb alignment, ligament status, and compartment-specific differences on clinical outcomes after meniscal substitution. A more comprehensive understanding of these factors may contribute to improved patient selection, optimized surgical planning, and more durable long-term results, moving toward a more personalized approach to meniscus preservation and restoration.

Conclusions

This thesis demonstrated that both scaffolds and MAT can improve symptoms after meniscectomy, but outcomes are strongly influenced by specific risk factors. For scaffolds, cartilage status and previous surgeries are decisive, while for MAT, donor–recipient sex mismatch is a novel and independent predictor of failure. Overall, the results emphasize the importance of personalized approaches in meniscus surgery, moving from a one-size-fits-all model toward precision medicine.

8. References

1. Clark CR, Ogden JA. Development of the menisci of the human knee joint. Morphological changes and their potential role in childhood meniscal injury. *J Bone Joint Surg Am*. 1983;65(4):538-547.
2. Papageorgiou CD, Gil JE, Kanamori A, Fenwick JA, Woo SL, Fu FH. The biomechanical interdependence between the anterior cruciate ligament replacement graft and the medial meniscus. *Am J Sports Med*. 2001;29(2):226-231. doi:10.1177/03635465010290021801
3. Śmigielski R, Becker R, Zdanowicz U, Ciszek B. Medial meniscus anatomy-from basic science to treatment. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(1):8-14. doi:10.1007/s00167-014-3476-5
4. Fenn S, Datir A, Saifuddin A. Synovial recesses of the knee: MR imaging review of anatomical and pathological features. *Skeletal Radiol*. 2009;38(4):317-328. doi:10.1007/s00256-008-0570-0
5. Papalia R, Simonetta R, Di Vico G, et al. Tears of popliteomeniscal fascicles, diagnostic and clinical implications. A review of the evidence. *J Biol Regul Homeost Agents*. 2016;30(4 Suppl 1):99-106.
6. Gupte CM, Bull AM j, Thomas RD, Amis AA. A review of the function and biomechanics of the meniscomfemoral ligaments. *Arthroscopy*. 2003;19(2):161-171. doi:10.1053/jars.2003.50011
7. LaPrade CM, Ellman MB, Rasmussen MT, et al. Anatomy of the anterior root attachments of the medial and lateral menisci: a quantitative analysis. *Am J Sports Med*. 2014;42(10):2386-2392. doi:10.1177/0363546514544678
8. Johannsen AM, Civitarese DM, Padalecki JR, Goldsmith MT, Wijdicks CA, LaPrade RF. Qualitative and quantitative anatomic analysis of the posterior root attachments of the medial and lateral menisci. *Am J Sports Med*. 2012;40(10):2342-2347. doi:10.1177/0363546512457642
9. Herwig J, Egner E, Buddecke E. Chemical changes of human knee joint menisci in various stages of degeneration. *Ann Rheum Dis*. 1984;43(4):635-640. doi:10.1136/ard.43.4.635
10. Ingman AM, Ghosh P, Taylor TK. Variation of collagenous and non-collagenous proteins of human knee joint menisci with age and degeneration. *Gerontologia*. 1974;20(4):212-223. doi:10.1159/000212017
11. Masouros SD, McDermott ID, Amis AA, Bull AMJ. Biomechanics of the meniscus-meniscal ligament construct of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2008;16(12):1121-1132. doi:10.1007/s00167-008-0616-9

12. Arnoczky SP, Warren RF. Microvasculature of the human meniscus. *Am J Sports Med.* 1982;10(2):90-95. doi:10.1177/036354658201000205
13. Benedetto KP, Glötzer W, Künzel KH, Gaber O. [The vascularization of the menisci. Morphological basis for the repair]. *Acta Anat (Basel).* 1985;124(1-2):88-92.
14. Renström P, Johnson RJ. Anatomy and biomechanics of the menisci. *Clin Sports Med.* 1990;9(3):523-538.
15. Baratz ME, Fu FH, Mengato R. Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. *Am J Sports Med.* 1986;14(4):270-275. doi:10.1177/036354658601400405
16. Fairbank TJ. Knee joint changes after meniscectomy. *J Bone Joint Surg Br.* 1948;30B(4):664-670.
17. Allen CR, Wong EK, Livesay GA, Sakane M, Fu FH, Woo SL. Importance of the medial meniscus in the anterior cruciate ligament-deficient knee. *J Orthop Res.* 2000;18(1):109-115. doi:10.1002/jor.1100180116
18. Bozkurt M, Elhan A, Tekdemir I, Tönük E. An anatomical study of the menisofibular ligament. *Knee Surg Sports Traumatol Arthrosc.* 2004;12(5):429-433. doi:10.1007/s00167-003-0450-z
19. Kopf S, Beaufils P, Hirschmann MT, et al. Management of traumatic meniscus tears: the 2019 ESSKA meniscus consensus. *Knee Surg Sports Traumatol Arthrosc.* 2020;28(4):1177-1194. doi:10.1007/s00167-020-05847-3
20. Beaufils P, Becker R, Kopf S, et al. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. *Knee Surg Sports Traumatol Arthrosc.* 2017;25(2):335-346. doi:10.1007/s00167-016-4407-4
21. Sun J, Vijayavenkataraman S, Liu H. An Overview of Scaffold Design and Fabrication Technology for Engineered Knee Meniscus. *Materials (Basel).* 2017;10(1):29. doi:10.3390/ma10010029
22. Rodkey WG, Steadman JR, Li ST. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthop Relat Res.* 1999;(367 Suppl):S281-292. doi:10.1097/00003086-199910001-00027
23. Stone KR, Steadman JR, Rodkey WG, Li ST. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data. *J Bone Joint Surg Am.* 1997;79(12):1770-1777. doi:10.2106/00004623-199712000-00002
24. Verdonk P, Beaufils P, Bellemans J, et al. Successful treatment of painful irreparable partial meniscal defects with a polyurethane scaffold: two-year safety and clinical outcomes. *Am J Sports Med.* 2012;40(4):844-853. doi:10.1177/0363546511433032
25. Reale D, Lucidi GA, Grassi A, Poggi A, Filardo G, Zaffagnini S. A Comparison Between Polyurethane and Collagen Meniscal Scaffold for Partial Meniscal Defects: Similar Positive Clinical Results at a Mean of 10 Years of Follow-Up. *Arthroscopy.* 2022;38(4):1279-1287. doi:10.1016/j.arthro.2021.09.011

26. A Cavendish P, DiBartola AC, Everhart JS, Kuzma S, Kim WJ, Flanigan DC. Meniscal allograft transplantation: a review of indications, techniques, and outcomes. *Knee Surg Sports Traumatol Arthrosc.* 2020;28(11):3539-3550. doi:10.1007/s00167-020-06058-6
27. Getgood A, LaPrade RF, Verdonk P, et al. International Meniscus Reconstruction Experts Forum (IMREF) 2015 Consensus Statement on the Practice of Meniscal Allograft Transplantation. *Am J Sports Med.* 2017;45(5):1195-1205. doi:10.1177/0363546516660064
28. Grassi A, Di Paolo S, Coco V, et al. Survivorship and Reoperation of 324 Consecutive Isolated or Combined Arthroscopic Meniscal Allograft Transplants Using Soft Tissue Fixation. *Am J Sports Med.* 2023;51(1):119-128. doi:10.1177/03635465221131522
29. Novaretti JV, Patel NK, Lian J, et al. Long-Term Survival Analysis and Outcomes of Meniscal Allograft Transplantation With Minimum 10-Year Follow-Up: A Systematic Review. *Arthroscopy.* 2019;35(2):659-667. doi:10.1016/j.arthro.2018.08.031
30. Liu JN, Gowd AK, Redondo ML, et al. Establishing Clinically Significant Outcomes After Meniscal Allograft Transplantation. *Orthop J Sports Med.* 2019;7(1):2325967118818462. doi:10.1177/2325967118818462
31. Reale D, Previtali D, Andriolo L, et al. No differences in clinical outcome between CMI and Actifit meniscal scaffolds: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* Published online April 16, 2021. doi:10.1007/s00167-021-06548-1
32. Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up study. *Am J Sports Med.* 2011;39(5):977-985. doi:10.1177/0363546510391179
33. Monllau JC, Gelber PE, Abat F, et al. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. *Arthroscopy.* 2011;27(7):933-943. doi:10.1016/j.arthro.2011.02.018
34. Grassi A, Lucidi GA, Filardo G, et al. Minimum 10-Year Clinical Outcome of Lateral Collagen Meniscal Implants for the Replacement of Partial Lateral Meniscal Defects: Further Results From a Prospective Multicenter Study. *Orthop J Sports Med.* 2021;9(5):2325967121994919. doi:10.1177/2325967121994919
35. Lucidi GA, Grassi A, Agostinone P, et al. Risk Factors Affecting the Survival Rate of Collagen Meniscal Implant for Partial Meniscal Deficiency: An Analysis of 156 Consecutive Cases at a Mean 10 Years of Follow-up. *Am J Sports Med.* 2022;50(11):2900-2908. doi:10.1177/03635465221112635
36. Phua SKA, Tham SY, Ho SWL. Does laterality matter? a systematic review and meta-analysis of clinical and survival outcomes of medial versus lateral meniscal scaffolds. *Knee.* 2022;40:227-237. doi:10.1016/j.knee.2022.11.020
37. Grassi A, Macchiarella L, Lucidi GA, et al. Long-term Outcomes and Survivorship of Fresh-Frozen Meniscal Allograft Transplant With Soft Tissue Fixation: Minimum 10-Year Follow-up Study. *Am J Sports Med.* 2020;48(10):2360-2369. doi:10.1177/0363546520932923
38. Grassi A, Bailey JR, Filardo G, Samuelsson K, Zaffagnini S, Amendola A. Return to Sport Activity After Meniscal Allograft Transplantation: At What Level and at What Cost? A

Systematic Review and Meta-analysis. *Sports Health*. 2019;11(2):123-133.
doi:10.1177/1941738118819723

39. Richmond JC. Editorial Commentary: Return to Sport Should Not Be Your Goal Following High Tibial Osteotomy With Concomitant Medial Meniscal Allograft Transplantation. *Arthroscopy*. 2019;35(11):3097-3098. doi:10.1016/j.arthro.2019.07.017
40. Spalding T, Getgood A. Defining outcome after meniscal allograft transplantation: Is buying time a valid measure of success? *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1424-1426. doi:10.1007/s00167-016-4128-8
41. Vannini F, Spalding T, Andriolo L, et al. Sport and early osteoarthritis: the role of sport in aetiology, progression and treatment of knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(6):1786-1796. doi:10.1007/s00167-016-4090-5
42. Gelber PE, Isart A, Erquicia JJ, Pelfort X, Tey-Pons M, Monllau JC. Partial meniscus substitution with a polyurethane scaffold does not improve outcome after an open-wedge high tibial osteotomy. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(1):334-339. doi:10.1007/s00167-014-3206-z
43. Houck DA, Kraeutler MJ, Belk JW, McCarty EC, Bravman JT. Similar clinical outcomes following collagen or polyurethane meniscal scaffold implantation: a systematic review. *Knee Surg Sports Traumatol Arthrosc*. 2018;26(8):2259-2269. doi:10.1007/s00167-018-4838-1
44. Frank R, Gilat R, Haunschild ED, et al. Do Outcomes of Meniscal Allograft Transplantation Differ Based on Age and Sex? A Comparative Group Analysis. *Arthroscopy*. 2022;38(2):452-465.e3. doi:10.1016/j.arthro.2021.05.029
45. Grassi A, Di Paolo S, Coco V, et al. Survivorship and Reoperation of 324 Consecutive Isolated or Combined Arthroscopic Meniscal Allograft Transplants Using Soft Tissue Fixation. *Am J Sports Med*. 2023;51(1):119-128. doi:10.1177/03635465221131522
46. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, et al. Two-Year Clinical Results of Lateral Collagen Meniscus Implant: A Multicenter Study. *Arthroscopy*. 2015;31(7):1269-1278. doi:10.1016/j.arthro.2015.01.025
47. Getgood A, LaPrade RF, Verdonk P, et al. International Meniscus Reconstruction Experts Forum (IMREF) 2015 Consensus Statement on the Practice of Meniscal Allograft Transplantation. *The American Journal of Sports Medicine*. 2017;45(5):1195-1205. doi:10.1177/0363546516660064
48. Condello V, Dei Giudici L, Perdida F, et al. Polyurethane scaffold implants for partial meniscus lesions: delayed intervention leads to an inferior outcome. *Knee Surg Sports Traumatol Arthrosc*. 2021;29(1):109-116. doi:10.1007/s00167-019-05760-4
49. Rodkey WG, DeHaven KE, Montgomery WH, et al. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. *J Bone Joint Surg Am*. 2008;90(7):1413-1426. doi:10.2106/JBJS.G.00656
50. Wang DY, Lee CA, Zhang B, et al. The immediate meniscal allograft transplantation achieved better chondroprotection and less meniscus degeneration than the conventional delayed transplantation in the long-term. *Knee Surg Sports Traumatol Arthrosc*. 2022;30(11):3708-3717. doi:10.1007/s00167-022-06982-9

51. Song JH, Bin SI, Kim JM, Lee BS, Son DW. Does Age Itself Have an Adverse Effect on Survivorship of Meniscal Allograft Transplantation? A Cartilage Status and Time From Previous Meniscectomy-Matched Cohort Study. *Am J Sports Med.* 2020;48(7):1696-1701. doi:10.1177/0363546520916727
52. Hirschmann A, Schiapparelli FF, Schenk L, Keller L, Amsler F, Hirschmann MT. The Genovese grading scale is not reliable for MR assessment of collagen meniscus implants. *Knee.* 2017;24(1):9-15. doi:10.1016/j.knee.2016.10.011
53. Kovacs BK, Huegeli R, Harder D, et al. MR variability of collagen meniscal implant remodelling in patients with good clinical outcome. *Knee Surg Sports Traumatol Arthrosc.* 2021;29(1):90-99. doi:10.1007/s00167-019-05715-9