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Orlando José de Almeida Branco Simões

Anterior Knee Pain and Sensitivity Deficits after Anterior Cruciate Ligament Reconstruction: BTB vs 4ST/G vs All-Inside

MARÇO, 2020

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Anterior Knee Pain and Sensitivity Deficits after Anterior Cruciate Ligament Reconstruction: BTB vs 4ST/G vs All-Inside

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E sob a Coorientação de:

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Anterior Knee Pain and Sensitivity Deficits after Anterior Cruciate Ligament Reconstruction: BTB vs 4 ST/G vs All-Inside

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Faculdade de Medicina da Universidade do Porto, 30/03/2021

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Anterior Knee Pain and Sensitivity Deficits after Anterior Cruciate Ligament Reconstruction: BTB vs 4ST/G vs All-Inside

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Abstract

Purpose

To study pain and sensory alterations of 75 (three cohorts of 25 patients) athletic patients that underwent different anatomic arthroscopic ACLr surgery techniques. The cohorts were divided in the bone-patellar tendon-bone autograft cohort, the quadruple strand semitendinosus and gracilis autograft cohort and the quadruple strand semitendinosus autograft all-inside cohort.

Methods

We conducted a retrospective cohort study of pain and sensory alterations. All these patients followed a similar rehabilitation protocol, being 2 years the minimal follow-up time. Pain was characterized by duration and anatomical location and sensory deficits were evaluated concerning duration and affected area. Patients also scored on 3 different subjective tests: KWT; LKSS and IKDC-SKF and were divided according to its TALS.

Results

The mean AKP duration amongst the 3 cohorts was 1.8 ± 4.5 months and was significantly smaller in the 4ST/G cohort. The majority of patients of the BTB cohort located pain on the patellar tendon while patients in the 4ST/G and All-Inside cohorts referred that it was diffuse. At 15 days' post-surgery, hypoesthesia was reported by 42 patients and was significantly higher on the BTB cohort and less in the All-Inside cohort. At 2-year follow-up, the All-Inside cohort had no patients with hypoesthesia. In the BTB cohort, the sensitive alterations were only located on the area innervated by the IPBSN. The 4ST/G cohort located the hypoesthesia in the area innervated by the IPBSN and in the area of the LSCN. The All-Inside group located the sensitive alterations mostly in the LSCN. The KWT was painful in BTB and 4ST/G patients and reported 0% for the All-Inside cohort. No statistic relevance was found for the IKDC-SKF and LKSS tests.

Conclusions

All cohorts referred pain and sensitive alterations. The arthroscopic ACLr using BTB autograft seems to condition a higher number of anterior knee pain and hypoesthesia on medium post-operative outcomes and KWT was more often reported. The 4ST/G group had the smallest duration of AKP. The All-Inside cohort showed, globally, a lower number of complaints and a shorter time of symptom persistence, namely in terms of sensory deficit in the postoperative period.

Level of evidence

III

Key words: ACL reconstruction; autograft; pain; sensory deficits; all-inside; hypoesthesia

List of abbreviations: ACL – anterior cruciate ligament; ACLr – anterior cruciate ligament reconstruction; BTB – bone-patellar tendon-bone; HT – hamstring; 4ST/G – 4 strand semitendinosus-gracilis; 4ST – 4-strand semitendinosus; AKP – anterior knee pain; IPBSN – infrapatellar branch of the saphenous nerve; LSCN – lateral sural cutaneous nerve; MCBSN – medial crural cutaneous branches of saphenous nerve; KWT – Knee Walking Test; LKSS – Lysholm Knee Scoring Scale; IKDC-SKF – International Knee Documentation Committee-Subjective Knee Form; TALS – Tegner Activity Level Scale; BTB/G – bone-patellar tendon-bone plus gracilis.

1. Introduction

Anterior cruciate ligament (ACL) injuries are common in accidents and sports activities and its reconstruction is necessary to restore the static and dynamic stability of the knee because it usually leads to post-traumatic arthritis and muscle weakness [1, 2]. The aim of the surgical procedure is to create a replica of the preexistent ACL, but that is not possible due to the tridimensional structure of the ligament. On the other hand, it is possible to make a ligament reconstruction (ACLr) using grafts that are similar to the ACL, respecting its anatomy, isometry and biomechanical properties. There are several intricacies in the procedure that are not consensual: different incision types, tunnels' orientation, distinct grafts available [3-5], among others, and there are several published papers advocating different outcomes and defending the advantages and disadvantages of different techniques.

Surgery techniques have evolved throughout time and have been correlated with functional outcomes [6-11]. For example, incisions for graft harvesting are nowadays more minimally invasive techniques. The advantages of these techniques are decreased nerve complaints such as hypoesthesia or dysesthesia, improved cosmesis, decreased surgical site pain or morbidity, and, in the case of hamstring (HT) harvesting, easier tendon identification. Complications during harvesting of the graft can include nerve injury, postoperative pain, fracture, insufficient graft harvest, soft tissue injury, and contaminated graft [12].

Being one of the most common orthopedic procedures, ACLr is usually accompanied by moderate-to-severe post-operative pain [13], and its successful management is an important component to full recovery, adequate rehabilitation and overall patient contentment [14]. Sensory alterations are also a relatively common morbidity in ACLr, being that the selected graft, the surgery technique and the rehabilitation program play a lead role in this problematic [15, 16]. It has also been documented that the main neurological complication of ACLr is the iatrogenic lesion of the infra-patellar branches of the saphenous nerve [17].

In our study we addressed three different surgical procedures. The first used a bone-patellar tendon-bone (BTB) autograft; the second one used a 4-strand semitendinosus-gracilis (4ST/G) autograft; and the third one used an All-Inside technique using a 4-strand semitendinosus autograft (4ST). Current knowledge shows that BTB and 4ST/G carry out similar outcomes in knee stability and functionality, however, BTB has a substantially higher risk of anterior knee pain (AKP) [18-20]. The All-Inside technique is a minimally invasive approach with low graft failure rates and has produced good outcomes in knee function and stability, although it is not yet certain to provide consistently better outcomes when compared to the full tunnel techniques [21-24]. Studies have shown that it causes less pain when compared to the classical approaches [25] but are still scarce when presenting sensory deficits.

The purpose of this study was to assess pain and sensory deficits that arise after ACLr. We aim to assess its evolution in time, anatomical location and rate of occurrence, as well as its repercussions on the patient rehabilitation, the return to sports and physical activity and functional knee score, in three distinct cohorts, which have had ACLr performed by the same surgeon. This paper is a continuation of a previous study where BTB and 4ST/G autografts were used for ACLr, and the previously referred parameters where evaluated between these two groups [18]. Since this study was carried out, a novel All-Inside technique was further developed, and a new cohort of patients was used for new data and comparison [8].

2. Materials and Methods

We conducted a retrospective cohort study with a total of 75 patients, all male, age ranging from 17 to 44, with sports motivation, with an ACL injury and a subsequent anatomic arthroscopic ACLr performed by the

same surgeon. All these patients followed a similar rehabilitation protocol, being 2 years the minimal follow-up time. The three cohorts were divided as such: the first cohort included patients where a BTB autograft was used; the second cohort included patients where a 4ST/G was used; and the third cohort consisted of an All-Inside using a 4ST autograft. Each of the cohorts was composed of 25 patients.

Patients of the three cohorts underwent an anatomic arthroscopic ACLr and there were no revision procedures. In the BTB and 4ST/G cohorts, the femoral tunnel was made with 110º of knee flexion by the in-out technique, the placement of both tunnels was made concordantly with the single anatomic bundle concept and the grafts were fixed using bioabsorbable interference screws. For the BTB autograft a central longitudinal incision was made with 5 to 6 cm, sparing the infrapatellar branch of the saphenous nerve (IPBSN) as possible. The peritendon was identified and then sutured at the end. The BTB autograft was shaped as a parallelepiped bone block which was 10 mm thick and the bone defect of the patella was fulfilled by autograft collected from the tunnels, in the end. On the 4ST/G group an oblique 3 to 4 cm incision was made, with the knee flexed at 90º with an externally rotated hip. After identifying the semitendinosus and the gracilis, these were separated from the adhesions and an open tendon stripper was used while maintaining the knee at 90º of flexion. The All-Inside cohort had the surgery as described by Noronha and Oliveira [8]. Two similar arthroscopic portals were used (anteromedial and anterolateral), no tourniquet was used in the surgery. A semitendinosus graft was harvested with a 90º flexed knee and with a 3 to 4 cm vertical incision over the pes anserinus. A closed tendon stripper was used while keeping the knee at 90º flexion and external rotation of the hip. The ST is then quadrupled and fashioned into a double loop. The tibial socket is made using a 55º tibial drill guide and in an inside-out fashion, a flexible reamer was used to create a socked of approximately 25 mm. The femoral socket was created by initially identifying the femoral footprint and marking the center at 90º flexion. Then, at 120º flexion, a low-profile reamer is used to create a socket with 25 mm as well.

The patients of the BTB and 4ST/G groups were invited to participate in the study via physical letter and the first 50 to answer positively were included. The patients in the All-Inside group were contacted via phone call and the first 25 to give consent and answer the full questionnaire were included. All efforts were done to attain and confirm a maximum veracity level on the answers and avoid miscommunication.

Pain and sensory alterations were the main subject of the evaluation. Patients were studied at 15 days post-op and after more than 2 years of follow-up. Pain was characterized by duration and anatomical location and the sensory deficits were evaluated by duration as well and by the affected area and its correlation with a different relevant nerve branchs (IPBSN; lateral sural cutaneous nerve (LSCN) and the medial crural cutaneous branches of saphenous nerve (MCBSN)).

Patients also scored on 3 different subjective tests: the Knee Walking Test (KWT); the Lysholm Knee Scoring Scale (LKSS) [26] and the International Knee Documentation Committee-Subjective Knee Form (IKDC-SKF) [27] and were divided according to its Tegner activity level scale (TALS) [28].

This specific study protocol was approved by the relevant ethics committee and all patients gave full informed consent regarding the participation in this study. Patients' results were recorded on a database and statistical analysis was performed using IBM SPSS Statistics version 27.0. A p-value < 0.05 was considered for statistical relevance. The chi-square independence test, the Anova One-Way test and the Kruskal-Wallis test were used in this study. The normality of the distribution was analyzed using the Shapiro-Wilk test, while the homogeneity of variances was analyzed with the Levene test. When the homogeneity of variances was not satisfied, the Anova One-Way with Welch's correction was used. The Kruskal-Wallis test was used as an alternative to the Anova One-Way when the normal distribution was not satisfied. The Chi-square assumption that there should be no more than 20% of cells with expected frequencies below 5 was analyzed and when not

satisfied, the Chi-square test by Monte Carlo simulation was used. The differences were analyzed with the support of standardized adjusted waste.

3. Results

Population demographics and questionnaire results are shown on table 1, table 2, table 3 and table 4. The three cohorts showed statistically significant differences for age (p=0.001). The average of ages was 25.8±5.3 [18-36], 33.0±8.1 [17-44] and 31.0±8.8 [17-44], respectively for the BTB, 4ST/B and All-inside cohorts. The Tukey's multiple posterior comparison test indicates that the athletes of the BTB cohort is significantly younger than the 4ST/G and All-Inside cohorts (25.84 vs 32.96 vs 31.0).

The mean time elapsed between injury and surgery was 3.0±2.2 months (minimum -1 and maximum - 8) in the BTB cohort, 5.2±3.8 months (minimum - 1 and maximum - 12) in the 4ST/G cohort and 5.9±10.1 (minimum – 1 and maximum – 49) with no statistically significant differences between the cohorts (p = 0.082). The high standard deviation (SD) observed with the All-Inside cohort is the result that included two athletes that were operated after 24 and 49 months. The mean time will be 3.3±2.0 months if these two data points are excluded.

For the BTB cohort, the mean value of the TALS pre-injury was 7.6±1.1 and currently is 7.2±1.3; for the 4ST/G cohort, the mean value of the TALS pre-injury was 6.6 ± 1.0 and currently is 6.0±1.0; and for the All-Inside cohort, the mean value of the TALS pre-injury was 7.3±1.1 and currently is 7.0±1.3. For pre-injury (χ^2_{KW} (2) = 11.272, p =0.004) and current (χ^2_{KW} (2)=12.599, p=0.002) TALS, the paired comparison test indicates that the values are significantly lower in the 4ST/G cohort when compared with the BTB and All-Inside cohorts.

The authorization to return to practice sports without restrictions was, respectively, 6.5±1.8 months, 6.9±1.4 months and 7.6±2.3 months for the BTB, 4ST/G and All-Inside cohorts, with no statistically significant differences between the three surgical techniques (p = 0.131).

All (100%) patients of the BTB cohort referred pain just after surgery. Less (88%) was referred by patients of the All-Inside cohort. In a 2-week evaluation, less (20%) patients of the 4ST/G cohort referred pain. The same percentage (32%) was referred by patients of the BTB and All-Inside cohorts. The mean AKP duration amongst the 3 cohorts was 1.8 ± 4.5 months and it was significantly smaller in the 4ST/G group (0.8±1.3). The paired comparison test (χ^2_{KW} (2) = 13.252) indicates that the values are significantly lower in the All-Inside cohort when compared to the BTB cohort and is statistically significant the differences between the three surgical techniques (p = 0.001).

The majority of patients of the BTB (n = 11; 44%) cohort located pain on the patellar tendon while patients in the 4ST/G (n = 15; 65.2%) and All-Inside (n = 15; 68.2%) referred that it was diffuse. None of the patients of these last cohorts referred pain on the patellar tendon.

At 15 days' post-surgery, hypoesthesia was reported by 42 patients (58%) and was significantly more reported on the BTB (84%) cohort and less reported in the All-Inside (28%) and is statistically significant the differences between the three surgical techniques (p = 0.001). At 2-year follow-up, the All-Inside (0%) cohort had no patients with hypoesthesia compared to 10 (40%) in BTB cohort and 5 (20%) in the 4ST/G cohort and is statistically significant the differences between the three surgical techniques (p = 0.002).

As for duration of hypoesthesia (χ^2_{KW} (2) = 18.371), the All-Inside cohort reported the lowest duration (1.3±2.3), followed by the 4ST/G (6.6 ± 9.6) cohort and then by the BTB (12±10.6) cohort and is statistically significant the differences between the three surgical techniques (p = 0.001).

In the BTB cohort, the sensitive alterations were only located on the area innervated by the IPBSN (n = 21; 84%). The 4ST/G cohort located the hypoesthesia in the area innervated by the IPBSN (n = 7; 28%) and in the area of the LSCN (n = 6; 24%). The All-Inside group located the sensitive alterations mostly in the LSCN (n = 5; 20%), with a smaller number of patients locating it in the MCBSN (n = 2; 8%).

The KWT was painful in a significantly larger group of patients in the BTB (72%) (χ2 KW (2) = 29.640) and 4ST/G (28%) cohorts, while it was reported 0% for the All-Inside cohort, with statistically significant differences between the three cohorts (p = 0.001).

The average value of the IKDC-SKF was 94.6 ± 3.9, 95.9 ± 3.4 and 96.5 ± 2.3, respectively for the BTB, 4ST/G and All-Inside cohorts with no statistically significant differences between the three cohorts (p=0.072).

The average value of the LKSS was 97.4 ± 4.1, 98.7 ± 2.0 and 97.6 ± 3.9, respectively for the BTB, 4ST/G and All-Inside cohorts with no statistically significant differences between the three cohorts (p = 0.256).

4. Discussion

Pain and sensory deficits after an ACLr are issues of complex interpretation since its sources are multifactorial and evaluation based on a questionnaire includes unavoidable subjectivity on the symptoms. Even though, type of graft assumes an important key role in the painful syndrome [4, 29-31] and is highly studied, it still is an exceedingly debated topic. It is well documented that ACLr outcomes depend on type of graft and there are contradicting conclusions when comparing the most common grafts, BTB and HT autografts. For some researchers, optimal graft selection is not only dependent on graft properties, but on patient characteristics and expectations as well [30]. For Cardona-Ramirez et al. [32], there are differences in the biologic responsiveness of cells from the tendon grafts used in ACLr, which are dependent on strain levels and graft source, suggesting that the biologic properties of the tissue used should be considered when selecting graft source.

For Thaunat et al. [31], there is no perfect graft and each one has its role in ACLr. However, these authors refer that donor-site morbidity can be a problem in BTB grafting, which is not to be recommended for patients who kneel frequently in their work. This finding is supported by our study since the BTB cohort evidenced the highest percentage of positive KWT.

The discussion of results obtained within our study can suffer from the fact that not much work has been published on the All-Inside technique with a 4-strand semitendinosus (4ST) graft. The majority of studies compare surgery techniques that use BTB autografts and HT autografts, more specifically 4ST/G autografts. It seems consensual that HT autograft remains a popular graft choice for ACLr. Although there are a variety of autograft and allograft options available, advantages of HT autografts include decreased postoperative knee pain and an overall easier surgical recovery compared with bone BTB autograft [33].

Widner et al. [4], reviewed current literature and discussed the reported outcomes for the most common graft choices (BTB, HT, quadriceps tendon). Most large studies report either no significant difference or a small difference in failure rate and outcome scores between the different autograft choices. These authors refer that

HT might have a slightly higher re-tear rate when compared with BTB (2.84 versus 2.80), but BTB has a higher rate of anterior knee and kneeling pain in the short- and mid-term follow-up.

Chee et al. [34] performed a comprehensive systematic review and meta-analysis for papers that compared clinical outcomes of BTB versus HT. They analyzed outcome measures that included rate of rerupture, KT-1000, IKDC grade, Lachman, pivot shift, LKSS, TALS, AKP, and discomfort on kneeling. The main conclusion of this study is that contemporary 4SHT is comparable with the BTB technique in terms of clinical stability and postoperative functional status. However, the HT technique carries lower risk of postoperative complications such as AKP, kneeling discomfort, and extension deficit [35], which is in agreement with our results.

The work of Kouloumentas et al. [36] compared the All-Inside technique for ACLr using a short, 4ST autograft and suspensory cortical fixation on both the femoral and tibial side (similar fixation method to the one used in our All-Inside cohort) versus the conventional technique using a 4ST/G autograft fixed with a suspensory device on the femoral side and with an interference screw on the tibial side, in terms of clinical and functional outcomes. They concluded that 4ST autografts is a viable alternative to the conventional technique, because it affords preservation of knee flexor strength, which is of advantage when treating athletes with ACL injury. A better clinical and laximetric results at the minimum 3-year follow-up was obtained for the ST4 group [37]. In the study of Roger et al. [38], 4ST graft with adjustable femoral and tibial cortical fixation produced good outcomes compared to an 4ST/G autograft with femoral pin transfixation and tibial bioscrew fixation and no significant between-group differences were found for mean postoperative subjective IKDC. The 4ST technique spares the gracilis tendon, which thus preserves the medial sided muscle and thereby could improve function and limit donor-side morbidity.

4SHT grafts are among the strongest grafts biomechanically. Although the technique of HT autograft harvest is relatively straightforward, it is critical to pay attention to several technical steps to avoid iatrogenic neurovascular damage as well as to avoid premature amputation of the graft while using a tendon stripper [33]. Complications on the BTB graft can be related to diminish patellar vascularity. Recent anatomic studies have suggested that the dominant arterial supply of the patella enters through the inferior pole [39].

An important concern has to do with the use of the gracilis tendon for the 4ST/G graft for arthroscopic ACLr. Aggarwal et al. [40] studied functional outcome of the 4ST All-Inside technique and the 4ST/G. These authors made a prospective cohort study in which 68 patients with isolated ACL tear and with knee instability were enrolled and used the LKSS preoperatively and postoperatively at 1 year. They concluded that 4ST graft is a viable alternative to ST/G graft for ACLr, and preserving gracilis tendon results in better knee flexion, which means that it is important to preserve the gracilis tendon whenever possible.

Noronha and Oliveira [8] describe a modification of the original All-Inside technique, as used in All-Inside patients of our study, both maintaining the cortical bone in an intact state and avoiding the retrograde drill aiming device. A limitation of the described technique is the impossibility of preserving the ACL tibial remnant, which we know contributes to its proprioception and vascularization, biomechanically protecting the graft [41]. Therefore, when the ACL rupture leaves a large tibial remnant, to preserve it, it is recommended alternative techniques like complete outside-in tibial tunnel [42].

Is seems consensual that BTB autograft significantly increases the risk of kneeling pain as compared with HT regardless of age [43]. In fact, within the results of our study, we can observe that patients of the BTB cohort referred pain feeling in a higher percentage postoperatively and 2-weeks after. After 2 years, pain disappeared, independently of the type of autograft.

In the study of Smith et al. [22], patients with BTB reported significantly greater postoperative pain scores at days 2 ($p = 0.049$), 3 ($p = 0.004$), and 7 ($p = 0.015$) and had significantly greater kneeling pain at 2 years ($p< 0.019$). A return to sport questionnaire at 2 years revealed no significant difference between the groups for returning to preoperative level of sport activity (83% All-Inside quadrupled semitendinosus, 74% BTB; $p = 0.415$). In our study, all patients experienced pain, essentially during the first 2 weeks (32% for the BTB cohort; 20% for the 4ST/G cohort and 32% for the All-Inside technique) but totally disappeared after 2 years. Benea et al. [25] evaluated the pain level through the Visual Analogical Scale and referred a value of 3.2±5.5 for the All-Inside group (with retrograde drill aiming device and ST harvest only) and 8.6±10 for the classical group (4ST/G with interference screws) and there were no significant differences in the mean IKDC subjective score at 6 months. These authors concluded that the All-Inside technique is a reliable procedure with very good results for pain, stability and knee function [25]. Our results also allow to reach a similar conclusion, using a modified All-Inside technique that allowed an additional benefit of it being substantially less costly.

Concerning overall prevalence of AKP, Niki et al. [44], analyzed BTB plus gracilis (BTB/G) tendon in 56 knees, ST in 71 knees and ST/G in 44 knees and refer that AKP at 3 months and 2 years postoperatively were 42.0 and 11.1%, respectively. The use of BTB/G graft represented the highest prevalence of AKP between the 3 different grafts ($p = 0.001$), but this statistical significance disappeared at 2-years postoperatively. These results correlate well with our findings. In fact, the prevalence of AKP was higher for the BTB cohort ($p = 0.001$) and statistical significance also disappeared at 2 years postoperatively.

The All-Inside technique is a relatively new development in ACL surgery. Some features of this technique include closed-socket tunnels, dual suspensory graft fixation, decreased bone removal, and smaller skin incisions. According to Connaughton et al. [45], the All-Inside ACL appears to have similar overall results on subjective and objective outcomes studies compared to standard ACL techniques and may be associated with decreased post-operative pain as observed in our study. However, for the same authors, there is also a concern for a higher graft failure rate with the All-Inside technique. At 2-years, no graft failure was observed in the All-Inside cohort of our study.

Hypoesthesia is intrinsically related to the autografts and regions were they are collected. There is debate concerning the geometry of the incision (vertical vs horizontal vs oblique). Several authors have studied the influence of the type of incision and refer that sensory changes are frequently found after ACLr. Minimally-invasive technique reduces the risk of cutaneous hypoesthesia, but does not prevent anterior pain related to harvesting the PT and a good-quality transplant can be obtained if the anterior tibial tuberosity is prominent [46].

Ruffilli et al. [47] found that a vertical incision significantly affects the presence of hypoesthesia and the extent of the area of sensory loss and the anatomical course of the nerve along with the results obtained in the available studies seems to suggest lower rate of neurological impairment adopting an oblique incision and may therefore be preferred in the routine clinical practice. Oblique incision evidences lower risk of nerve damage and is recommended for graft harvesting [48-50]. Hardy at el. [51] conducted a systematic review of literature to define the incidence of complications related to graft harvesting and the methods to prevent these complications. For these authors, main complication of HT harvesting was sensory deficit because of damage to the IPBSN. This complication occurred in 40% to 88% of patients. The main complication following BPB harvesting is AKP, reported in up to 46% of patients. In our study this complication was up to 28% for the 4ST/G patients and 84% for the BTB patients. Only 4% of the All-Inside patients referred complications. According to these authors the risk of HT harvesting can be reduced by using a horizontal or oblique incision. This conclusion is in contradiction with our findings since vertical incisions were used to harvest the ST graft in our All-Inside patients, while the 4ST/G cohort had the autograft harvested through an oblique incision, and still resulted in better outcomes for the All-Inside cohort regarding hypoesthesia frequency and duration.

Mochizuki et al. [16], refer that blunt exposure for harvesting the tendons failed to decrease the occurrence of the sensory change was frequently found using medial hamstring tendons with a vertical incision. Harvesting tendon autografts by vertical incisions can have high prevalence of saphenous nerve branches injury with a minor possibility for complete recovery within the first year [52]. It is likely to dissipate with time [15]. However, there were more patients in the HT group that reported on partial recovery and the loss of sensation was perceived by patients as a minor complication [52]. What concerns this topic of the study, there may be other factors that can affect the sensory changes besides incision geometry. Even though, it seems that injury to IPBSN is not related to age, gender, physique, education, delay from injury to reconstruction and injury frequency did not increase [48, 53]. Vertical incision has highest incidence of IPBSN injury, persistent hypoesthesia, largest area of sensory loss and poorest subjective outcome [50]. In the study of Sabat et al. [50], the SBSN injury is equally common in vertical, oblique and horizontal incisions, but better outcome was noted for the oblique incision group.

However, these observations are not consensual, since, e.g., Leiter et al. [54] did not find differences between a vertical and an oblique incision with respect to incidence or area of sensory loss. These authors, through a cadaveric study also refer that it was not possible to identify a safe zone that would prevent transection of all nerve branches of the IBSN.

In our study, the BTB technique was mainly applied to young athletic patients and with lower mean time elapsed between injury and surgery. The question of time to return to sport activities is an important factor and although it was smaller for the BTB patients, the differences to the 4ST/G and 4ST All-Inside are not significant, since differences were 1.6 weeks and 4.4 weeks respectively. Concerning this analysis, it is not adequate to refer any supremacy of the BTB technique.

According to the IKDC findings of our study, we conclude that the functional outcomes are not very different, independently of the portal technique and graft used. Other studies refer the same conclusion [7]. Kim et al. [7], using a prospective, randomized controlled trial with a minimum 2-year follow-up show that, with the exception of the functional test of IKDC objective score, clinical results, second-look arthroscopic findings, and MRI findings did not differ significantly between the outside-in and transportal techniques, although femoral tunnel geometries differed significantly.

The study of Lee et al. [55] determined the effects of single ST harvesting for anterior cruciate ligament ACLr by comparing outcomes of single ST and ST/G harvesting in a 3-year follow-up. Subjective assessments included subjective IKDC score, Lysholm score, and Tegner activity scale score. Objective assessments included isokinetic strength and functional tests. No statistically significant differences were seen for the subjective measurements. The ST group showed significantly less deficit in deep flexor strength and tended to show better clinical results at the last follow-up than the ST/G group. Single ST harvesting is effective in minimizing flexor weakness and functional deficits and shows great potential for regeneration [55].

We acknowledge the limitations of our study. Since it is a retrospective study, patients' recollection of data and symptoms may not be the most accurate. There might have been a selection bias, identified by the main surgeon, where the younger patients were more prone to be selected for the BTB surgery. The subjectivity of the used tests is unavoidable and there might be communication misunderstanding since the BTB and 4ST/G cohorts responded to the questionnaire in person, while All-Inside cohort responded by phone call. The findings of our study may lack in external validity, since the modified All-Inside technique used is different from the conventional ones and thus infrequently used in published studies which prevents us from accurately compare results.

Conclusions

All cohorts referred pain and sensitive alterations. The arthroscopic ACLr using BTB autograft seems to condition a higher number of anterior knee pain and hypoesthesia on medium post-operative outcomes and KWT was more often reported. The 4ST/G group had the smallest duration of AKP. The All-Inside cohort showed, globally, a lower number of complaints and a shorter time of symptom persistence, namely in terms of sensory deficit in the postoperative period. Graft choice should ultimately be based on surgeon comfort, experience and individual patient characteristics.

Anterior knee pain and sensory deficits are a reality in surgery arthroscopic reconstruction of the ACL and it is important to understand that its existence depends on the graft options and that this will have implications for some functional results. A better understanding of its origin may allow for modified techniques to reduce its incidence and improve the final outcome results.

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Table 1. Population demographics

	BTB	4 ST/G	All-Inside	*P*-value
Age (years)	25.8 ± 5.3	33.0 ± 8.1	30.8 ± 8.8	<0.001
BMI (kg/m^2)	24.4 ± 2.2	23.8 ± 1.8	24.1 ± 2.6	0.630
Lesion to surgery (months)	3.0 ± 2.2	5.2 ± 3.8	5.9 ± 10.0	0.082
Sports aetiology	23 (92%)	20 (80%)	25 (100%)	0.059
Right dominant limb	16 (64%)	15 (60%)	15 (60%)	1.000
TALS preoperative	7.6 ± 1.1	6.6 ± 1.0	7.3 ± 1.1	0.004

BTB - bone-tendon tendon-bone cohort. 4 ST/G – quadruple strand semitendinosus and gracilis cohort. All-Inside – quadruple strand semitendinosus with all-inside technique cohort. BMI – body mass index. TALS – Tegner Activity Level Scale,

Table 2. Hypoesthesia questionnaire results

	BTB	4 ST/G	All-Inside	*P*-value
Hypoesthesia				
15 days postoperative	21 (84%)	14 (56%)	7 (28%)	<0.001
2 years postoperative	10 (40%)	5 (20%)	0 (0%)	0.002
Hypoesthesia duration (months)	12 ± 10.6	6.6 ± 9.6	1,3 ± 2.3	<0.001
Location				
IPBSN	21 (84%)	7 (28%)	0 (0%)	
LSCN	0 (0%)	6 (24%)	5 (20%)	
MCBSN	0 (0%)	0 (%)	2 (8%)	

BTB - bone-tendon tendon-bone cohort. 4 ST/G – quadruple strand semitendinosus and gracilis cohort. All-Inside – quadruple strand semitendinosus with all-inside technique cohort. IPBSN – infrapatellar branches of the saphenous nerve. LSCN – lateral sural cutaneous nerve. MCBSN – medial crural cutaneous branches of saphenous nerve.

Table 3. Anterior Knee Pain questionnaire results

	BTB	4 ST/G	All-Inside	*P*-value
Anterior Knee Pain				
15 days postoperative	8 (32%)	5 (20%)	8 (32%)	0.551
2 years postoperative	1 (4%)	0 (0%)	0 (0%)	
Anterior Knee Pain duration (months)	2.7 ± 7.3	0.8 ± 1.3	1.7 ± 2.0	0.001
Location				
Diffuse	7 (28%)	15 (65.2%)	15 (68.2%)	
Patella	4 (16%)	0 (0%)	0 (0%)	
ATT	1 (4%)	0 (0%)	0 (0%)	
Patellar Tendon	11 (44%)	0 (0%)	0 (0%)	
Tibial Tunnel	2 (8%)	8 (34.8%)	7 (31.8%)	
KWT (+)	18 (72%)	7 (28%)	0 (0%)	0.001

BTB - bone-tendon tendon-bone cohort. 4 ST/G – quadruple strand semitendinosus and gracilis cohort. All-Inside – quadruple strand semitendinosus with all-inside technique cohort. ATT – anterior tibial tuberosity. KWT – knee walking test.

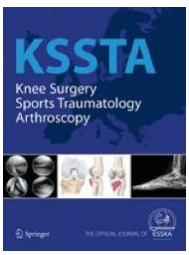
Table 4. TALS and subjective scores

	BTB	4 ST/G	All-Inside	*P*-value
TALS postoperative	7.2 ± 1.3	6.0 ± 1.0	7.0 ± 1.3	0.002
TALS preoperative=postoperative	17 (68%)	15 (60%)	21 (84%)	0.169
Sports authorization (months)	6.5 ± 1.8	6.9 ± 1.4	7.6 ± 2.3	0.131
LKSS	97.4 ± 4.1	98.7 ± 2.0	97.6 ± 3.9	0.256
IKDC-SKF	94.6 ± 3.9	95.9 ± 3.4	96.5 ± 2.3	0.072

BTB - bone-tendon tendon-bone cohort. 4 ST/G – quadruple strand semitendinosus and gracilis cohort. All-Inside – quadruple strand semitendinosus with all-inside technique cohort. TALS – Tegner Activity Level Scale. LKSS – Lysholm Knee Scoring Scale. IKDC-SKF - International Knee Documentation Committee-Subjective Knee Form.

ANEXO

1. Guidelines de submissão



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Text

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References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

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  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

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- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Doe J (1999) Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. Available via DIALOG. http://www.rsc.org/dose/title of subordinate document.

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Tables

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- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

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Artwork and Illustrations Guidelines

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- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

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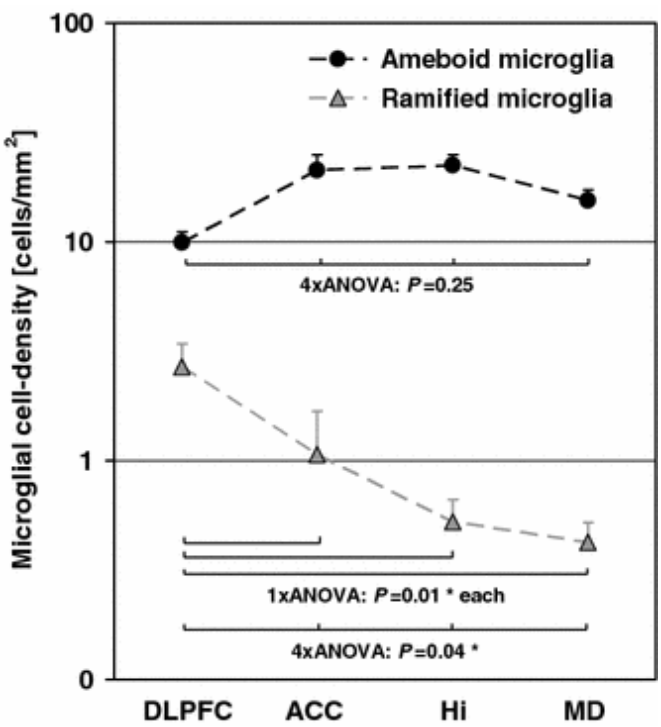

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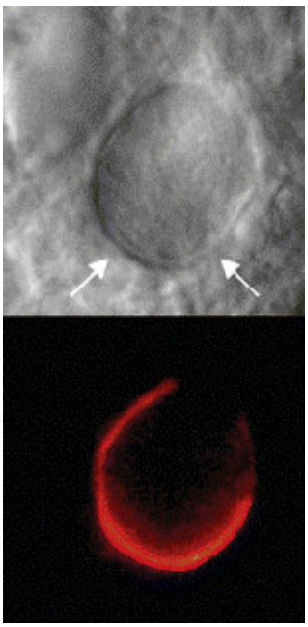

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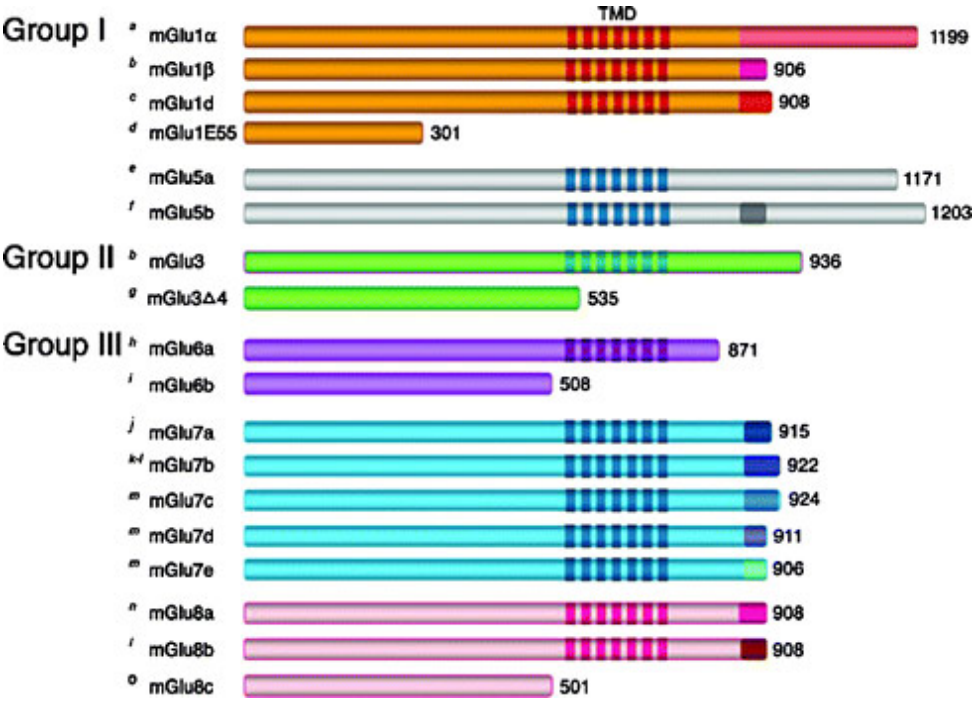

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* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

Data transparency

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

Role of the Corresponding Author

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

- ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;
- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For **review articles** where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the **student's dissertation or thesis**, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

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Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

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For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

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In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

Confidentiality

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

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Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

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Authors are requested to disclose interests *that are directly or indirectly related to the work submitted for publication*. Interests within the last 3 years of beginning the work (conducting the research and preparing the work for submission) should be reported. Interests outside the 3-year time frame must be disclosed if they could reasonably be perceived as influencing the submitted work. Disclosure of interests provides a complete and

transparent process and helps readers form their own judgments of potential bias. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate.

Interests that should be considered and disclosed but are not limited to the following:

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Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through publication of this manuscript. This includes multiple affiliations (if applicable).

Financial interests: Stocks or shares in companies (including holdings of spouse and/or children) that may gain or lose financially through publication of this manuscript; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication of this manuscript.

It is difficult to specify a threshold at which a financial interest becomes significant, any such figure is necessarily arbitrary, so one possible practical guideline is the following: "Any undeclared financial interest that could embarrass the author were it to become publicly known after the work was published."

Non-financial interests: In addition, authors are requested to disclose interests that go beyond financial interests that could impart bias on the work submitted for publication such as professional interests, personal relationships or personal beliefs (amongst others). Examples include, but are not limited to: position on editorial board, advisory board or board of directors or other type of management relationships; writing and/or consulting for educational purposes; expert witness; mentoring relations; and so forth.

Primary research articles require a disclosure statement. Review articles present an expert synthesis of evidence and may be treated as an authoritative work on a subject. Review articles therefore require a disclosure statement. Other article types such as editorials, book reviews, comments (amongst others) may, dependent on their content, require a disclosure statement. If you are unclear whether your article type requires a disclosure statement, please contact the Editor-in-Chief.

Please note that, in addition to the above requirements, funding information (given that funding is a potential conflict of interest (as mentioned above)) needs to be disclosed upon submission of the manuscript in the peer review system. This information will automatically be added to the Record of CrossMark, however it is **not added** to the manuscript itself. Under 'summary of requirements' (see below) funding information should be included in the '**Declarations**' section.

Summary of requirements

The above should be summarized in a statement and included on **a title page that is separate from the manuscript** with a section entitled "**Declarations**" when submitting a paper. Having all statements in one place allows for a consistent and unified review of the information by the Editor-in-Chief and/or peer reviewers and may speed up the handling of the paper. Declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data, Materials and/or Code availability and Authors' contribution statements. **Please use the title page for providing the statements.**

Once and if the paper is accepted for publication, the production department will put the respective statements in a distinctly identified section clearly visible for readers.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

When all authors have the same (or no) conflicts and/or funding it is sufficient to use one blanket statement.

Provide "**Funding**" as a heading (**see template**)

- Partial financial support was received from [...]
- The research leading to these results received funding from […] under Grant Agreement No[…].
- This study was funded by […]
- This work was supported by […] (Grant numbers […] and […]

In case of no funding:

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- No funding was received to assist with the preparation of this manuscript.
- No funding was received for conducting this study.
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Provide "**Conflicts of interest/Competing interests**" as a header (**see template**)

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  Non-financial interests: Author C is an unpaid member of committee Z.

- **Financial interests:** The authors declare they have no financial interests.

  Non-financial interests: Author A is on the board of directors of Y and receives no compensation as member of the board of directors.

- **Financial interests:** Author A received a speaking fee from Y for Z. Author B receives a salary from association X. X where s/he is the Executive Director.

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  Non-financial interests: Author D has served on advisory boards for Company M, Company N and Company O.

When authors have nothing to declare the following statement may be used:

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- The authors have no conflicts of interest to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
- The authors have no financial or proprietary interests in any material discussed in this article.

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Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

Cell Line: RST307 cell line **RRID:CVCL_C321**

Antibody: Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

Plasmid: mRuby3 plasmid **RRID:Addgene_104005**

Software: ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

Clinical Trial Registration

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

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Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal’s Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

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Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Conflicts of interest/competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

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2. Reporting guidelines

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3, 4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5, 6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5, 6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	6, 7, 8, 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6, 7, 8, 9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.