PRP does not improve the objective outcomes of anterior cruciate ligament reconstruction

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PRP does not improve the objective outcomes of Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analyses.

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Abstract:	Purpose : Platelet rich plasma (PRP) has been used in association with ACLR to improve rehabilitation. The purpose was to systematically review the literature in order to compare the effects of PRP on ACLR in its objective and subjective outcomes. Methods: A systematic review of the MEDLINE, Web of Science, Embase, Scopus, and Cochrane databases was performed. Two independent reviewers included all the English language literature of patients undergoing primary ACLR with autograft combined with PRP. The outcomes analyzed were graft ligamentization (MRI), tibial and femoral tunnel widening (MRI), knee laxity, IKDC, Lysholm, Tegner activity scale and visual analog scale. Results: Nine studies were included with a total of 525 patients. PRP did not improve ligamentization of graft (standardized mean difference: 0.01 [95%CI: -0.37; 0.39]), neither in the form lesser tunnel widening (standardized mean difference: 0.71 [95% CI: -0.12; 1.54), or lesser knee laxity (raw mean difference: 0.33 [95% CI: -0.84; 0.19). Although there was statistical significance of PRP effects on Lysholm score and VAS (p<0.01), their magnitude was limited. Conclusion: PRP showed no improvement in objective outcomes like ligamentization and less tunnel widening, while it showed just small improvements in terms of Lysholm, VAS and knee laxity. Therefore, there is not enough evidence to support a recommendation in favor of PRP and more research is needed. Level of evidence: Level I.
Response to Reviewers:	It was attached to answer point by point.
Keywords:	Anterior cruciate ligament; Knee surgery; anterior cruciate ligament reconstruction; Platelet enriched plasma; Autologous platelet concentrate; Lysholm; International knee documentation committee; Ligamentization; Pain; Visual analog scale; Tunnel enlarge

Thanks for the opportunity of this fourth review!
Please, find our answer highlighted in yellow.

COMMENTS TO THE AUTHOR:
"PRP does not improve the objective outcomes of Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analysis"

Comments to Authors

GENERAL

This is the fourth version. I have still several comments and corrections that are needed.

TITLE

In fact you could show that PRP was not useful. Why not say it in the title?
Answer: We understand that even the results of a meta-analysis of RCTs is not an absolute truth and many things can make our results lead to different conclusion in the future. Thus, it is important to mention exactly what we found in the title without our opinion/conclusion or extrapolation over it! What is not clinically relevant for subjective measurements could be studied in deep in the future in different scenarios and have another meaning; or if PRP is applied in the donor site it could be beneficial; or different populations or doses (PRP protocols), as well as future modern technologies that could show different utilities. In other words, even though a meta-analysis of RCTs offer the higher level of evidence, the strength of this evidence should be based on other variables that we did not assess (such as aspects of the participants' preferences, costs and resources used, or other more assistance aspects that goes beyond our scope), thus we cannot do recommendations with this type of work.

ABSTRACT

Conclusion section: Same comment about PRP, not being useful. You can state this clearly in the Conclusion section here.
Answer: We understand we stated very clearly what we can conclude based only on our findings (Line 20-24).

Line 89: You write "describe but not take into account". There is something missing in this sentence. As it is now it doesn't make any sense.
Answer: We tried to make it clearly, adding more specificity to the sentence and explaining we followed the guidelines (Lines 88 and 89).

Line 107: Please use passive voice.
Answer: We adapted the sentence for passive voice.

Line 172: How was PRP associated with Lysholm?
Answer: We clarified the type of test used (Line 175).

Line 189: Please use passive voice.

Answer: We adapted the sentence for passive voice (193).

Line 194: It should be assesses.
Answer: We corrected (Line 198).

Line 216: Of course there is no PRP effect on Tegner activity scale. You cannot write like this. There might be an association but not an effect.
Answer: We tried to write it more adequately (Line 220).

Line 244: “there is not enough evidence” I think you should be much stronger and clearly state that PRP is not useful and should be advised against.
Answer: As clinicians we totally agree that we won`t recommend PRP based on our results, but advisements and recommendations are beyond our scope and other type of studies such as guidelines, expert panel might base their recommendations in our meta-analysis as well as other different important factors.

Reference #5: Who are the authors and how can this book be found?
Answer: We are not sure that we understand the question, but the authors are: Borenstein M, Hedges L, Higgins J, Rothstein H. and It can be found, for exemple, on Amazon: https://www.amazon.com.br/Introduction-Meta-Analysis-Michael-Borenstein/dp/0470057246.

Reference #9: It should only be Arthroscopy. Delete J Arthrosc Relat Surg.
Answer: We corrected it (Line 287).

Are references updated?
Answer: In our point of view the references are updated since most of them are from the last five years, with the only exception of the validation and classic studies that deserve to be cited.

Regarding figures, you have included several forest plots. They are good per se, but you must give much better figure legends for each of the figures. What do they show?
Answer: We added the figure legends for each forest plot after the references.

Regarding Tables, please make sure that you avoid repetitions.
Answer: Ok.

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Title Page

PRP does not improve the objective outcomes of Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analyses.

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Conflict of Interest: the authors declare they have no conflict of interest.

PRP does not improve the objective outcomes of Anterior Cruciate Ligament Reconstruction: A Systematic Review and Meta-Analyses.

Abstract

Purpose: Platelet rich plasma (PRP) has been used in association with ACLR to improve rehabilitation. The purpose was to systematically review the literature in order to compare the effects of PRP on ACLR in its objective and subjective outcomes.

Methods: A systematic review of the MEDLINE, Web of Science, Embase, Scopus, and Cochrane databases was performed. Two independent reviewers included all the English language literature of patients undergoing primary ACLR with autograft combined with PRP. The outcomes analyzed were graft ligamentization (MRI), tibial and femoral tunnel widening (MRI), knee laxity, IKDC, Lysholm, Tegner activity scale and visual analog scale.

Results: Nine studies were included with a total of 525 patients. PRP did not improve ligamentization of graft (standardized mean difference: 0.01 [95%CI: -0.37; 0.39]), neither in the form lesser tunnel widening (standardized mean difference: 0.71 [95% CI: -0.12; 1.54), or lesser knee laxity (raw mean difference: 0.33 [95% CI: -0.84; 0.19). Although there was statistical significance of PRP effects on Lysholm score and VAS ($p<0.01$), their magnitude was limited.

Conclusion: PRP showed no improvement in objective outcomes like ligamentization and less tunnel widening, while it showed just small improvements in terms of Lysholm, VAS and knee laxity. Therefore, there is not enough evidence to support a recommendation in favor of PRP and more research is needed.

Level of evidence: Level I.

Keywords: Anterior cruciate ligament, Knee surgery, Anterior cruciate ligament reconstruction, Platelet enriched plasma, Autologous platelet concentrate.

Introduction

The platelet rich plasma (PRP) has been used to improve the autologous graft ligamentization and the regenerative process after ACLR [2, 14, 15]. PRP is a small amount of blood whose platelets are above the blood baseline values. These platelets act during inflammation, releasing coagulation adhesive proteins, protease inhibitors and growth factors [8]. The content of the platelet, primarily the growth factor are known to cause angiogenesis, cell proliferation and collagen deposition that modulates the inflammation and the regeneration/repair process [3, 22].

A few controlled trials have tried to address PRP effects on ACLR. Two studies [25, 26] suggested benefits of PRP on tunnel widening/enlargement, visual analog scale (VAS) and knee functions, while others showed no significant effect [24, 30]. Although the literature is conflicting, many discursive reviews defend the potential benefit of PRP during ACLR in graft ligamentization, tunnel widening, visual analog scale (VAS), and knee functional scores [4, 17, 35]. Thus, to bring a consensus to the literature the aim of the present study was to meta-analyze the randomized controlled trials testing PRP effects on ACLR recovery.

Materials and Methods

A systematic search was conducted on MEDLINE, Web of Science, Embase, Scopus, and Cochrane with the last up- date on December of 2019. The search combined “anterior cruciate ligament reconstruction” and “Platelet-Rich Plasma” descriptors. The flowchart of study selection was detailed in Figure 1. The inclusion criteria was: (1) studies comparing ACLR with PRP on injury side compared to a control group when they reported measures for at least one of the main outcomes of the ACLR: ligamentization (assessed by MRI), tunnel widening (assessed by MRI), pain (VAS), Lysholm, Tegner, IKDC and knee laxity; (2) articles written in English; and (3) full text available. The exclusion criteria were: (1) papers not published in English; (2) reviews; and (3) laboratory studies. Thus, 7 meta-analyses were made, one for each of the main outcomes mentioned.

Studies were selected independently by two investigators. After the overall screening, 10 studies were included and each PRP group within the studies were treated as a separated study against their control group for meta-analyses. Different time points of assessment within the studies were also considered different studies for subgroup analyses.

please, insert figure 1 here

Briefly, among the studies included, during the surgery, PRP was prepared manually or by a machine. The amount of blood necessary was obtained from the patient using a syringe with an anticoagulant and processed according to author’s protocol. When the protocol did not use a machine to separate the platelets, the blood was centrifuged and the PRP obtained. The PRP was applied in the bone tunnels and in the graft before it was inserted into the knee. The PRP used in the studies were classified according to the MARSPILL classification [13], the categories were: the method, activation, red blood cells, spin, platelet number, image guided, leukocyte concentration and light activation.

The PEDro scale quantified the quality of the studies and the scores on PEDro scale ranged from 0 (very low methodological quality) to 10 (high methodological quality). The first of the 11 questions (Eligibility criteria specified) was just qualitatively described but not take into the sum, according to its guidelines [16]. All studies attend the 4º criterion (groups similar at baseline), since the prognosis of the injury was the complete ligament torn, therefore all participants had exactly the same injury. The quality of the studies was used only for qualitative purpose and was not an exclusion criterion. Egger's tests were performed to check the risk of publication bias in each meta-analysis [7].

Statistical analysis

Mean, standard deviation (SD) and sample number (n) were used for analysis. Median and interquartile range (IQR) were replaced respectively by mean and SD according to the equation SD = (IQR / 1.35) [10]. Two studies presented the range for variation description [30, 32], thus its SD was estimated based on the range rule SD (SD=(maximum-minimum)/4).

The seven meta-analyses were performed using Comprehensive Meta-Analysis software, version 3.3.070. The effect was calculated based on difference between: 1) PRP and control groups at post-surgery (Ligamentization and Pain score); 2) PRP and control groups mean change from pre to post interventions (knee laxity, IKDC, Lysholm and Tegner); 3) difference between the PRP and control groups mean change from immediately post to longer time post ACLR (tunnel widening). Raw mean difference (RMD) and 95% confidence interval was used for Lysholm, IKDC, Tegner, knee laxity, VAS, considering the variables were presented by the same unit of measurements among all studies. On the other hand, for ligamentization and tunnel widening we used standardized mean difference (SMD), due to the different type of measures across studies.

When there was no statistical significance for heterogeneity, fixed effect models were selected for analyses (Ligamentization, IKDC, Knee Laxity, Lysholm and Pain Score) and when there was statistical significance for heterogeneity, randomized effect models were selected for analyses (Tunnel widening and Tegner). Conservative pre-post correlations of 0.5 were assumed [5].

Subgroup analysis was performed to compare different time points of assessments and also the difference between tunnel widening at tibia or femur.

Results

The quality of the studies was assessed by PEDro scale. Most studies using random allocation, having similar values between groups at baseline, using inter-group statistical comparisons, presenting central point measures and variability measures of the data, and did not perform concealed allocation of participants or had blinded subjects (Supplementary Table 1). This led to scores ranging from 4 to 8 among all studies. MARSPILL classification for each study were described at Supplementary files (Supplementary Table 2).

Table 1 shows details of the studies included in the meta-analyses. Most studies included both men and women in the same analysis, including young adults, testing PRP effects from 10 weeks to more than 48 weeks. Regarding the fixation technique, the most used were the biodegradable cross pins for the femoral tunnel and interference screws in the tibial tunnels. The different rehabilitation protocols could be a confounding factor for PRP effects analyses, however, the use of a control group in each study contributes to the isolation of PRP effects.

please, insert table 1 here.

Legend: NR: Not reported in the original paper; y: years; ACLR: Anterior cruciate ligament reconstruction.

The forest plots of the 7 meta-analyses are presented from figure 2 to 8 and the subgroup analysis described in table 2. Ligamentization, IKDC and Tegner were not different between PRP and control. Lysholm was significantly increased with PRP in comparison to control (RMD=5.4 [95%CI: 2.16;8.60], p<0.001). This increase occurred in each of the time points it was assessed, at 12, 24 and >48 weeks, without differences among them (n.s.). VAS was significantly lower post PRP compared to control (p=0.002). Despite no overall difference between PRP and control for Knee laxity in the main analysis, there were significant lower laxity for PRP than control at 12 weeks and 24 weeks, but not for >48 weeks (n.s.).

Analyzing the tunnel widening differences at 12 weeks and >48 weeks, the higher tunnel widening for PRP occurred only at >48 weeks post ACLR (SMD=1.58 [95%CI: 0.19; 2.98], p=0.03) and it was significantly different between groups (p=0.03).

please, insert Figure 2 here
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please, insert Figure 4 here
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please, insert Figure 6 here
please, insert Figure 7 here
please, insert Figure 8 here

please, insert table 2 here

Discussion

The main finding was that Platelet Rich Plasma applied during ACLR surgery did not improve ligamentization, enlargement of the femoral and tibial tunnels, knee laxity, IKDC and Tegner. However, PRP was associated with Lysholm and the visual analog scale of pain (VAS).

After ACLR, a rehabilitation of 6-9 months is common for a return to the complete routine of physical activities and also competitive sports, this time is necessary to avoid reinjury during the integration of the graft to the knee. Following this safety time for complete recovery the physicians might check objective criteria through MRI such as the ligamentization of the graft and the non-widening of the bone tunnels; and also evaluate the knee laxity. In the present meta-analyses, we found no significant differences between PRP and control groups for these objective outcomes (ligamentization, tunnel widening and knee laxity). Although the subgroups of 12 weeks and 24 weeks significantly reduced knee laxity in the PRP compared to control, the higher weight of the studies testing PRP >48 weeks post ACLR, might have contributed to the null overall effects of PRP on knee laxity at this time point. Furthermore, PRP might have short duration effects, in which can be proved around 24 weeks, but long-lasting effect is not clear. This is an important information, considering the neoligament might be more required after this time, when the patients are released to return to their normal physical activities and sports.

Evidence of the functional scales importance have been shown [1]; distinguishing between patients returning and not returning to play after ACLR. In the present meta-analyses, the null effect of PRP on IKDC could be due to the lack of specificity of this assessment for ACLR, considering it tests knee function independently of any lesion; while Lysholm score could be more adequate, since it assessed the knee function in ligament injured knees [11]. Although we found a mean of 5.38 [2.16; 8.60] higher Lysholm score for PRP than control, the minimal clinical important difference (MCID) of this effect might be taken into account [28]. The MCID is the smallest change perceived as important by the patient, and the MCID for Lysholm score is 8.9 for patients with different knee conditions including ACLR [9]. Thus, the 95% confidence interval of the present meta-analysis can not be considered clinically relevant.

Although PRP resulted in significant reduction of pain (VAS), Norman et al. [21], stated that an effect size lower than 0.5 on VAS does not improve quality of life. In this way, converting the raw values of our meta-analysis to SMD values, a VAS of -0.29 (95%CI: -0.84; 0.25) was found; which suggests a clinically non-significant result. Despite many studies have pointed to PRP benefits on pain in a variety of lesions [6, 18], it still unclear which physiological mechanisms would explain such findings. Johal et al. [12], did not find evidence that leukocyte concentration, platelet concentration, or the use of an exogenous activating agent affects the overall effectiveness of PRP. Other studies, not included in this review, due to the lack of quantifiable results, performed an arthroscopy revision and histological analysis of the graft submitted to PRP [23, 24]. Sanchez et al.[23] found the PRP application influences collagen deposition, extracellular matrix and blood vessels at the bone tunnel site as well as they showed higher frequency of a synovial enveloping with connective tissue around the ligament, while Silva et al. [24] reported just a general ligament improvement for the PRP group compared to control between 24 weeks and 2 years.

The use of PRP did not lead to different Tegner activity scale scores. It is possible that the scale was not sensitive enough to capture the differences between PRP effects and control by the time it was assessed (around 12 months). In fact, at 12 months the majority of patients would be able to undergo their normal life physical activities without restrictions, being all in the same level.

Another limitation was the estimation of mean and SD from median and interquartile range values. However, it can be a good estimation considering the SD in bell shaped curves have approximately the same size of the range and two SD away from the mean captures nearly all of the data.

The variety of PRP methods and classifications among studies might have led to heterogeneous results for some variables, despite the large homogeneity for most of them. Unfortunately, the number of studies in each analysis did not allow comparisons between all these methods. Thus, the conclusions were limited to general PRP effects, and future studies might investigate which PRP method could be more or less effective for ACLR.

The results regarding ligamentization and VAS were restricted to a cross-sectional comparison as they had no follow-up. It is expected since there is no interest in researchers to assess ligamentization and VAS immediately after surgery, and accordingly we just pointed the comparison between PRP and control at one time point.

Conclusion

The present meta-analyses showed no difference between ACLR with and without PRP in the ligamentization, tunnel widening, knee laxity, IKDC and Tegner, however, the low number of studies included in each analysis suggest further investigation in this topic. Although there were positive effects of the PRP on VAS and Lysholm scores, the magnitudes of these effects were too small to lead to an important clinical effect. Therefore, there is not enough evidence to support the recommendation in favor of PRP and the use of PRP in day by day clinical work must be reviewed. In addition, since the results are based in a low number of studies, more research would be important to confirm these results.

Conflict of interest: The authors declare that they have no conflict of interest.

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Figure legends

Figure 2. Forest plot of the effect of PRP on Ligamentization. SMD: Standardized mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 3. Forest plot of the effect of PRP on Tunnel widening. SMD: Standardized mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 4. Forest plot of the effect of PRP on Knee Laxity. RMD: Raw mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 5. Forest plot of the effect of PRP on IKDC (International Knee Documentation Committee) . Raw mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 6. Forest plot of the effect of PRP on Lysholm Score. Raw mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 7. Forest plot of the effect of PRP on Tegner Score. Raw mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 8. Forest plot of the effect of PRP on VAS (visual analog scale). Raw mean difference; LCL: Lower confidence limit (95%); UCL: Upper confidence limit (95%); I^2: Inconsistency between studies; $P < 0.05$ means significant effect of PRP.

Figure 4

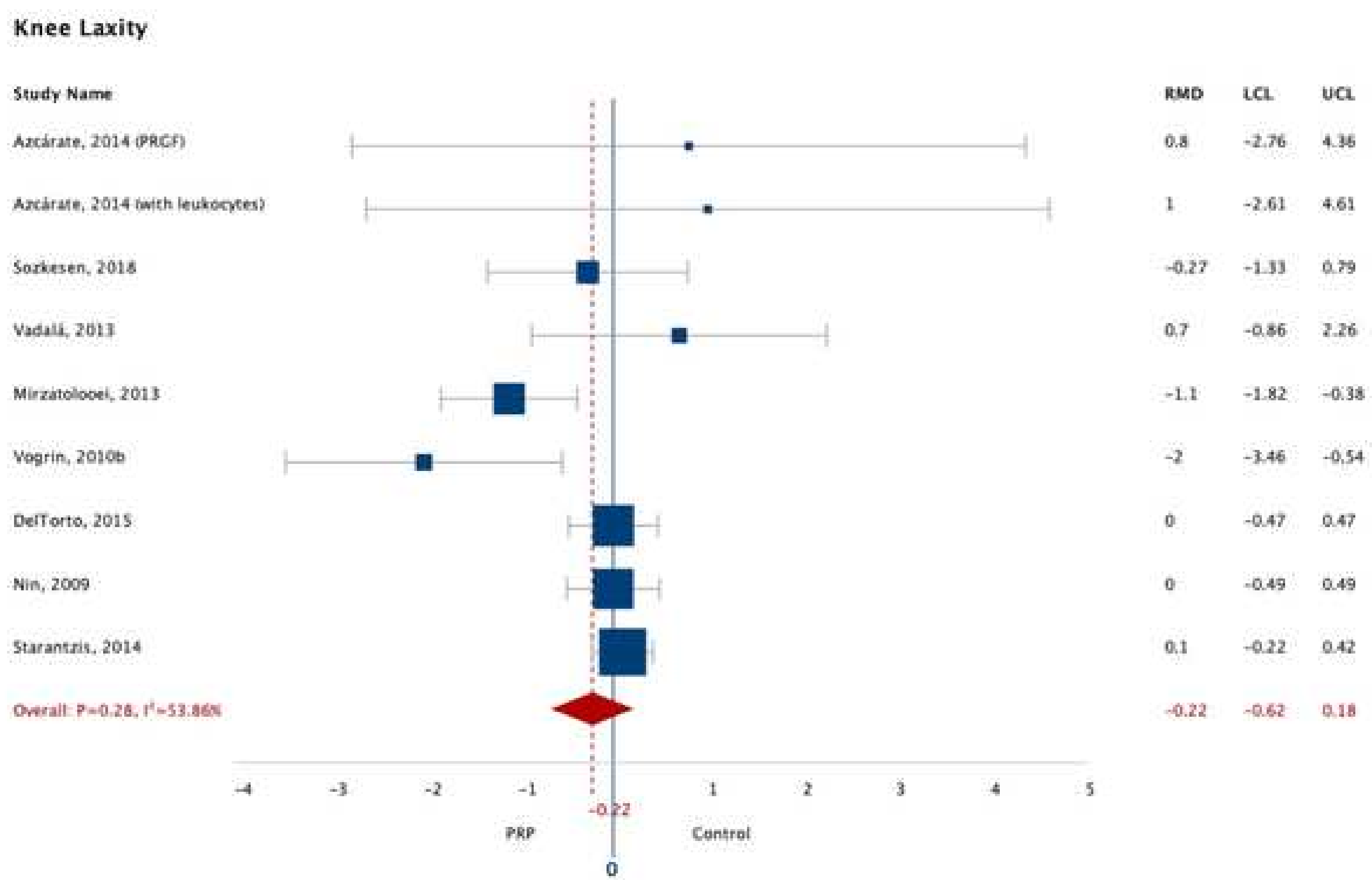
Knee Laxity
Study Name
RMD
LCL
UCL
Azcárate, 2014 (PRGF)
0.8
-2.76
4.36
Azcárate, 2014 (with leukocytes)
1
-2.61
4.61
Sozkesen, 2018
-0.27
-1.33
0.79
Vadalá, 2013
0.7
-0.86
2.26
Mirzatolooei, 2013
-1.1
-1.82
-0.38
Vogrin, 2010b
-2
-3.46
-0.54
DelTorto, 2015
0
-0.47
0.47
Nin, 2009
0
-0.49
0.49
Starantzis, 2014
0.1
-0.22
0.42
Overall: P=0.28, I²=53.86%
-0.22
-0.62
0.18
-4
-3
-2
-1
1
2
3
4
5
-0.22
PRP
Control
0

Figure 5

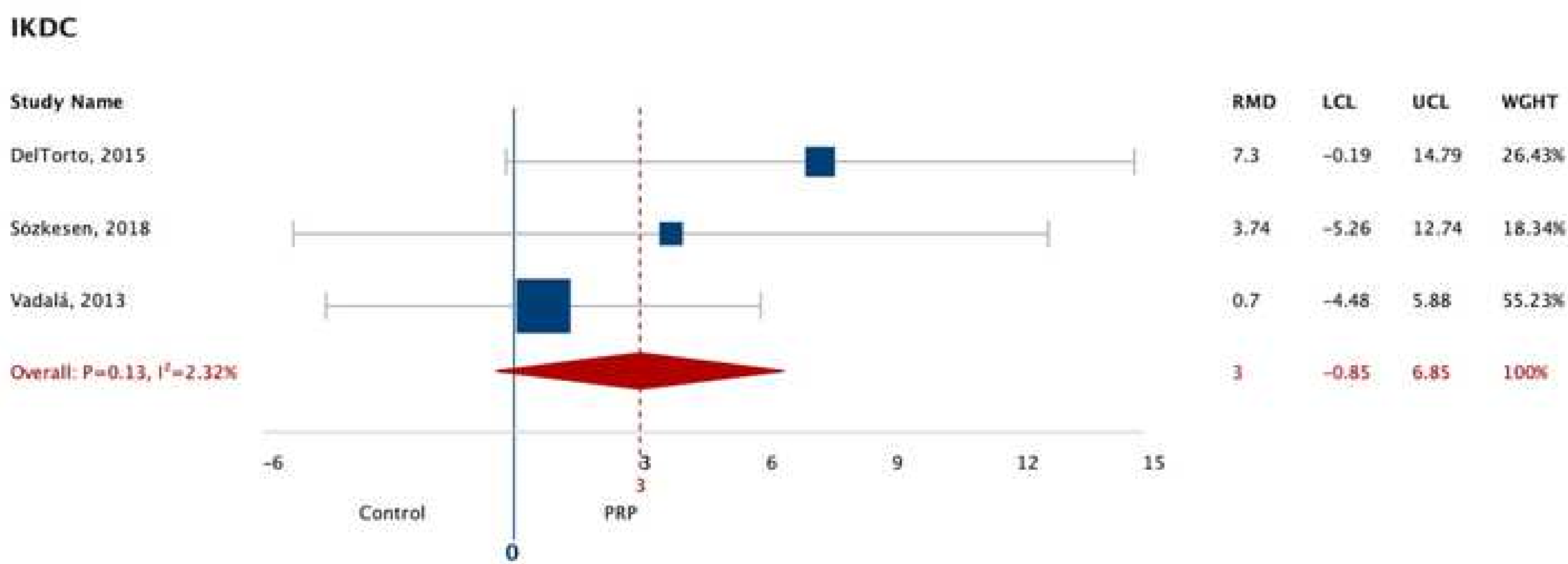
IKDC
Study Name
RMD
LCL
UCL
WGHT
DelTorto, 2015
7.3
-0.19
14.79
26.43%
Sózkesen, 2018
3.74
-5.26
12.74
18.34%
Vadalá, 2013
0.7
-4.48
5.88
55.23%
Overall: P=0.13, I²=2.32%
3
-0.85
6.85
100%
-6
3
6
9
12
15
3
Control
PRP
0

Figure 6

Click here to access/download;Figure;Lysholm fig6.jpg

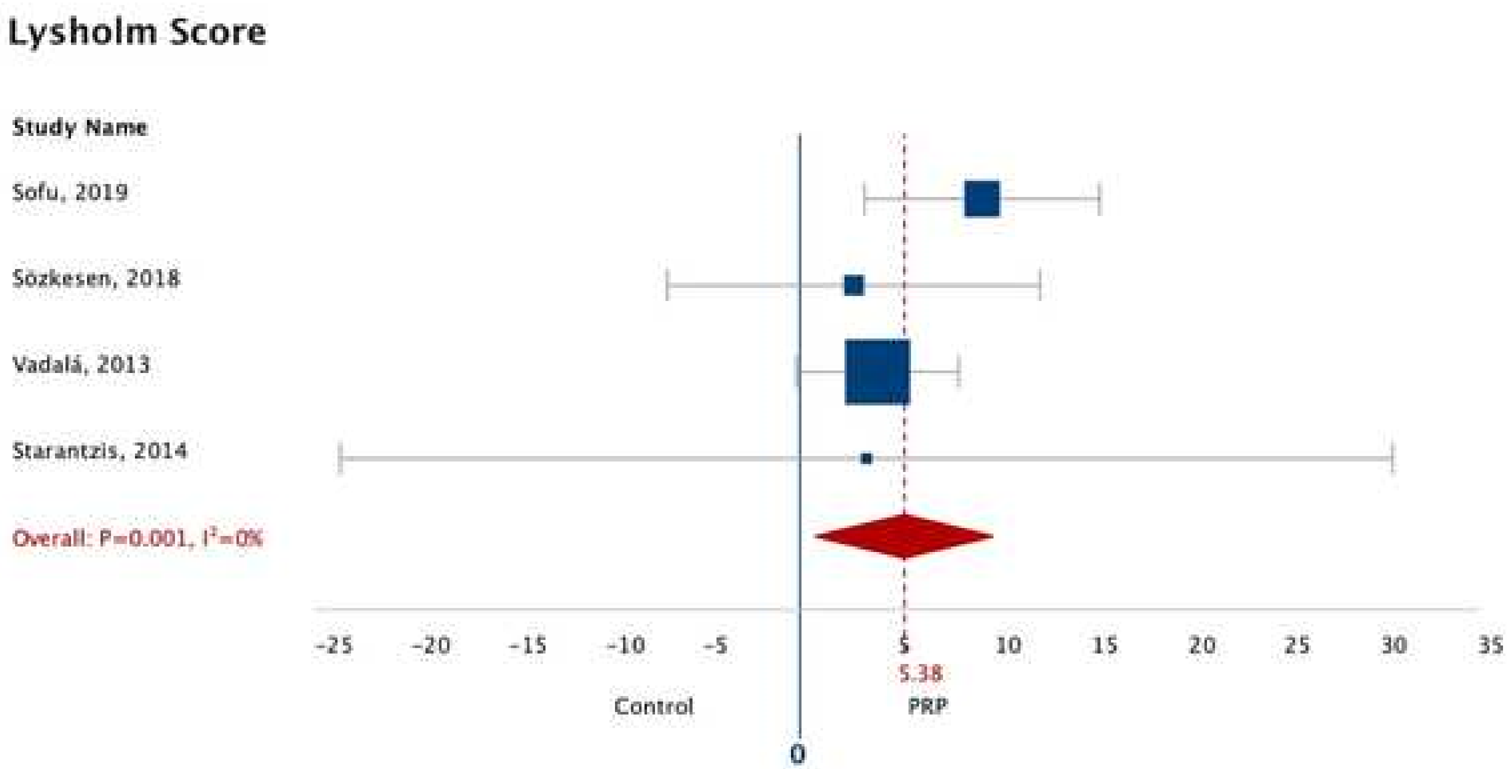

Figure 7

Click here to access/download;Figure;tegnerfig7.jpg

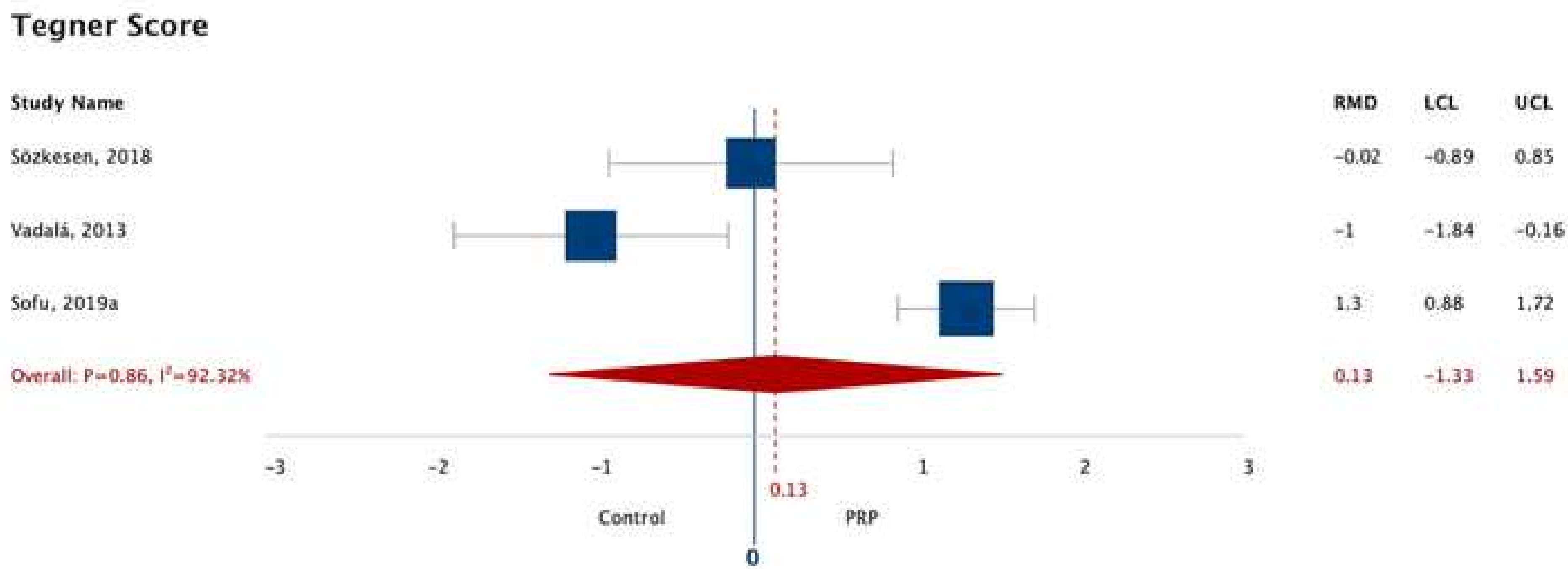

Figure 8 Click here to access/download;Figure;VASfig8.jpg

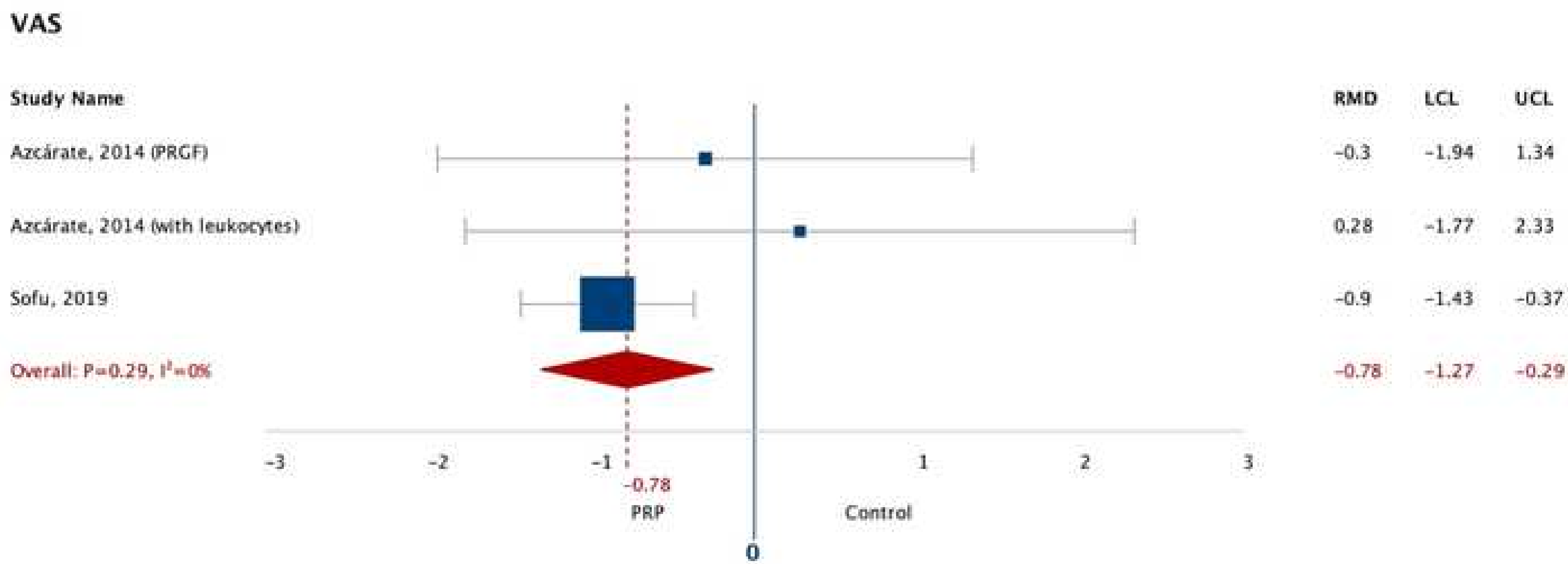

Figure 2

Click here to access/download;Figure;ligamentizationfig2.jpg

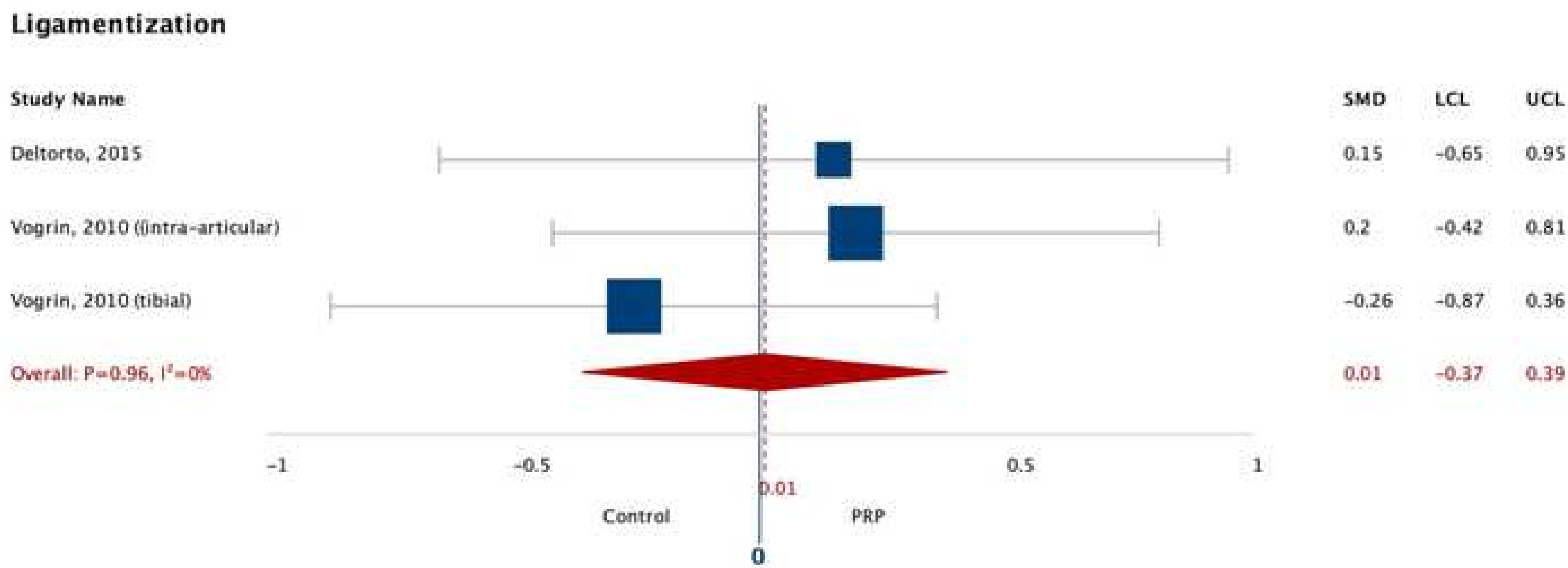

Figure 3

Click here to access/download;Figure;tunnel widening fig3.jpg

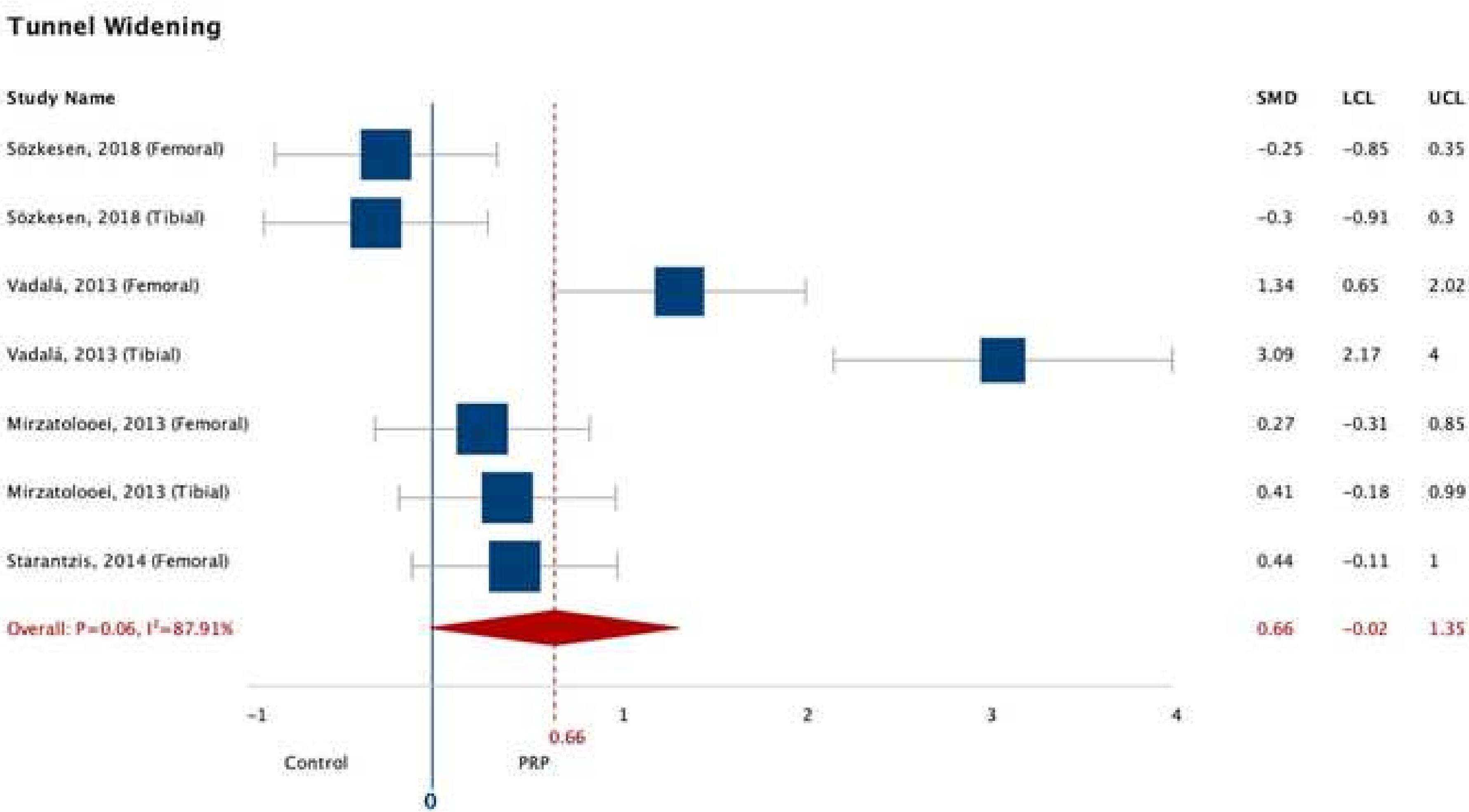

Figure 1

Figure 1. Flowchart of the study`s selections.

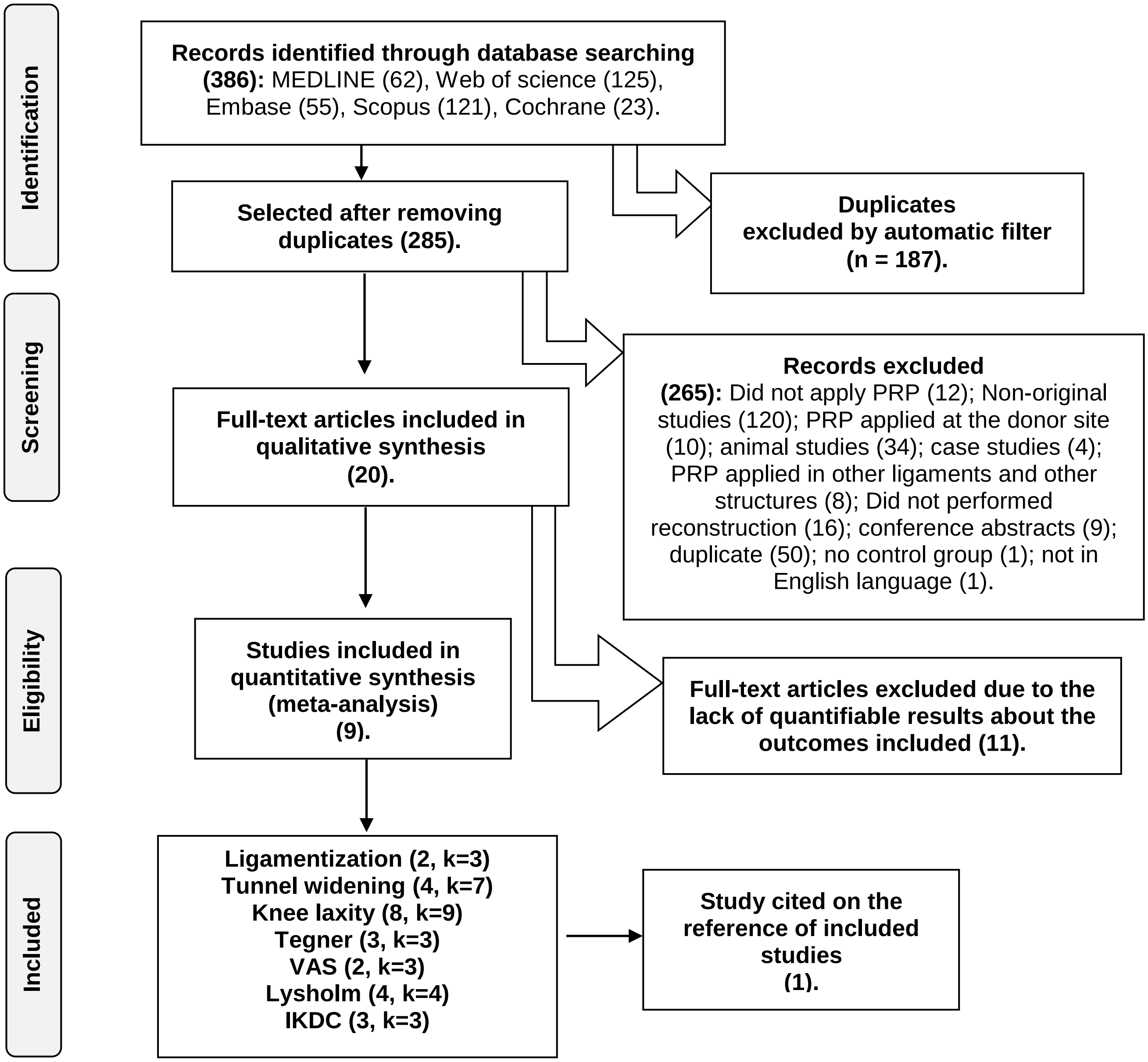

Table 1

Table 1. Characteristics of studies included.

First author, year	n	Sex. Group age (y).	Assessments time point	Graft type	Fixation
Azcárate, 2014 [31]	150	Both. 26.1 Control, 26.1 PRP (with leukocytes), 27.4 PRGF.	24wk post ACLR.	Patellar tendon allograft.	Two cross pins to fixate the femoral bone and a interference screw for the tibial.
Del torto, 2015 [29]	24	Both. Age NR.	Before, 24wk post, 48wk post and 96wk post ACLR.	Gracilis and semitendinosus tendon.	Femoral tunnel was fixed with two cross-pin and in the tibial tunnel an interference screw was used.
Mirzatolooei, 2013 [19]	46	Both. 26.9 Control, 26.4 PRP.	Before, immediatly post and 12wk post ACLR.	Hamstring quadrupled graft.	Femoral tunnel was fixed with a cross-pin and in the tibial tunnel a bio-absorbable interference screw was used.
Nin, 2009 [20]	100	Both. 26.6 (range, 15 to 59) Control, 26.1 years (range, 14 to 57) PRP.	Before, 96wk post ACLR	Patellar tendon allograft.	Two cross pins to fixate the femoral bone and a tibial interference screw.

Sofu, 2019 [25]	39	Both. 26 ± 6.5 Control, 31.3 ± 8.4 PRP.	Before, 12wk post, 24wk post and 48wk post ACLR.	Hamstrings autograft.	NR
Sözkesen, 2018 [26]	44	Both. 26.54 ± 7.93 Control, 26 ± 6.96 PRP.	Immediatly post and 12wk post ACLR.	Hamstrings autograft.	Femoral suspension device for ACL
Starantzis, 2014 [27]	60	Both. 31.3±8.0 Control, 29.4±7.3 PRP.	Preoperatively and 56wk post ACLR	Hamstrings tendons (Semitendinosus and Gracilis)	Femoral tunnel was fixed with cross pins or endobutton, and the tibial tunnel was fixed with nterference screw plus bone bridge suture anchoring
Vadala, 2013 [30]	40	Men.	Immediatly post and 56wk post ACLR.	Hamstring autograft.	Femoral suspension device for ACL and modified interference screw in the tibial tunnel.
Vogrin, 2010 [34]	41	Both. 32.6 ± 12.3 Control, 37.2 ± 8.4 PRP.	4-6wk post and 10-12wk post ACLR.	Double-looped semitendinosus and gracilis tendon autograft.	Fixed with 2 cross pins in the femoral tunnel and with 1 interference screw in the tibial tunnel.

Vogrin, [33]	2010	41		Both. 32.6 ± 12.3 Control, 37.2 ± 8.4 PRP.	Before, 12wk post and 24wk post ACLR.	Double-looped semitendinosus and gracilis tendon autograft.	Fixed with 2 cross pins in the femoral tunnel and with 1 bioabsorbable interference screw in the tibial tunnel.

Legend: NR: Not reported in the original paper; y: years; ACLR: Anterior cruciate ligament reconstruction.

Table 2

Table 2. Subgroup analysis.

Tunnel widening			
Time point	**k**	**ES [LCL; UCL]**	**p-value**
12wk	5	0.05 [-0.22; 0.31]	n.s.
>48wk	3	1.58 [0.19; 2.98]	
Local	**k**	**ES [LCL; UCL]**	**p-value**
tibial	3	1.03 [-0.68; 2.73]	n.s.
femoral	4	0.44 [-0.16; 1.03]	
Lysholm			
Local	**k**	**ES [LCL; UCL]**	**p-value**
12wk	2	7.31 [1.82; 12.79]	n.s.
24wk	1	9.70 [3.61; 15.79]	
>48wk	3	5.71 [2.29; 9.12]	
Knee laxity			
Local	**k**	**ES [LCL; UCL]**	**p-value**
12wk	4	-0.51 [-1.26; -0.23]	n.s.
24wk	3	-1.27 [-2.54; -0.01]	
>48wk	3	0.03 [-0.30; 0.36]	

Legend: ES: Effect size; k: number of trials; LCL: lower confidence limit; UCL: upper confidence limit. The p-values represent the significance for difference between categories of subgroups.