



OPEN Effects of rehabilitation interventions on time to return to play and reinjury rate in athletes with acute hamstring strain injuries

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Despite the high prevalence and recurrence of acute hamstring strain injuries in athletes, the optimal rehabilitation strategy balancing rapid time to return to play (TTRTP) with durable re-injury protection remains unclear. We searched PubMed, Cochrane Library, Web of Science, Scopus, Embase, and Google Scholar from inception to January 2026 for English-language randomized controlled trials (RCTs) evaluating exercise-based rehabilitation, adjunctive biological modalities, or other approaches for acute hamstring strains in athletes. TTRTP was the primary outcome; re-injury rate was secondary. Certainty was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Models were selected based on heterogeneity and clinical plausibility of pooling. 14 RCTs (693 athletes) were included. A lengthening-focused exercise protocol (L-protocol) based on two trials may shorten TTRTP versus conventional rehabilitation (moderate certainty) without increasing re-injury risk (low certainty). Progressive agility and trunk stabilization (PATS) did not accelerate TTRTP (low certainty); the re-injury estimate was inconclusive (RD -0.35, 95% CI -0.74 to 0.03; $I^2 = 72\%$; very low certainty; 2 trials), with the confidence interval including both a potential reduction and no effect. For adjunctive therapies, we analyzed Platelet-Rich Plasma (PRP) as a separate meta-analysis (three trials) and described radial extracorporeal shockwave therapy (rESWT) and low-level laser therapy (LLLT) as single-trial evidence. PRP showed heterogeneous effects ($I^2 = 70\%$), rESWT modest benefit (one trial), and LLLT no added benefit (one trial). Pain-threshold rehab enhanced strength without delaying TTRTP (moderate certainty; one trial). Trial Sequential Analysis (TSA) indicated that the lengthening-focused exercise protocol (L-protocol) TTRTP benefit exceeded the monitoring boundary, suggesting sufficient evidence to rule out random error; however, this does not eliminate clinical heterogeneity or concerns about external validity. Lengthening-focused eccentric exercise may shorten TTRTP. Evidence for PATS and adjunctive modalities remains uncertain, warranting high-quality RCTs. Decisions should prioritize evidence certainty over statistical significance.

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Keywords Hamstring strain injuries, Eccentric loading, Progressive agility and trunk stabilization, PRP, Time to return to play, Re-injury rate

Hamstring strains (HSIs) are one of the most common injuries experienced by athletes in both contact and non-contact sports, with reported frequencies reaching up to 37% in some athletic populations^{1–4}. Similar high injury rates have been observed in physically demanding occupational training, with up to 41% of recruits affected during initial phases⁵. Hamstring strains typically occur during movements involving extreme hip flexion and knee extension such as sprinting, jumping, or stretching³. The long head of the biceps femoris (BFLh) is most frequently affected, with injuries typically occurring 0–6 cm proximal to the myotendinous junction¹. Acute HSIs present with localized pain and muscle fibre disruption (Grade I–III) of varying severity, which is associated with functional deficits^{2,6}. This condition is distinct from proximal hamstring tendinopathy (an overuse disorder

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presenting with chronic deep gluteal pain during loaded activities), tendon avulsions (partial or complete detachment from the ischial tuberosity, often requiring surgical repair), recurrent strains (a repeat injury following an index strain), and delayed-onset posterior-thigh pain (non-traumatic muscle soreness without structural injury). These conditions differ in pathophysiology, natural history, and clinical management¹. The high rates of HSI have persisted for several decades, with some surveillance data indicating an approximate 4% annual increase in incidence in professional football populations⁷. HSIs occur more frequently during training than during competition and result in substantial time loss from sport, diminished athletic performance, and considerable economic burden⁸. Additionally, with a recurrence rate of 12–31%, HSIs present a significant challenge for athletes and clinicians alike⁹.

Physical modalities and therapeutic exercises have been the subject of much research as traditional treatment options for HSIs over the last 20 years^{10,11}. However, surgical intervention is usually only indicated for more serious or complicated cases^{12,13}. The overall aim of rehabilitation from an HSI is the safe and timely return to athletic participation while reducing the chance of re-injury. This dual objective restoring function while mitigating recurrence risk is grounded in biomechanical principles that inform both performance optimization and injury prevention strategies. Therefore, clinicians treating athletes must be knowledgeable in evidence-based rehabilitation techniques to provide the athlete with the best possible therapeutic treatments, as well as improve their performance^{14–17}.

A range of adjunctive therapies, including orthobiologics such as platelet-rich plasma (PRP) and electrophysical agents such as low-level laser therapy (LLLT), radial extracorporeal shockwave therapy (rESWT), capacitive-resistive energy transfer (TECAR) and transcutaneous electrical nerve stimulation (TENS), is frequently employed alongside active rehabilitation^{12,18–20}. However, these interventions differ substantially in their biological rationale, mechanisms of action and clinical objectives, and therefore should not be considered interchangeable²¹. PRP has been studied for its potential to deliver growth factors to injured tissue^{22,23}. rESWT has been shown to help reduce TTRTP and increase recovery of strength²⁴. Both TECAR and TENS have been shown to provide better short-term pain relief and improve flexibility than complete rest. However, studies examining the long-term efficacy of these modalities have produced limited data²⁵. While physical modalities are used widely, their effectiveness as the sole treatment method is questionable at best; therefore, most studies examined physical modalities as part of a structured exercise program, and therefore the incremental benefit from exercise alone varies greatly by specific modality and stage of injury.

Therapeutic exercise constitutes the cornerstone of HSI rehabilitation, grounded in a strong physiological rationale for restoring muscle strength, flexibility, neuromuscular control, and tissue capacity^{26,27}. Contemporary exercise-based approaches have shifted from simple stretching and concentric strengthening toward more sophisticated protocols. Eccentric loading, particularly exercises performed at long muscle lengths has gained prominence due to its ability to increase fascicle length and enhance eccentric strength²⁸. Another approach combines progressive agility exercises with trunk stabilization training (PATS), focusing on lumbopelvic control and movement patterns that mimic sporting actions^{18,29}. Stretching exercises have traditionally been incorporated to restore range of motion; however, contemporary evidence suggests that static stretching alone provides limited functional benefit^{20,30,31}. Current guidelines recommend stretching as an adjunct rather than a standalone intervention, with emphasis shifting toward eccentric loading and neuromuscular retraining³².

The recent trend in clinical practice and research is towards combining physical modalities with exercise-based rehabilitation^{33,34}, on the rationale that physical modalities may modulate pain and inflammation in the acute phase, thereby creating a more favorable environment for early loading³⁵. In contrast, exercise therapy addresses the neuromuscular and biomechanical deficits that predispose athletes to recurrence-deficits that cannot be resolved by physical modalities alone. Preliminary evidence suggests that combined approaches may result in faster recovery than exercise alone, without increasing re-injury risk^{18,19,36}. However, the optimal timing, sequencing, and combination of specific modalities with specific exercise protocols remain undefined, primarily due to variability in study design and outcome measures.

Several recent systematic reviews have synthesized evidence on hamstring rehabilitation, but none have provided a stratified synthesis that separates exercise-based interventions from adjunctive therapies rather than pooling them, nor interpreted findings through both GRADE and TSA. This systematic review and meta-analysis therefore aimed to evaluate the efficacy of rehabilitation interventions for acute hamstring strain injuries in athletes, including eccentric loading, PATS and adjunctive biological and physical therapies. The primary outcome was time to return to play; secondary outcomes were re-injury rate, pain and functional recovery. Through this stratified synthesis, we sought to guide clinical decision making by evidence certainty rather than statistical significance alone.

Methods

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement³⁷.

Inclusion criteria

Studies were selected based on the following PICOS criteria. Population: competitive or recreational athletes with acute hamstring strain injuries, diagnosed clinically or by imaging; Intervention: (1) exercise-based rehabilitation programmes (eccentric loading, PATS, stretching); (2) adjunctive biological or physical therapies (PRP, rESWT, LLLT) when combined with structured rehabilitation; (3) stand-alone physical modalities (TECAR, TENS) evaluated as isolated treatments. Stand-alone modalities were included only for narrative synthesis and were not pooled in meta-analyses; Comparison: conventional rehabilitation, placebo, or alternative protocols; Outcomes: TTRTP (primary), re-injury rate, pain, and function (secondary); Study design: published RCTs (English-language only, due to resource constraints; acknowledged in Limitations).

Exclusion criteria

(1) Unpublished RCTs (including systematic reviews, meta-analyses, cross-sectional studies, observational studies, conference abstracts, case reports or non-randomized controlled trials). One master’s thesis was exceptionally included for narrative synthesis only because it provided unique data on an intervention not covered elsewhere (spinal adjustive therapy); its poor methodological quality (PEDro score 4) is acknowledged in the Limitations and it was not included in any pooled meta-analysis; (2) Studies where participants were not diagnosed with hamstring strain injury; (3) Studies that did not report any training or intervention measures; (4) Studies that did not report at least one of the prespecified outcomes (TTRTP, re-injury rate, pain, or functional outcomes); (5) Studies on chronic tendinopathy, tendon avulsions, or delayed-onset posterior-thigh pain.

Literature search

The search was conducted in accordance with the Cochrane Handbook and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines³⁷. Two reviewers (JZ and SH) independently performed the search and screened all retrieved records. The protocol for this review was registered with PROSPERO in May 2026 (CRD420261387775). The literature search was completed prior to registration, but screening against eligibility criteria and data extraction had not yet commenced. Screening began immediately after registration. The final analytical approach was consistent with the registered protocol, except for the post-hoc disaggregation of physical modalities (PRP, rESWT, LLLT), which is explicitly described in the Results. All other methods (eligibility criteria, outcomes, subgroup categories, analytical models, minimum clinically important difference, GRADE decisions, and TSA analyses) were established before screening began. From database inception to January 2026, PubMed, Cochrane Library, Web of Science, Scopus, Embase and Google Scholar databases were searched. The full search strategies for all databases, including controlled vocabulary, free-text terms, Boolean operators, field tags, and limits, are provided in Supplementary Table 1. In addition, three additional records were identified through screening the reference lists of included studies and relevant reviews. All studies were retrieved and imported into the citation database (EndNote 21), and duplicates were removed. The search terms are listed in Table 1.

Quality and risk of bias assessment

The risk of bias in the included RCTs was assessed using the Cochrane RoB 2 tool as the primary instrument³⁸, with assessments conducted at the outcome level. Two reviewers independently evaluated each study across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as “low risk of bias”, “some concerns” or “high risk of bias” following standard RoB 2 guidance. Domain-level justifications are provided in Supplementary Table 2. Judgements for selective reporting were based on available trial registrations or published protocols where accessible; otherwise, the domain was rated as “some concerns” in the absence of a pre-registered protocol. For exercise-based trials, lack of blinding of participants and personnel was not automatically rated as high risk; rather, ratings reflected whether protocol deviations (e.g. differential co-interventions or progression decisions influenced by knowledge of allocation) were judged likely given the trial context, consistent with RoB 2 guidance³⁸. In addition, we used the PEDro scale to describe the methodological quality of included studies as a supplementary descriptive measure, not as a primary risk-of-bias tool.

Data analysis

Data from the fourteen studies were independently extracted by two reviewers and recorded in Microsoft Excel 2025 spreadsheets to facilitate the comparison and interpretation of research findings. The extracted data encompassed participant characteristics (age, sex, and type of exercise), sample sizes for each assigned group, administered intervention protocols, and the follow-up duration. A consensus on all extracted data was reached by both authors prior to subsequent analysis. We preferentially extracted intention-to-treat data when available. For the single study reporting medians and IQRs (Hamilton et al.³⁹), the SD was estimated using IQR/1.35. No authors were contacted for missing data, and no imputation was required. Inter-reviewer agreement was high (Cohen’s κ = 0.92). Data analysis was performed using Review Manager (RevMan) version 5.4. Model selection followed a prespecified strategy: random-effects models were used as the primary approach for all meta-analyses where clinical transitivity was judged adequate, to account for anticipated clinical and methodological heterogeneity across the included trials, including variations in study populations, intervention protocols, and outcome definitions. Fixed-effects models were used only in sensitivity analyses to assess the robustness of findings under an alternative modelling assumption. For TTRTP analyses, we used random-effects models with

Patient, Population or Problem	Intervention	Outcome	Study design
hamstring* injur* strain* rupture tear	therapy	Pain	Randomized control trial (RCT)
“hamstring muscle*”	exercise	“return to play”	
“posterior thigh”	“therapeutic exercise”	“return to sport*”	
“Biceps Femoris” Semimembranosus	“training intervention” “physical modalit*”	“reinjury”	
Semitendinosus	“physical		
	instrument*”		

Table 1. PICOS framework for eligibility criteria.

inverse variance weighting. For re-injury analyses, we used Mantel-Haenszel risk difference with random-effect models as the primary approach, consistent with recommendations for sparse binary data⁴⁰. The random-effects estimator was DerSimonian-Laird, with confidence intervals based on the standard normal approximation. Heterogeneity was assessed using the I^2 statistic; $I^2 > 50\%$ was considered a guide for substantial heterogeneity, but clinical and methodological heterogeneity particularly variations in return-to-play definitions and re-injury surveillance periods was assessed qualitatively before examining statistical heterogeneity. In the analysis evaluating the impact of hamstring eccentric loading and the hamstring strengthening program combined with progressive agility and trunk stabilization on TTRTP, the weighted mean difference (WMD) was employed to calculate the pooled effect size, owing to the utilization of identical measurement criteria. Risk difference (RD) was utilized to evaluate the re-injury rates between the intervention and control groups. Risk ratio (RR) was applied in subgroup analyses to examine the influence of follow-up duration on re-injury rates⁴¹. Heterogeneity among studies was assessed using the Q statistic and the I^2 index, with the significance level established at $p < 0.05$. The I^2 index quantifies heterogeneity, with values of $\leq 25\%$, $> 25\%$ to $\leq 50\%$, and $> 50\%$ indicative of low, moderate, and high heterogeneity, respectively.

In sensitivity analyses, we additionally applied Peto odds ratio, which is more stable with sparse events^{42,43}. Studies with zero events in both arms were not estimable and did not contribute to pooled estimates. For outcomes with few studies and events, results were interpreted with emphasis on confidence intervals rather than p-values. Sensitivity analyses examined the influence of effect measure (RD versus OR) and model choice on conclusions. For multi-arm trials, only relevant arms were included: for the three-arm Hamilton trial, we used only the PRP and no-injection groups to avoid double-counting. No missing data required imputation, as all continuous outcomes were reported as means with standard deviations. Outcomes were extracted at the primary TTRTP endpoint prespecified in each trial. The analytical approach followed the PROSPERO-registered protocol, except for the post-hoc disaggregation of physical modalities (PRP, rESWT, LLLT), which is explicitly described in the Results. For the three-arm Hamilton trial (PRP, PPP, and no injection), we included only the PRP and no-injection groups in the meta-analysis. The PPP arm was excluded to avoid double-counting, and the no-injection group was selected as the comparator because it represented rehabilitation alone, consistent with the other PRP trials. No participants were double-counted.

Synthesis without meta-analysis

For outcomes and intervention categories that could not be pooled in meta-analysis (pain-threshold rehabilitation, stand-alone physical modalities, stretching exercises, and spinal adjustable therapy), we conducted a narrative synthesis following the Synthesis Without Meta-analysis (SWiM) reporting guideline⁴⁴. Findings are presented descriptively with effect estimates and confidence intervals transcribed verbatim from the original reports. No additional statistical pooling was performed for these comparisons.

Sensitivity analyses

To assess robustness, we compared fixed-effects versus random-effects models, RD versus Peto OR as alternative effect measures, and examined the influence of continuity correction (adding 0.5 to all cells) for zero-event studies. Results were considered robust if direction and significance remained consistent across sensitivity analyses. Fixed-effects models were applied as a sensitivity analysis to examine whether the primary findings were robust to alternative modelling assumptions. Results were considered robust if the direction and magnitude of effect remained consistent across random- and fixed-effects models.

Trial sequential analysis

Trial sequential analysis (TSA) was performed to quantify the risk of random error in cumulative meta-analyses⁴⁵, thereby serving as a robustness check for the primary meta-analytic conclusions. The required information size (RIS) was calculated using $\alpha = 0.05$, $\beta = 0.20$, with control event proportions and effect estimates derived from the included trials; diversity-adjusted RIS was used for TTRTP outcomes to account for heterogeneity, while the re-injury analyses used the control event proportion from the pooled data due to sparse events. RIS values are provided in the figure legends for each TSA plot. The O'Brien-Fleming monitoring boundary was applied for all TSA plots; futility boundaries were not used. Conventional meta-analysis declares statistical significance when the Z-curve crosses ± 1.96 (the conventional boundary for $P < 0.05$). TSA imposes more stringent O'Brien-Fleming boundaries: crossing the monitoring boundary before reaching RIS indicates sufficient evidence; crossing the conventional 1.96 boundary but not the TSA boundary suggests potential false-positive results due to sparse data⁴⁶. TSA was conducted using TSA 0.9.5.10 Beta, with trials entered in chronological order for each meta-analysis.

Grading of evidence quality using the GRADE approach

To evaluate the overall certainty of evidence for TTRTP and Re-injury outcomes, we applied the GRADE framework. Two reviewers independently rated the evidence using GRADEpro, with disagreements resolved by a third reviewer^{47,48}. Evidence quality was downgraded for serious limitations in risk of bias (RoB 2), inconsistency ($I^2 > 50\%$), indirectness, or imprecision. Publication bias was not formally assessed due to the limited number of studies per comparison (≤ 5). Upgrading was not applied as all evidence originated from RCTs, which begin at high certainty. For TTRTP, we prespecified a 7-day MCID. This threshold was established a priori in our PROSPERO protocol, is consistent with sample-size calculations used in prior hamstring rehabilitation trials³⁹, and reflects the clinical judgment that a one-week reduction in RTP time is meaningful in athletic populations. Imprecision was judged by whether the 95% confidence interval crossed this MCID threshold, in addition to examining confidence interval width.

Results

Search results

The search strategy was conducted following PICOS guidelines⁴⁹. Figure 1 shows the PRISMA 2020 flow diagram for study selection. A total of 5473 articles were retrieved from PubMed, the Cochrane Library, Web of Science, Scopus, Embase and Google Scholar databases. Two reviewers (JZ and SH) independently screened all titles and abstracts. Full texts of potentially eligible studies were then independently assessed by the same two reviewers. Disagreements at either stage were resolved through discussion or, if necessary, by consultation with a third reviewer (SL). Of the 30 full-text articles assessed, 16 were excluded for reasons presented in the PRISMA flow diagram (Fig. 1). The remaining 14 articles were included in the quantitative synthesis.

Quality and risk of bias assessment

As a supplementary descriptive measure, PEDro scores for the 14 included studies ranged from 4 to 9 (Table 2), with corresponding descriptive categories based on established thresholds (9–10 = excellent, 6–8 = good, 4–5 = fair, ≤ 3 = poor). One study scored 4 (fair), six studies scored 5–6 (five fair, one good), and seven studies scored 8–9 (good). These PEDro totals are presented for descriptive purposes only; all primary methodological quality assessments and GRADE downgrading decisions were based on the RoB 2 tool (Fig. 2; Supplementary Table 2).

The RoB 2 assessment revealed substantial heterogeneity in methodological quality across the 14 included RCTs (Fig. 2). For each study, the overall risk-of-bias judgement was derived from the domain-level assessments of the primary outcome (TTRTP); for the small number of studies that also reported re-injury as a secondary outcome, the overall judgement did not differ materially, as the domains affecting TTRTP (randomization, deviations, and measurement) applied equally to the re-injury outcome. Figure 2 presents the overall study-level judgement; domain-level justifications are provided in Supplementary Table 2. Regarding specific domains, the randomization process was predominantly low risk, although approximately one-third showed some concerns due to unclear allocation concealment or baseline imbalances. Deviations from intended interventions constituted the major source of bias; in exercise-based trials, blinding of participants and personnel was unfeasible, which contributed to “some concerns” or “high risk” ratings when protocol deviations were judged likely to have arisen from the trial context (e.g. differential co-interventions or progression decisions influenced by knowledge of group allocation), consistent with RoB 2 guidance. Missing outcome data were generally low risk, with complete follow-up in most studies. Outcome measurement was largely low risk owing to assessor blinding, and selective reporting was judged as low risk for studies with available protocols, or some concerns where protocols were unavailable (see Supplementary Table 2 for domain-level justifications). These findings

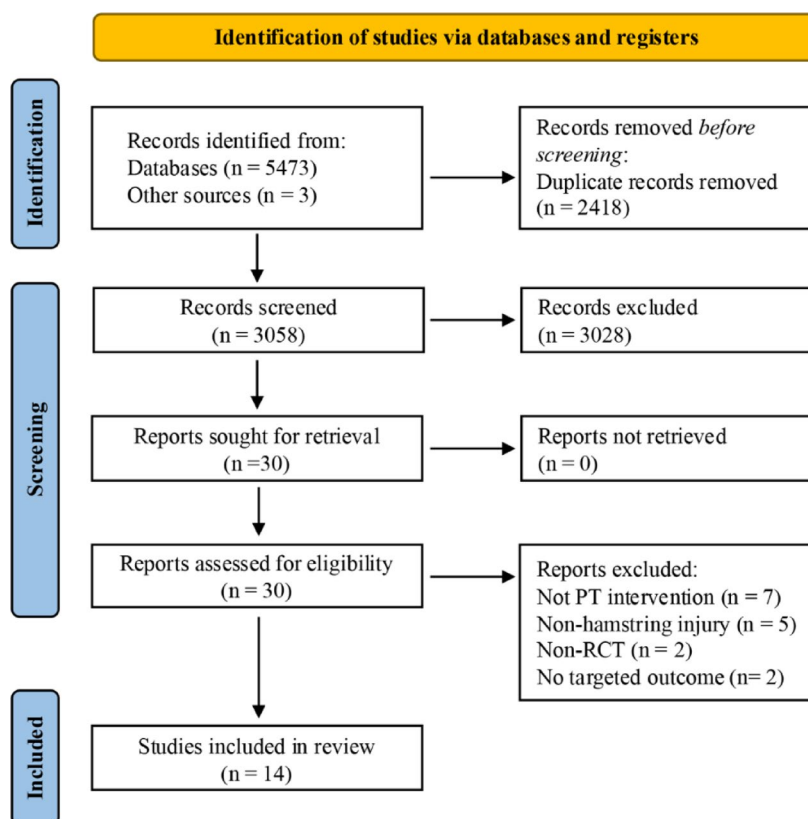


Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Author & Year	Subjects & Background	Experimental group	Control group	Follow-up/TTRTP	Outcomes & Key findings	PEDro Score
Kelli et al., 2025 ²⁵ (RCT)	75 sprinters or soccer players (mean age: TECAR, 22.1 ± 2.5 yr; TENS, 23.4 ± 3.0 yr; CON, 22.7 ± 2.8 yr); r/a: 26/24, 26/26, 26/25	TECAR (n = 24), TENS (n = 26), CON (n = 25)	Instructed to rest only	24 h post, 48 h post; Not reported	TECAR group showed greater improvements in VAS, FASH, SLR and STR	8
Askling et al., 2013 ³⁰ (RCT)	75 (68 males, 7 females) elite football players (mean age: L-protocol 25 ± 5 yr; C-protocol, 25 ± 6 yr); r/a: 37/37, 38/38	L-protocol (n = 37)	C-protocol (n = 38)	12 months; Return to full team training	A L-protocol significantly reduced TTRTP after acute hamstring injury compared to C-protocol	5
Askling et al., 2014 ⁵¹ (RCT)	56 Swedish elite sprinters and jumpers with MRI-verified acute hamstring injury; r/a: 28/28, 28/28	L-protocol (n = 28)	C-protocol (n = 28)	12 months; Return to full participation in training	A L-protocol resulted in significantly shorter TTRTP compared to C-protocol	5
Silder et al., 2013 ⁵² (RCT)	25 (19 males, 5 females in completers) athletes (mean age: 24 ± 9 yr); r/a: 16/13, 13/12	PATS group (n = 16)	PRES group (n = 13)	12 months; Return to sport clearance	Both rehabilitation programs yielded similar recovery outcomes	8
Sherry et al., 2004 ⁵³ (RCT)	24 completed (18 males, 6 females) athletes (mean age: STST 24.3 ± 12.4 y, PATS 23.2 ± 11.1 y, range 14–49); r/a: 16/13, 12/11	PATS group (n = 13)	STST group (n = 11)	2 weeks and 12 months; Return to full sport participation	A PATS is more effective than STST. It promotes return to sport and significantly reduces re-injury rates	5
Dhlamini et al., 2009 ⁵⁴ (RCT)	40 (range: 15–34 yr) professional soccer players with history of grade I or II hamstring strain; r/a: 20/20	Group A (n = 20)	Group B (n = 20)	After fifth treatment; Not reported	Spinal adjustive therapy (L4/5) combined with ultrasound improved hamstring contractile strength	4
Sefiddashti et al., 2018 ⁵⁵ (RCT)	37 elite athletes (mean age: 24.7 ± 4.1, range 18–40) with acute grade I or II hamstring strain (within 48 h); r/a: 18/17, 19/18	Cryostretching group (n = 18)	Cryotherapy group (n = 19)	1–6 days, after 5 sessions; Not reported	Cryostretching (ice plus gentle stretching) improved function and passive knee extension ROM	6
Medeiros et al., 2020 ⁵⁶ (RCT)	24 male amateur athletes (mean age: LLLT 30.4 ± 7.1 y, Placebo 28.0 ± 7.4 y, range 18–40); r/a: 12/11, 12/11	LLL group (n = 11)	Placebo group (n = 11)	6 months; Return to sport without pain and with full strength	LLL didn't enhance functional recovery or accelerate return to sport following HSIs	8
Desouza et al., 2025 ⁵⁷ (RCT)	60 athletes (mean age: PRP 24.5 ± 3.8 y, Control 25.1 ± 4.1 y); r/a: 30/30, 30/30	PRP group (n = 30)	Control group (n = 30)	24 months; Return to unrestricted training + full competitive match play	PRP with standard rehabilitation significantly reduced TTRTP in acute grade 2 HSIs	8
Hickey et al., 2020 ⁵⁸ (RCT)	43 (all male) athletes (mean age: pain-free 27.4 ± 5.2 y, pain-threshold 24.9 ± 5.3 y, range 18–40); r/a: 21/21, 22/21	Pain-threshold group (n = 21)	Pain-free group (n = 22)	2-month and 6-month; Return-to-play clearance per predefined criteria	Pain-threshold didn't accelerate TTRTP but improved knee flexor strength and muscle architecture without increasing re-injury risk	9
Crupnik et al., 2025 ⁵⁹ (RCT)	36 semi-professional athletes analyzed (mean age: rESWT 25.0 ± 4.9 y, sham 26.7 ± 4.8 y, range 18–34); r/a: 20/18, 20/18	rESWT + RP group (n = 18)	Sham rESWT + RP group (n = 18)	6-month; Return to full competition readiness	rESWT combined with rehabilitation reduced TTRTP and improved strength recovery in acute HSIs	9
Malliaropoulos et al., 2004 ⁶⁰ (RCT)	80 (52 males, 28 females) Greek athletes (Mean age: Group A 20.6 ± 3.7 y, Group B 20.3 ± 3.3 y); r/a: 40/40, 40/40	Group B (n = 40)	Group A (n = 40)	Return to full training; Return to unrestricted athletic activities	Increased frequency of static stretching accelerates ROM recovery and shortens overall rehabilitation time in grade II HSIs	5
Hamilton et al., 2015 ³⁹ (RCT)	90 (all male) professional athletes (mean age: PRP 26.6 ± 5.9 y, PPP 25.6 ± 5.8 y, No injection 25.5 ± 5.7 y, range 18–50); r/a: 30/28, 30/30, 30/27	PRP group (n = 30)	PPP group (n = 30); No injection group (n = 30)	2- and 6-months; Return to sport clearance upon rehabilitation completion	Single PRP didn't reduce TTRTP versus intensive rehabilitation alone in acute hamstring injuries.	9
Hamid et al., 2014 ⁶¹ (RCT)	28 enrolled; 24 completed athletes (median 21.0 y, range 17–49); r/a: 14/12, 14/12	PRP group (n = 14, 12 analyzed)	Control group (n = 14, 12 analyzed)	26 weeks and 39 weeks; Return to full training and competition readiness	Single autologous PRP injection combined with PATS rehabilitation significantly reduced time to TTRTP, and pain severity	6

Table 2. Results of the evidence synthesis from the selected RCTs. *RCT* randomized controlled trial, *TECAR* Transfer energy capacitive and resistive, *TENS* Transcutaneous electrical nerve stimulation, *VAS* visual analogue scale, *FASH* functional assessment for acute hamstring injuries, *SLR* straight leg raise, *STR* sit-and-reach test, *TTRTP* time to return to play, *L-protocol* lengthening protocol, *C-protocol* conventional protocol, *PATS* Progressive agility and trunk stabilization, *PRES* Progressive running and eccentric strengthening, *STST* stretching and strengthening, *ROM* range of motion, *rESWT* radial extracorporeal shock wave therapy, *RP* rehabilitation program, *PRP* platelet-rich plasma, *PPP* platelet-poor plasma, *WB* whole blood, *r/a* randomized/analyzed.

indicate that methodological quality varied considerably, underscoring the need for cautious interpretation of meta-analytic results, particularly from studies with high risk of bias, and highlight the importance of improved reporting standards in future trials.

Study characteristics

According to Table 2, a total of 693 participants diagnosed with hamstring injuries were included in this study, with mean participant ages across studies ranging from 20.3 years to 46.6 years. Most of the participants were professional, and semi-professional athletes engaged in sports such as football and track and field, and most diagnoses (10/14 studies) were confirmed by magnetic resonance imaging (MRI) or ultrasound imaging. Most included studies reported TTRTP and re-injury rate as primary or secondary outcomes; two studies^{25,54} reported only short-term functional outcomes without formal TTRTP data and were therefore excluded from

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Kelli et al, 2025	+	-	+	+	+	-
	Askling et al, 2013	+	-	+	-	+	-
	Askling et al, 2014	+	-	+	-	+	-
	Silder et al, 2013	+	+	+	+	+	+
	Sherry et al, 2004	+	X	+	-	+	X
	Dhlamini et al, 2009	-	-	X	-	-	X
	Sefiddashti et al, 2018	-	X	+	-	+	X
	Medeiros et al, 2020	+	+	+	+	+	+
	Desouza et al, 2025	+	-	+	+	+	-
	Hickey et al, 2020	+	+	+	+	+	+
	Crupnik et al, 2025	+	+	-	+	+	-
	Malliaropoulos et al, 2004	-	X	+	-	+	X
	Hamilton et al, 2015	+	+	+	+	+	+
	Hamid et al, 2014	+	X	+	+	+	X

Judgement

 High
 Some concerns
 Low

Fig. 2. Risk of bias assessment (RoB 2 domains: (1) Randomization process; (2) Deviation from intended interventions; (3) Missing outcome data; (4) Measurement of the outcome; (5) Selection of the reported result; (6) Overall risk of bias). Domain-level justifications are provided in Supplementary Table 2.

the quantitative synthesis. TTRTP definitions varied across studies and are detailed in Table 2. Re-injury was generally defined as a repeat hamstring injury after return to sport, with follow-up periods of 2–24 months. Except for Hickey et al.⁵⁸, who included the degree of pain as an element in their study, all the other trials' intervention items were carried out without pain. A part of the included studies mainly focused on evaluating the effects of therapeutic rehabilitation training, including strength enhancement and stretching load exercises. Two studies evaluated the hamstring loading training performed during stretching exercises^{50,51}. Two studies evaluated the hamstring strengthening training program combined with progressive agility and trunk stability training^{52,53}. Five studies evaluated the effect of combining rehabilitation programs with physical therapy^{39,56,57,59,61}. Among them, three studies were about PRP^{39,57,61}, one was about rESWT⁵⁹, and one was about LLLT⁵⁶. Kelli et al.²⁵ evaluated the therapeutic effects of TECAR, TENS on HSLs from a single modality perspective. Regarding stretching, Sefiddashti et al.⁵⁵ and Malliaropoulos et al.⁶⁰ respectively evaluated the therapeutic effects of combining cold therapy with stretching and increasing the frequency of stretching. One more research report presented the therapeutic effect of spinal adjustive therapy⁵⁴.

Meta-analysis results

The data synthesis was structured according to the primary intervention categories identified in the included studies: (I) hamstring eccentric loading; (II) hamstring strengthening combined with progressive agility and trunk stabilization; (III) rehabilitation program combined with PRP. For each category, the effects on TTRTP, re-injury rate, and pain/functional outcomes were analyzed separately. Heterogeneity was assessed using the I^2 statistic, and effect sizes were calculated as weighted mean difference (WMD), standardized mean difference (SMD), risk difference (RD) or risk ratio (RR) as appropriate.

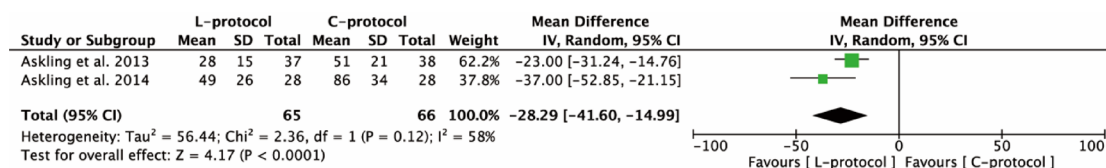


Fig. 3. Forest plot of the impact of L-protocol and C-protocol on TTRTP of HSIs; *TTRTP* time to return to play; *WMD* weighted mean difference; *CI* confidence interval.

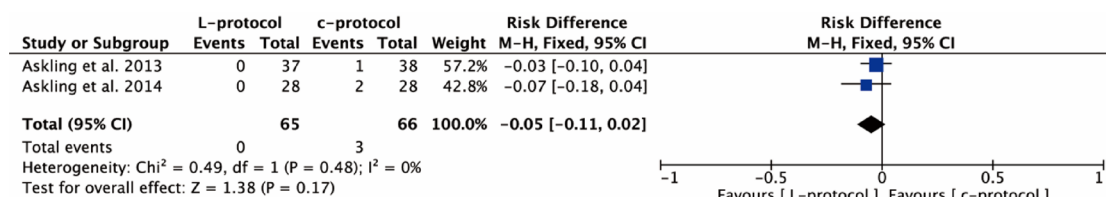


Fig. 4. Forest plot of the impact of L-protocol and C-protocol on re-injury rate of HSIs; *RD* risk difference; *CI* confidence interval.

Hamstring eccentric loading

TTRTP

Two randomized controlled trials^{50,51} evaluated the effect of a lengthening-protocol (L-protocol) compared with a conventional protocol (C-protocol) on TTRTP following acute hamstring strains. A random-effects meta-analysis was conducted due to moderate heterogeneity ($I^2 = 58\%$, $P = 0.12$). The pooled results showed that the L-protocol significantly reduced TTRTP compared with the C-protocol, with a weighted mean difference (WMD) of -28.29 days (95% CI -41.60 to -14.99, $p < 0.0001$; Fig. 3). Askling et al.⁵⁰ reported a mean difference of -23.00 days (95% CI -31.24 to -14.76) in elite football players, while Askling et al.⁵¹ observed a larger effect (-37.00 days, 95% CI -52.85 to -21.15) in Swedish elite sprinters and jumpers. These findings indicate that a rehabilitation protocol emphasizing lengthening exercises (L-protocol) may accelerate TTRTP compared with conventional rehabilitation.

Re-injury rate

These two studies^{50,51} reported re-injury rate following L-protocol versus C-protocol in athletes with HSIs. A fixed-effects meta-analysis using MH-RD was performed ($I^2 = 0\%$, $P = 0.48$). No significant difference was found between groups (RD -0.05, 95% CI -0.11 to 0.02, $p = 0.17$; Fig. 4). No re-injuries occurred in the L-protocol group (0/65), whereas the C-protocol group had three (3/66). A sensitivity analysis using Peto OR confirmed the null finding (OR 0.13, 95% CI 0.01 to 1.30, $p = 0.08$), supporting robustness. These findings indicate a trend toward reduced re-injury risk with the L-protocol compared with conventional rehabilitation.

Pain and functional outcomes

Neither of the two included studies on hamstring eccentric loading systematically reported quantitative pain scores (e.g. visual analogue scale) or standardized functional outcome measures (e.g. functional assessment for HSIs) as primary or secondary endpoints. Both studies used pain-guided rehabilitation progression, where exercises were performed without pain provocation. Clinical recovery was monitored weekly through manual assessment of flexibility (passive straight leg raise) and isometric strength, with the absence of localised palpation pain and pain during isometric contraction serving as criteria for advancing to the next rehabilitation stage⁵⁰. Additionally, the Askling H-test-a dynamic test assessing the player's confidence and absence of insecurity during a simulated high-speed running movement-was applied prior to return to sport. In the L-protocol group, 35% of players (13/37) experienced insecurity and required an average extension of 7.5 days ($SD \pm 2.8$) of rehabilitation, compared with 71% (27/38) in the C-protocol group (mean extension 6.7 days, $SD \pm 2.7$)⁵⁰. These findings suggest that the L-protocol was associated with fewer functional deficits at the time of return-to-play testing; however, due to the absence of uniform pain or functional scales, a quantitative meta-analysis was not feasible for this outcome domain.

Hamstring strengthening program combined with progressive agility and trunk stabilization

For PATS analyses, the two included trials used different control interventions STST (stretching and strengthening) and PRES (progressive running and eccentric strengthening) both of which represent conventional rehabilitation approaches. We considered pooling these comparisons clinically appropriate as both reflect standard care against which PATS was evaluated.

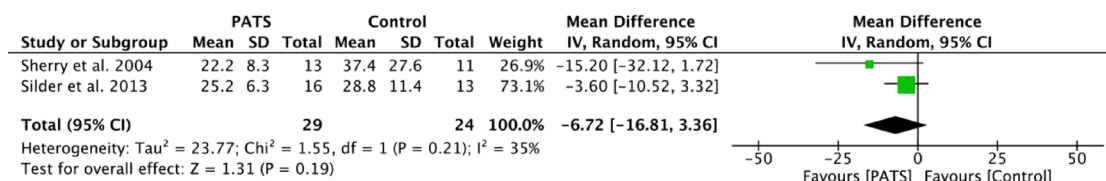


Fig. 5. Forest plot of the impact of PATS and control programs (STST or PRES) on TTRTP of HSIs; TTRTP time to return to play; WMD weighted mean difference; CI confidence interval.

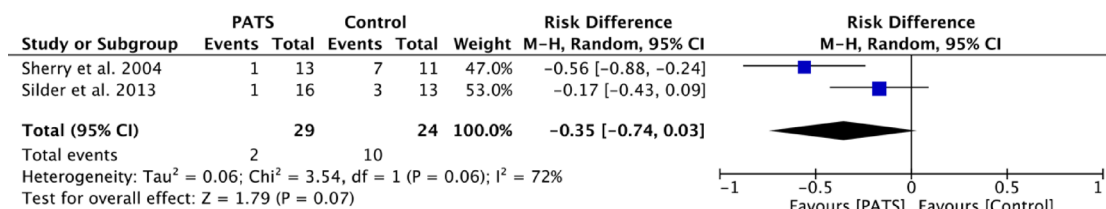


Fig. 6. Forest plot of the impact of PATS and control programs (STST or PRES) on re-injury rate of HSIs; RD risk difference; CI confidence interval.

TTRTP

Two randomized controlled trials^{52,53} evaluated the effect of a PATS compared with STST or PRES on TTRTP following HSIs. A random-effects meta-analysis was performed due to moderate heterogeneity ($I^2 = 35\%$, $P = 0.21$). The pooled analysis showed no significant difference in TTRTP between the PATS group and the control groups, with a WMD of -6.72 days (95% CI -16.81 to 3.36 , $p = 0.19$; Fig. 5). Sherry et al.⁵³ reported a mean difference of -15.20 days (95% CI -32.12 to 1.72) favoring PATS over STST, whereas Silder et al.⁵² found a smaller, non-significant difference of -3.60 days (95% CI -10.52 to 3.32) when comparing PATS with PRES. These findings indicate that, compared with conventional strengthening and stretching or eccentric running programs, the addition of progressive agility and trunk stabilization does not significantly accelerate return to sport after HSIs.

Re-injury rate

These two studies^{52,53} reported re-injury rate following PATS compared with STST or PRES. A random-effects meta-analysis using risk difference was conducted due to substantial heterogeneity ($\tau^2 = 0.06$; $\chi^2 = 3.54$, $df = 1$, $P = 0.06$; $I^2 = 72\%$). The pooled analysis showed no statistically significant difference in re-injury rate between PATS and control groups (RD -0.35 , 95% CI -0.74 to 0.03 , $p = 0.07$; Fig. 6). Across both studies, two re-injuries occurred in the PATS groups ($n = 29$) compared with ten in the control groups ($n = 24$). Individual trial results ranged from RD -0.56 (95% CI -0.88 to -0.24) in Sherry et al.⁵³ to RD -0.17 (95% CI -0.43 to 0.09) in Silder et al.⁵². A sensitivity analysis using Peto odds ratio ($I^2 = 0\%$) yielded a larger effect estimate (OR 0.08 , 95% CI 0.02 to 0.38), but the statistical significance of this estimate should be interpreted with caution. The Peto odds ratio can produce unstable estimates in the presence of very large treatment effects and sparse event data, as is the case here. The primary analysis using risk difference (RD -0.35 , 95% CI -0.74 to 0.03 , $p = 0.07$) was statistically inconclusive, and the inconsistent findings across the two analytical approaches indicate that the evidence for PATS on re-injury prevention remains uncertain. We therefore emphasize the absolute event counts (2/29 vs. 10/24) and the width of the RD confidence interval, which crosses the null, as more informative than the point estimate of the Peto OR.

Pain and Functional Outcomes

Sherry et al.⁵³ conducted a battery of functional tests at the TTRTP, including hop tests (hop for height, hop for distance, 4-hop crossover test) and 40-yard sprint times. No significant differences were observed between the PATS and STST groups for any functional measure (all $p > 0.05$). Furthermore, functional test performance did not differ between athletes who subsequently sustained a re-injury and those who did not ($P = 0.07$ – 0.97), suggesting that these tests had limited predictive value for re-injury risk. Silder et al.⁵² reported that at the TTRTP, nearly all subjects in both groups had resolution of pain with palpation and during manual muscle strength testing. However, 11 of 25 subjects (44%) who completed rehabilitation reported remaining hamstring symptoms (e.g. pain, tightness), with no significant difference between groups (7/13 in PATS vs. 4/12 in PRES, $P = 0.444$). Twelve subjects (48%) did not feel they had returned to their pre-injury level of performance, though only three (12%) attributed this limitation to their hamstring injury, with general deconditioning being the most common limiting factor. ROM measures (passive straight leg raise) showed no significant between-group differences at final examination ($P = 0.337$). Importantly, despite meeting clinical return-to-sport criteria (no pain, full strength), no subject in either group showed complete resolution of injury on MRI, indicating ongoing tissue healing^{52,53}.

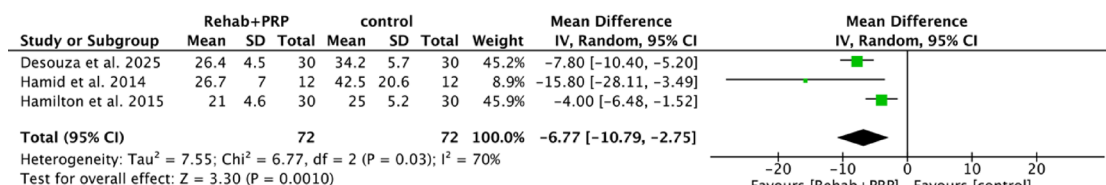


Fig. 7. Forest plot of the impact of PRP combined with rehabilitation versus rehabilitation alone (no injection) on TTRTP of HSIs; TTRTP time to return to play; WMD weighted mean difference; CI confidence interval.

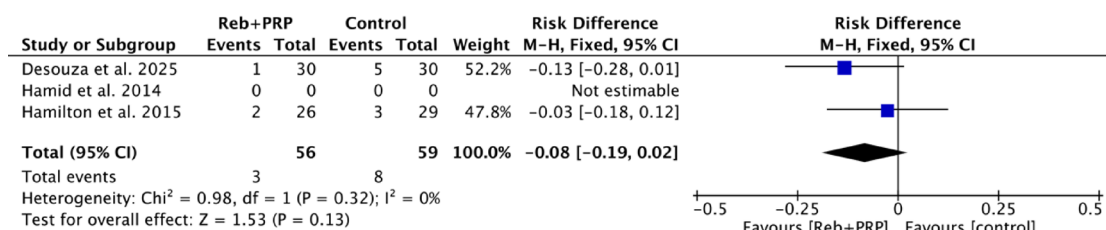


Fig. 8. Forest plot of the impact of PRP combined with rehabilitation versus rehabilitation alone (no injection) on re-injury rate of HSIs; RD risk difference; CI confidence interval.

Taken together, these findings indicate that PATS and control programs yield comparable improvements in pain and functional performance at the TTRTP. However, residual symptoms and functional deficits may persist despite clinical clearance, underscoring the need for continued monitoring and gradual return to full activity.

Rehabilitation programs combined with physical modalities

Five randomized controlled trials^{39,56,57,59,61} evaluated the effect of rehabilitation programs combined with physical modalities on TTRTP following HSIs. Due to substantial differences in biological rationale, mechanism of action, and clinical objectives, we did not pool these interventions into a single estimate. Instead, we conducted a meta-analysis for PRP, for which three trials were available, and narratively described the single-trial evidence for rESWT and LLLT.

Rehabilitation programs combined with PRP

TTRTP

A random-effects meta-analysis of the three PRP trials (PRP combined with rehabilitation versus rehabilitation alone or placebo injection) showed that PRP suggestively reduced TTRTP compared with control, with a weighted mean difference (WMD) of -6.77 days (95% CI -10.79 to -2.75, $p = 0.0010$; Fig. 7). Heterogeneity was substantial ($I^2 = 70\%$, $p = 0.03$). Individual trial effects ranged from WMD -4.00 days (95% CI -6.48 to -1.52) in Hamilton et al.³⁹ to WMD -15.80 days (95% CI -28.11 to -3.49) in Hamid et al.⁶¹, with Desouza et al.⁵⁷ reporting an intermediate effect (WMD -7.80 days, 95% CI -10.40 to -5.20). The substantial heterogeneity may reflect differences in PRP preparation (leukocyte-rich versus leukocyte-poor), injection timing, rehabilitation protocols, or definitions of return to sport across studies.

Re-injury rate

The three PRP trials reported re-injury rates over follow-up periods ranging from 6 to 24 months. A fixed-effects meta-analysis ($I^2 = 0\%$, $p = 0.32$) showed no significant difference between PRP and control groups (RD -0.08, 95% CI -0.19 to 0.02, $p = 0.13$; Fig. 8). Across the three trials, three re-injuries occurred in the PRP groups ($n = 56$) versus eight in controls ($n = 59$). Sensitivity analyses using Peto OR (OR 0.40, 95% CI 0.12 to 1.34, $p = 0.14$) and random-effects models (OR 0.39, 95% CI 0.11 to 1.36) confirmed the null finding. Desouza et al.⁵⁷ reported one re-injury in the PRP group versus five in controls (RD -0.13, 95% CI -0.28 to 0.01); Hamilton et al.³⁹ reported two versus three (RD -0.03, 95% CI -0.18 to 0.12); Hamid et al.⁶¹ reported no re-injuries in either group and did not contribute to the pooled estimate.

Pain and functional outcomes

Hamid et al.⁶¹ assessed pain using the Brief Pain Inventory-Short Form (BPI-SF). Patients in the PRP group demonstrated significantly lower pain severity scores across all follow up time points compared with controls ($\beta = -0.390$, 95% CI -0.67 to -0.11, $p = 0.007$). However, no significant between-group difference was observed for pain interference with daily activities ($\beta = -0.185$, 95% CI -0.44 to 0.07, $p = 0.157$). Hamilton et al.³⁹ evaluated isokinetic knee flexor strength at return to sport and found no significant differences between PRP and control groups for concentric strength at 60°/s, 300°/s, or eccentric strength at 60°/s (all $p > 0.05$). Desouza et al.⁵⁷ did not report standardized pain or functional outcome measures. Due to the heterogeneity in outcome reporting across studies, a quantitative synthesis for pain and functional outcomes was not feasible.

Rehabilitation programs combined with rESWT

TTRTP

The rESWT group showed a significantly shorter TTRTP compared with the sham group (25.4 ± 3.5 days versus 28.3 ± 4.5 days; mean difference -2.90 days, 95% CI -5.63 to -0.17 ; SMD -0.70 , 95% CI -1.38 to -0.03).

Re-injury rate

One re-injury occurred in each group over the 6-month follow-up period (1/16 versus 1/16), with no significant between-group difference. Due to single-trial nature, formal meta-analysis was not performed.

Pain and functional outcomes

Crupnik et al.⁵⁹ assessed isometric knee flexor strength post-treatment using two-way repeated measures ANOVA. A significant leg effect (previously injured versus contralateral uninjured leg) was observed ($p = 0.005$), but no significant treatment effect was detected ($p = 0.899$). Post-hoc testing showed that in the sham rESWT group, the previously injured leg was significantly weaker than the contralateral uninjured leg ($p = 0.014$), whereas no such difference was observed in the rESWT group. However, the treatment-by-leg interaction was not reported; therefore, these findings should be interpreted cautiously and do not establish that rESWT restores strength symmetry.

Rehabilitation programs combined with LLLT

TTRTP

The study found no significant benefit of LLLT over placebo for TTRTP (mean difference -0.80 days, 95% CI -11.22 to 9.62 ; SMD -0.06 , 95% CI -0.90 to 0.77).

Re-injury rate

No re-injuries occurred in either group during the 6-month follow-up period (0/11 versus 0/11). With zero events in both arms, the effect estimate was not estimable.

Pain and functional outcomes

Medeiros et al.⁵⁶ assessed hamstring flexibility (passive straight leg raise, knee extension test, maximal hip flexion active knee extension) and isometric strength (inner, mid, and outer range) using a handheld dynamometer. Both the LLLT and placebo groups showed significant improvements over time (time effect $p < 0.05$), but no significant group-by-time interactions were observed for any flexibility or strength outcome (all $p > 0.05$), with between-group effect sizes ranging from trivial to moderate (Cohen's $d = 0.04$ – 0.61). These findings indicate that LLLT provided no additional benefit over placebo for pain, flexibility, or strength recovery.

Trial sequential analysis

The graphics illustrate the trial sequential analysis for both studies^{50,51} (Fig. 9). The meta-analysis of the trial results for the TTRTP outcome is represented in panel A. The cumulative Z-curve exceeded the conventional boundary of 1.96 at an early stage and subsequently crossed the O'Brien-Fleming monitoring boundary, having reached the required information size. This finding supports the robustness of the cumulative meta-analytic conclusion regarding the 28-day reduction in return time, indicating that the observed effect is unlikely to be a type I error arising from sparse data. Panel B illustrates the re-injury analysis. The Z-curve for the re-injury rate remained within the monitoring boundaries and did not accumulate sufficient information to meet the required information size. Consequently, the available data do not support either the acceptance or rejection of a moderate risk difference; the non-significant estimate should therefore be regarded as tentative until further evidence emerges from adequately powered trials.

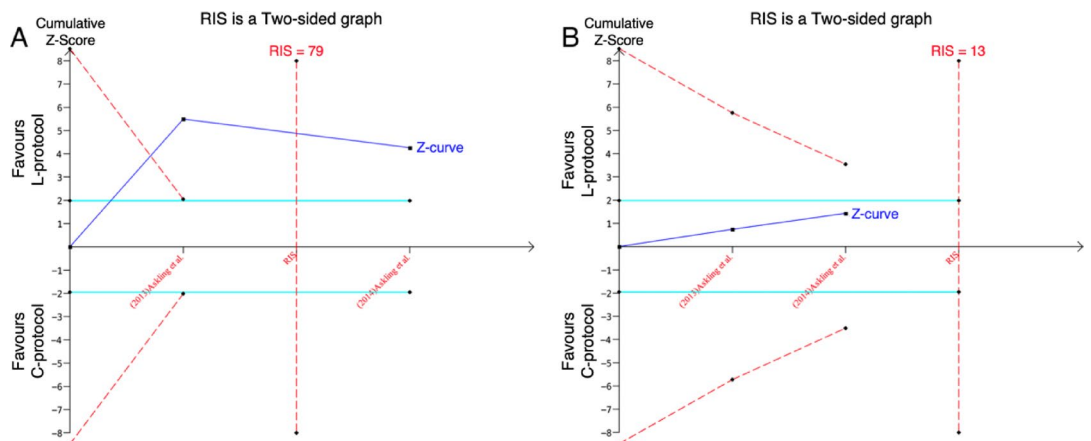


Fig. 9. Trial sequential analysis of eccentric loading (L-protocol) versus conventional rehabilitation for TTRTP (A) and re-injury rate (B); RIS required information size; O'Brien-Fleming boundary; Z-curve.

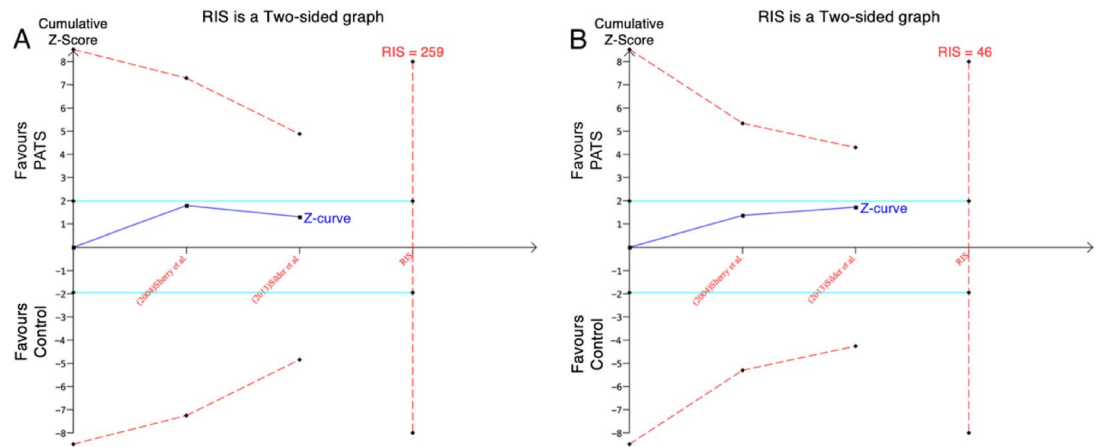


Fig. 10. Trial sequential analysis of progressive agility and trunk stabilization versus control programs for TTRTP (A) and re-injury rate (B); *RIS* required information size; O'Brien-Fleming boundary; Z-curve.

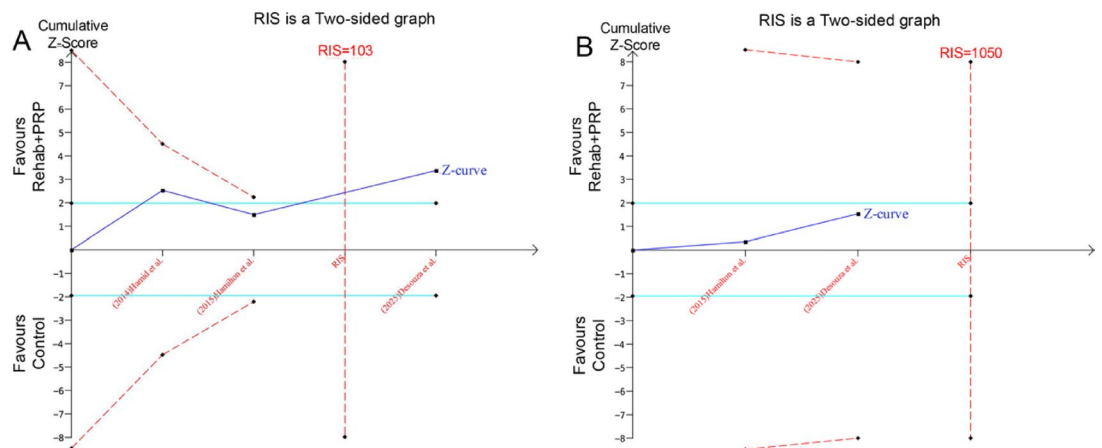


Fig. 11. Trial sequential analysis of rehabilitation combined with physical modalities versus control for TTRTP (A) and re-injury rate (B); *RIS* required information size; O'Brien-Fleming boundary; Z-curve.

The cumulative Z-curve for the two PATS trials^{52,53} did not cross either the conventional threshold of 1.96 or the O'Brien-Fleming monitoring boundary, indicating that the null finding from the current meta-analysis remains inconclusive; the available evidence cannot definitively rule out a clinically meaningful difference (Fig. 10). The Z-curve for the re-injury rate also did not cross either boundary, or did it accumulate sufficient information to meet the required information size. Although the point estimate favors PATS for re-injury reduction, the evidence is insufficient to eliminate the risk of random error; consequently, the observed risk reduction should be interpreted as preliminary rather than definitive, and further large-scale trials are warranted to confirm these findings.

Trial sequential analysis was conducted for the three PRP trials comparing PRP combined with rehabilitation versus control^{39,57,61} (Fig. 11). For TTRTP (Panel A), the cumulative Z-curve crossed the conventional boundary of 1.96 and reached the required information size, but did not cross the O'Brien-Fleming monitoring boundary. This indicates that, although the cumulative information is sufficient to exclude random error as the sole explanation for the observed effect, the evidence does not meet the more stringent threshold required for conclusive confirmation of the TTRTP benefit. The result should therefore be interpreted as suggestive but not definitive, warranting confirmation in future trials. For re-injury rate (Panel B), the Z-curve remained within the monitoring boundaries and accumulated information fell substantially short of the required information size. Consequently, the available data do not permit firm conclusions regarding the impact of PRP on re-injury risk. The non-significant estimate should therefore be regarded as tentative until further evidence emerges from adequately powered trials. TSA was not performed for rESWT or LLLT as each was evaluated in a single trial.

Narrative synthesis of non-pooled studies

For intervention categories that were not amenable to quantitative meta-analysis specifically pain-threshold rehabilitation, stand-alone physical modalities, stretching exercises, and spinal adjustive therapy we performed a narrative synthesis following the SWiM framework⁴⁴. For each intervention, we report the direction of effect,

effect size with confidence intervals, p-values, study design and sample size, risk of bias (RoB 2), and GRADE certainty where applicable. All numerical values were directly extracted from the original trial reports; no statistical pooling, re-analysis, or recalculation was performed.

Pain-threshold rehabilitation

TTRTP

Median time from injury to TTRTP clearance was 15 days (95% CI 13 to 17) in the pain-free group and 17 days (95% CI 11 to 24) in the pain-threshold group. Hickey et al.⁵⁸ reported the hazard ratio for achieving TTRTP clearance in the pain-threshold group relative to the pain-free group was 0.75 (95% CI 0.40 to 1.40, $p=0.37$), indicating no significant difference between protocols. All participants in the pain-threshold group (21/21) and 21 of 22 participants in the pain-free group met TTRTP clearance criteria.

Re-injury rate

Over the 6-month follow-up period after TTRTP clearance, two reinjuries occurred in each group (pain-free: 2/22; pain-threshold: 2/21). The hazard ratio for re-injury in the pain-threshold group was 1.05 (95% CI 0.14 to 7.47, $p=1.00$), demonstrating no significant difference in recurrence risk between protocols.

Pain and functional outcomes

Hickey et al.⁵⁸ compared isometric knee flexor strength, BFlh fascicle length, and fear of movement between pain-threshold (pain $\leq 4/10$) and pain-free rehabilitation. At return-to-play clearance and 2-month follow-up, the pain-threshold group showed significantly greater strength recovery at 90° hip/90° knee flexion (mean difference 15% at both time points; 95% CI 1–28% and 1–29%, respectively). No between-group differences were observed at 0° hip/0° knee flexion. BFlh fascicle length increased more in the pain-threshold group from baseline to 2-month follow-up (mean difference 0.91 cm, 95% CI 0.34 to 1.48). Fear of movement (Tampa Scale) decreased similarly in both groups, with no significant between-group differences. No adverse events occurred, and no rehabilitation-period reinjuries were reported. Thus, pain-threshold rehabilitation enhances strength at long muscle lengths and architectural adaptations without increasing fear or risk.

Physical modalities

TTRTP

No data on TTRTP were available for stand-alone physical modalities. The included study focused on short-term (up to 48 h) symptomatic and functional outcomes without defining return-to-sport criteria or recording the time from injury to full sport participation²⁵.

Re-injury rate

The study did not systematically report hamstring re-injury rate. Kelli et al.²⁵ did not follow participants beyond 48 h after the single intervention session, precluding any assessment of injury recurrence.

Pain and functional outcomes

Kelli et al.²⁵ compared a single session of TECAR ($n=24$), TENS ($n=26$), or rest ($n=25$) in athletes with acute HSIs. TECAR produced significantly greater reductions in VAS (–38.8% to –63.3%) and greater improvements in FASH (28.6–48.2%) and flexibility (SLR/STR) than TENS (–16.7% to –25.0% for VAS) or rest (all $p<0.05$). These findings suggest that TECAR may offer short-term pain relief and functional improvement in the acute phase, although the long-term benefits remain unclear due to the absence of extended follow-up.

Stretching exercise

TTRTP

Only Malliaropoulos et al.⁶⁰ reported a return-to-play relevant outcome: the time required for full rehabilitation (return to unrestricted athletic activities). The higher-frequency stretching group (Group B) achieved full rehabilitation significantly faster than the lower-frequency group (Group A) (mean $\pm$ SD: 13.27 $\pm$ 0.71 days vs. 15.05 $\pm$ 0.81 days, $p<0.001$). Additionally, the time to normalize active knee extension range of motion was shorter in Group B (5.57 $\pm$ 0.71 days vs. 7.32 $\pm$ 0.53 days, $p<0.001$). Sefiddashti et al.⁵⁵ did not report TTRTP. No meta-analysis was performed due to the absence of uniform TTRTP definitions across studies.

Re-injury rate

Neither study systematically reported hamstring re-injury rates. Malliaropoulos et al.⁶⁰ followed athletes only until return to full training without providing long-term recurrence data. Sefiddashti et al.⁵⁵ assessed outcomes immediately after the 5-day intervention period and did not report follow-up beyond the post-treatment assessment.

Pain and functional outcomes

Sefiddashti et al.⁵⁵ assessed pain at rest and during activity using a 10-point VAS and functional status using the Lower Extremity Functional Scale (LEFS). Both the cryostretching ($n=18$) and cryotherapy ($n=19$) groups improved from baseline to post-treatment, but between-group differences were not significant for pain at rest or during activity ($p>0.05$). For passive knee extension range of motion (PKE), the cryostretching group showed a significantly larger improvement than the cryotherapy group ($p<0.05$), whereas improvements in active knee extension (AKE) did not differ significantly between groups. Functional status (LEFS) improved to a significantly greater extent in the cryostretching group compared with the cryotherapy group ($p<0.05$), with the change exceeding the minimal detectable change (4.2 points), indicating a clinically meaningful improvement.

Malliaropoulos et al.⁶⁰ did not use standardized pain or functional questionnaires but reported that the higher-frequency stretching group achieved faster normalization of active knee extension range of motion, which was used as a proxy for recovery of flexibility and functional capacity.

Taken together, these findings suggest that incorporating static stretching into early rehabilitation, particularly when applied at higher frequency, accelerates the restoration of range of motion and shortens overall rehabilitation time. Cryostretching (ice plus stretching) provides additional benefits for passive flexibility and self-reported function compared with cryotherapy alone, without significant additional pain reduction.

Spinal adjunctive therapy

TTRTP

The study⁵⁴ did not report time to return to play as an outcome measure. Therefore, no data were available for meta-analysis or qualitative synthesis for this outcome.

Re-injury rate

This study did not report re-injury rate. Follow-up was limited to the post-treatment assessment after the fifth session, with no long-term surveillance for injury recurrence.

Pain and functional outcomes

Using a Cybex system 2000, the primary outcome is hamstring muscle contractile strength during knee flexion. Although the groups had different baselines for contractile strength (due to age and body weight), both groups had increases in contractile strength after intervention. Group A (spinal adjustment + ultrasound) had greater increases in overall muscle contraction of the previously injured leg compared to Group B (ultrasound only). The study did not report pain scores (e.g. VAS) or functional status questionnaires. Due to no reported TTRTP, re-injury, or standardized pain/function measures, this study was excluded from the quantitative synthesis. The data indicate that spinal adjustment may provide more benefit to improving hamstring strength, yet further research with relevant clinical outcomes is needed.

GRADE assessment

The GRADE assessment revealed marked variability in evidence certainty across intervention categories and outcomes (Table 3). For TTRTP outcomes, downgrading for imprecision was applied when the 95% confidence interval crossed the MCID threshold of 7 days or when the optimal information size was not met; for re-injury outcomes, imprecision was assessed based on event counts and confidence interval width crossing the null. Inconsistency was downgraded when I^2 exceeded 50% and the direction of effects varied substantially, and risk of bias downgrades were based on the proportion of information from studies with “some concerns” or “high” RoB 2 ratings exceeding 33.3%. Moderate certainty evidence was confirmed for eccentric loading on TTRTP (downgraded solely for risk of bias), for Rehab + LLLT on TTRTP (downgraded for imprecision due to small sample size), and for pain-threshold rehabilitation on TTRTP (downgraded for risk of bias). Single-trial evidence does not automatically imply low certainty rather, certainty reflects the confidence in the effect estimate based on the trial’s methodological quality and precision. Low certainty evidence was observed for eccentric loading on re-injury rate (imprecision), PATS on TTRTP (risk of bias and imprecision), Rehab + PRP on both TTRTP (inconsistency, $I^2 = 62\%$) and re-injury rate (imprecision), Rehab + rESWT on both TTRTP and re-injury rate (risk of bias and imprecision), Rehab + LLLT on re-injury rate (zero events, very small sample), and pain-threshold rehabilitation on re-injury rate (risk of bias and imprecision). PATS for re-injury reduction was downgraded to very low certainty, reflecting serious inconsistency ($I^2 = 72\%$) and imprecision, with trial sequential analysis indicating inconclusive evidence. Collectively, these findings indicate that, aside from the TTRTP benefits of eccentric loading, Rehab + LLLT, and pain-threshold protocols (moderate certainty), most estimates remain provisional, underscoring an urgent need for high-quality, adequately powered RCTs to improve confidence in clinical recommendations.

Discussion

It is important to note that TTRTP alone should not be interpreted as a marker of complete recovery. Return to sport particularly return to competition or full performance requires restoration of strength, neuromuscular control, and sport-specific function, which may not be fully captured by TTRTP criteria alone. Throughout our GRADE assessment, we prioritized clinical relevance (whether the 95% CI crossed the 7-day MCID) over nominal statistical significance (whether $p < 0.05$), consistent with the principle that statistically significant effects may be clinically trivial, and non-significant effects may still be clinically meaningful when estimates are imprecise but suggest potential benefit. Interpretation of the pooled TTRTP findings is further complicated by variation in return-to-play definitions across the included studies. These definitions ranged from return to full training or unrestricted activity to return to match play or competitive sport and return to full sport participation or medical clearance. These thresholds represent different stages of functional recovery and may systematically influence the observed treatment effects. For instance, studies using earlier return-to-training criteria may yield shorter TTRTP estimates than those requiring match-play clearance, independent of the intervention’s true efficacy. This variation should be considered when comparing results across intervention categories and when interpreting the clinical applicability of the pooled estimates. Formal subgroup analysis by TTRTP definition level was not feasible due to the limited number of studies per category, and this constitutes a limitation of the current synthesis. In addition to recovering muscle strength, the mechanisms of protection from eccentric loading appear to involve numerous structural changes. When eccentrically loaded in a muscle lengthened state, the muscle is induced to generate new sarcomeres through the sequential addition of sarcomeres which results in an increase in fascicle length, thereby changing the muscle’s length-tension relationship towards the

Intervention Category	Outcome	No. of Studies/Participants	Study Design Grade	Risk of Bias (Downgrade if ≥ 50% domains with 'some concerns' or 'high' on RoB 2)	Indirectness (Downgrade if significant PICO differences)	Inconsistency (Downgrade if wide variance, non-overlapping CIs, or I ² > 50%)	Imprecision (Downgrade if 95% CI cross null; or OIS not reached)	Publication Bias	Certainty of Evidence (High/Moderate/Low/Very Low)
Lengthening-focused protocol (L-protocol vs. C-protocol)	TTRTP	2 RCTs (n = 131)	High	-1	0	0	0	0	⊕⊕⊕○ Moderate
Lengthening-focused protocol (L-protocol vs. C-protocol)	Re-injury Rate	2 RCTs (n = 130)	High	-1	0	0	-1	0	⊕⊕○○ Low
PATS vs. Control (STST or PRES)	TTRTP	2 RCTs (n = 49)	High	-1	0	0	-1	0	⊕⊕○○ Low
PATS vs. Control (STST or PRES)	Re-injury Rate	2 RCTs (n = 49)	High	-1	0	-1	-1	0	⊕○○○ Very Low
Rehab+ PRP	TTRTP	3 RCTs (n = 144)	High	-1	0	-1	0	0	⊕⊕○○ Low
Rehab+ PRP	Re-injury Rate	3 RCTs (n = 115)	High	-1	0	0	-1	0	⊕⊕○○ Low
Rehab+ ESWT	TTRTP	1 RCT (n = 36)	High	-1	N/A	0	-1	0	⊕⊕○○ Low
Rehab+ ESWT	Re-injury Rate	1 RCT (n = 36)	High	-1	N/A	0	-1	0	⊕⊕○○ Low
Rehab+ LLLT	TTRTP	1 RCT (n = 24)	High	0	N/A	0	-1	0	⊕⊕⊕○ Moderate
Rehab+ LLLT	Re-injury Rate	1 RCT (n = 24)	High	0	N/A	0	-2	0	⊕⊕○○ Low
Pain-Threshold Rehabilitation vs. Pain-Free	TTRTP	1 RCT (n = 43)	High	-1	0	0	0	0	⊕⊕⊕○ Moderate
Pain-Threshold Rehabilitation vs. Pain-Free	Re-injury Rate	1 RCT (n = 43)	High	-1	0	0	-1	0	⊕⊕○○ Low

Table 3. Summary of GRADE evidence certainty for primary outcomes. Certainty symbols: ⊕⊕⊕⊕ high, ⊕⊕⊕⊕ moderate, ⊕⊕⊕○○ low, ⊕○○○○ very low. Imprecision was downgraded by one level (−1): When the 95% confidence interval crossed the null or when the total sample size was small, but events were not zero; Imprecision was downgraded by two levels (−2): When zero events occurred in both groups with a very small total sample size.

longer length range of operation, which is especially important for the biceps femoris long head as it experiences maximal musculotendon strain while the hamstrings are activated and lengthened at the terminal swing phase of a sprint²⁸. This type of architectural remodeling may allow the hamstrings to better absorb eccentric loads, reducing their risk of injury at specific joint angles during high-speed running⁶². While these mechanisms are biologically plausible, they are derived from physiological studies and should be distinguished from the clinical evidence of reduced TTRTP. The L-protocol is also thought to be less likely than other aggressive eccentric regimes to create premature overloads and/or iatrogenic re-injuries because it utilizes moderate levels of intensity and is guided by pain to progress the program. Though existing data affirms eccentric loading, a few considerations must be borne in mind. The pooled estimate of -28.29 days reflects the weighted average of two trials with differing effect sizes (-23 days in footballers⁵⁰ and -37 days in sprinters/jumpers⁵¹). The L-protocol trials included mostly male elite footballers and sprinters, rendering it uncertain whether findings can be generalized to female athletes, masters' competitors, or recreational populations⁶³. Moreover, Vermeulen et al.⁶⁴ did not find significant differences in TTRTP from introducing lengthening exercises early versus late (adjusted HR 0.95, 95% CI 0.56 to 1.60), suggesting that the timing of eccentric loading may be less important than once accepted-provided the exercises are ultimately incorporated. Future trials will then need to explore parameters governing optimal dosing (volume, frequency, and progression rate) and explore whether individual factors like injury grade, age, and baseline fascicle architecture modulate treatment response. Moderate-certainty evidence suggests that a lengthening-focused protocol (L-protocol) may expedite TTRTP when this is the clinical priority, although the evidence on re-injury prevention remains low certainty.

Although eccentric loading schemes depend on a quick return to activity, rehabilitation techniques that utilize PATS are developed for a unique clinical focus: prevention of re-injury over the long-term. The results of our meta-analysis indicate that PATS programs do not reduce TTRTP significantly compared to control programs (STST or PRES). However, reconciling pooled risk with re-injury, an absolute risk reduction of 35% indicates a clinically meaningful effect. The point estimate (RD -0.35) suggests a potential reduction, but the 95% CI (-0.74 to 0.03) is wide and crosses the null; combined with very low certainty, high heterogeneity ($I^2 = 72\%$), and inconclusive TSA, this finding should not be interpreted as evidence of efficacy. The potential prophylactic effect of PATS may be related to its capacity to address biomechanical and neuromuscular deficits, although mediator data directly linking lumbopelvic control improvements to re-injury reduction are not available. Isolated hamstring strengthening, while effective for restoring local muscle force-generating capacity, fails to remediate the broader kinetic chain dysfunctions that contribute to tissue overload during sport-specific movements^{65–67}. In contrast, PATS incorporates progressive trunk stabilization exercises designed to enhance lumbopelvic control—a factor increasingly recognized as integral to hamstring injury etiology. During the terminal swing phase of high-speed running, the biceps femoris long head undergoes peak musculotendon strain while actively lengthening to decelerate the lower limb. Insufficient lumbopelvic stability may allow excessive anterior pelvic tilt and trunk rotation, increasing the eccentric demand on the hamstrings and predisposing the muscle to overload injury. By improving lumbopelvic control, PATS may reduce compensatory pelvic motion and thereby mitigate eccentric hamstring strain during high-velocity running movements. A narrative review by Badrinath et al.⁶⁸ concluded that athletes returning to sport after conventional rehabilitation exhibit persistent neuromuscular inhibition of both the hamstring and lumbopelvic musculature, manifesting as impaired myoelectric activity in the biceps femoris and altered activation patterns in the gluteal and trunk stabilizers. These residual deficits, undetectable by standard clinical clearance criteria (pain-free palpation, full isometric strength), may explain the alarmingly high early re-injury rates observed in protocols that neglect lumbopelvic retraining. The PATS re-injury analysis illustrates the challenge of interpreting sparse event data. The primary RD analysis was inconclusive, whereas the Peto OR sensitivity analysis suggested a large effect. This discrepancy likely reflects the instability of Peto OR under extreme effect sizes and sparse events, as well as the marked difference in baseline risk between the two studies. Given this uncertainty, the PATS finding should be considered hypothesis-generating rather than confirmatory.

Despite the compelling evidence, important limitations temper clinical translation. Despite near-universal acceptance of lumbo-pelvic training in elite sport, interventions exploring its effect on hamstring injury rates have not measured stability in any meaningful way, and prospective risk factor studies examining lumbopelvic motion during sprinting remain scarce⁶⁹. Furthermore, the London International Consensus and Delphi Study on hamstring injuries reported that 91% of experts agreed it is “important to assess, treat and prescribe exercises addressing the whole kinetic chain”, yet consensus on specific exercise selection and progression criteria remains elusive. Future trials must define standardized PATS protocols and evaluate whether individual patient characteristics—including baseline lumbopelvic control, sport-specific biomechanical demands, and injury chronicity—modulate treatment response.

Physical modalities—including PRP, rESWT, and LLLT are frequently employed as adjuncts to exercise-based rehabilitation in athletes with hamstring strain injuries. However, these passive interventions do not restore eccentric strength, neuromuscular control, or sport-specific functional movement patterns, which are prerequisites for safe return to sport. Their appeal lies in the theoretical potential to modulate pain, accelerate tissue repair, and create a permissive environment for early loading. However, despite decades of clinical application, the evidence supporting their routine use remains inconsistent, and their role in hamstring strain injury management continues to generate considerable debate. Our stratified analyses demonstrate that these modalities should not be considered interchangeable. PRP has garnered particular interest due to its theoretical capacity to deliver concentrated growth factors to the injury site. A systematic review of six RCTs ($n = 277$) from 2026 found that PRP reduced TTRTP by a mean difference of -8.6 days (95% CI -3.04 to -0.03 , $p = 0.045$) compared with control, though heterogeneity was high ($I^2 = 94.1\%$) and re-injury rate did not differ (15% vs. 16%, $p = 0.722$). Similarly, Liu et al.⁷⁰ demonstrated shorter TTRTP with PRP plus physical therapy versus physical therapy alone (MD -2.29 , 95% CI -4.11 to -0.47 , $p = 0.01$). Beyond PRP, Crupnik et al.⁵⁹ reported that rESWT

added to an 8-week rehabilitation program reduced TTRTP by approximately three days (25.4 ± 3.5 vs. 28.3 ± 4.5 days, $p=0.037$) while preserving strength symmetry in the injured leg. While there are positive indicators to support their use, several caveats should be pointed out before recommending their use. This study was unable to conclude whether there are any clinical benefits from stretching programs or physical modality interventions according to Jankaew et al.⁷¹. The LLLT RCT also demonstrated no advantage over exercise, indicating that not all modalities provide equivalent benefits. Furthermore, heterogeneity among PRP preparation (leukocyte-rich, leukocyte-poor, activated, un-activated), injection times and image-guide protocols make interpretation more difficult. Standardized protocols and controlled trials comparing head-to-head the clinical effectiveness and cost effectiveness of the various modalities; if applicable, will further clarify those that are beneficial beyond optimal continued rehabilitation through an exercise programme. Although PRP preparation protocols (leukocyte-rich versus leukocyte-poor) and injection timing varied across the three trials, we considered pooling them clinically appropriate because all evaluated PRP as an adjunct to structured rehabilitation in acute hamstring injuries, shared comparable outcome definitions (time to return to sport), and used similar control conditions (rehabilitation alone or placebo injection). The substantial statistical heterogeneity ($I^2 = 70\%$) reflects the clinical diversity in PRP formulations and rehabilitation contexts, which limits the precision of the pooled estimate but does not invalidate the overall direction of effect. The clinical heterogeneity across PRP studies, including differences in injection protocols, rehabilitation programmes, and athlete populations, means that the pooled estimate should be viewed as a summary of available evidence rather than a precise effect size applicable to all clinical settings. Compared with recent systematic reviews¹⁰, which synthesized evidence on therapeutic exercises and modalities without stratification, our review provides a stratified synthesis that separates exercise-based interventions from adjunctive therapies. Unlike previous meta-analyses that pooled PRP across heterogeneous trials without GRADE or TSA contextualization⁷⁰, we analyzed PRP separately from other modalities and interpreted findings according to evidence certainty rather than nominal statistical significance. Our findings on PRP are more conservative than those reported in recent meta-analyses⁷⁰, which generally reported statistically significant effects based on pooled p-values without GRADE or TSA contextualization. This difference likely reflects our stricter eligibility criteria (acute injuries only, excluding tendinopathy), our stratified analytical approach (PRP analyzed separately from rESWT and LLLT), and our use of GRADE and TSA to distinguish suggestive from definitive evidence. Our incremental contribution lies in this stratified, certainty-based interpretation rather than in the identification of new primary studies.

Pain threshold rehabilitation appears to be an effective rehabilitation method that is safe. Hickey et al.⁵⁸ did not find any cases of adverse events or re-injuries during rehabilitation and demonstrated a similar decline in fear of movement scores in the two groups, suggesting that the presence of pain would not promote kinesiophobia. The consistency of these findings with the larger body of literature on tendinopathy supports the generalizability of the pain threshold principle for other forms of musculoskeletal injury⁷², although the evidence for tendinopathy is indirect and should not be extrapolated to acute hamstring strains without caution. The application of this principle requires clinical judgement: pain $\leq 4/10$ that resolves within 24 h of exercise is acceptable; however, if pain continues or worsens, then the athlete's loads should be reduced. The use of pain threshold rehabilitation may reduce functional deficits and decrease the likelihood of future hamstring strains⁶². Future studies are needed to determine if individual variables, such as injury severity, pain catastrophizing, and psychosocial readiness, affect the optimal pain threshold, and whether recurrent injuries occur after 6 months have passed. Overall, the available evidence supports that pain threshold rehabilitation is a safe, biologically based method for improving tissue adaptation without slowing the recovery process or increasing injury risk.

The future of HSI rehabilitation lies in precision medicine: leveraging multimodal data streams to stratify athletes by individual risk profiles and tailor interventions dynamically. Wearable sensors and AI may support personalized rehabilitation, but standardized algorithms and sensor-placement protocols are currently lacking⁷³. Imaging biomarkers also show promise for objective injury assessment^{74,75}, though translation into practice requires standardized protocols and external validation⁷⁶. These technologies are promising but remain in development and were not evaluated in this review. Nevertheless, the convergence of risk stratification, wearable monitoring, and AI-enabled analytics heralds a shift towards more personalized, technology-augmented care pathways.

Limitations

Several limitations warrant consideration. Moderate to high heterogeneity (I^2 up to 72%) arose from variations in interventions, follow-up durations, and outcome definitions. Performance bias was unavoidable due to inability to blind participants and personnel in exercise-based trials. For re-injury outcomes, sparse events constrained precision; despite multiple analytical approaches, statistical power remains limited, with zero-event (LLLT) and single-study (rESWT) estimates precluding definitive conclusions. GRADE certainty for most outcomes ranged from low to very low, with only eccentric loading, LLLT, and pain-threshold rehabilitation on TTRTP reaching moderate certainty. Differences in TTRTP criteria, re-injury surveillance periods (2–24 months), and post-return sport exposure limited comparability; the small number of studies precluded formal subgroup analyses to assess the impact of definitional heterogeneity on pooled estimates, making heterogeneity estimates unreliable and requiring cautious interpretation of single-study and two-trial findings. The pooled L-protocol TTRTP effect should be interpreted as population-specific rather than universally applicable, given the inclusion of elite male athletes and the larger effect observed in sprinters/jumpers. Standardized functional outcomes were largely absent, precluding meta-analysis. Female and recreational athletes were underrepresented. TSA revealed inconclusive evidence for PATS on re-injury and PRP on both outcomes (PRP TTRTP reached RIS but not the O'Brien-Fleming boundary). One included study (Dhlamini et al.) was a master's thesis with a low PEDro score (4/10; fair); its grey-literature status and poor methodological quality limit its interpretability, and it was therefore included only in narrative synthesis, consistent with our protocol. The English-language restriction

may have contributed to language bias. Adherence to prescribed rehabilitation protocols was not uniformly reported across trials, which may contribute to heterogeneity in treatment effects. Adverse events were not systematically reported in most trials, precluding formal safety assessment.

Conclusions

Moderate-certainty evidence based on two trials suggests a lengthening-focused protocol (L-protocol) may shorten TTRTP. PATS shows a non-significant trend toward re-injury reduction (very low certainty), but this finding is preliminary. Among adjunctive therapies, rehab + PRP may offer modest TTRTP acceleration (low certainty), rESWT shows preliminary promise requiring replication, and LLLT does not appear to add benefit. Pain-threshold rehabilitation enhances strength without delaying TTRTP (moderate certainty, single trial). Most evidence remains low or very low certainty. These findings support intervention-specific decision-making based on clinical priorities, while acknowledging that current evidence does not identify a single strategy that reliably optimizes both rapid return and durable protection. Future trials should use standardized injury and return-to-sport definitions, report exposure-adjusted recurrence and adverse events, include sex-balanced samples, and register protocols before recruitment.

Data availability

All data supporting the findings of this systematic review and meta-analysis are presented within the main manuscript and its tables. Specifically, the characteristics of each included study are detailed in Table 2, the effect estimates and summary statistics for individual studies and syntheses are presented in the forest plots (Figs. 3, 4, 5, 6, 7 and 8), and the certainty of evidence assessments are provided in Table 3. No additional raw patient-level data were collected, as this is a review of previously published aggregate data.

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Author contributions

Authors' Contributions All Seven authors contributed to the design and implementation of the study; J.Z. completed the analysis of the results and original writing of the manuscript; S.H., S.L., X.H., L.Z., D.G. and X.P. edited and reviewed the writing of the manuscript; J.Z. was responsible for study supervision and project administration. All authors have read and approved the final version of the manuscript and agree to be accountable for the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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