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Surgery and Research

SYSTEMATIC REVIEW

Open Access



# Efficacy and safety of platelet-rich plasma combined with hyaluronic acid versus platelet-rich plasma alone for knee osteoarthritis: a systematic review and meta-analysis

Qing Zhang, Tuodong Liu, Yuan Gu, Yongquan Gao and Jiangdong Ni\*

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# Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

*Clinical Sports Medicine Update*

## Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis CME

### A Systematic Review and Meta-analysis of Randomized Controlled Trials

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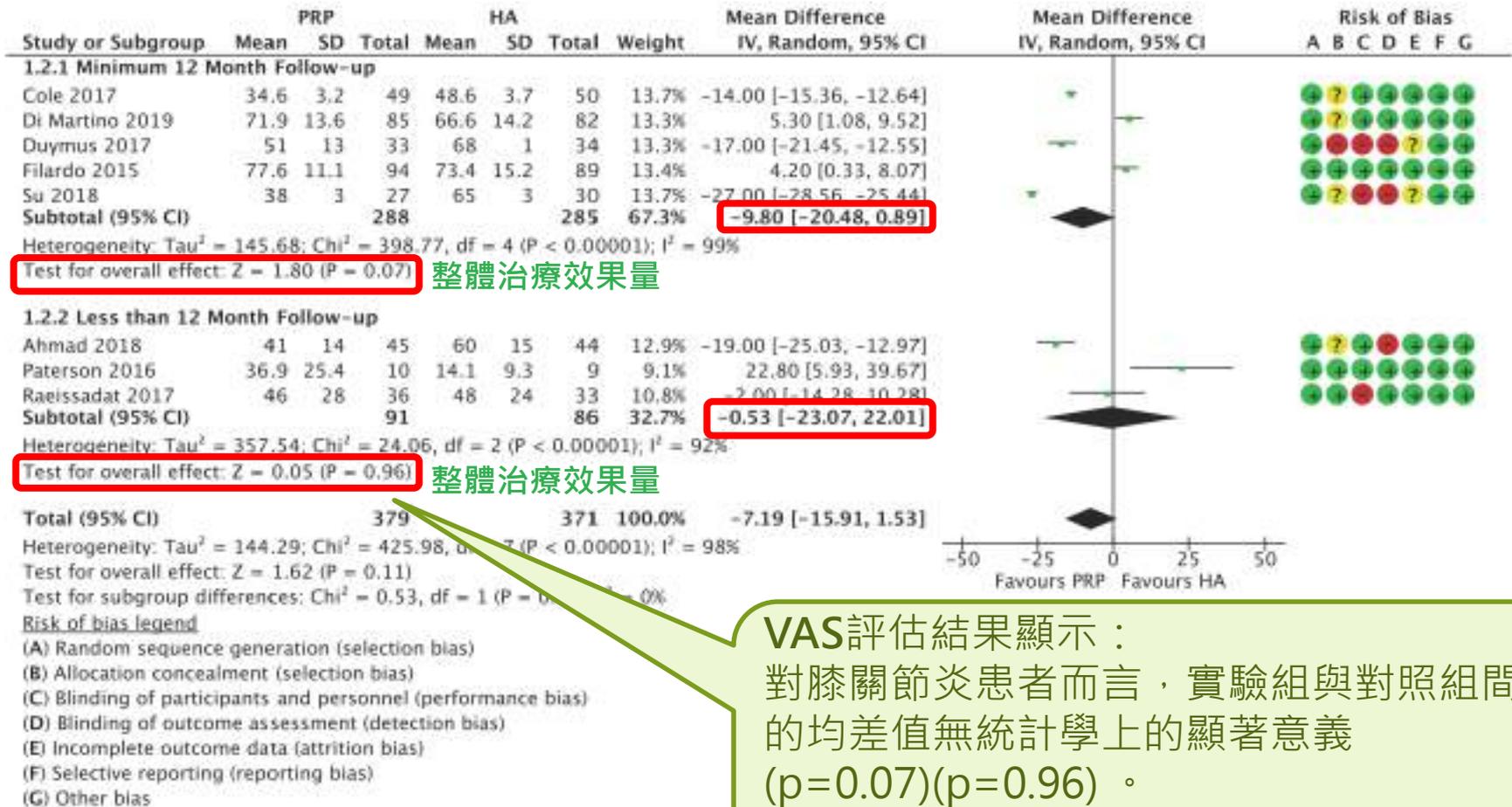
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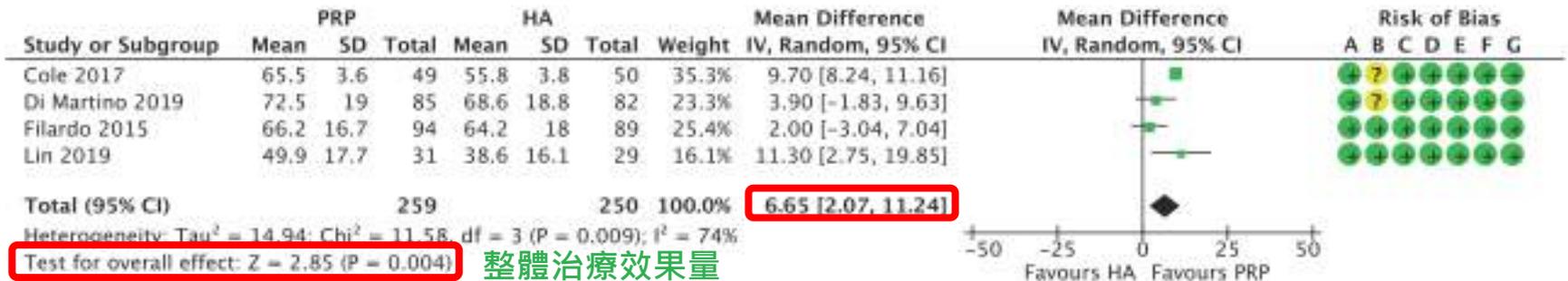
# Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials



VAS評估結果顯示：  
對膝關節炎患者而言，實驗組與對照組間的均差值無統計學上的顯著意義 (p=0.07)(p=0.96)。  
→ 症狀改善效果PRP無異於HA

Figure 4. Forest plot of VAS scores. HA, hyaluronic acid; IV, inverse variance; PRP, platelet-rich plasma; VAS, visual analog scale.

# Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials



### Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

IKDC評估結果顯示：

對膝關節炎患者而言，注射PRP的疼痛改善效果比注射HA顯著( $p < 0.05$ )。

→ 症狀改善效果PRP優於HA

**Figure 5.** Forest plot of Subjective IKDC scores. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; IV, inverse variance; PRP, platelet-rich plasma.

# 臨床情境

- 一位78歲女性右膝疼痛，經診斷為退化性膝關節炎第二級，目前規律在骨科門診定期追蹤並施打半年三劑短效玻尿酸，因家住4樓舊式公寓，最近上下樓梯右膝蓋又感疼痛難受。兒子最近看到一篇網路文章，宣稱注射高濃度血小板血漿(PRP)+玻尿酸(HA)可以有效緩解膝蓋疼痛，因此兒子帶母親來門診複診時詢問骨科醫師是否建議注射高濃度血小板血漿(PRP)？

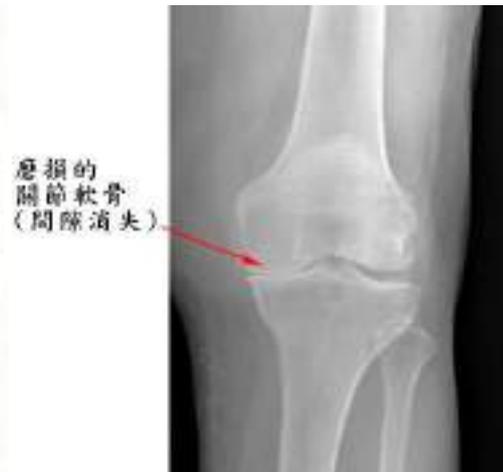
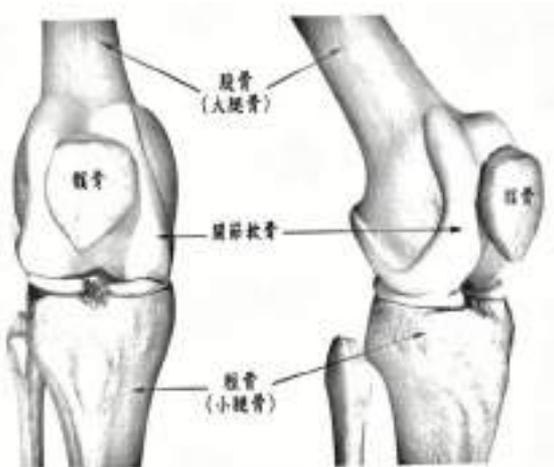


# 背景資料 *Background Knowledge*

## • 什麼是退化性膝關節炎？

- 膝關節軟骨**退化磨損失去彈性**，而產生關節疼痛、僵硬、影響活動功能。

## • 膝關節的結構



F3100042-109-12-C 退化性膝關節炎，我該怎麼辦？(SDM)-骨科



# 根據Kellgren-Lawrence Grading System 將退化性膝關節炎分為五級

## Stages of knee osteoarthritis



Stage I



Stage II



Stage III



Stage IV

疑似有骨刺生成

軟骨輕度磨損，可見骨刺生成，關節腔間隙輕微狹窄

軟骨中度磨損，多處骨刺生成，關節腔間隙明顯狹窄

軟骨嚴重磨損，關節腔間隙幾乎消失，硬骨磨損變形



# 退化性膝關節炎各分級適合的治療方式

退化等級	第一期	第二期	第三期	第四期
保守治療				
生活型態改變	😊	😊		
復健治療	😊	😊		
藥物止痛	😊	😊	😊	
玻尿酸注射	😊	😊		
輔具使用	😊	😊		
手術治療				
全膝人工關節置換			😊	😊
部分人工膝關節置換			😊	😊
高位脛骨截骨手術			😊	😊
關節鏡手術	😊	😊	😊	

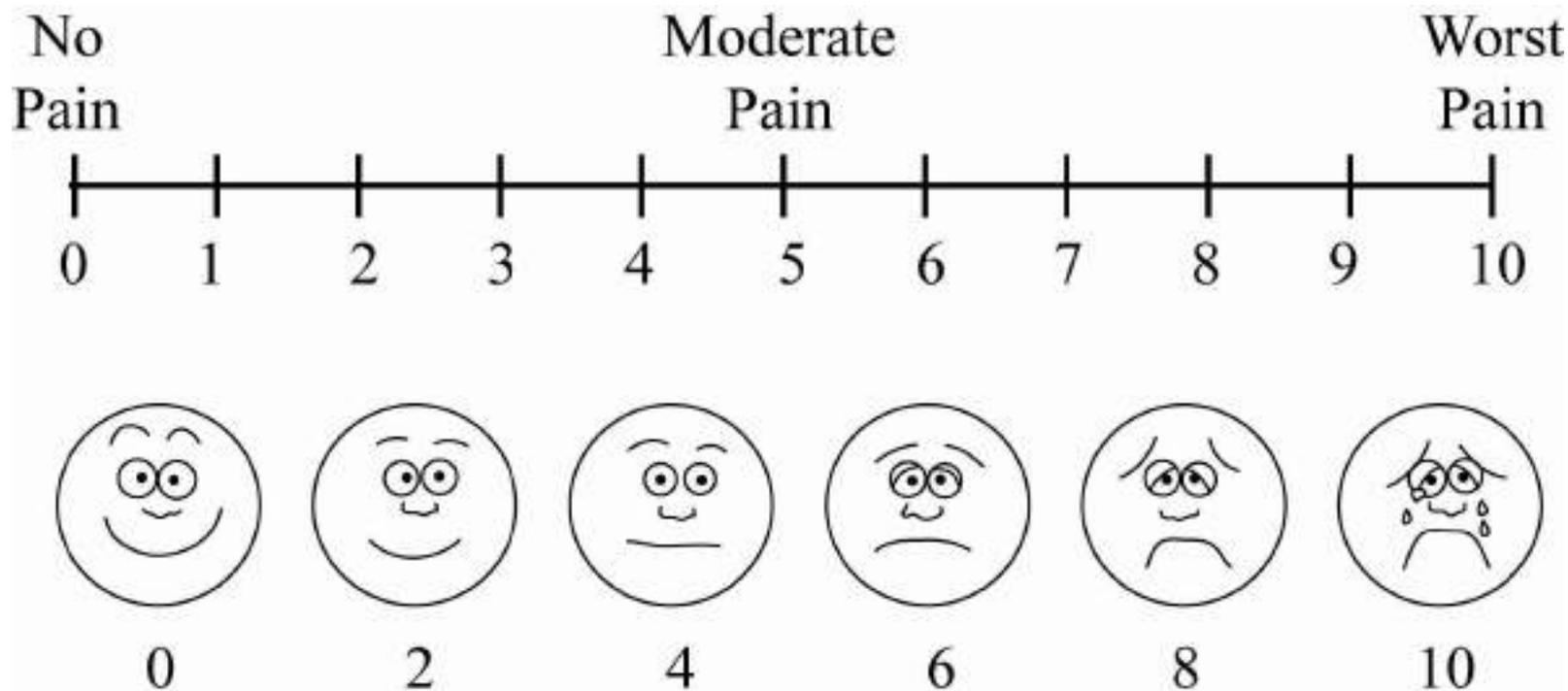
治療	玻尿酸 (Hyaluronic Acid, HA)	高濃度血小板血漿 (Platelet-rich plasma, PRP)
成份	主要是一種 <b>多醣鏈</b> ，它是關節裡的成份之一，是 <b>關節的潤滑劑</b> 。	抽取 <b>自己身體血液離心</b> ，從離心後的血液萃取血小板、血漿、生長因子，接著 <b>根據不同組合作為增生劑</b> 。
原理	<b>潤滑受損軟骨 抗發炎</b>	<b>富含豐富生長因子 協助組織癒合</b>
療程	1.每半年三劑短效(575元/劑) 2.每半年一劑中長效(2,889元/劑) 3.每一年一劑長效(5,516元/劑)	醫師會建議一年打一個療程，一個療程打1-2劑。 這部分因為缺乏完整的研究，所以每位醫師的做法也不一樣。
費用	1.健保給付 2.自費	1.PRP：15,000元/支 2.Acti-PRP(亞恩液體/血球細胞分離器) 14,300元/支 3.AHC PRP：18,500元/支

備註：1.限經同一院所保守治療及一般藥物治療時間累計達6個月(含)以上均無效後，至未達需置換人工膝關節之標準且經診斷為退化性膝關節疼痛患者使用。  
 2.病患於注射關節內注射劑期間不得使用NSAID鎮痛消炎藥、類固醇注射劑及置換人工膝關節，亦不可併做同一部位之復健治療。



# 背景資料 *Background Knowledge*

- VAS(visual analogue scale)視覺類比量表
  - 受試者會看到一條10公分的線，最左邊為不痛，最右邊為最痛，由受試者評估自身的疼痛程度並畫於線上。



# 背景資料 *Background Knowledge*

## • WOMAC(Western Ontario and McMaster University Osteoarthritis Index)

- 針對髌關節炎與膝關節炎的評分系統，共24個項目，分為「疼痛」5項、「僵硬」2項、「關節功能」17項，以此三大方面進行評估。
- 每項分數以0-4分計算，**總分越高表示有更嚴重的疼痛、僵硬及功能限制。**

Severity, on average, during the last 48 hours, of:

Pain	None	Slight	Moderate	Severe	Extreme
Pain – Walking	<input type="checkbox"/>				
Pain – Stair climbing	<input type="checkbox"/>				
Pain – Nocturnal	<input type="checkbox"/>				
Pain – Rest	<input type="checkbox"/>				
Pain – Weightbearing	<input type="checkbox"/>				

Stiffness:

	None	Slight	Moderate	Severe	Extreme
Morning Stiffness	<input type="checkbox"/>				
Stiffness occurring during the day	<input type="checkbox"/>				

Level of difficulty performing the following functions, on average, during the last 48 hours:

	None	Slight	Moderate	Severe	Extreme
Descending stairs	<input type="checkbox"/>				
Ascending stairs	<input type="checkbox"/>				
Rising from sitting	<input type="checkbox"/>				
Standing	<input type="checkbox"/>				
Bending to the floor	<input type="checkbox"/>				
Walking on flat	<input type="checkbox"/>				
Getting in/out of a car	<input type="checkbox"/>				
Going shopping	<input type="checkbox"/>				
Putting on socks	<input type="checkbox"/>				
Rising from bed	<input type="checkbox"/>				
Taking of socks	<input type="checkbox"/>				
Lying in bed	<input type="checkbox"/>				
Getting in/out of bath	<input type="checkbox"/>				
Sitting	<input type="checkbox"/>				
Getting on/off toilet	<input type="checkbox"/>				
Performing heavy domestic duties	<input type="checkbox"/>				
Performing light domestic duties	<input type="checkbox"/>				

The WOMAC parameters are:

0 – none, 1 – slight, 2 – moderate, 3 – severe, 4 – extreme.

The index is out of a total of 96 possible points, with 0 being the best and 96 being the worst



# 背景資料 Background Knowledge

## • KOOS(Knee injury and Osteoarthritis Outcome Score)

- 評估膝關節損傷和骨關節炎患者的短期和長期症狀與功能，包含「疼痛」、「其他症狀」、「日常生活功能」、「運動及娛樂功能」、「膝關節相關的生活品質」5個部分共42個項目。
- 每項分數以0-4分計算並換算百分制。
- 最終分數越低表示損傷程度越嚴重；越高表示損傷程度較輕微。

A10. Rising from bed	None, mild, moderate, severe, extreme
A11. Taking off socks/stockings	None, mild, moderate, severe, extreme
A12. Lying in bed (turning over, maintaining knee position)	None, mild, moderate, severe, extreme
A13. Getting in/out of bath	None, mild, moderate, severe, extreme
A14. Sitting	None, mild, moderate, severe, extreme
A15. Getting on/off toilet	None, mild, moderate, severe, extreme
A16. Heavy domestic duties (shoveling, scrubbing floors, etc.)	None, mild, moderate, severe, extreme
A17. Light domestic duties (cooking, dusting, etc.)	None, mild, moderate, severe, extreme
<b>Sport and recreation function</b>	
What difficulty have you experienced the last week...?	
Sp1. Squatting	None, mild, moderate, severe, extreme
Sp2. Running	None, mild, moderate, severe, extreme
Sp3. Jumping	None, mild, moderate, severe, extreme
Sp4. Turning/twisting on your injured knee	None, mild, moderate, severe, extreme
Sp5. Kneeling	None, mild, moderate, severe, extreme
<b>Knee-related quality of life</b>	
Q1. How often are you aware of your knee problems?	Never, monthly, weekly, daily, always
Q2. Have you modified your lifestyle to avoid potentially damaging activities to your knee?	Not at all, mildly, moderately, severely, totally
Q3. How troubled are you with lack of confidence in your knee?	Not at all, mildly, moderately, severely, extremely
Q4. In general, how much difficulty do you have with your knee?	None, mild, moderate, severe, extreme
Scoring: Each item is scored 0 to 4 and the raw score for each section is the sum of item scores. Scores are then transformed to a 0 to 100 scale. A higher score indicates fewer problems.	

Scale	Raw score	Transformed score	MDC <sub>95</sub>
Pain	/16	$100 - \frac{\text{Actual raw score} \times 100}{\text{Possible raw score range}}$ Example: a pain raw score of 16 would be transformed as follows: $100 - \frac{(16 \times 100)}{36} = 56$	12 points
Symptoms	/28		8 points
ADL	/48		18 points
Sport/Rec	/20		19 points
QoL	/16		13 points

(Copyright 1998, Journal of Orthopaedic & Sports Physical Therapy. Reprinted from Reos EM, Reos HP, Lehmann LR, Ekblad C, Beynon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS) – Development of a Self-Administered Outcome Measure. J Orthop Sports Phys Ther. 1998; 28(2):88-96, with permission of the Orthopaedic and Sports Physical Therapy Sections of the American Physical Therapy Association.)



# 背景資料 *Background Knowledge*

- IKDC(International Knee Documentation Committee)
  - 一種針對膝部疾病患者主觀感受的評量，分為「膝部症狀」、「運動活動」、「關節功能」三個部分。
    - ✓ 膝部症狀主要評估膝關節的疼痛、僵硬、腫脹情形。
    - ✓ 運動活動著重在功能評估如：上下樓梯、從椅子上站起來、蹲下和跳躍。
    - ✓ 關節功能則詢問患者一個簡單的問題：膝關節目前的情況和受傷前相比如何。
  - 加總各項分數並轉換成百分制，最終分數越高表示越好的功能或較輕微的症狀。



# 背景資料 Background Knowledge

## • IKDC(International Knee Documentation Committee)

**orthotoolkit**

**International Knee Documentation Committee Subjective Knee Form**

Patient Name: \_\_\_\_\_ Affected Knee: R L (Circle One)  
 Date: \_\_\_\_\_

**A: Symptoms**  
 Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

Very strenuous activities like jumping or pivoting as in basketball or soccer [+4]  
 Strenuous activities like heavy physical work, skiing, or tennis [+3]  
 Moderate activities like moderate physical work, running, or jogging [+2]  
 Light activities like walking, housework, or yard work [+1]  
 Unable to perform any of the above activities due to knee pain [+0]

2. During the past 4 weeks, or since your injury, how often have you had pain?

Never | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Constant

3. If you have pain, how severe is it?

No Pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

Not at all [+4]  
 Mildly [+3]  
 Moderately [+2]  
 Very [+1]  
 Extremely [+0]

5. What is the highest level of activity you can perform without significant swelling in your knee?

Very strenuous activities like jumping or pivoting as in basketball or soccer [+4]  
 Strenuous activities like heavy physical work, skiing, or tennis [+3]  
 Moderate activities like moderate physical work, running, or jogging [+2]  
 Light activities like walking, housework, or yard work [+1]  
 Unable to perform any of the above activities due to knee pain [+0]

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

Yes [+0]  No [+1]

7. What is the highest level of activity you can perform without significant giving way in your knee?

Very strenuous activities like jumping or pivoting as in basketball or soccer [+4]  
 Strenuous activities like heavy physical work, skiing, or tennis [+3]  
 Moderate activities like moderate physical work, running, or jogging [+2]  
 Light activities like walking, housework, or yard work [+1]  
 Unable to perform any of the above activities due to knee pain [+0]

### B: Sports Activities

8. What is the highest level of activity you can participate in on a regular basis?
- Very strenuous activities like jumping or pivoting as in basketball or soccer [+4]  
 Strenuous activities like heavy physical work, skiing, or tennis [+3]  
 Moderate activities like moderate physical work, running, or jogging [+2]  
 Light activities like walking, housework, or yard work [+1]  
 Unable to perform any of the above activities due to knee pain [+0]

### 9. How does your knee affect your ability to:

	Not difficult at all	Minimally difficult	Moderately difficult	Extremely difficult	Unable to do
A. Go up stairs	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
B. Go down stairs	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
C. Stand on the front of your knee	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
D. Squat	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
E. Sit with your knee bent	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
F. Rise from a chair	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
G. Go straight ahead	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
H. Turn and bend on your involved leg	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]
I. Stop and start quickly	<input type="checkbox"/> [+4]	<input type="checkbox"/> [+3]	<input type="checkbox"/> [+2]	<input type="checkbox"/> [+1]	<input type="checkbox"/> [+0]

### C: Function

10. How would you rate the function of your knee on a scale of 0 to 10 with 0 being normal, excellent function and 10 being the inability to perform any of your usual daily activities which may include sports?

Function prior to your knee injury:

Couldn't perform daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (No limitations in daily activities)

Current function of your knee:

Couldn't perform daily activities | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 (No limitations in daily activities)

### Scoring Instructions

Question 2: The responses are reverse-scored such that "Constant" is assigned a score of 0 points and "Never" is assigned a score of 10 points.

Question 3: The responses are reverse-scored such that "Worst pain imaginable" is assigned a score of 0 points and "No pain" is assigned a score of 10 points.

Question 10: Only include the "Current function of your knee" when scoring.

All other questions: Use points listed in parenthesis

$$IKDC \text{ Score} = \left[ \frac{\text{Sum of Items}}{\text{Maximum Possible Score}} \right] \times 100$$

IKDC Score = \_\_\_\_

# 背景資料 *Background Knowledge*

## • Lequesne index

- 一種評估膝關節炎病人疼痛指數的評分表，分為「疼痛及不舒服」、「最遠走路距離」、「每日關節活動能力」三部分。
- 總分0-24分，**分數越高表示越嚴重的疼痛及臨床症狀**。

### Section I: Pain or Discomfort

Parameter	Findings	Values	Points
Pain or discomfort during nocturnal bedrest (i.e. sleep)	None	0	
	Only on movement or in certain positions	1	
	Without movement	2	
Duration of morning stiffness or pain after getting up	None	0	
	< 15 minutes	1	
	>= 15 minutes	2	
Remaining standing for 30 minutes increases pain	No	0	
	Yes	1	
Pain on walking	None	0	
	Only after walking some distance	1	
	Early after starting (just when start walking)	2	
Pain or discomfort after getting up from sitting without use of arms	No	0	
	Yes	1	



# 背景資料 *Background Knowledge*

- Lequesne index

## Section II. Maximum Distance Walked

Parameter	Findings	Values	Points
Maximum distance walked	Unlimited	0.0	
	> 1 kilometer but limited	1.0	
	About 1 kilometer (about 15 minutes)	2.0	
	About 500 - 900 meters (about 8-15 minutes)	3.0	
	From 300 - 500 meters	4.0	
	From 100 - 300 meters	5.0	
	< 100 meters	6.0	
Walking aids required	None	0.0	
	One walking stick or crutch	1.0	
	Two walking sticks or crutches	2.0	

## Section III. Activities of Daily Living

Parameter	Findings	Values	Points
Able to climb up a standard flight of stairs	Easily	0.0	
	With mild difficulty	0.5	
	With moderate difficulty	1.0	
	With marked difficulty	1.5	
	Impossible	2.0	

# 背景資料 *Background Knowledge*

- Lequesne index

Parameter	Findings	Values	Points
Able to climb down a standard flight of stairs	Easily	0.0	
	With mild difficulty	0.5	
	With moderate difficulty	1.0	
	With marked difficulty	1.5	
	Impossible	2.0	
Parameter	Findings	Values	Points
Able to squat or bend at the knee	Easily	0.0	
	With mild difficulty	0.5	
	With moderate difficulty	1.0	
	With marked difficulty	1.5	
	Impossible	2.0	
Parameter	Findings	Values	Points
Able to walk on uneven ground	Easily	0.0	
	With mild difficulty	0.5	
	With moderate difficulty	1.0	
	With marked difficulty	1.5	
	Impossible	2.0	
<b>Index of severity = Sum of points for all parameters</b>			

# ★符合PICO ★年代最新 ★符合研究設計

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SYSTEMATIC REVIEW

Open Access



**Efficacy and safety** of platelet-rich plasma combined with hyaluronic acid versus platelet-rich plasma alone for knee osteoarthritis: a systematic review and meta-analysis

Qing Zhang, Tuodong Liu, Yuan Gu, Yongquan Gao and Jiangdong Ni\*

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2021 JOURNAL IMPACT FACTOR

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JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS

2.485

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Journal Citation Indicator (JCI)

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0.87

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CATEGORY  
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JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
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2021	43/86	Q2	50.58	
2020	41/82	Q2	50.61	
2019	46/82	Q3	44.51	
2018	37/76	Q2	51.97	
2017	43/77	Q3	44.81	

### Rank by Journal Citation Indicator (JCI)

Journals within a category are sorted in descending order by Journal Citation Indicator for each category in which the journal is listed in JCR. Data for the most recent year is in chronological order. [Learn more](#)

CATEGORY  
ORTHOPEDICS  
41/127

JCR YEAR	JCI RANK	JCI QUARTILE	JCI PERCENTILE
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2021	41/127	Q2	68.11	
2020	41/119	Q2	65.97	
2019	41/119	Q2	65.97	
2018	39/118	Q2	67.37	
2017	45/117	Q2	61.97	



## SR Appraisal sheets(FAITH)

# Appraisal Tool

## [系統性文獻回顧Systematic Review]

步驟1: 系統性文獻回顧探討的問題為何? (PICO)

步驟2: 系統性文獻回顧的品質如何? (內在效度)

步驟3: 結果為何? (效益)

## 步驟1: 系統性文獻回顧探討的問題為何？

P

- Knee osteoarthritis
- 退化性膝關節炎患者

I

- Platelet-rich plasma combined with hyaluronic acid
- 高濃度血小板血漿合併玻尿酸

C

- Platelet-rich plasma
- 高濃度血小板血漿

O

- Pain , Adverse events
- 疼痛、不良事件



## SR Appraisal sheets(FAITH)

# Appraisal Tool

## [系統性文獻回顧Systematic Review]

步驟1: 系統性文獻回顧探討的問題為何? (PICO)

步驟2: 系統性文獻回顧的品質如何? (內在效度)

步驟3: 結果為何? (效益)

## FAITH - 研究是否找到(Find)所有的相關證據？

評讀結果：是 否 不清楚

Page 2 of 13

### Methods

#### Search strategy

This meta-analysis was following the Preferred Reporting Items for Systematic Review and Meta-Analysis statement (Additional file 1: PRISMA) [15]. Two independent researchers (QZ and YG) searched PubMed, EMBASE, Cochrane Library and CNKI up to January 15, 2022. Search terms were used including “platelet-rich plasma,” “hyaluronic acid,” “knee osteoarthritis.” The database retrieval strategies are illustrated in Additional file 2.

使用一般檢索詞彙搜尋，未使用MeSH字串搜尋



# FAITH - 研究是否找到(Find)所有的相關證據？

評讀結果：是 否 不清楚

Inclusion and exclusion Page 3 of 13

## Inclusion criteria

(1) Studies: RCTs or cohort studies were included (2) Population: patients diagnosed with KOA; (3) Intervention: PRP+HA therapy; Comparator: PRP treated alone; and (4) At least one of the outcome indicators, including Visual Analogue Scale (VAS) scores, Western Ontario and McMaster Universities Arthritis Index (WOMAC) total scores, Knee Injury and Osteoarthritis Outcome Scores (KOOS), and the American Society of Sports Medicine (ASSM) Committee (IKDC) scores, as well as adverse events.

1. 資料庫初搜尋獲得文獻 513篇，由其他途徑補充相關文獻2篇。
2. 經二位獨立審查者篩選後最終納入13篇文獻進行研究成果整合。  
(9篇RCT, 4篇世代研究)

## Exclusion criteria

(1) The studies that were not associated with treatment for KOA; (2) Laboratory or animal articles; (3) Duplicate publications, secondary publications or articles with similar data; and (4) Reviews, meeting abstracts, case reports, letters to the editor or commentaries.

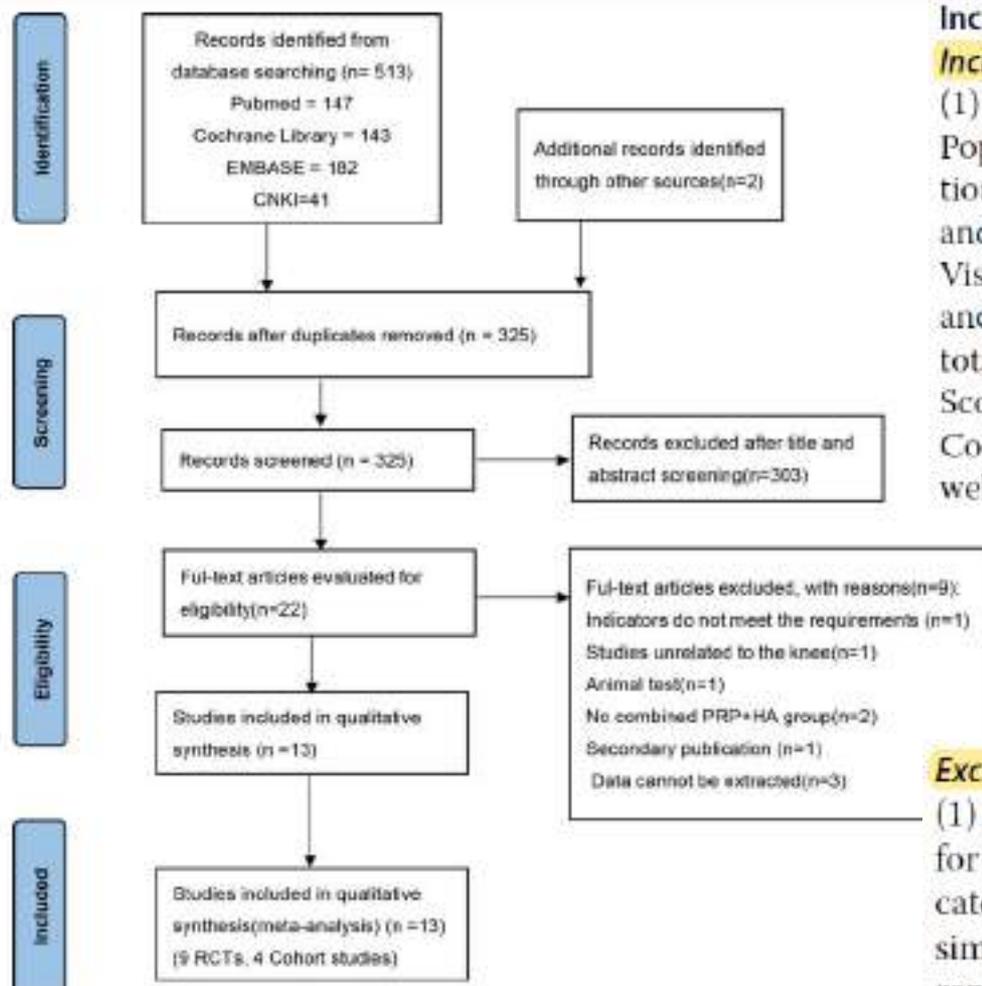


Fig. 1 PRISMA search flow diagram (last search: January 2022)

## FAITH - 文獻是否經過嚴格評讀(Appraisal) ?

評讀結果：是 否 不清楚

### Risk of bias assessment

Two independent researchers (TDL and YQG) evaluate the risk of bias for RCTs by using the Cochrane Risk of Bias tool [16]. Each study was evaluated based on the following 7 areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, as well as other biases. Two independent researchers (TDL and YQG) performed the quality assessment of cohort studies by using Newcastle–Ottawa Scale (NOS). The scale was divided into 3 items: selection, comparability, and exposure.

1. 使用Cochrane Risk of Bias tool 進行9篇RCT 研究文章品質評估。
2. 使用Newcastle-Ottawa Scale(NOS) 進行4篇Cohort 研究文章品質評估。

### Literature screening and data extraction

The relevant data from articles were abstracted by two researchers (TDL and YQG) independently using a prepared data extraction form. Information that was extracted from the selected studies consisted of publication year, authors, patient characteristics, study design, number of included patients, interventions, follow-up time, as well as outcomes. Any disagreement would be resolved through discussion with a third investigators.

由二位研究員獨立進行評讀，意見不一致時透過和第三位研究員進行討論採共識決。

# FAITH - 文獻是否經過嚴格評讀(Appraisal) ?

評讀結果：是 否 不清楚

Page 5 of 13

Fig. 2 Risk of bias summary

	Zhao, 2018	Yu, 2018	Xu, 2021	Sun, 2021	Rao, 2020	Lana, 2016	Ke, 2016	Jacob, 2017	Ding, 2017	
Random sequence generation (selection bias)										
Allocation concealment (selection bias)										
Blinding of participants and personnel (performance bias)										
Blinding of outcome assessment (detection bias)										
Incomplete outcome data (attrition bias)										
Selective reporting (reporting bias)										
Other bias										

- 高風險偏差 (high risk)
- 不明風險(unclear risk)
- 低風險 (low risk)

# FAITH - 文獻是否只納入(included)具良好效度的文章？

評讀結果：是 否 不清楚

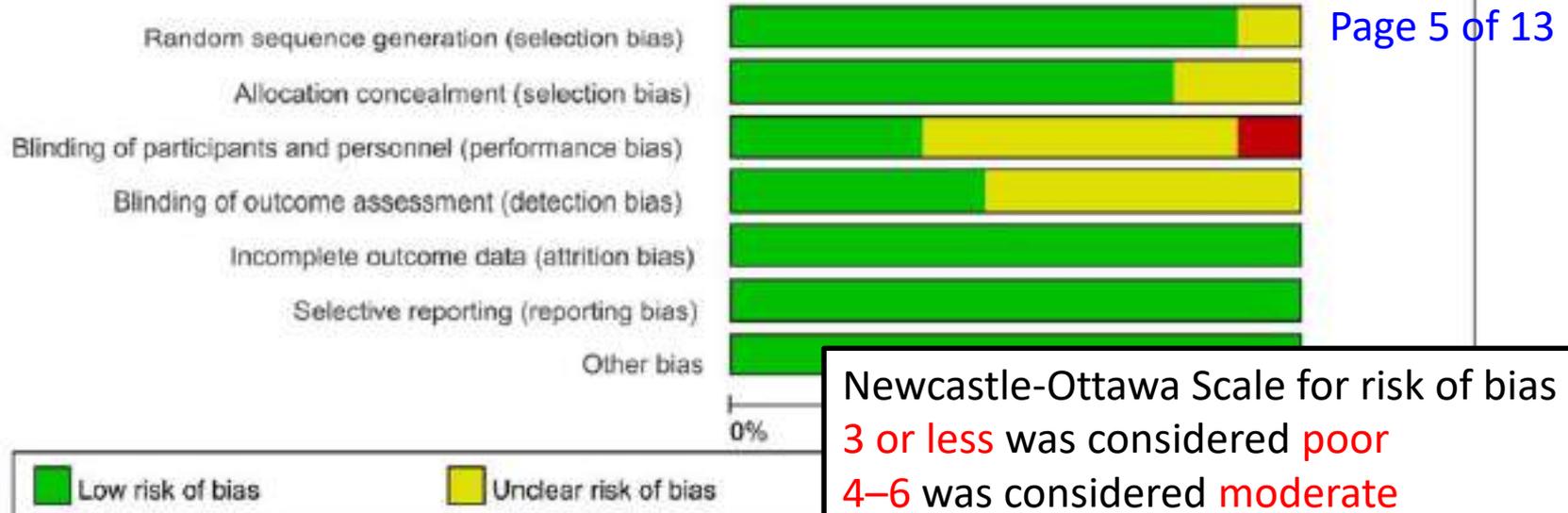


Fig. 3 Risk of bias graph

Newcastle-Ottawa Scale for risk of bias  
 3 or less was considered **poor**  
 4–6 was considered **moderate**  
 7–9 was deemed **high quality**

Table 2 Newcastle-Ottawa Scale for risk of bias assessment of cohort studies included in the meta-analysis

Page 6 of 13

Study	Selection				Comparability	Outcome			Overall
	Representativeness of exposed cohort	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start		Assessment of Outcome	Adequate Follow-Up Length	Adequacy of Follow-Up	
Huang [27]	★	★	★	★	★★	★	★	★	9
Guo [28]	★	★	★	★	★★	★	★	☆	8
Abate [29]	★	★	★	★	★★	★	★	★	9
Palco [30]	★	★	★	★	★	★	★	☆	7

High quality

# FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？

評讀結果：是 否 不清楚

**Table 1** Important characteristics of patients enrolled in the included studies

Page 4 of 13

Study, year	Study design	Sample size		Gender (M/F)		Age, years		Kellgren-Lawrence score (I:II:III:IV)		Clinical outcomes	Follow-up periods
		PRP + HA	PRP	PRP + HA	PRP	PRP + HA	PRP	PRP + HA	PRP		
Zhao [19]	RCT	62	62	35/27	37/25	55.73 ± 7.18	56.32 ± 8.13	-	-	①	5 weeks
Rao [20]	RCT	20	20	-	-	73.3 ± 7.2	73.3 ± 7.2	-	-	①	5 weeks
Ke [21]	RCT	50	50	25/25	24/26	57.80 ± 6.90	53.9 ± 7.1	5:11:20:14	6:12:20:12	②③④⑤	12 months
Ding [22]	RCT	20	27	2/18	8/19	56.75 ± 9.536	62.11 ± 12.50	9:6:5:0	10:11:6:0	①②③⑤	6 months
Yu [14]	RCT	104	96	46/50	54/50	46.50 ± 7.50	46.20 ± 8.60	-	-	②	12 months
Jacob [23]	RCT	20	31	-	-	-	-	-	-	①/④	6 months
Sun [24]	RCT	39	39	21/18	17/22	60.6 ± 8.4	58.4 ± 8.1	0:39:0:0	0:39:0:0	①②⑥	6 months
Lana [25]	RCT	33	36	6/27	7/29	62 ± 6.1	60.9 ± 7	5:14:14:0	9:14:13:0	⑥	12 months
Xu [26]	RCT	48	40	-	-	57.9 ± 4.1	56.9 ± 4.2	0:25:23	0:19:21	⑥	24 months
Huang [27]	Co. P	31	33	8/23	8/25	63 ± 7.02	65.03 ± 7.10	0:10:10:11	0:9:15:9	⑤⑥	6 months
Guo [28]	Co. R	63	63	45/18	51/12	61.2 ± 9.6	60.7 ± 10.1	17:28:18:0	15:31:17:0	①②⑥	12 months
Abate [29]	Co. R	40	40	31/9	21/19	56.7 ± 11.2	60.90 ± 9.0	0:23:17:0	0:19:21:0	①③	6 months
Palco [30]	Co. R	28	23	12/16	12/11	62.71 ± 7.88	54.04 ± 10.4	0:8:20:0	0:10:13:0	①③	12 months

RCT randomized control trail, Co Cohort study, P prospective study, R retrospective study. PRP platelet-rich plasma, HA hyaluronic acid

① VAS scores, ② WOMAC total scores, ③ KOOS, ④ IKDC scores, ⑤ Lequesne index scores, ⑥ Adverse events

# 量表類別與量測時間

量表/測量時間	1 Month	3 Months	6 Months	12 Months
VAS Visual Analogue Scale 疼痛視覺類比量表	●	●	●	●
WOMAC Western Ontario and McMaster Universities Osteoarthritis Index 骨關節炎指數		●	●	
KOOS Knee Injury and Osteoarthritis Outcome Score 膝關節功能評估量表	●	●	●	
IKDC International Knee Documentation Committee 主觀膝部評估表			●	
Lequesne index score 膝關節炎病人疼痛指數		●	●	

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

VAS scores at 1 month

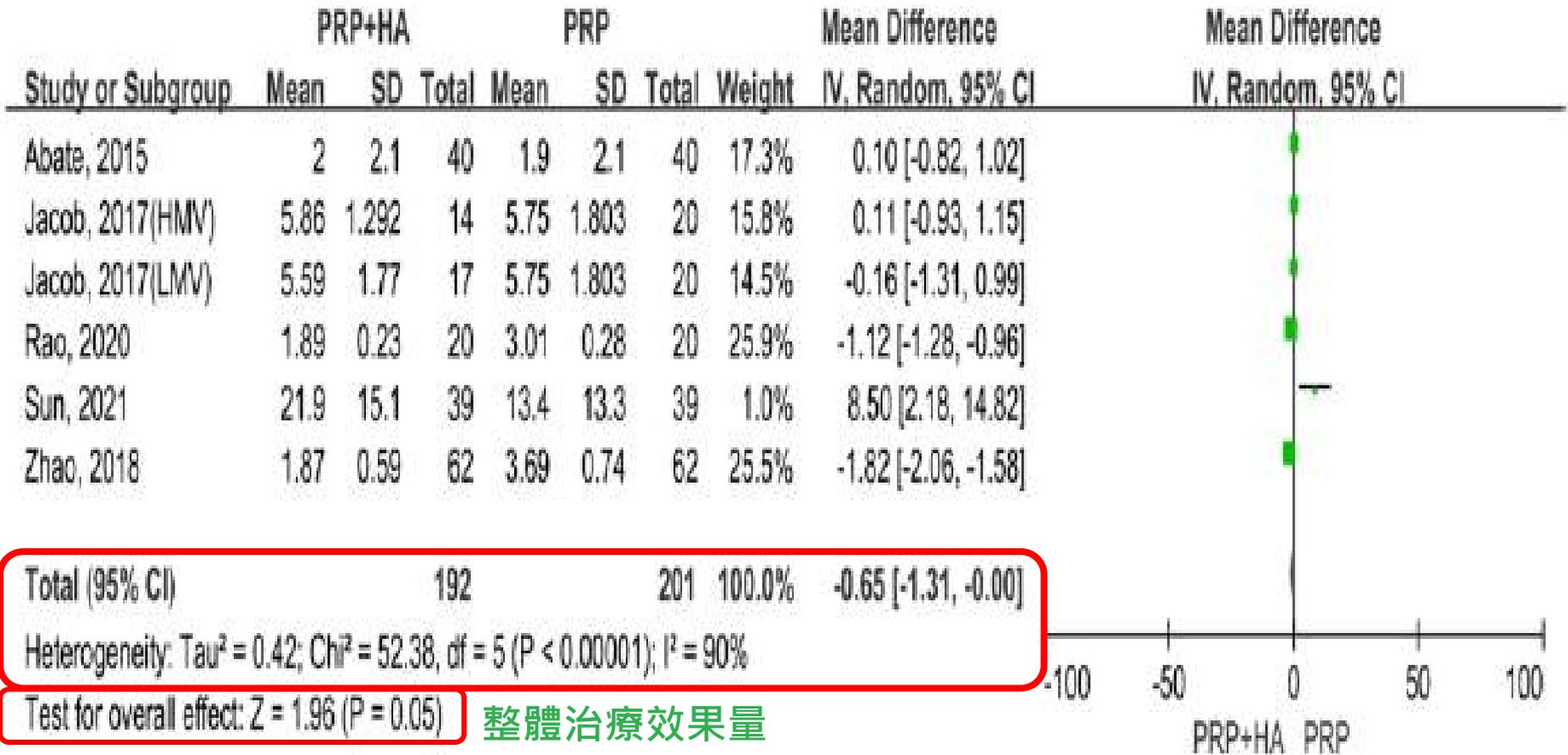


Fig. 4 Forest plot and meta-analysis of VAS score (1 month)

PRP+HA組在1個月後測得疼痛指數下降0.65分，  
 實驗組與對照組之間的均差值差異未達統計學上  
 顯著意義( $p=0.05$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

VAS scores at 3 months

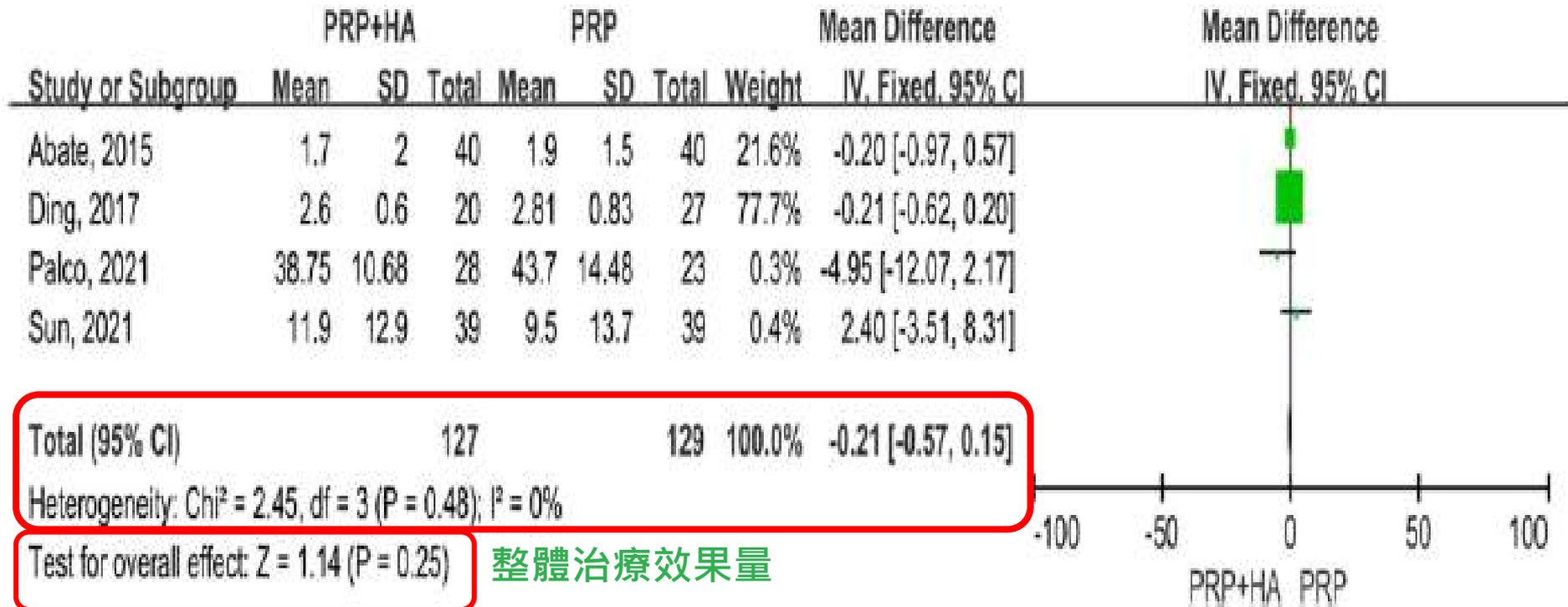


Fig. 5 Forest plot and meta-analysis of VAS scores (3 months)

PRP+HA組在3個月後測得疼痛指數下降0.21分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.25$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

VAS scores at 6 months

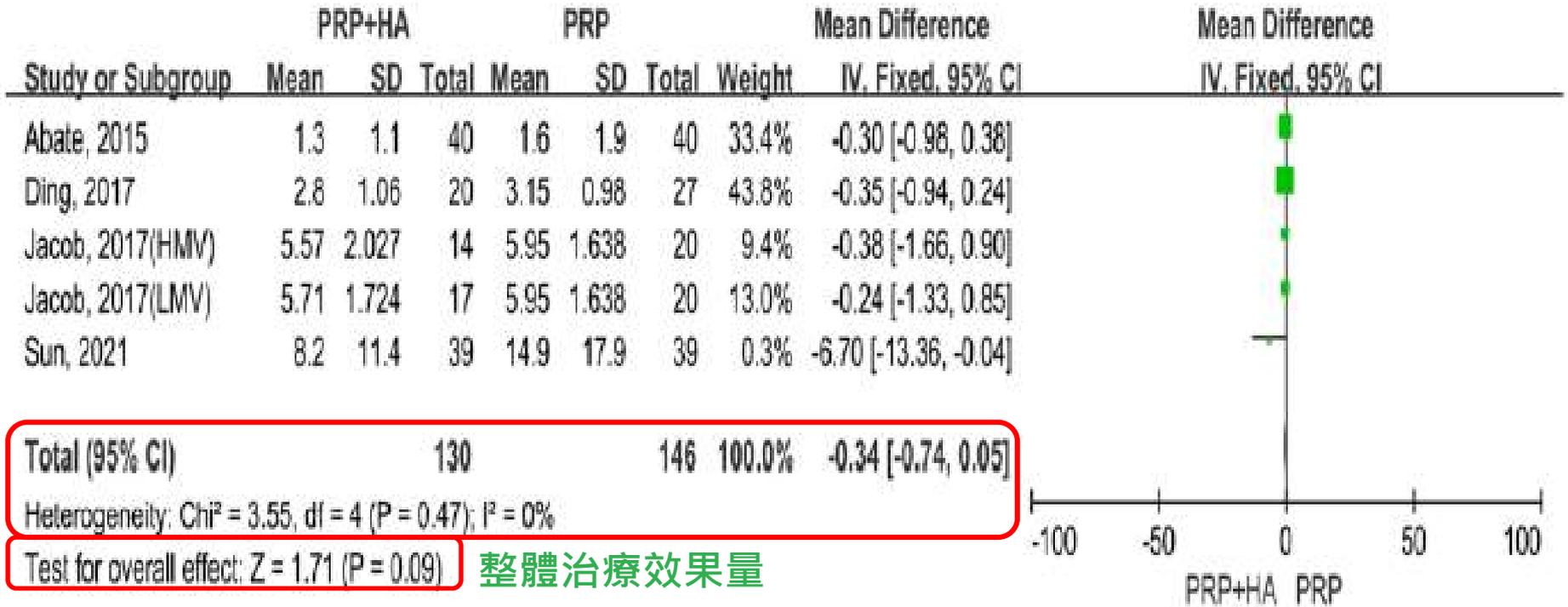


Fig. 6 Forest plot and meta-analysis of VAS scores (6 months)

PRP+HA組在6個月後測得疼痛指數下降0.34分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.09$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

VAS scores at 12 months

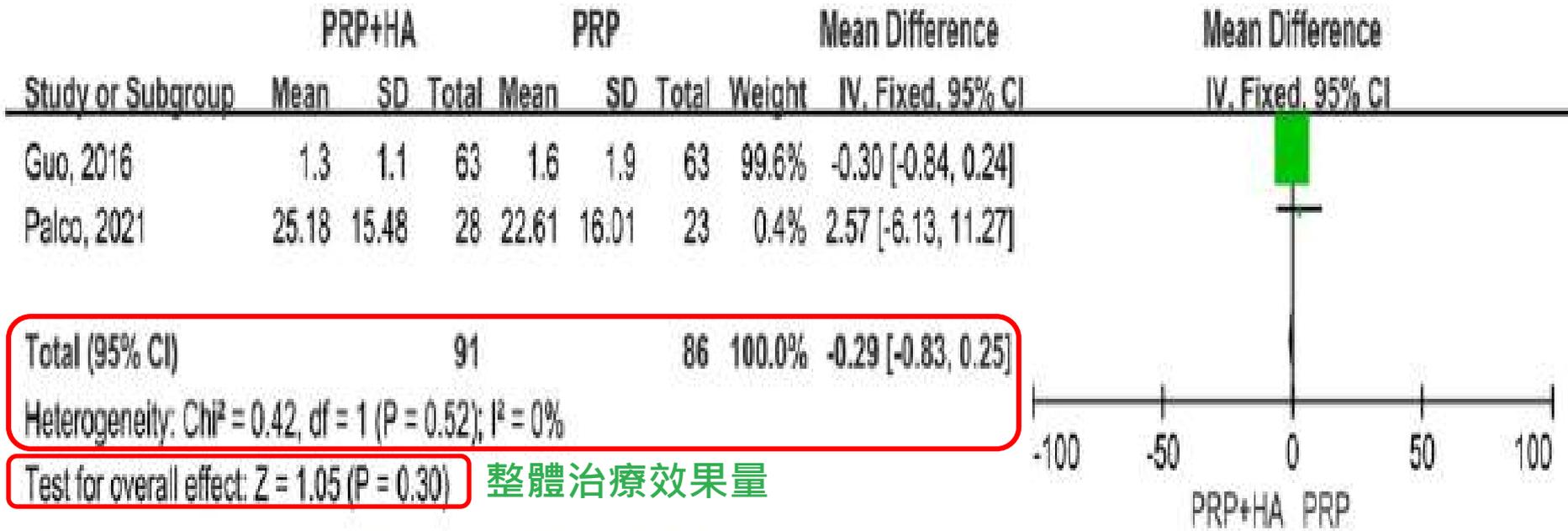


Fig. 7 Forest plot and meta-analysis of VAS scores (12 months)

PRP+HA組在12個月後測得疼痛指數下降0.29分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.30$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**WOMAC scores at 3 months**

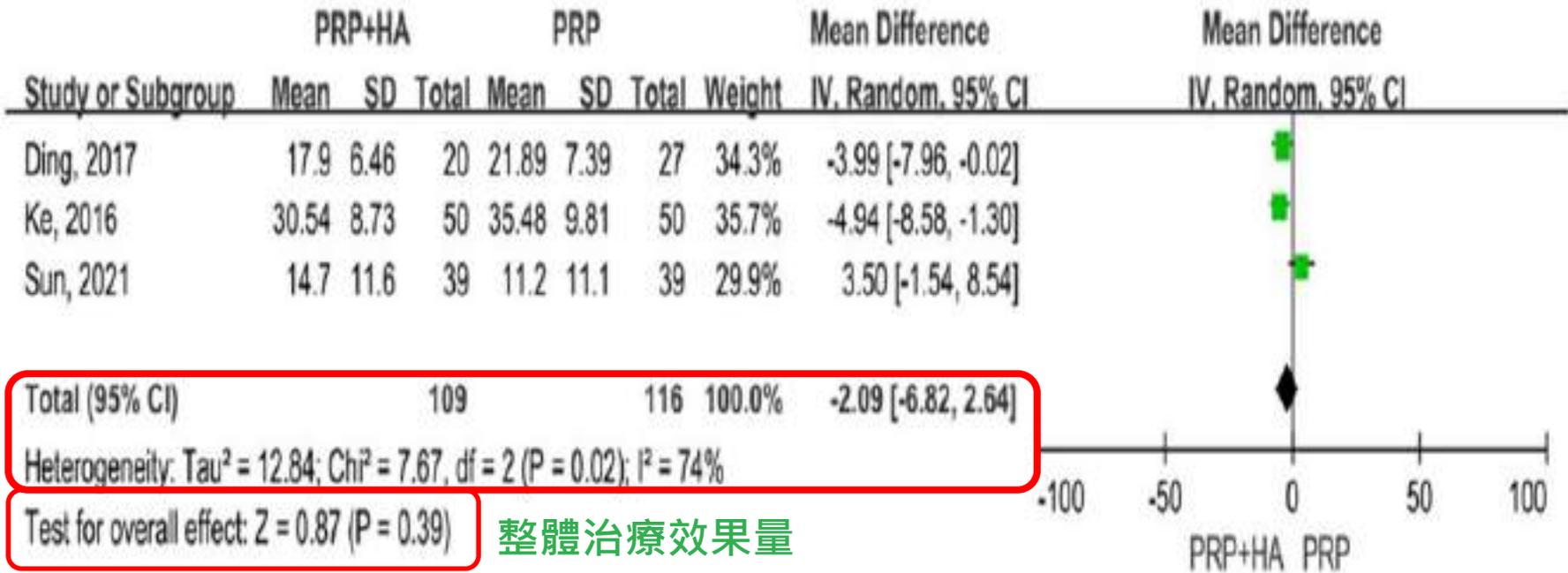


Fig. 8 Forest plot and meta-analysis of WOMAC total scores (3 months)

PRP+HA組在3個月後測得骨關節炎疼痛指數下降2.09分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.39$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**WOMAC scores at 6 months**

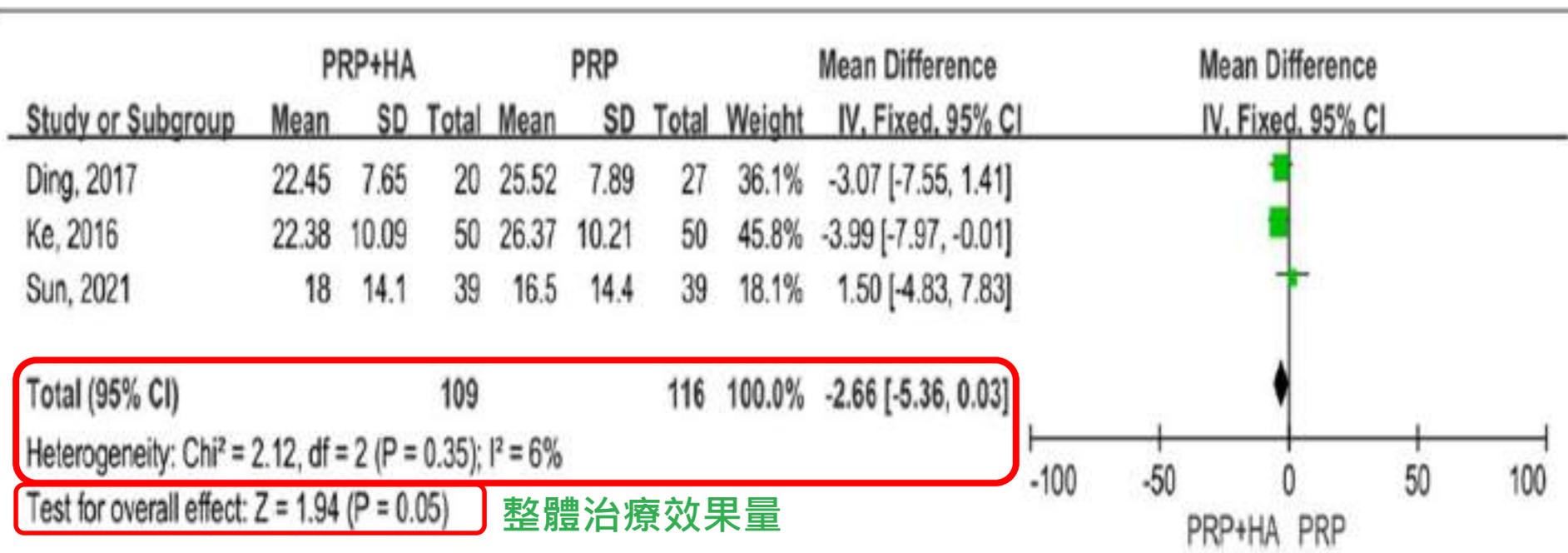


Fig. 9 Forest plot and meta-analysis of WOMAC total scores (6 months)

PRP+HA組在6個月後測得骨關節炎疼痛指數下降2.66分，實驗組與對照組之間的均差值差異未達統計學上顯著意義(p=0.05)

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**KOOS scores at 1 month**

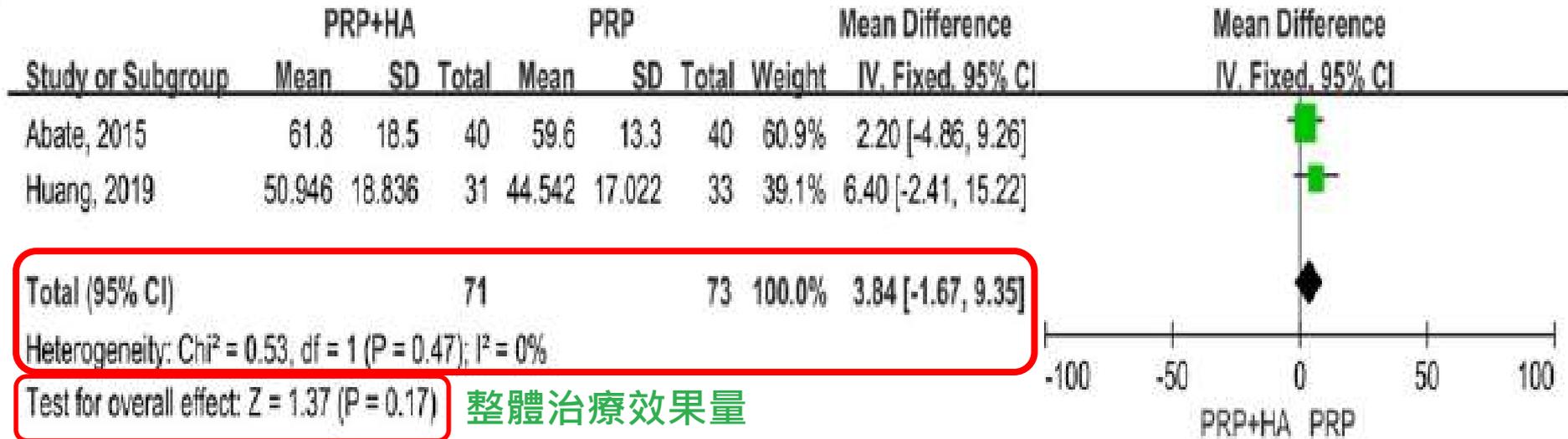


Fig. 10 Forest plot and meta-analysis of KOOS (1 month)

PRP+HA組在1個月後測得膝關節功能評估上升3.84分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.17$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**KOOS scores at 3 months**

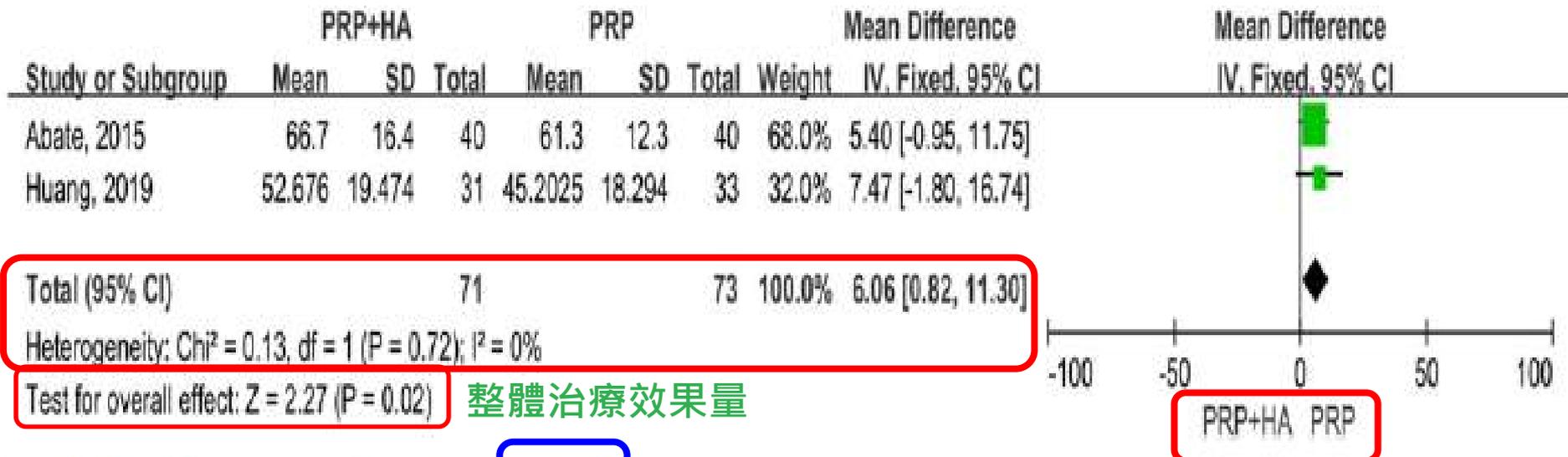


Fig. 11 Forest plot and meta-analysis of KOOS (3 months)

圖表與內文不一致

PRP+HA組在3個月後測得膝關節功能評估上升6.06分，實驗組與對照組均差值差異達統計學上顯著意義( $p=0.02 < 0.05$ )，但沒有超過最小臨床重要差異值(MCID: 10)，故無臨床治療意義

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**KOOS scores at 6 months**

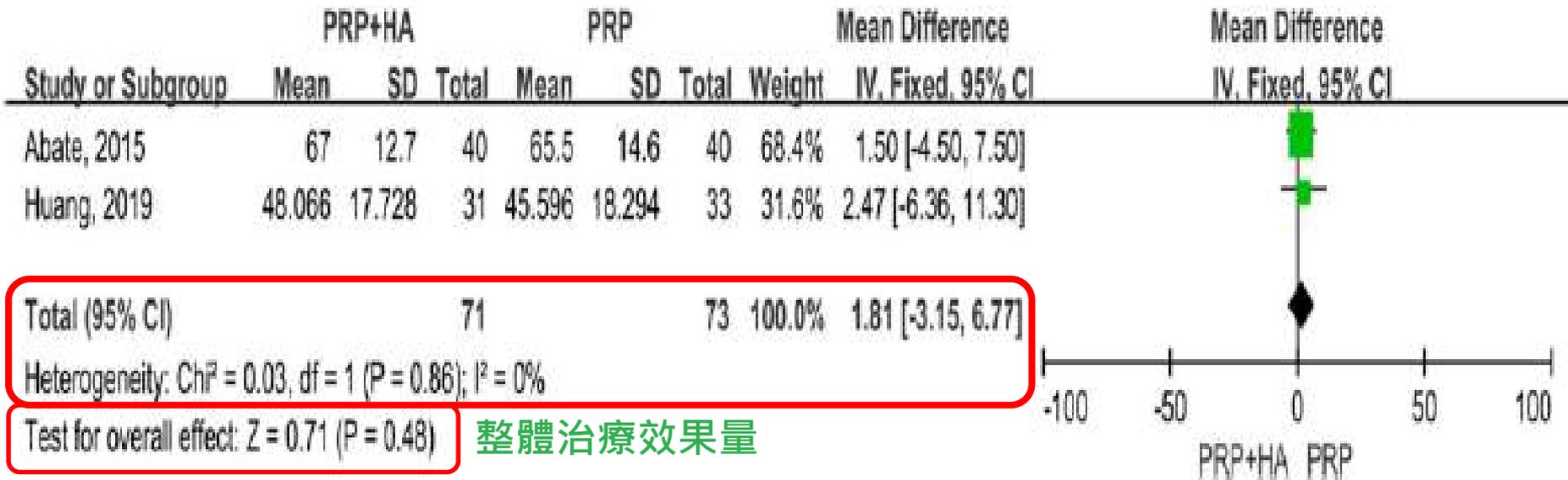


Fig. 12 Forest plot and meta-analysis of KOOS (6 months)

PRP+HA組在6個月後測得膝關節功能評估上升1.81分，實驗組與對照組之間的均差值差異未達統計學上顯著意義( $p=0.48$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**IKDC at 6 months**

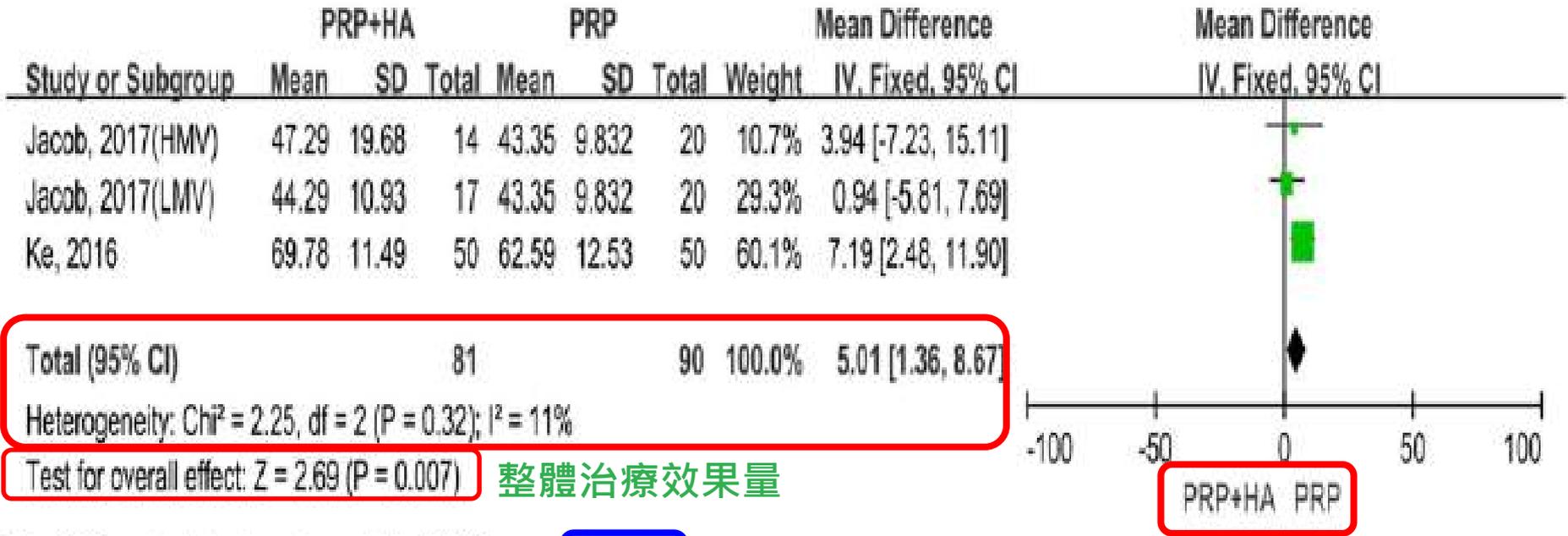


Fig. 13 Forest plot and meta-analysis of IKDC scores (6 months)

圖表與內文不一致

PRP+HA組在6個月後主觀膝部評估量表得分上升5.01分，實驗組與對照組均差值差異達統計學上顯著意義( $p=0.007 < 0.05$ )，但沒有超過最小臨床重要差異值(MCID：11.5)，故無臨床治療意義

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**Lequesne index scores at 3 months**

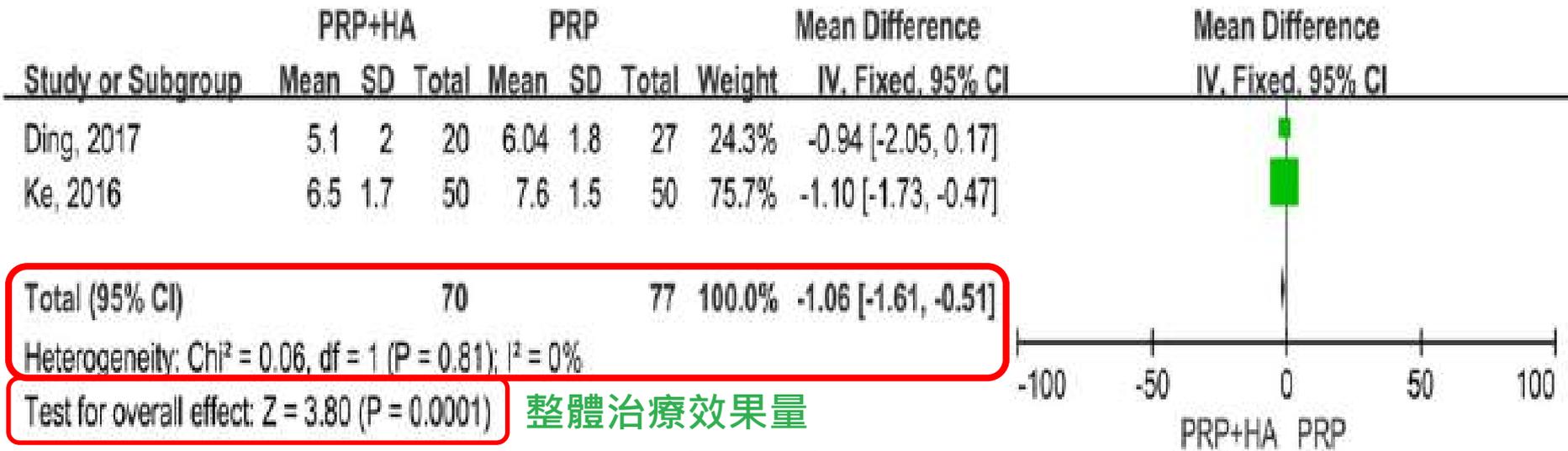


Fig. 14 Forest plot and meta-analysis of Lequesne index scores (3 months)

PRP+HA組在3個月後膝關節炎疼痛指數下降1.06分，實驗組與對照組均差值差異達統計學上顯著意義( $p=0.0001 < 0.05$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

**Lequesne index scores at 6 months**

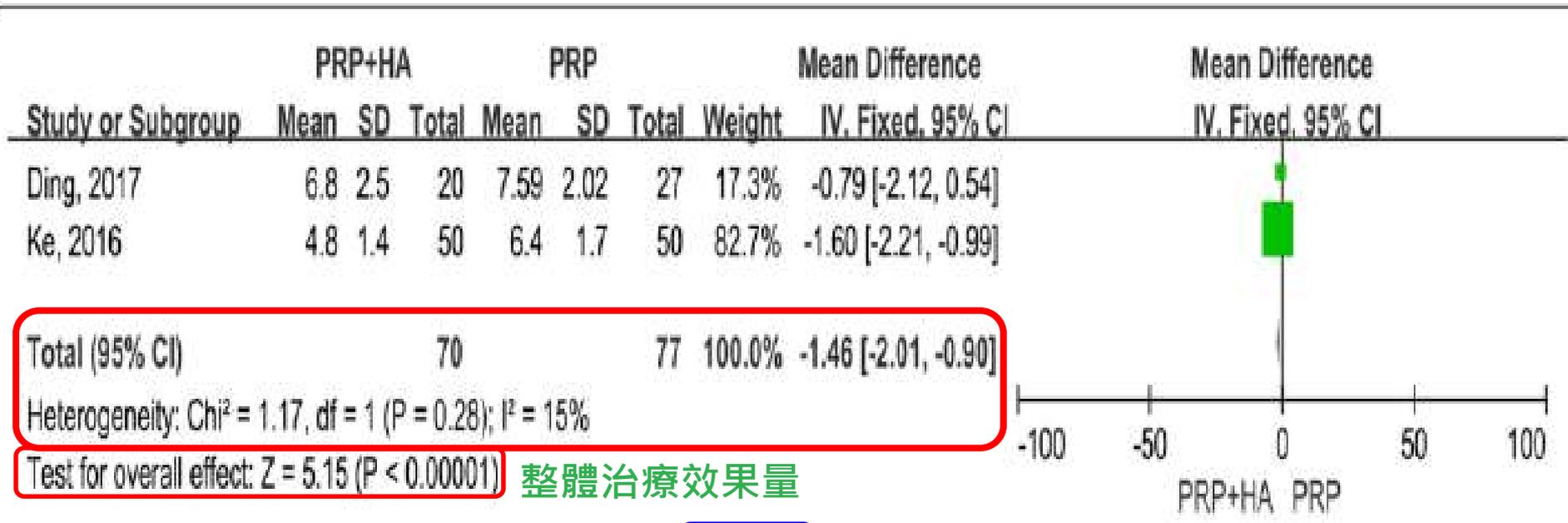


Fig. 15 Forest plot and meta-analysis of Lequesne index scores (6 months)

PRP+HA組在6個月後膝關節炎疼痛指數下降1.46分，實驗組與對照組均差值差異達統計學上顯著意義( $p=0.00001 < 0.05$ )

FAITH-作者是否以表格和圖表「總結」(total up)試驗結果？  
 FAITH-試驗的結果是否相近-異質性 (Heterogeneity)？

## Adverse events

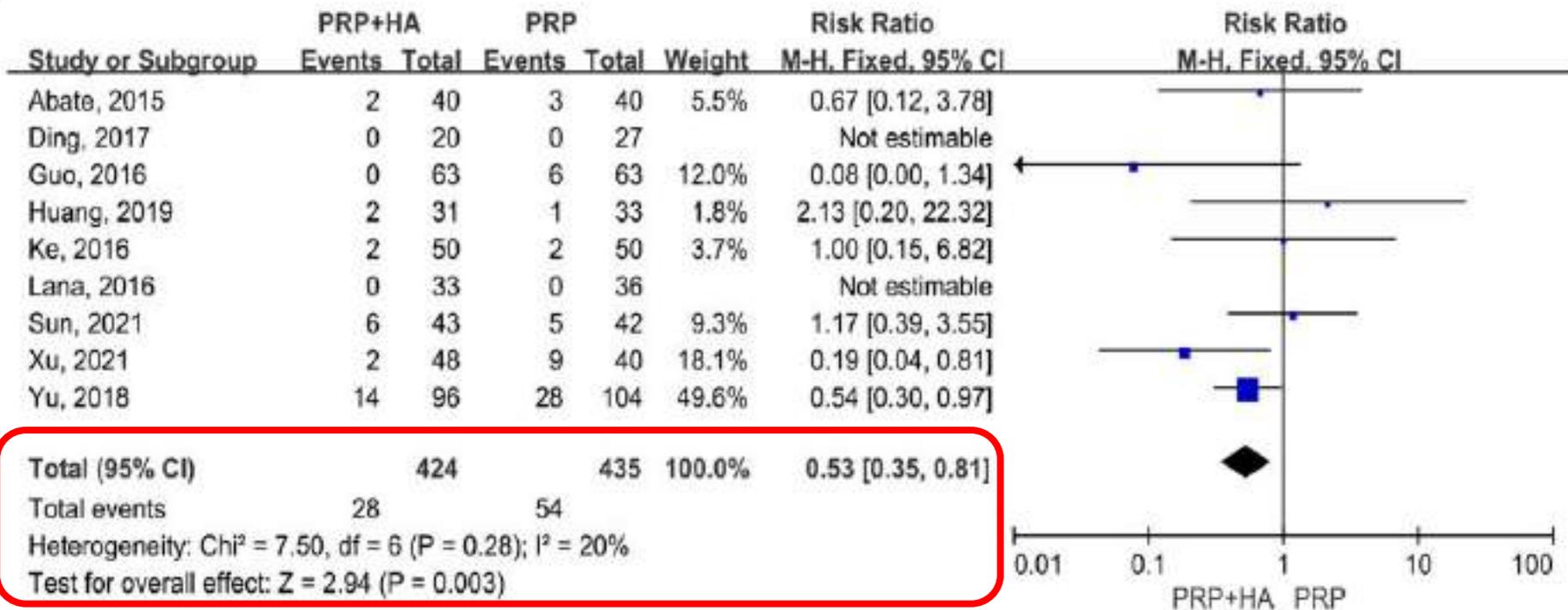


Fig. 16 Forest plot and meta-analysis of Adverse events

PRP+HA組比單一只注射PRP組發生不良反應事件風險比為0.53 [0.35, 0.81] · 統計學上達顯著意義(p=0.003)

## Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1 <sup>+</sup> )	Step 2 (Level 2 <sup>+</sup> )	Step 3 (Level 3 <sup>+</sup> )	Step 4 (Level 4 <sup>+</sup> )	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

\* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

\*\* As always, a systematic review is generally better than an individual study.

## How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group\*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

\* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson



## SR Appraisal sheets(FAITH)

# Appraisal Tool

## [系統性文獻回顧Systematic Review]

步驟1: 系統性文獻回顧探討的問題為何? (PICO)

步驟2: 系統性文獻回顧的品質如何? (內在效度)

步驟3: 結果為何? (效益)

# 結果為何? 使用何種評估方式，療效有多大(是否來自隨機效果)？

量表/測量時間	1 Month	3 Months	6 Months	12 Months
VAS Visual Analogue Scale 疼痛視覺類比量表	●	●	●	●
WOMAC Western Ontario and McMaster Universities Osteoarthritis Index 骨關節炎指數		●	●	
KOOS Knee Injury and Osteoarthritis Outcome Scores 膝關節功能評估量表	●	★	●	
IKDC International Knee Documentation Committee 主觀膝部評估表			★	
Lequesne index scores 膝關節炎病人疼痛指數		★	★	

## 其他說明：最小臨床重要差異值(minimum clinically important difference, MCID)之概念

Page 5 of 13

### MCID

Based on previous work, the MCID for both the pain VAS scores and the WOMAC total scores was set at 20% [19–22]. Therefore, based on the baseline values of each outcome in the included studies, the MCID of the pain VAS scores was calculated to be 1.16, and the WOMAC total score was 7.86. In addition the mean difference between the two groups was compared with the MCID for each score reported in the literature: 11.5/100 for the IKDC scores [31] and 10/100 for the KOOS subscale [32].

# 其他說明：最小臨床重要差異值(minimum clinically important difference, MCID)之概念

- 一. 定義：對臨床有重要意義之**最小改變量**。
  1. 以研究方面，療效的判斷常以是否具有「統計顯著(statistical significance)」判定，然而具有統計顯著之差異值，不一定具有「臨床意義(clinical significance)」。
  2. MCID值可協助臨床/研究人員判斷評估**結果之改變量是否超過臨床認為有意義之最小閾值**。
- 二. MCID值設定：
  1. 通常以研究做為佐證，若找不到相關研究，也應該有專業共識。
  2. MCID值可作為判斷群組分數改變/差異（組內(within-group)/組間(between-group)）是否具有臨床重要意義的最小閾值。
- 三. 舉例說明：

若降血壓新藥可以降低平均血壓2 mmHg，達統計上顯著差異，但學理 (或專業共識) 上認為藥物有效的 MCID值要達到10 mmHg，則此新藥就不具有降低血壓的臨床意義。
- 四. 影響因素：

個案之初始分數：**初始分數不同的個案，對於一樣的進/退步量感受不同**。

**[例如：疼痛7→4分仍需處理；疼痛4→1分可不處理]**

# 總評(Summary)

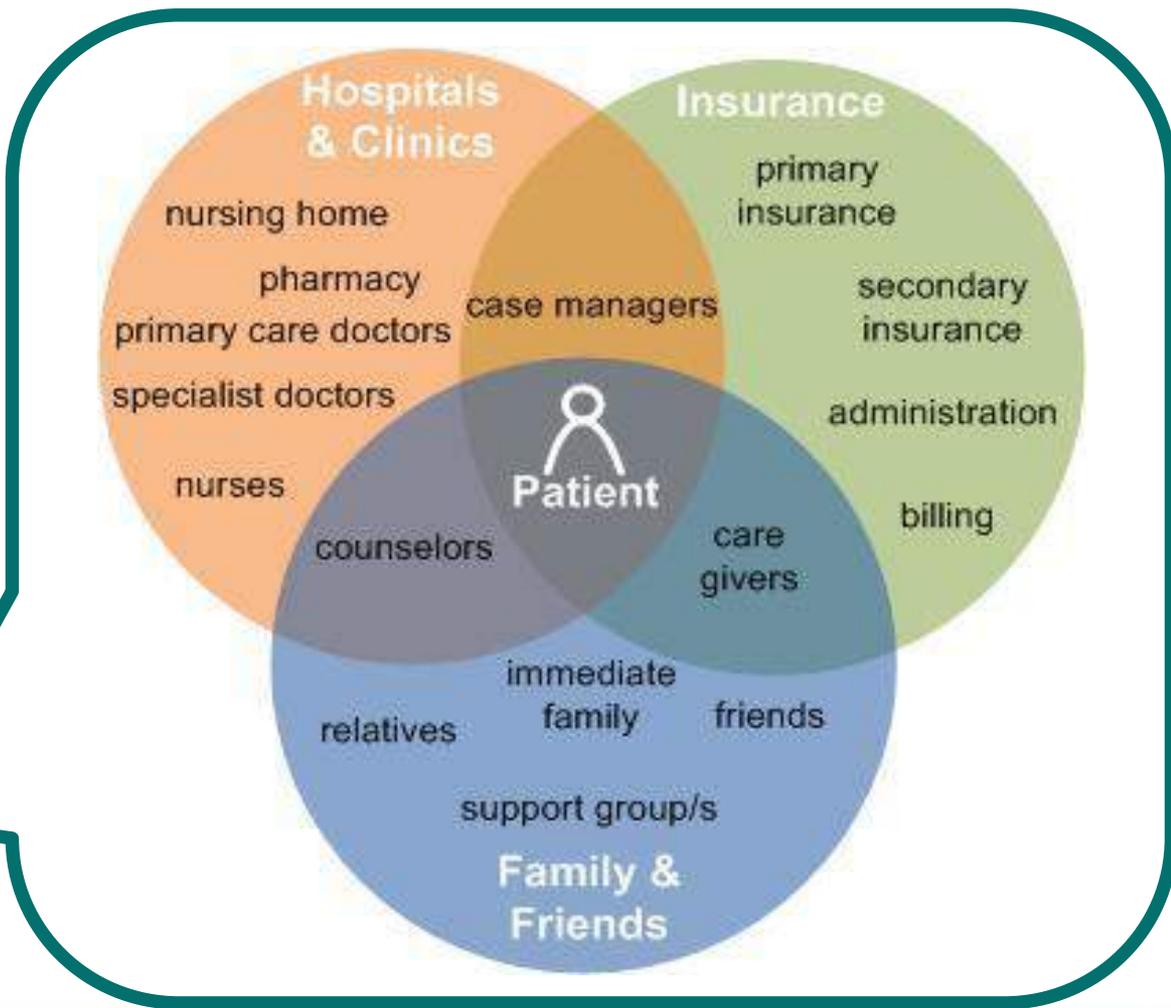
## FAITH系統性文獻回顧快速評讀表

結果

F	研究是否找到 (Find) 所有的相關證據？	至少二個主要資料庫(PubMed, EMBASE, and Cochrane Library), 加上文獻引用檢索(Web of Science), 不限英文, 使用MeSH字串及一般檢索詞彙(text words)	是
A	文獻是否經過嚴格評讀 (Appraisal)？	以the Cochrane Risk of Bias assessment tool進行嚴格評讀, 並以表格呈現各篇納入文獻品質	是
I	是否只納入 (Included) 具良好效度的文章？	由二位研究員獨立進行評讀, 意見不一時和第三位研究員進行討論採共識決	是
T	作者是否以表格和圖表「總結」(Total up)？	Table (characteristics of enrolled studies, subgroup analysis), forest plot of probiotics overall effects and adverse events	是
H	試驗的結果是否相近 - 異質性 (Heterogeneity)？	因異質性大套用random effects model, 進行sensitivity analyses and subgroup analyses, funnel plot、Begg test、Egger test to assess publication bias	是



# 這篇文獻的實證證據可以用於本院嗎？



## 臨床情境

- 一位78歲女性右膝疼痛，經診斷為退化性膝關節炎第二級，目前規律在骨科門診定期追蹤並施打半年三劑短效玻尿酸，因家住4樓舊式公寓，最近上下樓梯右膝蓋又感疼痛難受。兒子最近看到一篇網路文章，宣稱注射高濃度血小板血漿(PRP)+玻尿酸(HA)可以有效緩解膝蓋疼痛，因此兒子帶母親來門診複診時詢問骨科醫師是否建議注射高濃度血小板血漿(PRP)？



# 討論

- **Expectations(病人期待)**
  - 退化性膝關節炎患者希望**減緩疼痛程度**。
  - 退化性膝關節炎患者期待**身體活動功能自如**。
- **Evidence(研究證據)**
  - 9篇隨機對照試驗(RCT)
  - 4篇世代研究(Cohort study)
  - **主觀測量問卷量表**
    - VAS,WOMAC,KOOS,IKDC,Lequesne index scores
    - 最小臨床重要差異值(minimum clinically important difference, MCID)可幫助研究人員和臨床工作者判斷分數的改變是否達到臨床上重要的差異。
- **Expertise(臨床專家)**
  - 復健科：許庭瑄住院醫師(PRPR原理)
  - 中醫科：蔡宗儒醫師
  - 骨科：吳正淳醫師
- **成本效益：**
  - PRP(自費)：14,300元/15,000元/18,500元
  - 玻尿酸半年3劑：健保或自費(575元/支+注射費：135=2,130)
  - 玻尿酸半年1劑：健保或自費(2,889元/支+注射費：135=3,024)
  - 玻尿酸一年1劑：健保或自費(5,516元/支+注射費：135=5,651)



## 臨床應用

- 退化性膝關節炎第二級的患者，注射「高濃度血小板血漿(PRP)+玻尿酸(HA)」是否安全且能有效緩解退化性膝關節炎引起的疼痛？



■ 同意：1票    ■ 待評估：22票    ■ 不同意：2票



感謝聆聽!

