SEMMELWEIS EGYETEM

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Ph.D. értekezések

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című program

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NEW FRONTIERS IN DISEASE ACTIVITY MONITORING AND THERAPY IN THE FIELD OF DERMATOLOGY AND RHEUMATOLOGY

Ph.D. Thesis

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Translational Medicine Program

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"There is no greater misfortune in the world than the loss of reason."

Mikhail Bulgakov, The Master and Margarita

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1. LIST OF ABBREVIATIONS

AA	alopecia areata
ACPA	anti-citrullinated peptide antibody
ADA	adalimumab
APG	autologous platelet gel
bDMARD	biological disease-modifying antirheumatic drug
c.c.	correlation coefficient
CDAI	Clinical Disease Activity Index
CI	confidence interval
COR	correlation
CRP	C-reactive protein
CsA	cyclosporin A
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DAM	disease activity measure
DAS28	Disease Activity Score with 28-joint count
DMARD	Disease-Modifying Anti-Rheumatic Drug
DP	dermal papilla
EGF	epidermal growth factor
ESR	erythrocyte sedimentation rate
ETN	etanercept
EULAR	European Union League Against Rheumatism
FA	folic acid
GC	glucocorticoid
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HAQ	Health Assessment Questionnaire
HCQ	hydroxychloroquine
HF	hair follicle
IFX	infliximab

IGF-1	insulin-like growth factor
IL-6	interleukin-6
ILC	innate lymphoid cell
IMID	immune-mediated inflammatory disease
IP	immune privilege
MBDA	multi-biomarker disease activity
MD	mean difference
MMP	matrix metalloproteinase
MTX	methotrexate
N/A	no data available
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	odds ratio
PBO	placebo
PC	platelet concentrate
PDGF	platelet-derived growth factor
PDUS	synovial power dopplers score based on ultrasonography
PICO	population-intervention-control-outcome
POS	prospective observational study
PPP	platelet-poor plasma
PRF	platelet-rich fibrin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	platelet-rich plasma
PtGA	Patient Global Assessment of Disease Activity
QUIPS	Quality In Prognosis Studies
RA	rheumatoid arthritis
RCT	randomized clinical trial
ReOS	retrospective observational study
RF	rheumatoid factor
RoB 2	Revised tool for assessing the risk of bias

ROS	reactive oxygen species
RP	radiographic progression
RTX	rituximab
SAA	serum amyloid A
SALT	Severity of Alopecia Tool
SDAI	Simplified Disease Activity Index
SJC28	Swollen Joint Count of 28 joints
SMD	standardized mean difference
SSZ	sulfasalazine
SvdH	Sharp/van der Heijde
TCZ	tocilizumab
TGF-ß	transforming growth factor ß
TJC28	Tender Joint Count of 28 joints
TNFi	TNF-alpha-inhibitor
TNFRI	tumor necrosis factor receptor type I
TrA	triamcinolone acetonide
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve patient care, thus enhance the quality of life for patients with chronic dermatological and rheumatological conditions.

My mission is to urge the implementation of novel disease modifying and monitoring methods in clinical practice.

My specific goals include the investigation of the utility of MBDA score for the monitoring of rheumatoid arthritis, as well as the assessment of the efficacy of PRP in chronic wound management and in the treatment of alopecia areata.

2.2. Scientometrics

Number of all publications:	13
Cumulative IF:	26.20
Av IF/publication:	2.01
Ranking (Sci Mago):	D1: 2, Q1: 3, Q2: 5
Number of publications related to the subject of the thesis:	3
Cumulative IF:	14.10
Av IF/publication:	4.70
Ranking (Sci Mago):	D1: 1, Q1: 2, Q2: -
Number of citations on Google Scholar:	39
Number of citations on MTMT (independent):	11
H-index:	3

The detailed bibliography of the student can be found on page 75.

2.3. Future plans

My future plans revolve around the dual goals of continuing my research and gaining valuable experience in patient care as well.

I firmly believe that a comprehensive understanding of healthcare requires more than theoretical expertise alone. To enhance my skill set and broaden my perspective, I am keen on actively participating in patient care. By engaging directly with patients, I aspire to gain firsthand experience in addressing their unique needs, challenges, and concerns.

By integrating research and patient care, I aim to forge a career that not only advances scientific knowledge but also directly contributes to the well-being and improved healthcare outcomes of patients.

3. SUMMARY OF THE PH.D.

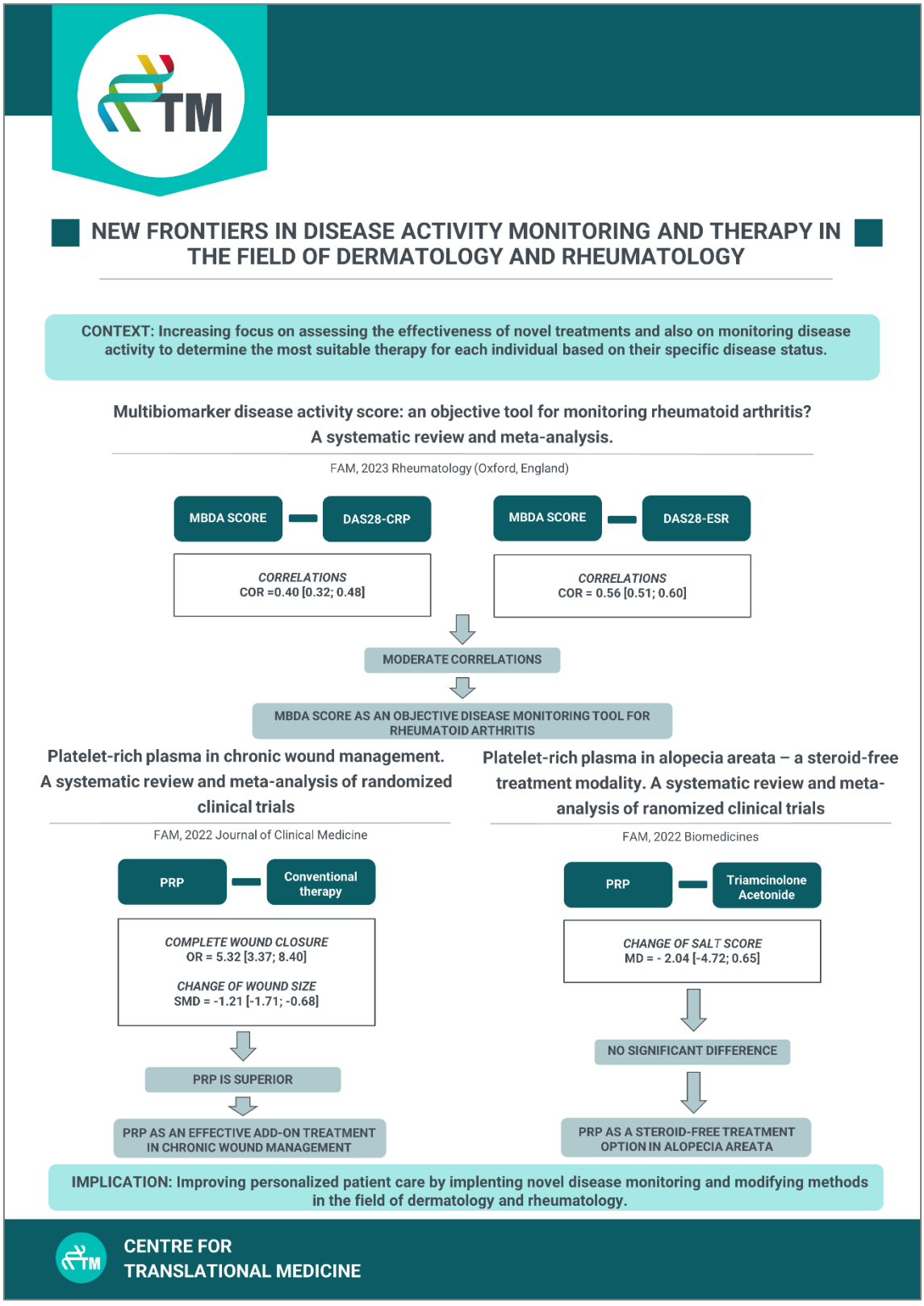
The advancements achieved in dermatology and rheumatology call for an assessment of the efficacy of novel treatments, while also highlight the importance of monitoring disease activity to facilitate personalized treatment.

To advance clinical practice by promoting innovative disease-modifying and monitoring methods we conducted three meta-analyses. These analyses evaluated the effectiveness of the multi-biomarker disease activity (MBDA) score as a monitoring tool for rheumatoid arthritis (RA), as well as the efficacy of platelet-rich plasma (PRP) in treating two dermatological conditions, chronic wounds and alopecia areata (AA).

Our results showed moderate correlations between the MBDA score and conventional disease activity measures both at baseline and at follow-up. Regarding the efficacy of PRP, our findings demonstrated that the odds for complete wound closure were significantly higher in the PRP group compared to the control group when treating chronic wounds. When comparing the PRP and triamcinolone acetonide groups for the treatment of AA, the pooled MDs from the four studies of the quantitative analysis did not demonstrate a significant difference in the mean change of the SALT score.

In conclusion, our findings demonstrated the utility of MBDA score for the monitoring of RA and highlighted the potentials of PRP in the treatment of chronic wounds and alopecia areata. By implementing the use of MBDA score in clinical practice, the personalized treatment of RA patients could be further improved, while PRP could providing a potential treatment option for a wide range of patients.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Our main focus is the assessment of the utility of novel disease monitoring and modifying methods in the field of dermatology and rheumatology.

5.1.2. What is the problem to solve?

The progress made in the fields of dermatology and rheumatology necessitates the evaluation of the effectiveness of innovative therapies, while also emphasizing the significance of monitoring disease activity to enable tailored treatment approaches.

5.1.3. What is the importance of the topic?

Dermatological and rheumatological conditions can have a profound impact on patients' quality of life as well as on society as a whole. These conditions often bring about physical discomfort, pain, and visible symptoms, which can lead to significant psychological distress and emotional challenges for patients. Moreover, these conditions impose a financial burden on the healthcare system and society as the long-term management of these conditions often requires ongoing medical care, specialized treatments, and medications.

5.1.4. What would be the impact of our research results?

Through the assessment of the effectiveness of new therapies and the facilitation of widespread adoption of objective disease monitoring systems, the quality of life for patients can be significantly improved. The evaluation of the efficacy of emerging treatments allows healthcare professionals to determine the most suitable interventions for patients, leading to enhanced outcomes and better overall well-being. Additionally, the implementation of objective disease monitoring systems provides clinicians with valuable data on the progression and response to treatment, enabling personalized and timely adjustments to patient care plans.

5.2. Inflammation – a key player in dermatology and rheumatology

Understanding the role of inflammation is critical in the diagnosis and management of dermatologic and rheumatologic conditions: serum markers of inflammation can help diagnosis, while anti-inflammatory agents can be valuable tools in disease management.

Inflammation can be both the trigger and the maintainer of a disease, often without the clear separation of the two phenomena. In case of autoimmune and immune-mediated inflammatory diseases (IMIDs), two common and well-known disease groups in the field of dermatology and rheumatology, it is usually both.

Alopecia areata (AA) is a non-scarring alopecia, mainly described as an autoimmune disease in the field of dermatology, characterized by inflammation-induced hair loss, which can affect the scalp, the beard, or even the whole body, leading to a serious deterioration in patients' quality of life (1). The loss of the immune privilege (IP) of the hair follicles (HF) plays a key role in the pathomechanism of AA, resulting in the influx of pro-inflammatory cells responding to the exposed HF autoantigens that induce HF damage (2-5). The reason behind the loss of IP is heavily investigated: the role of an autoimmune component with the ectopic expression of HF antigens, promoting the activation of autoreactive CD8+ T cells, resulting IP collapse is widely accepted (2, 3, 6, 7). However, the theory of the non-autoimmune form of AA, where an environmental stress-induced reactive oxygen species (ROS) buildup in HF keratinocytes promotes pro-inflammatory activity from the innate immune system, resulting IP collapse, is also described in the literature (2, 3, 8, 9).

Inflammation is also a hallmark of several rheumatological autoimmune and immune mediated inflammatory diseases, such as rheumatoid arthritis (RA), a chronic disease that primarily affects the joints, causing inflammation, pain, and damage. The pathogenesis of RA is complex and multifactorial. Although the initial triggers for the breakdown of immune tolerance are yet to be identified, several genetic factors, such as epigenetic modifications and genetic polymorphisms affecting the immune function and environmental factors, including cigarette smoke, have been described in the literature (10, 11). In response to the initial trigger, the activation of the immune system leads to the production of autoantibodies and the release of pro-inflammatory cytokines that lead

to a systemic inflammation and also target the synovial tissue, causing the destruction of the joint cartilage and bone (10, 12).

As the maintainer of the condition, inflammation also plays a significant role in chronic wounds. Chronic wounds are common conditions that greatly impact patients' quality of life (13). They place a heavy burden on the healthcare system as the cost of wound management is estimated to account for 5.5% of all healthcare expenditures (14). Although a wide range of causes, including arterial and venous insufficiency, neuropathy, microangiopathy, and several additional factors underlie ulceration, the healing process consists of the same phases (15, 16). After the hemostasis, the phase of inflammation ensures the breakdown of the tissue and the clean-up of cellular, extra-cellular and pathogen debris (16, 17). The healing continues with the proliferative phase and ends with tissue remodeling (16, 17). The inflammation is an essential step of wound healing, however, in case of chronic wounds, the healing cascade is not as well defined as in case of acute trauma (16). Due to tissue hypoxia combined with the host response to repetitive stress, a chronic inflammation is sustained and the progression to the proliferative phase is consequently delayed, preventing the healing (16, 18).

5.3. The implementation of innovative disease-monitoring and modifying methods in dermatology and rheumatology

The therapeutic landscape is expanding both in the field of dermatology and rheumatology, mainly driven by the emergence and widespread adoption of biological therapies. While the availability of multiple treatment options is noteworthy, the paramount objective is to optimize patient care by selecting the most effective therapy. Consequently, there is an escalating emphasis on monitoring disease activity to guide the selection of the optimal treatment based on individual disease status. Furthermore, the evaluation of novel therapies' efficacy, even besides biologics, remains imperative.

5.3.1. Multi-biomarker disease activity score, a novel disease monitoring system

The Multi-biomarker Disease Activity (MBDA) score is an objective tool using only serum biomarker levels for the assessment of disease activity in RA. The validated test that calculates MBDA score with an algorithm is commercially available as the Vectra® DA test, resulting a score from 0 to 100. It was created through the testing of 130 potential

biomarkers in feasibility studies. From these, 25 biomarkers were chosen to train the algorithm and 12 (interleukin-6 [IL-6], tumor necrosis factor receptor type I [TNFRI], vascular cell adhesion molecule 1 [VCAM-1], epidermal growth factor [EGF], vascular endothelial growth factor A [VEGF-A], YKL-40, matrix metalloproteinase 1 [MMP-1], MMP-3, C-reactive protein [CRP], serum amyloid A [SAA], leptin, and resistin) were selected as final biomarkers (19).

As per the recommendations of the European Union League Against Rheumatism (EULAR), the objective of therapy for rheumatoid arthritis (RA) is to attain either remission or, at least, minimize disease activity. (20). Current guidelines recommend early initiation of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and employing a treat-to-target therapeutic approach to prevent long-term functional decline by minimizing damage to cartilage and bone (21-23).

Currently, the available options for monitoring disease activity and progression are predominantly subjective or lack specificity. The Disease Activity Score with 28-joint count (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) are widely used but incorporate subjective evaluations of disease activity reported by either the patient or the healthcare provider (24-26). While non-specific inflammatory markers like CRP or erythrocyte sedimentation rate (ESR) are utilized in the calculation of DAS28 and SDAI, the inclusion of a scoring system that combines inflammatory markers with additional biomarkers could enhance the objectivity of disease activity measurement.

Assessing structural damage, a significant determinant of disease progression, can be achieved through radiography and quantified using the Sharp/van der Heijde (SvdH) score system (27). Several established risk factors for radiographic progression have been identified, including elevated disease activity monitored through non-specific inflammatory markers like CRP, seropositivity for rheumatoid factor (RF), and anti-citrullinated peptide antibody (ACPA) (28). Nevertheless, nor RF or ACPA are suitable for monitoring disease activity (29).

The utilization of the MBDA score as an objective disease monitoring system can play a significant role in tailoring personalized therapeutic plans and modifications aligned with

contemporary medical perspectives. Apart from its ability to monitor disease activity, the MBDA score also holds potential in predicting radiographic progression (30-33).

5.3.2. Platelet-rich plasma, a novel disease-modifying treatment modality

Platelet-rich plasma (PRP) is a relatively new, presently evolving treatment modality. The term PRP was first described as a treatment alternative of thrombocytopenia and was used as a synonym of the category "platelet concentrate" (PC) (34). Since the appearance of the denser, second-generation PCs, such as platelet-rich fibrin (PRF) or autologous platelet gel (APG), PRP is also used as a subcategory of PCs to describe formulations with lower density (35, 36). PRP is prepared from whole blood by a centrifugation process to achieve a product that is rich in platelets, growth factors, and cytokines. PRP was shown to stimulate stem cell regeneration and tissue remodeling, promote cell proliferation in the dermal papilla (DP), increase DP cell survival through antiapoptotic effects, and stimulate hair regrowth by prolonging the anagen phase of the hair cycle (37-39).

Due to its beneficial effects on tissue regeneration, PRP is widely used in several fields of medicine, such as ortopedics, sports medicine, ophthalmology, oral surgery, gynecology, and urology (40-46). It has also been utilized in plastic surgery and dermatology for facial rejuvenation and for therapeutic purposes such as the treatment of androgenic alopecia, acne scars, or chronic wounds (47-50).

Depending on the format of the PC, it can be either injected, applied topically after a pre-treatment such as microneedling or CO2 laser treatment, or applied in a gel format.

Both the management of chronic wounds and the treatment of AA are challenging. The key element of chronic wound management is the treatment of the underlying cause, however, promoting the wound healing through professional wound care is also essential; the gold standard methods are smart dressings and compression therapy (51). In the management of AA, a diverse range of topical and systemic treatments are employed. However, due to the variable response of the disease to therapy, there is a lack of consensus on a standardized treatment approach (52). According to guidelines, the first line of treatment in limited patchy AA is triamcinolone acetonide (TrA) administered intralesionally (53, 54). In addition to the often-debated effectiveness of TrA treatment,

common side effects like skin atrophy, telangiectasiae, and hypopigmentation are frequently observed. Moreover, the use of steroids can evoke concern in many, leading to a phenomenon known as steroid phobia (55). These factors further emphasize the need to explore alternative topical steroid-free treatment options.

6. OBJECTIVES

6.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis

Although several studies have evaluated the utility of the MBDA score, and a meta-analysis has been conducted on the correlation of the MBDA score with conventional DAMs; the predictive and discriminative value of the MBDA score was yet to be analyzed in a comprehensive manner (56). Therefore, our aim was to conduct a systematic review and meta-analysis assessing the predictive and discriminate value of MBDA score besides its correlation with conventional DAMs.

6.2. Study II. – Investigating the efficacy of PRP in chronic wound management

The effects of PRP on wound healing are heavily investigated, however, the current evidence is inconclusive (49). Therefore, we aimed to evaluate the efficacy of PRP in chronic wound management.

6.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata

PRP showed promising results in the treatment of AA(57-62), but as there was no systematic evaluation of randomized trials reporting on the therapeutic effect of PRP on AA, we aimed to summarize the latest data on the efficacy of PRP in AA comprehensively.

7. METHODS

Our systematic reviews and meta-analyses are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement (63). The Cochrane Handbook's recommendations for Systematic Reviews of Interventions Version 6.1.0 (64) and Cochrane Prognosis Methods Group (65) were followed and the review protocols were registered on PROSPERO (Study I.: *CRD42021279474;* Study II.: *CRD42021287881;* Study III.: *CRD42021282807*).

7.1. Literature search and eligibility criteria

We performed a systematic literature search in five databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Web of Science and Scopus for Study I, and four medical databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, and Web of Science for Study II. and Study III. The dates of the searches and the queries used are detailed in the original publications (66-68).

Original articles reporting on the performance of the MBDA score's correlation with conventional DAMs, or the predictive and the discriminative value of the MBDA score for radiographic progression, therapy response, remission, and relapse were included for Study I. Randomized clinical trials (RCTs) reporting on patients with chronic wounds treated with PRP, comparing additional PRP treatment with conventional ulcer therapy alone were included for Study II., while RCTs reporting on patients with AA treated with PRP, comparing PRP with TrA or placebo for Study III.

7.2. Study selection and data collection

We used EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for the articles' selection. Two independent authors screened the publications separately for the title, abstract, and full text, and disagreements were resolved by a third author.

Two authors independently extracted data into a predefined Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA), and a third reviewer resolved the discrepancies.

The following data were collected from each eligible article: data regarding the article (first author, year of publication, DOI, language, study design, study duration, original study/data source), data regarding participants (demographics and subject characteristics:

age, sex, treatment applied, subgroups examined), data regarding outcomes (all possible data of the investigated outcomes were collected). Multiple reports of the same population were linked together.

7.3. Quality assessment

The risk of bias assessment was carried out separately by two reviewers by using the Quality In Prognosis Studies (QUIPS) tool for Study I. (69) and the revised tool for assessing the risk of bias (RoB 2) (70) for Study II. and III. Disagreements were resolved by a third reviewer. To assess the quality of the evidence for Study II. and Study II., we followed the recommendation of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup and used GRADEPro Guideline Development Tool for visualization (71, 72).

7.4. Data synthesis and analysis

The statistical analyses were performed with R (R Core Team 2022, v4.2.1) (73). Forest plots were used to graphically summarize the results. For calculations and plots we used the meta (Schwarzer 2022, v5.5.0) (74) and dmetar (Cuijpers, Furukawa, and Ebert 2022, v0.0.9000) (75) packages.

Random-effects meta-analyses were performed on the different datasets as we anticipated considerable between-study heterogeneity.

For dichotomous outcomes the odds ratio (OR) with 95% confidence interval (CI) was used for the effect measure; to calculate the OR, the total number of patients in each group and those with the event of interest were extracted from each study. Raw data from the selected studies were pooled using a random effect model with the Mantel-Haenszel method (76-78). For the pooled results exact Mantel-Haenszel method (no continuity correction) was used to handle zero cell counts (79). At individual studies zero cell count problem was adjusted by treatment arm continuity correction (80). In case of continuous outcomes, mean difference (MD) and standardized mean difference (SMD) with 95% CI were calculated as effect size. In case of correlations, the correlations retrieved from the studies belonged to three categories: Pearson's correlation coefficient (c.c.), Spearman's c.c. and those that the type of c.c. was not mentioned in the article. These three were analyzed separately as Pearson's c.c. and Spearman's c.c. are calculated differently, thus

analyzing them together or trying to transform them into each other might introduce some distortion to our results, undermining the reliability of the conclusions. For the meta-analyses, Fisher's z-transformation was carried out on the collected c.c.-s, which were then retransformed for the reporting of the results.

Between-study heterogeneity was described by the Higgins & Thompson's I^2 statistics (81).

8. RESULTS

8.1. Search and selection, characteristics of the included studies

8.1.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis

Our systematic search provided 1190 records; after duplicate removal we screened 708 duplicate-free publications. Thirty eligible studies (30-33, 82-107) were identified after title, abstract and full-text selection, and two additional studies (108, 109) during citation search. Of these studies, we included 24 in the quantitative (30-32, 82-84, 86-88, 90, 91, 93-97, 99, 100, 102, 103, 105, 106, 108, 109) and eight only in the qualitative (33, 85, 89, 92, 98, 101, 104, 107) analysis. The summary of the selection process is shown in **Figure 1**.

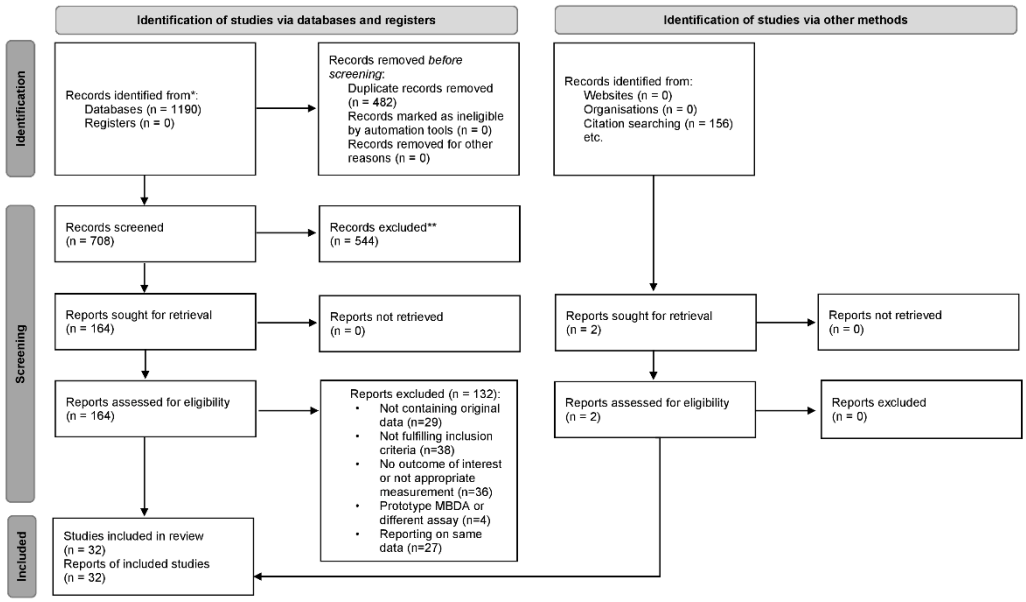


Figure 1. PRISMA Flow Diagram of the screening and selection process for Study I. (66)

Characteristics of the identified studies for the systematic review and meta-analysis are detailed in **Table 1.**

Table 1. Main characteristics of the included studies for Study I. (66)

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Studies included in the meta-analysis						
Baker, 2021 (82)	US (Pennsylvania)	journal article	POS	MTX, bDMARD, GC	Spearman's correlation with conventional DAMs	baseline*
Bakker, 2012 (30)	Netherlands	journal article	RCT	MTX, CsA, intraarticular GC, NSAID	Pearson's correlation with conventional DAMs^{++}, predicting radiographic progression, remission^{++}	baseline*, month 1,3,6*, year 2^{+}
Bechman, 2018 (83)	UK	journal article	POS	csDMARD, bDMARD, GC	Spearman's correlation with conventional DAMs, relapse^{++}	month 3, 6, 9, 12*
Bijlsma, 2013 (84)	Netherlands	conference abstract	RCT	group A: MTX+PBO group B: MTX+GC	Spearman's correlation with conventional DAMs	baseline*, month 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12*

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Bouman, 2017 (86)	Netherlands	journal article	RCT	MTX, csDMARD, ADA, ETN, NSAID, GC	Spearman's correlation with conventional DAMs, predicting radiographic progression^{++}, relapse^{++}	baseline*, month 3, 6, 9, 12, 15, 18
Brahe, 2016 (87)	Denmark	conference abstract	RCT	group A: MTX+PBO group B: MTX+ADA	Spearman's correlation with conventional DAMs	baseline*, month 3*, 6, 12*
Brahe, 2019 (31)	Denmark	journal article	RCT	group A: MTX+PBO group B: MTX+ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression, remission^{++}	baseline*, month 1, 2, 3*, 6*, 9, 12
Genovese, 2017 (88)	US	conference abstract	RCT	group A: MTX+PBO group B: MTX+100 mg filogitinib group C: MTX+200 mg filogitinib	Spearman's correlation with conventional DAMs	baseline*, week 12*

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Hambardzumyan, 2013 (90)	Sweden	conference abstract	RCT	MTX, other DMARD, IFX	Spearman's correlation with conventional DAMs	baseline*, year 1*
Hambardzumyan, 2015 (32)	Sweden	conference abstract	RCT	MTX, HCQ, SSZ, IFX	predicting radiographic progression	month 3, year 1^{+}
Hirata, 2013 (108)	Netherlands, Japan	journal article	RCT	DMARD, IFX	Spearman's correlation with conventional DAMs, remission^{++}	baseline*, year 1*
Hirata, 2015 (109)	Japan	journal article	REOS	ADA, ETN, IFX, MTX	Spearman's correlation with conventional DAMs, therapy response^{++}	baseline*, week 24, 52*
Hirata, 2016 (93)	Japan	journal article	REOS	MTX, ADA, ETN, IFX	Spearman's correlation with conventional DAMs, predicting radiographic progression^{++}	baseline*, week 52*
Jurgens, 2020 (94)	Netherlands	journal article	RCT	MTX, GC, CsA, ADA, PBO	Spearman's correlation with conventional DAMs	baseline*, month 1, 2, 3*, 4, 5, 6, 7, 8, 9, 10, 11, 12

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Krabbe, 2017 (95)	Denmark	journal article	POS	MTX, ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression^{++}	baseline*, week 26, 52*
Lee, 2016 (96)	USA (Massachusetts)	journal article	POS	csDMARD, bDMARD	Spearman's correlation with conventional DAMs	baseline*
Li, 2013 (97)	Sweden	conference abstract	POS	MTX	Spearman's correlation with conventional DAMs, therapy response^{++}	baseline*, month 3*
Ma, 2014 (100)	UK	conference abstract	POS	N/A	Spearman's correlation with conventional DAMs	baseline*, year 1*
Maijer, 2013 (102)	Netherlands	conference abstract	POS	N/A	Spearman's correlation with conventional DAMs	baseline*

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Reiss, 2016 (105)	USA (California)	journal article	RCT	TCZ, MTX, GC	Spearman's correlation with conventional DAMs	baseline*, week 4, 12, 24*
Roodenrijs, 2018 (106)	Netherlands, UK	journal article	POS	RTX, GC	Spearman's correlation with conventional DAMs, therapy response^{++}	baseline*, month 6*
Studies included in the systematic review						
Boeters, 2019 (85)	Netherlands	journal article	POS	csDMARDS, bDMARDS	relapse	annually
Hambardzumyan, 2019 (89)	Sweden	journal article	RCT	MTX, HCQ, SSZ, IFX	therapy response	month 0, 3
He, 2020 (91)	US	conference abstract	database analysis	DMARD	Pearson's correlation with conventional DAMs	baseline*
Hirata, 2012 (92)	Netherlands	conference abstract	RCT	N/A	remission	baseline, year 1
Li, 2016 (98)	Netherlands	journal article	POS	csDMARD, TNFi	predicting radiographic progression	annually

First author, year of publication	Country	Type of publication	Original study type	Treatment	Outcome	Timepoints of study
Luedders, 2020 (99)	USA (Nebraska)	journal article	POS	MTX, FA, GC, NSAID	Pearson's correlation with conventional DAMs, remission	baseline*, week 8, 16*
Ma, 2020 (101)	UK, Singapore	journal article	POS	csDMARDs, TNFi, GC	remission	baseline, month 3,6
Markusse, 2014 (33)	Netherlands	journal article	RCT	csDMARD, IFX, GC	predicting and discriminating radiographic progression	baseline, year 1
Moghadam, 2018 (107)	Netherlands	journal article	RCT	csDMARD	relapse	baseline, month 3, 6, 9, 12
Razmjou, 2020 (103)	USA (California)	journal article	POS	csDMARD,To facitinib	Pearson's correlation with conventional DAMs	baseline*, week 2, 6, 12*
Rech, 2016 (104)	Germany	journal article	RCT	csDMARDS, bDMARDS	relapse	baseline, month 3, 6, 9, 12

ADA-adalimumab; CsA-cyclosporin A; bDMARD-biological disease-modifying antirheumatic drug; csDMARD- conventional synthetic disease-modifying antirheumatic drug; ETN-etanercept; FA-folic acid; GC-glucocorticoid; HCQ-hydroxychloroquine; IFX-infliximab; MTX-methotrexate; N/A-no data available; NSAID- NonSteroidal Anti-Inflammatory Drug; PBO-placebo; POS-prospective observational study; RCT-randomized clinical trial; ReOS-retrospective observational study; RTX-rituximab; SSZ-sulfasalazine; TCZ-tocilizumab;TNFi-TNF-alpha-inhibitor

* timepoint used for calculating correlation

[+] timepoint used for calculating radiological progression

[++] not included in the meta-analysis

8.1.2. Study II. – Investigating the efficacy of PRP in chronic wound management

Our systematic search provided a total of 2,688 articles; after duplicate removal, we screened 1,910 duplicate-free publications. Following the title, abstract and full-text selection, we identified 46 RCTs matching our population-intervention-control-outcome (PICO) framework (68-113) and two additional articles (114, 115) after citation search. The full text of 10 articles could not be retrieved even after contacting the authors (116-125). The summary of the selection process is shown in **Figure 2**.

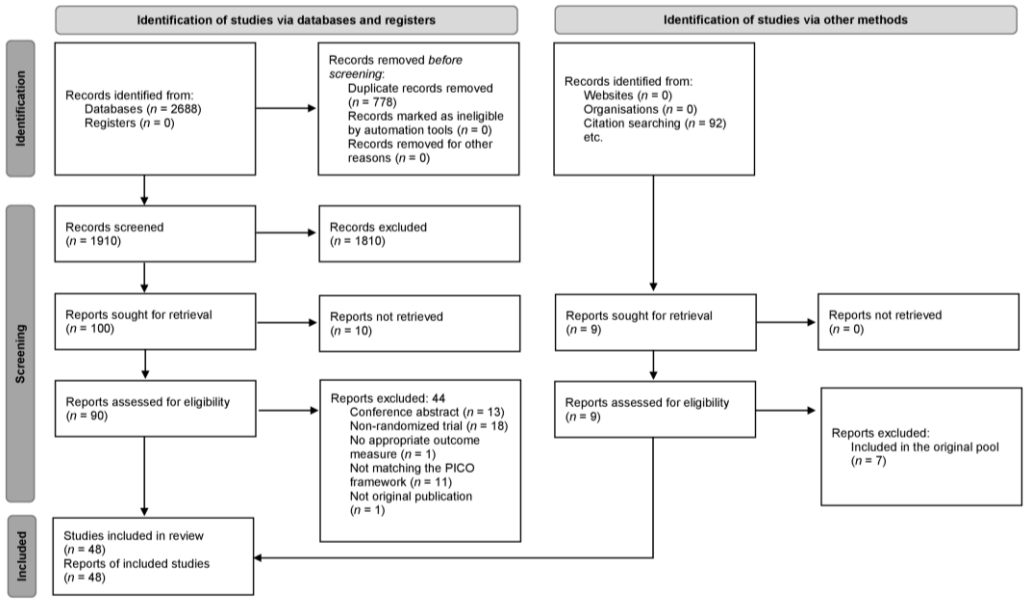


Figure 2. PRISMA Flow Diagram of the screening and selection process for Study II. (67)

The characteristics of the identified RCTs for the systematic review and meta-analysis are detailed in **Table 2.**

Table 2. Main characteristics of the included studies for Study II. (67)

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Studies included in the meta-analysis					
Abd El-Mabood, 2018 (110)	Egypt	diabetic	topical PRP + conventional therapy	conventional therapy	complete closure, healing rate, infection, and pain
Ahmed, 2017 (111)	Egypt	diabetic	topical PRP + conventional therapy	conventional therapy	complete closure, healing rate, and infection
Amato, 2020 (112)	Italy	mixed	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, infection, and pain
Burgos-Alonso, 2018 (113)	Spain	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, infection, pain, adverse events, and quality of life
Driver, 2006 (114)	US	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, healing rate, complete closure, healing time, and adverse events
Elbarbary, 2020 (115)	India	venous	topical/injected PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, healing time, and recurrence
Elgarhy, 2020 (116)	India	venous	topical/injected PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, and healing time

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Elsaid, 2020 (117)	Egypt	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, and healing time
Game, 2018 (118)	UK	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, healing time, infection, pain, amputation, and adverse events
Glukhov, 2017 (119)	Russia	venous	topical PRP + conventional therapy	conventional therapy	complete closure, and pain
Goda, 2018 1 (120)	Egypt	diabetic	topical PRP + conventional therapy	topical PPP + conventional therapy	healing rate, and complete closure
Goda, 2018 2 (121)	Egypt	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and complete closure
Gude, 2019 (122)	US	diabetic	topical PRP + conventional therapy	conventional therapy	complete closure, and amputation
Helmy, 2021 (123)	Egypt	venous	PRP injection + conventional therapy	conventional therapy	reduction of wound area, complete closure, healing time, pain, adverse events, and recurrence
Hongying, 2020 (124)	China	pressure	PRP injection + conventional therapy	conventional therapy	reduction of wound area, and complete closure

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Kakagia, 2007 (125)	Greece	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and complete closure
Karimi, 2016 (126)	Iran	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, and amputation
Li, 2015 (127)	China	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, healing time, infection, amputation, and adverse events
Moneib, 2018 (128)	Egypt	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, pain, and adverse events
Obolenskiy, 2014 (129)	Russia	mixed	topical PRP + conventional therapy	conventional therapy	complete closure, and healing time
Obolenskiy, 2017 (130)	Russia	mixed	topical PRP + conventional therapy	conventional therapy	healing rate, complete closure, and healing time
Rainys, 2019 (131)	Lithuania	N/A	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, infection, and adverse events
Ramos-Torrecilla, 2015 (132)	Spain	pressure	topical PRP + conventional therapy	conventional therapy	reduction of wound area, complete closure, and infection

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Saad Setta, 2011 (133)	Egypt	diabetic	topical PRP + conventional therapy	topical PPP + conventional therapy	complete closure, and healing time
Saha, 2020 (134)	India	leprosy	PRP injection + conventional therapy	conventional therapy	reduction of wound area, complete closure, and pain
Senet, 2003 (135)	France	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, healing rate, complete closure, infection, and adverse events
Singh, 2018 (136)	India	diabetic	PRP injection + conventional therapy	conventional therapy	complete closure, healing time, amputation, and adverse events
Singh, 2021 (137)	India	pressure	PRP injection + conventional therapy	conventional therapy	reduction of wound area
Sokolov, 2017 (138)	Bulgaria	not defined	topical PRP + conventional therapy	conventional therapy	complete closure
Somani, 2017 (139)	India	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and complete closure
Tsachiridi, 2019 (140)	Greece	pressure	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and healing rate

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Yang, 2017 (141)	China	diabetic	topical PRP + conventional therapy	conventional therapy	healing rate, healing time, infection, pain, and adverse events
Yuvasri, 2020 (142)	India	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and complete closure
Studies included in the systematic review					
Alamdari, 2021 (143)	Iran	diabetic	topical PRP + conventional therapy	conventional therapy	healing time, and amputation
Anitua, 2008 (144)	Spain	mixed	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and infection
Cardenosa, 2017 (145)	Spain	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, pain, and adverse events
Chandanwale, 2020 (146)	India	arterial	PRP injection + conventional therapy	conventional therapy	reduction of wound area
de Oliveira, 2017 (147)	Brazil	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and infection

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Khorvash, 2017 (148)	Iran	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area, infection, pain, and quality of life
Kulkarni, 2019 (149)	India	N/A	topical PRP + conventional therapy	conventional therapy	reduction of wound area, healing time, and adverse events
Milek, 2019 (150)	Poland	venous	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and complete closure
Mohammad, 2017 (151)	Iran	diabetic	topical PRP + conventional therapy	conventional therapy	reduction of wound area
Pires, 2021 (152)	Brazil	venous	topical PRP + conventional therapy	conventional therapy	infection
Pu, 2019 (153)	China	arterial	topical PRP + conventional therapy	conventional therapy	reduction of wound area, healing rate, and amputation
Qin, 2019 (154)	China	diabetic	topical/injected PRP + conventional therapy	conventional therapy	reduction of wound area
Semenic, 2018 (155)	Slovenia	mixed	topical PRP + conventional therapy	conventional therapy	reduction of wound area, and adverse events
Tsai, 2019 (156)	US	mixed	topical/injected PRP	conventional therapy	reduction of wound area

First author, year of publication	Country	Ulcer etiology	Intervention	Control	Outcome
Ucar, 2020 (157)	Turkey	pressure	topical PRP + conventional therapy	conventional therapy	reduction of wound area

PRP-platelet-rich plasma, PPP-platelet-poor plasm

8.1.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata

Our systematic search provided a total of 2747 articles; after duplicate removal, we screened 2002 duplicate-free records. After the title, abstract and full-text selection, we identified 6 RCTs matching our PICO framework (57-62); of these articles, we could use 4 RCTs for our quantitative synthesis (57, 59-61). The summary of the selection process is shown in **Figure 3**.

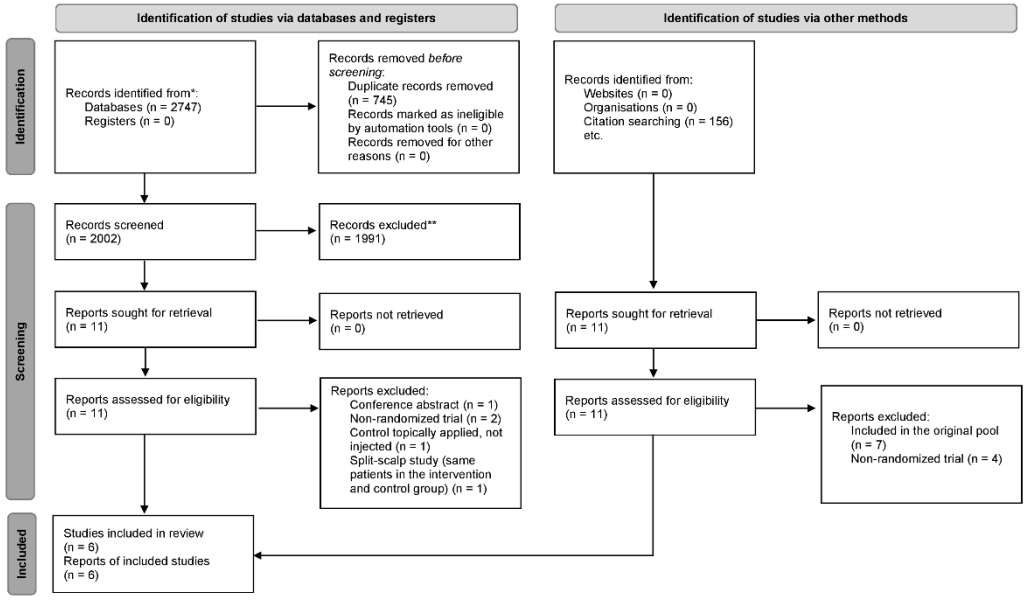


Figure 3. PRISMA Flow Diagram of the screening and selection process for Study III. (68)

Characteristics of the identified RCTs for the systematic review and meta-analysis are detailed in **Table 3**.

Table 3. Main characteristics of the included studies for Study III. (68)

First Author, Year of Publication	Country	Intervention	Control	Administration	Timepoints of evaluation (weeks)*
Studies included in the meta-analysis					
Albalat, 2019 (57)	Egypt	PRP injection (double-spin method)	TrA injection (5 mg/ml)	3-5 sessions, 2-week intervals	12
Fawzy, 2020 (59)	Egypt	PRP injection (single-spin method)	TrA injection (5 mg/ml)	3 sessions, 4-week intervals	12
Hegde, 2020 (60)	India	PRP injection (double-spin method)	TrA injection (10 mg/ml), placebo	3 sessions, 4-week intervals	16
Kapoor, 2020 (61)	India	PRP injection (single-spin method)	TrA injection (10 mg/ml)	4 sessions, 3-week intervals	3, 6, 9, 12^{+}, 24
Studies included in the systematic review					
Balakrishnan, 2020 (58)	India	PRP injection (double-spin method)	TrA injection (10 mg/ml)	3 sessions, 4-week intervals	0, 4, 8, 12
Trink, 2013 (62)	Italy	PRP injection (single-spin method)	TrA injection (2,5 mg/ml), placebo	3 sessions, 4-week intervals	8, 24, 48

* weeks after the first treatment session, $^{+}$timepoint used in our calculations
PRP-platelet-rich plasma, TrA-triamcinolone acetonide

8.2. Results of the quantitative analysis

8.2.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis

8.2.1.1. MBDA score for the assessment of disease activity

The studies that evaluated the utility of the MBDA score for monitoring disease activity examined the correlation between MBDA scores and conventional disease activity measures. Studies using Pearson's correlations could not be included in the meta-analysis due to a lack of statistical power, but are displayed in forest plots for visualization (see the Supplementary Material of the original publication) (66). The results of studies using Spearman's correlation are detailed below.

Six study groups of five publications (86, 88, 95, 105, 106) with a total of 667 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP (COR = 0.45, CI: 0.28-0.59; I^2 = 71.0%) (see **Figure 4A**). Excluding conference abstracts from the analysis, similar results were observed; four publications (86, 95, 105, 106) with a total of 324 subjects demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-CRP (COR = 0.46, CI: 0.10-0.72; I^2 = 81.0%) (66).

Assessing the correlations of baseline MBDA scores with baseline DAS28-ESR, a moderate correlation was found based on the results of two publications with a total of 127 subjects (COR = 0.55, CI: 0.19-0.78; I^2 = 0.0%) (see **Figure 4A**) (66).

Further metrics associated with disease activity (CRP, ESR, SJC28, TJC28, PtGA, CDAI, PDUS) showed low and moderate correlations, and are detailed in the Supplementary Material of the original publication (66).

Six study groups of four publications (88, 95, 105, 106) with a total of 287 subjects revealed a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP (COR = 0.44, CI: 0.28-0.57; I^2 = 70.0%) (see **Figure 4B**). After the exclusion of conference abstracts from the analysis, three articles (95, 105, 106) with a total of 137 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP (COR = 0.38, CI: -0.02-0.68; I^2 = 18.0%) (66).

The only study investigating the correlations of follow-up MBDA scores with follow-up DAS28-ESR found a moderate correlation (COR=0.49, CI: 0.22-0.69) between MBDA score and DAS28-ESR (**Figure 4B**) (66, 106).

Other parameters associated with disease activity (ESR, SJC28, TJC28, PtGA, PDUS) showed low-to-moderate correlations and are detailed in the Supplementary Material of the original publication (66).

Ten study groups of six articles (31, 87, 88, 95, 106, 109) with a total of 698 subjects demonstrated a moderate correlation between the change in MBDA score and the change of DAS28-CRP (COR = 0.40, CI: 0.32-0.48; I^2 = 19.0%). Seven study groups of six articles (84, 94, 97, 106, 108, 109) with a total of 543 subjects exhibited a moderate correlation between the change of MBDA score and the change of DAS28-ESR (COR = 0.56, CI: 0.51-0.60; I^2 = 71.0%) (see **Figure 4C**). Excluding conference abstracts from the analysis, similar results were recorded. The change of MBDA moderately correlates with the change of DAS28-CRP (COR = 0.43, CI: 0.25-0.59; I^2 = 47.0%) based on the results of six study groups of four publications (31, 95, 106, 109) with a total of 418 subjects, and with DAS28-ESR (COR = 0.52 CI: 0.43-0.60; I^2 = 0.0%) based on the results of four publications (94, 106, 108, 109) with a total of 298 subjects (66).

Further parameters linked to disease activity (CRP, CDAI, SDAI, HAQ) showed low-to-moderate correlations and are detailed in the Supplementary Material of the original publication (66).

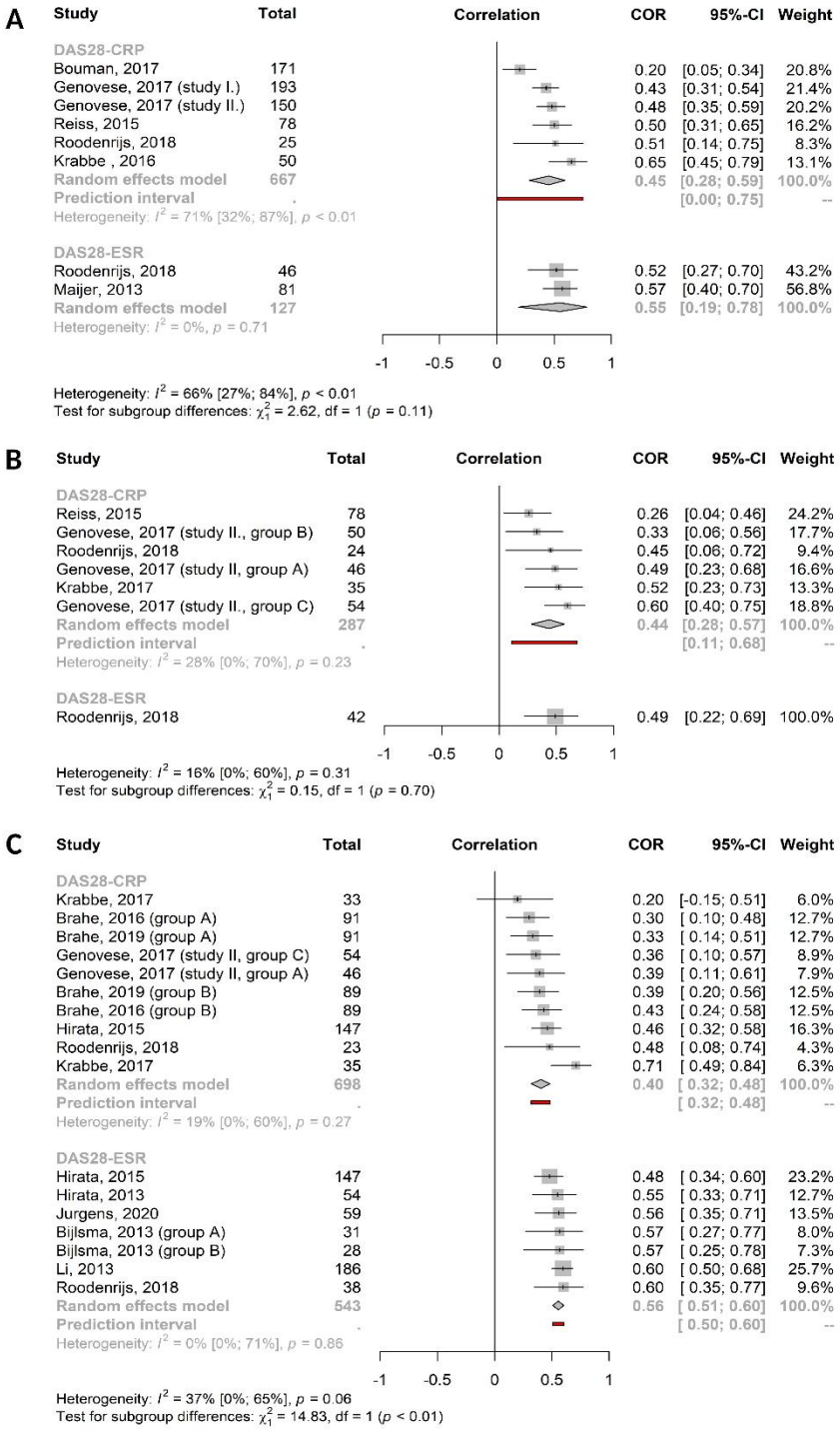


Figure 4. Forest plot for the correlation of MBDA score with DAS28-CRP/ESR **(A)** Forest plot for the correlation of baseline MBDA score with baseline DAS28-CRP/ESR **(B)** Forest plot for the correlation of follow-up MBDA score with follow-up DAS28-CRP/ESR **(C)** Forest plot for the change of baseline MBDA score with the change of DAS28-CRP/ESR (66)

8.2.1.2. MBDA score for the assessment of radiographic progression

Three study groups of three articles with a total of 22 subjects showed a low correlation between baseline MBDA score and baseline SvdH score (COR = 0.13, CI: -0.25-0.47; I^2 = 79.0%), and five study groups of four articles with a total of 307 subjects demonstrated a low correlation between the change of MBDA score and the change of SvdH score (COR = 0.08, CI: -0.06-0.21; I^2 = 79.0%) as well (see **Figure 5)** (66).

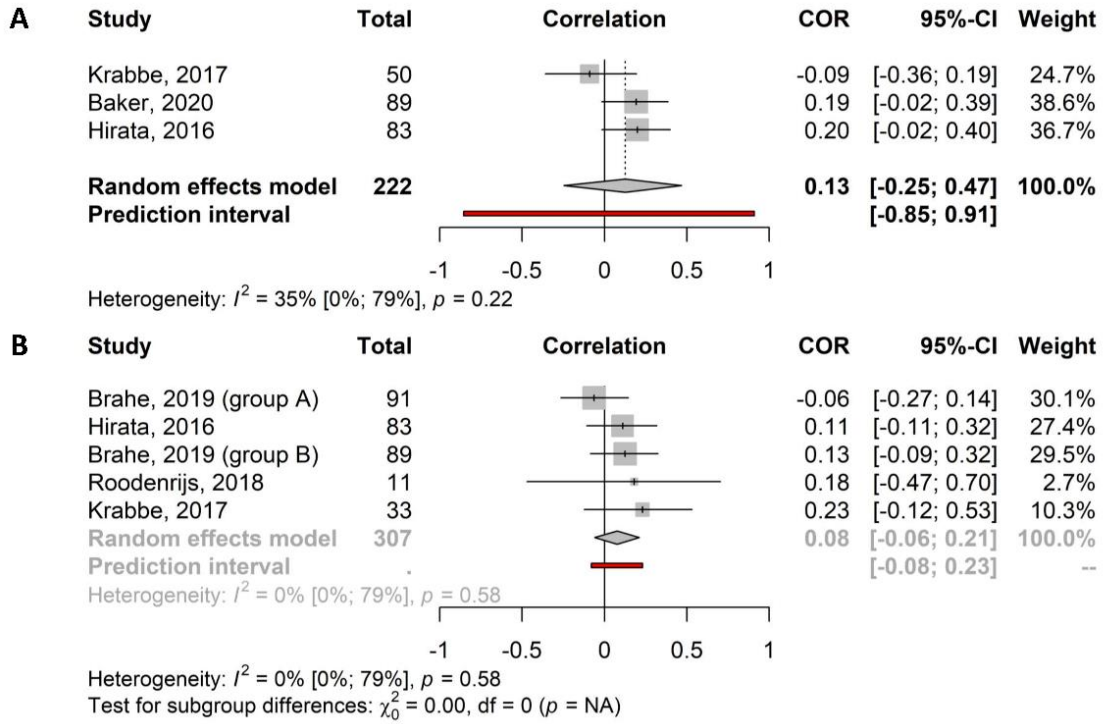


Figure 5. Forest plots for the correlations of MBDA score with SvdH score **(A)** Forest plot for the correlation of baseline MBDA score with baseline SvdH score **(B)** Forest plot for the correlation of the change of MBDA score with the change of SvdH score (66)

When evaluating the predictive value of MBDA score for radiographic progression, three studies (30-32) with a total of 481 subjects showed that the odds of radiographic progression are significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) (OR = 1.03, CI: 1.02-1.05; I^2 = 10.0%) (see **Figure 6A**). In contrast, the odds of progression for patients with a high baseline DAS28-CRP were not significantly higher than for patients with a low baseline DAS28-CRP (OR = 1.12, CI: 0.91-1.37; I^2 = 0.0%) (see **Figure 6B**) (66).

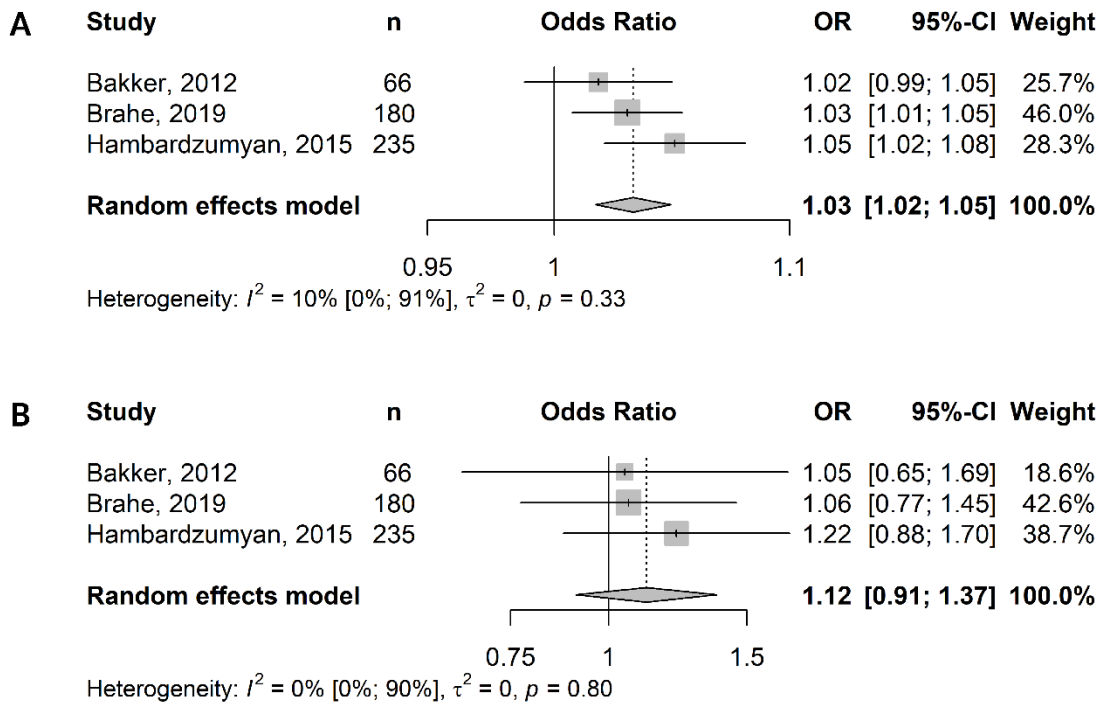


Figure 6. Forest plots for the predictive value of MBDA score and DAS28-CRP. for radiographic progression (**A**) Forest plot for the predictive value of MBDA score (**B**) Forest plot for the predictive value of DAS28-CRP (66)

The characteristics of the studies evaluating the predictive value of the MBDA score and DAS28-CRP for radiographic progression are detailed in **Table 4**.

Table 4. Characteristics of studies evaluating the predictive value of MBDA score and DAS28-CRP for radiographic progression (66)

First author, year of publication	Time of evaluating RP	Definition of RP	Low MBDA score	High MBDA score	Low DAS28-CRP	High DAS28-CRP
Studies included in the meta-analysis						
Bakker, 2012 (30)	2 years	>0 units increase of SvdH score	<30	>44	≤2.7	>2.7
Brahe, 2019 (31)	1 year	>2 units increase of SvdH score	<30	>44	≤5.1	>5.1
Hambardzumyan, 2015 (32)	1 year	>5 units increase of SvdH score	<30	>44	≤2.7	>4.1
Studies included in the systematic review						
Bouman, 2017 (86)	1.5 years	>0.5 units increase of SvdH score	<30	>44	<2.7	>4.1
Hirata, 2016 (93)	1 year	>3 units increase of SvdH score	<30	>44	≤3.2	>5.1
Krabbe, 2017 (95)	0.5, 1 year	N/A	<30	>44	≤3.2	>5.1
Li, 2016 (98)	1 year	>3 units increase of SvdH score	<30	>44	≤2.67	>4.09
Markusse, 2014 (33)	1 year	>0.5 units increase of SvdH score	<30	>44	≤2.4	>3.7

N/A-no data available; RP-radiographic progression; SvdH score- Sharp/van der Heijde score; MBDA score- Multi-biomarker Disease Activity score; CRP-C-reactive protein; : DAS28-CRP-Disease Activity Score with 28-joint count

8.2.2. Study II. – Investigating the efficacy of PRP in chronic wound management

8.2.2.1. Complete closure

Thirty-three study groups of 29 RCTs with a total of 2,198 wounds showed that the odds for complete closure were significantly higher in the PRP group than in the control group (OR=5.32; CI: 3.37; 8.40; I^2=58%) (see **Figure 6**) (67).

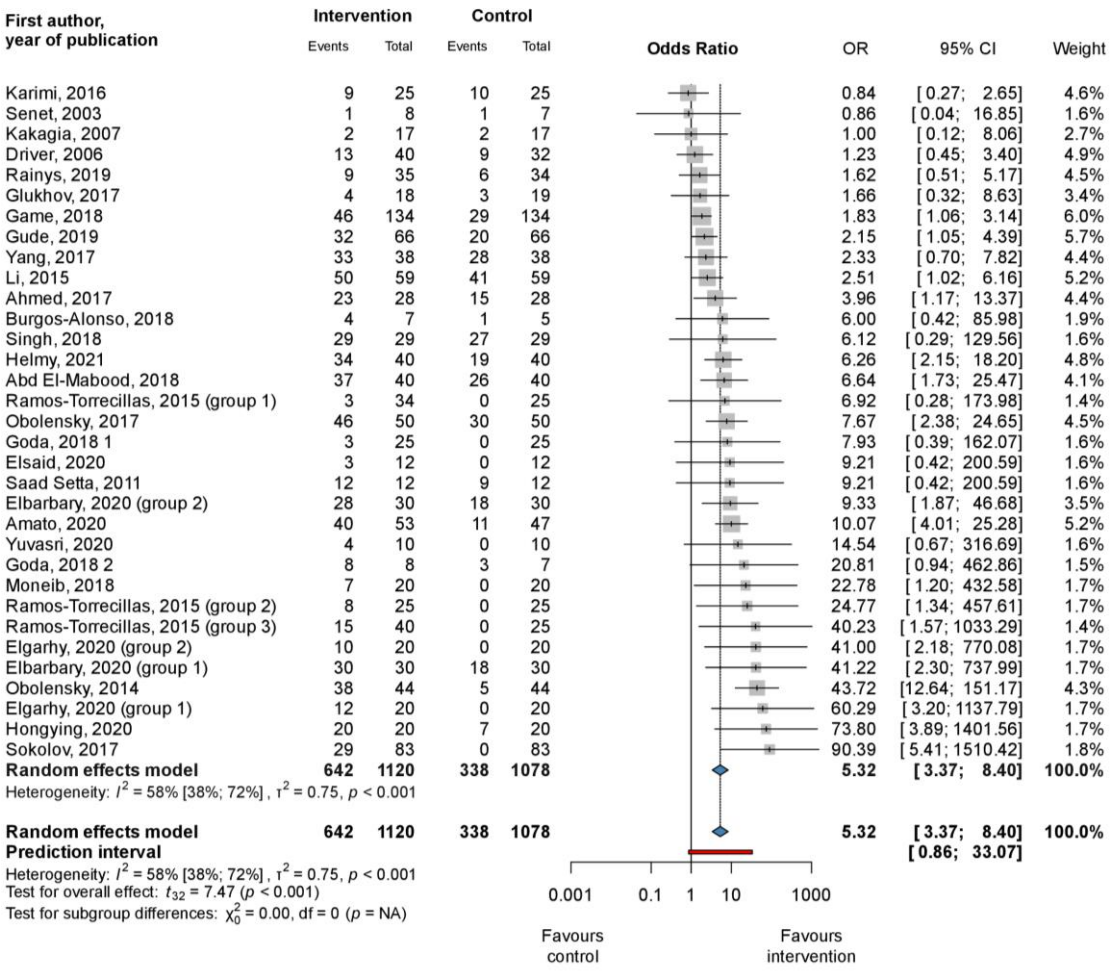


Figure 6. Forest plot for complete closure, platelet-rich plasma compared to conventional ulcer therapy (67)

The visualized results of the subgroup analysis are detailed in the Supplementary Material of the original publication (67).

When subgrouping was based on ulcer etiologies, the odds for complete closure were significantly higher in the PRP group than in the control group, both in diabetic foot ulcers

(OR=2.26; CI: 1.50; 3.41; I^2=12.0%) as well as venous leg ulcers (OR=8.02; CI: 3.63; 17.71; I^2=10.0%). The test for subgroup difference showed a significant difference between the two groups (χ^2=9.88; df=1; p=0.002), the odds for complete closure were significantly higher in venous ulcers than in the diabetic foot ulcers treated with PRP (67).

Subgrouping based on the way of the application of PRP showed similar results. The odds for complete closure were significantly higher both in the topically applied (OR=4.74; CI: 2.87; 7.83; I^2=60%) and injected (OR=9.42; CI: 3.32; 26.76; I^2=0%) PRP groups than in the control group, with no significant subgroup difference (χ^2=2.34; df=1; p=0.126) (67).

The odds for complete closure were significantly higher in the PRP group than in the control group in the short (OR=6.03; CI: 3.21; 11.33; I^2=47%), medium (OR=3.38; CI: 1.15; 9.89; I^2=73%), and long (OR=8.24; CI: 1.66; 40.87; I^2=0%) follow-up categories as well with no significant subgroup differences (χ^2=2.50; df=3; p=0.476) (67).

8.2.2.2. Reduction of wound area

Pooled SMDs from 18 study groups of 16 RCTs with a total of 1,062 wounds showed a significant difference between the post-treatment wound size of the PRP and the control groups (SMD = -1.21, CI: -1.74; -0.68; I^2 = 92.5%), the PRP group showing greater improvement (see **Figure 7**) (67).

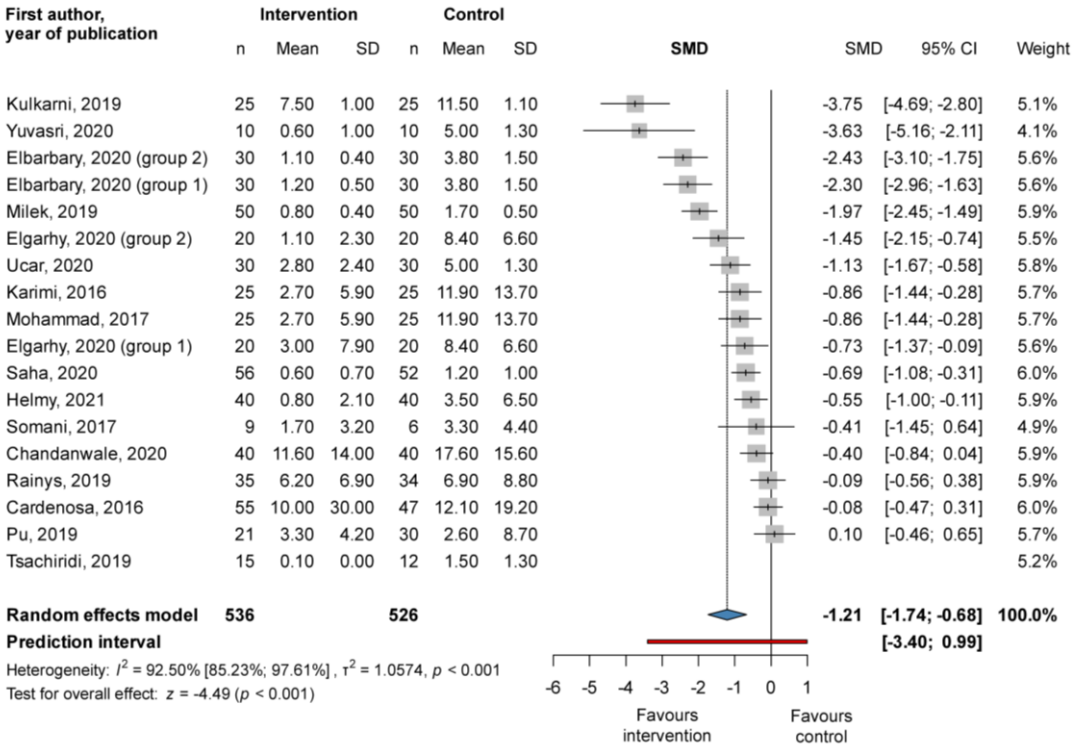


Figure 7. Forest plot for the reduction of wound area, platelet-rich plasma compared to conventional ulcer therapy (67)

The visualized results of the subgroup analysis are detailed in the Supplementary Material of the original publication (67).

Subgrouping based on ulcer etiology, application method, and follow-up length showed similar results (67). The post-treatment wound size was significantly smaller in the PRP group than in the control group in diabetic (SMD = -0.68, CI: -1.31; -0.06; I^2 =93.64%), venous (SMD = -1.26, CI: -2.28; -0.24; I^2=90.76%), topically applied (SMD = -0.94, CI: -1.43;-0.46; I^2=91.26%), and injected (SMD =-1.03, CI: -1.79;-0.26; I^2 =86.63%) subgroups, as well as in the short follow-up subgroup (SMD = -1.00, CI: -1.64;-0.35; I^2 = 89.41%). However, the difference between the PRP and the control groups was not significant in the medium (SMD = -1.38, CI: -2.96; 0.19; I^2 = 54.51%), and long (SMD = -0.63, CI: -1.64; 0.37; I^2 = 93.88%) follow-up groups. No significant subgroup differences were recorded (67).

8.2.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata

8.2.3.1. Reduction of SALT score

Two studies evaluated the post-treatment SALT score 12 weeks after the first treatment session (57, 59), one study 16 weeks after the first treatment session (60), and one at multiple timepoints: weeks 3, 6, 9, 12, and 24 (61) (see Table 1). We used the SALT score of the 12th week evaluation of this study for our meta-analytical calculations. Pooled MDs from four RCTs with a total of 201 subjects did not show a significant difference in mean change in SALT scores between the PRP and TrA groups (MD = - 2.04, CI: -4.72-0.65; I^2 = 80.4%, p = 0.14) (see **Figure 8**) (68).

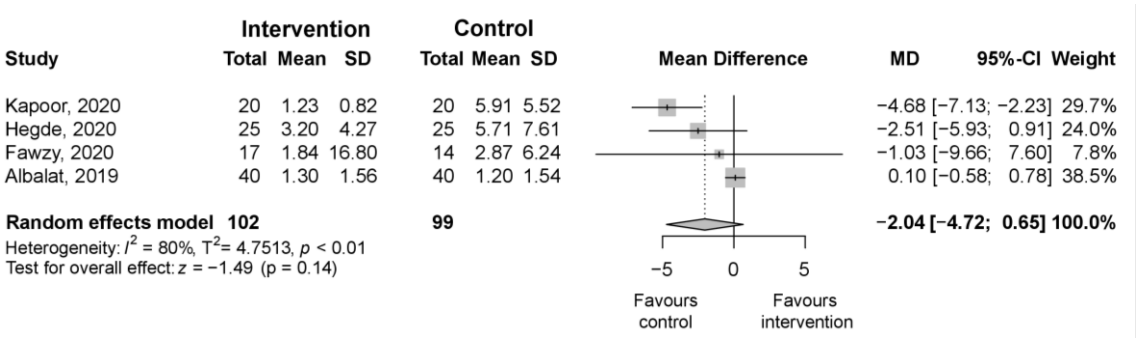


Figure 8. Forest plot for mean decrease of SALT score, platelet-rich plasma (PRP) compared to triamcinolone acetonide (TrA) (68)

8.3. Qualitative analysis

The results of the studies that could not be included in the quantitative analyses are detailed in the discussion and in the systematic review sections of the original publications (66-68).

8.4. Quality assessment

8.4.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis

The majority of the outcomes of the studies included in the meta-analysis (n=79) and the systematic review (n=37) were rated as having a low or moderate risk of bias. The risk of bias was low in 35 outcomes of the studies included in the meta-analysis and 29 outcomes

of studies included in the systematic review; moderate in 32 outcomes of the studies included in the meta-analysis and five outcomes of studies included in the systematic review; and a high risk of bias was determined in 12 outcomes of studies included in the meta-analysis and three outcomes of studies included in the systematic review. Common methodological limitations across studies were attrition rates, study confounding, and statistical analysis and reporting.

The quality assessment scores for all outcomes are shown in the supplementary material of the original publications (66).

8.4.2. Study II. – Investigating the efficacy of PRP in chronic wound management

None of the studies included in the meta-analysis was at high risk of bias. In 30 studies (111-114, 119, 122, 123, 125, 127-130, 132, 133, 135, 137-142, 144, 146, 149-151, 154-157) the 'randomization process' domain, in 12 studies (112, 122, 124, 125, 127, 129, 133, 136, 139, 151, 154, 157) the 'deviations from intended interventions' domain, in one study (144) the 'missing outcome data' domain, in five studies (124, 125, 133, 151, 154) the 'measurement of the outcome' domain, and in eight studies (111, 122, 131, 132, 136, 139, 142, 147) the 'selection of the reported result' domain were rated as 'some concerns' for our primary outcome.

The results of the risk of bias assessment and the Summary of Findings table can be found in the supplementary material of the original publication (67).

8.4.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata

None of the studies included in the meta-analysis were at high risk of bias. In 3 articles the randomization process (57, 59, 61) and in two articles the measurement of the outcome (60, 61) were ranked as "some concerns". Deviation from the intended intervention, missing outcome data, and selection of the reported results domains were at low risk of bias. The quality of evidence was low for the primary outcome.

The results of the risk of bias assessment are detailed in the supplementary material of the original publication (68).

9. DISCUSSION

9.1. Summary of findings, international comparisons

Given the growing therapeutic advancements in dermatology and rheumatology, there is an increasing focus on not only assessing the effectiveness of novel treatments but also on monitoring disease activity to determine the most suitable treatment for each individual based on their specific disease status.

As that the treat-to-target therapeutic approach is essential for the treatment of RA and necessitates close monitoring of disease activity, the importance of objective score systems is indisputable. Our objective in conducting a systematic review and meta-analysis was to evaluate the effectiveness of the MBDA score in assessing disease activity, radiographic progression, remission, and relapse. Through this analysis, we aimed to provide valuable insights to support clinical decision-making and determine the suitability of the MBDA score in practical clinical settings.

We observed moderate correlations when analyzing the correlations between the MBDA score and conventional disease activity measures using a random-effects model, consistent with the findings of the meta-analysis of Johnson *et al.* (56). Both DAS28-CRP and DAS28-ESR, the gold standard DAMs in RA, showed moderate correlations with MBDA at baseline and follow-up, as well as in the change of DAS28-CRP and DAS28-ESR with the change of MBDA. Other DAMs detailed in the supplement of the original publication showed weaker correlations with MBDA score, except for CRP, as the correlation between the MBDA score and CRP alone was found to be stronger than with DAS28-CRP. (66). It is not surprising that the MBDA score deviates from conventional disease activity measures, as it does not incorporate clinical assessment results. However, since the purpose of the MBDA score is to complement rather than replace conventional disease activity measures, its deviation from such measures can even offer advantages (158).

Considering that the MBDA score, in addition to the inflammatory markers found in currently-used disease activity measures like CRP, includes markers indicating cartilage and bone damage such as MMP-3, there is a realistic possibility that the MBDA score may surpass conventional measures in accurately predicting radiological progression

(159). Based on the findings of our meta-analysis, it appears that the MBDA score can serve as an independent predictor of radiological progression. Our results indicate a significant increase in the odds of radiographic progression for patients with a high baseline MBDA score compared to those with a low baseline MBDA score. In contrast, there was no significant difference in radiographic progression between low- and high-baseline DAS28-CRP groups. It should be noted, however, that the included studies utilized consistent cutoff values for defining high and low MBDA scores, while different cutoff values were employed for defining DAS28-CRP subgroups. This discrepancy in cutoff values may have an impact on the results, underscoring the need for further investigation in this area. Moreover, our analysis revealed a weak correlation between the SvdH score and the MBDA score at both baseline and follow-up, suggesting that caution should be exercised when interpreting these data. These findings align with the results of the studies included in our systematic review and are consistent with the previous meta-analysis by Curtis *et al.* and the systematic review by Abdelhafiz *et al.* (160, 161).

While the efficacy of the newly emerging biologics is indisputable, the significance of alternative treatments that are cost-effective, repeatable, and more widely available should not be overlooked. PRP therapy offers ease of application and demonstrates versatility in addressing various dermatological conditions, thereby providing a potential treatment option for a wide range of patients.

The management of chronic ulcers is a serious problem worldwide and places a heavy burden on the health care system. On the basis of our systematic review and meta-analysis, PRP is an effective add-on treatment modality to enhance wound healing. The PRP group demonstrated significantly higher odds of achieving complete wound closure compared to the control group. Additionally, PRP treatment led to a significantly greater reduction in wound area when compared to conventional therapy.

Subgroup analyses were conducted in order to reduce heterogeneity, and these analyses yielded similar results while also highlighting differences based on ulcer etiologies and PRP application methods. Injected PRP appeared to have a greater impact on improvement compared to topically applied PRP. However, it is important to exercise caution when drawing conclusions from this subgroup analysis due to the relatively small sample size. Regarding ulcer etiologies, PRP demonstrated superiority over conventional

therapy in terms of complete closure and reduction of wound area for both diabetic and venous ulcers, however, better outcomes were observed in the venous ulcer group. This phenomenon could be attributed to the fact that diabetic ulcers tend to be more challenging to heal. Additionally, the higher frequency of injected PRP administration in the venous ulcer group may have contributed to the better results observed in this subgroup. Furthermore, the effectiveness of PRP was demonstrated across various follow-up times, including short, medium, and long durations, in achieving complete closure of the ulcers.

PRP also showed promising results in the treatment of AA. The studies included in our systematic review and meta-analysis all showed a significant decrease in SALT score in in the PRP and TrA groups as well (57-62). Pooled MDs from the four RCTs did not show a significant difference in mean change in SALT score between the PRP and TrA groups. Although we could not conduct a meta-analysis comparing PRP to placebo, the included studies all concluded the superiority of PRP treatment (60, 62). The obtained results provide evidence of the effectiveness of PRP as an alternative steroid-free treatment approach, however, it is essential to consider various factors that might have influenced these outcomes, including variations in TrA dosages and differences in the duration of follow-up periods. The strength of the effect of TrA can be dose-dependent: RCTs investigating the optimal dilution of TrA have revealed that the 10 mg/ml dose elicits the most favorable therapeutic response. Nonetheless, considering the escalating risk of adverse effects associated with increasing doses, it is recommended to commence treatment with lower doses. (162, 163). Two of the four studies included in our meta-analysis used 5 mg/ml TrA, and two studies used 10 mg/ml TrA as a comparator (61). The decrease in SALT score was higher in the studies using a higher dose of TrA, however, one of the latter studies registered atrophy in five cases, assumably due to the higher doses of TrA. In contrast, PRP can be utilized for an unlimited number of treatment sessions without heightening the risk of adverse effects (57, 58, 60-62).

9.2. Strengths

There are several strengths of our studies. We implemented a rigorous methodology to achieve the highest quality of evidence and provide a structured analysis of the outcomes discussed in the literature. We provide a comprehensive summary on the utility of MBDA

score for the monitoring of RA disease activity and also the predictive and discriminative value of MBDA socre for radiographic progression, therapy response, remission and relapse. We summarized the latest evidence including only RCTs on the wound healing properties of PRP for the management of chronic wounds assessing the most objective outcome measure, the change of the wound area; and also on the efficacy of PRP in the treatment of AA.

9.3. Limitations

Our main limitation is the heterogeneity of the populations. In our first study, a wide range of anti-rheumatic drugs was used in the included publications, with potentially varying effects on the MBDA score: by inhibiting receptor binding, the IL-6 receptor-blocker tocilizumab may increase the serum level of IL-6, thus affecting the change in MBDA score via one of the 12 included biomarkers (105). TNF inhibitors can potentially have an indirect impact on the MBDA score as well, by reducing the serum level of TNF-alpha. Hirata *et al.* compared anti-TNF-alpha and anti-TNF-alpha-receptor drugs, revealing no significant difference between the two groups, however, additional research is required to evaluate the influence of targeted therapies on the serum levels of the biomarkers incorporated in the MBDA score, and consequently, their impact on the alteration of the MBDA score (93). Moreover, the utilization of varying follow-up times to evaluate disease activity can contribute to increased heterogeneity. In our second study, the principal factor for the substantial heterogeneity is likely the divergence in control groups, encompassing a wide array of dressings utilized as part of conventional therapy. In our third study, apart from the limited sample size, the heterogeneity could be attributed to the different PRP preparation methods employed across the included studies. Previous research has demonstrated the superiority of the double-spin preparation method over the single-spin method, which could potentially contribute to the observed heterogeneity (164, 165).

10. CONCLUSION

The utilization of the MBDA score in the management of RA patients holds significant value, serving as a valuable tool for monitoring disease activity and predicting radiological progression. However, to further enhance our understanding of the utility of the MBDA score and the specific contributions of individual biomarkers in disease activity monitoring, additional studies are warranted. These future investigations will provide valuable insights and contribute to the ongoing advancement of RA patient care

PRP has demonstrated both safety and efficacy as a modality for promoting wound healing. Its integration into clinical practice has the potential to transform it into a widely utilized and valuable tool. By leveraging the benefits of PRP, patients' quality of life can be enhanced while simultaneously reducing the healthcare burden associated with wound management.

PRP offers a promising alternative as a topical steroid-free treatment option for AA. While no significant difference was observed between PRP and conventional treatment (TrA), it is imperative to conduct further high-quality RCTs to better evaluate the efficacy of PRP and enhance the strength of the existing evidence.

11. IMPLEMENTATION FOR PRACTICE

The early application of research results in clinical practice has an unequivocal importance (166, 167).

By implementing the use of MBDA score in clinical practice, the personalized treatment of RA patients could be further improved. Applied together with the currently used DAMs, MBDA score would be an objective addition that could help clinicians' decision-making regarding therapy modifications. As a promising predictor of radiographic progression, MBDA score could also influence initial therapeutic choices following the establishment of the diagnosis, urging the earlier use of highly potent therapies in case of a potentially higher chance for radiographic progression.

Due to its wound healing properties, platelet-rich plasma could become a widely used, valuable tool in chronic wound management. PRP can be administered topically or intralesionally, and it can also be used in conjunction with a diverse range of smart dressings. This versatility allows for personalized treatment approaches, offering physicians a multitude of options to tailor the therapy according to individual patient needs. As a steroid free therapeutic modality for treatment of AA, PRP can be used in a virtually unlimited number of treatment sessions without increasing the risk of steroid-specific adverse effects (57, 58, 60-62). The adverse effects associated with TrA treatment, such as atrophy, teleangiectasiae, and hypopigmentation, can pose particular challenges when treating the facial region. Given that PRP is safely employed in facial rejuvenation procedures, it may present an optimal therapeutic option for localized AA affecting the face (55, 168, 169). In the context of the facial region and extensive cases of AA, employing PRP in conjunction with microneedling or fractional carbon dioxide laser treatment may offer a more tolerable way of administration (170).

12. IMPLEMENTATION FOR RESEARCH

To facilitate a more comprehensive analysis and promote the adoption of the MBDA score in daily clinical practice, future studies should consider including a larger patient cohort, standardizing the follow-up duration for evaluation, and establishing consistent cut-off values of DAS28-CRP for defining remission. These measures would enhance the assessment of the MBDA score's utility and provide a more robust foundation for its implementation in clinical settings.

To enable further comprehensive analysis on the efficacy of PRP in chronic wound management, it is important for future studies to report their outcomes in a standardized manner. Specifically, the change in wound size should be consistently recorded as the most objective measure of PRP efficacy, with baseline and post-treatment wound area always reported. However, there is a need for better reporting guidelines that include detailed descriptive statistics such as median and interquartile range in addition to mean and standard deviation. Moreover, the methods used to measure wound size can introduce bias. Chronic wounds commonly affect the leg, and simple photographic measurements may not account for the overall leg circumference affected by the wound. Additionally, assessing wound size solely based on width and length can yield inaccurate results due to the asymmetrical nature of ulcer areas. We suggest that a precise measurement approach involves tracing the wound outline on carbon paper, which can be digitalized for further calculations. In addition to baseline and post-treatment wound area, the number of completely closed wounds is a critical outcome measure that demonstrates treatment efficacy and should always be reported.

Regarding the use of PRP in AA, the limited evidence warrants further high-quality RCTs to accurately assess its efficacy. The implementation of objective and comparable outcome measurements beyond the SALT score could help evaluate complete remission, recurrence rates, and adverse effects more effectively. This would contribute to a better understanding of the benefits and drawbacks of each treatment modality and enable future systematic analyses using these parameters to enhance the quality of the existing evidence. Furthermore, future RCTs should focus on comparing PRP with different doses of TrA. While higher doses of TrA may lead to greater improvement, they can also increase the risk of adverse effects (162, 163). Opting for a steroid-free treatment such as

PRP as the primary choice can offer potential benefits, even if the rate of improvement is relatively slower. Implementing longer follow-up protocols extending beyond 4 months would allow for the observation of additional differences between the two treatment modalities. This extended duration would enable a more comprehensive assessment of complete remission and recurrence rates, providing a clearer understanding of the relative effectiveness of each approach.

13. IMPLEMENTATION FOR POLICYMAKERS

It is imperative for policymakers to emphasize the importance of disease monitoring and the integration of new therapies into healthcare systems. By recognizing the value of disease monitoring, policymakers can support its implementation and encourage healthcare facilities to adopt effective monitoring systems. This entails allocating resources to ensure the availability and accessibility of novel therapies in various healthcare settings, enabling patients to benefit from the latest advancements. Policymakers can also play a crucial role in revising and updating guidelines to reflect emerging evidence and best practices. By actively engaging in policy decisions, policymakers can facilitate the necessary changes to enhance disease monitoring and promote the integration of new therapies into clinical practice.

14. FUTURE PERSPECTIVES

Looking ahead, the future holds promising opportunities for the utilization of MBDA score and PRP. The adoption of objective disease monitoring systems, such as the MBDA score or similar methodologies, presents compelling possibilities within the realm of rheumatology. Furthermore, with its regenerative properties, PRP shows potential for delivering therapeutic benefits in a wide range of diseases.

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Systematic review and meta analysis

Clinical science

Multibiomarker disease activity score: an objective tool for monitoring rheumatoid arthritis? A systematic review and meta-analysis

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Abstract

Objectives: The multibiomarker disease activity (MBDA) score is an objective tool for monitoring disease activity in RA. Here we report a systematic review and meta-analysis of the clinical value of the MBDA score in RA.

Methods: We performed a systematic literature search in five medical databases—MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Scopus and Web of Science—from inception to 13 October 2021. Original articles reporting on the performance of the MBDA score's correlation with conventional disease activity measures or the predictive and discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse were included.

Results: Our systematic search provided a total of 1190 records. After selection and citation searches, we identified 32 eligible studies. We recorded moderate correlations between MBDA score and conventional disease activity measures at baseline [correlation (COR) 0.45 (CI 0.28, 0.59), $I^2 = 71.0\%$ for the 28-joint DAS with CRP (DAS28-CRP) and COR 0.55 (CI 0.19, 0.78), $I^2 = 0.0\%$ for DAS28 with ESR] and at follow-up [COR 0.44 (CI 0.28, 0.57, $I^2 = 70.0\%$ for DAS28-CRP) and found that the odds of radiographic progression were significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) [OR 1.03 (CI 1.02–1.05), $I^2 = 10.0\%$].

Conclusion: The MBDA score might be used as an objective disease activity marker. In addition, it is also a reliable prognostic marker of radiographic progression.

Keywords: RA, MBDA score, disease activity monitoring, radiographic progression

Rheumatology key messages

- The multibiomarker disease activity (MBDA) score is an objective tool for the monitoring of rheumatoid arthritis.
- The MBDA score showed moderate correlations with conventional disease activity measures.
- The MBDA score may be an independent predictor of radiological progression.

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Introduction

RA is a systemic autoimmune disease affecting ≈0.5–1% of the population [1]. According to the EULAR recommendations, the aim of the therapy in RA is to achieve remission, or at least low disease activity [2]. Early treatment with DMARDs and a treat-to-target treatment strategy are recommended by current guidelines and are considered to be the optimal way to prevent long-term functional decline by minimizing cartilage and bone damage [3–5].

Given that the treat-to-target therapeutic approach requires close monitoring of disease activity, the need for reliable, objective disease activity measures (DAMs) is undeniable. The currently available, widely used options for monitoring disease activity and progression are either subjective or non-specific: the 28-joint DAS (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) all include subjective assessments of disease activity by the patient and/or the provider [6–8]. Although non-specific inflammatory markers such as CRP and ESR are used to calculate the DAS28 and SDAI, the incorporation of a scoring system based on the combination of inflammatory markers and additional biomarkers could further objectify the measurement of disease activity. Structural damage, a major factor defining the course of the disease, can be assessed by radiography and quantified with the Sharp–van der Heijde (SvdH) scoring system [9]. There are several known risk factors for radiographic progression, including high disease activity monitored by non-specific inflammatory markers such as CRP, RF and ACPA seropositivity [10]. However, RF and ACPA are not suitable for monitoring disease activity [11].

The multibiomarker disease activity (MBDA) score system is an algorithm based on the serum level of 12 biomarkers [IL-6, TNF receptor type 1 (TNFR1), vascular cell adhesion molecule 1 (VCAM-1), epidermal growth factor (EGF), vascular EGF A (VEGF-A), YKL-40, matrix metalloproteinase-1 (MMP-1), MMP-3, CRP, serum amyloid A (SAA), leptin and resistin], resulting in a scale from 0 to 100 [12]. The MBDA score presents an objective disease monitoring system and thus may contribute to personalized therapeutic plans conforming to modern medical views. In addition to monitoring disease activity, the MBDA score may also predict radiographic progression [13–16].

Several studies have evaluated the utility of the MBDA score and a meta-analysis has been conducted on the correlation of the MBDA score with conventional DAMs; however, the predictive and discriminative values of the MBDA score has yet to be analysed in a comprehensive manner [17]. Here we report a systematic review and meta-analysis of the clinical value and utility of the MBDA score for monitoring RA by determining the correlation of the MBDA score with conventional DAMs and the predictive and the discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse.

Materials and methods

Our systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [18]. The recommendations of the Cochrane Prognosis Methods Group [19] were followed and the review protocol was registered on PROSPERO.

We performed a systematic literature search of five medical databases—MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Scopus and Web of Science—from inception to 13 October 2021. Original articles reporting on the performance of the unadjusted MBDA score's correlation with conventional DAMs or the predictive and discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse were included in the systematic review and meta-analysis. Single case reports were excluded.

RA was defined by the ACR 1987 [20] and ACR/EULAR 2010 [21] classification criteria. Radiographic progression was measured by the change in the SvdH score per time unit, therapy response was defined by the EULAR criteria for therapy response and remission and relapse were defined by the different cut-off values of conventional DAMs.

Study selection and data extraction were carried out by two independent reviewers and disagreements were resolved by a third reviewer. The quality assessment of the outcomes was carried out separately by two reviewers using the Quality In Prognosis Studies (QUIPS) tool for assessing the risk of bias [22].

Further details regarding the search and selection strategy, data extraction, data synthesis and analysis are detailed in the supplementary methods available at *Rheumatology* online.

Results

Search and selection and characteristics of the included studies

Our systematic search provided 1190 records; after duplicate removal we screened 708 duplicate-free records. Thirty eligible studies [13–16, 23–48] were identified after title, abstract and full-text selection and two additional studies [49, 50] during citation search. Of these studies, we included 24 in the quantitative analysis [13–15, 23–25, 27–29, 31, 32, 34–38, 40, 41, 43, 44, 46, 47, 49, 50] and 8 in the qualitative analysis [16, 26, 30, 33, 39, 42, 45, 48]. The summary of the selection process is shown in Fig. 1. We conducted a meta-analysis assessing the correlation of MBDA scores with conventional DAMs and the predictive value of the MBDA score for radiographic progression. Studies that could not be included in the meta-analysis and reports of other outcomes are detailed in the systematic review.

The characteristics of the identified studies for the systematic review and meta-analysis and the patient characteristics of included studies are detailed in Table 1 and Supplementary Table S1, available at *Rheumatology* online.

MBDA score for the assessment of disease activity

Studies assessing the utility of the MBDA score for disease activity monitoring calculated the correlation of MBDA scores with conventional DAMs. Studies using Pearson's correlations could not be included in the meta-analysis due to a lack of statistical power, but are displayed in forest plots for visualization (see Supplementary Figs S1–S3, available at *Rheumatology* online). The results of studies using Spearman's correlation are detailed below.

Six study groups in five publications [27, 29, 36, 46, 47] with a total of 667 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP [correlation (COR) 0.45 (CI 0.28, 0.59), $I^2 = 71.0\%$] (see

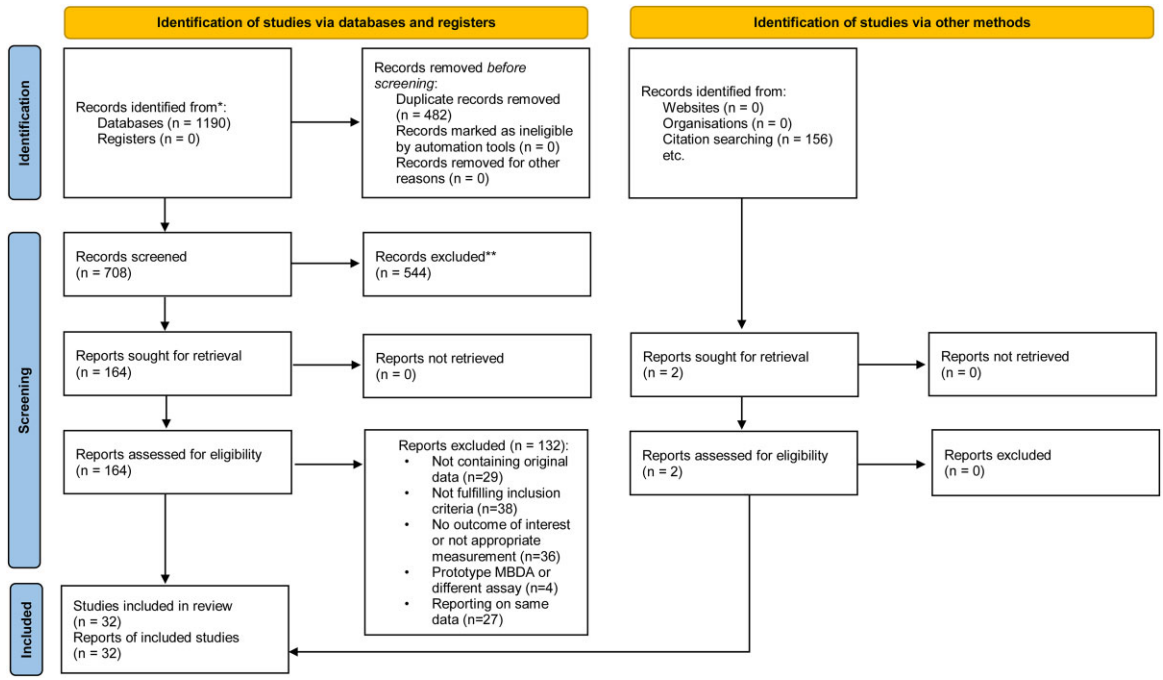

Figure 1. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines [18]

Fig. 2A). Excluding conference abstracts from the analysis, similar results were observed; four publications [27, 36, 46, 47] with a total of 324 subjects demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-CRP [COR 0.46 (CI 0.10, 0.72), $I^2 = 81.0\%$].

Assessing the correlations of baseline MBDA scores with baseline DAS28-ESR, a moderate correlation was found based on the results of two publications with a total of 127 subjects [COR 0.55 (CI 0.19, 0.78), $I^2 = 0.0\%$] (see Fig. 2A).

Further metrics associated with disease activity [CRP, ESR, 28-joint swollen joint count,28-joint tender joint count, patient global assessment (PtGA), CDAI, power Doppler ultrasound (PDUS)] showed low and moderate correlations and are detailed in Supplementary Fig. S4, available at *Rheumatology* online.

Six study groups from four publications [29, 36, 46, 47] with a total of 287 subjects revealed a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP [COR 0.44 (CI 0.28, 0.57), $I^2 = 70.0\%$] (see Fig. 2B). After the exclusion of conference abstracts from the analysis, three articles [36, 46, 47] with a total of 137 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP [COR 0.38 (CI −0.02, 0.68), $I^2 = 18.0\%$].

The only study investigating the correlations of follow-up MBDA scores with follow-up DAS28-ESR found a moderate correlation [COR 0.49 (CI 0.22, 0.69)] between MBDA score and DAS28-ESR (Fig. 2B) [47].

Other parameters associated with disease activity (ESR, SJC28, TJC28, PtGA, PDUS) showed low–moderate correlations and are detailed in Supplementary Fig. S5, available at *Rheumatology* online.

Ten study groups from six articles [14, 28, 29, 36, 47, 50] with a total of 698 subjects demonstrated a moderate correlation between the change in MBDA score and the change in DAS28-CRP [COR 0.40 (CI 0.32, 0.48), $I^2 = 19.0\%$]. Seven study groups from six articles [25, 35, 38, 47, 49, 50] with a total of 543 subjects exhibited a moderate correlation between the change in MBDA score and the change in DAS28-ESR [COR 0.56 (CI 0.51, 0.60), $I^2 = 71.0\%$] (see Fig. 2C). Excluding conference abstracts from the analysis, similar results were recorded. The change in MBDA score moderately correlates with the change in DAS28-CRP [COR 0.43 (CI 0.25, 0.59), $I^2 = 47.0\%$] based on the results of six study groups of four publications [14, 36, 47, 50] with a total of 418 subjects, and with DAS28-ESR [COR 0.52 (CI 0.43, 0.60), $I^2 = 0.0\%$] based on the results of four publications [35, 47, 49, 50] with a total of 298 subjects.

Further parameters linked to disease activity (CRP, CDAI, SDAI, HAQ) showed low–moderate correlations and are shown in Supplementary Fig. S6, available at *Rheumatology* online.

The results of the subgroup analysis based on the length of the follow-up showed similar results and are displayed in Supplementary Figs S7 and S8, available at *Rheumatology* online.

MBDA score for the assessment of radiographic progression

Three study groups of three articles with a total of 22 subjects showed a low correlation between baseline MBDA score and baseline SvdH score [COR 0.13 (CI −0.25–0.47), $I^2 = 79.0\%$] and five study groups of four articles with a total of 307 subjects demonstrated a low correlation between the change in MBDA score and the change in SvdH score [COR 0.08 (CI −0.06–0.21), $I^2 = 79.0\%$] as well (see Fig. 3).

When evaluating the predictive value of the MBDA score for radiographic progression, three studies [13–15] with a total of 481 subjects showed that the odds of radiographic progression are significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) [OR 1.03 (CI 1.02, 1.05), $I^2 = 10.0\%$] (see Fig. 4). In contrast, the odds of progression

Table 1. Characteristics of included studies

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Studies included in the meta-analysis									
Baker, 2021 [23]	Journal article	POS	Pennsylvania and Philadelphia VA Medical Centre	–	N/A	Baseline[a]	USA (Pennsylvania)	MTX, bDMARD, GC	Spearman's correlation with conventional DAMs
Bakker, 2012 [13]	Journal article	RCT	CAMERA	N/A	2 years	Baseline[a], month 1,3,6[a], year 2[b]	Netherlands	MTX, CsA, intra-articular GC, NSAID	Pearson's correlation with conventional DAMs[c] predicting radiographic progression and remission[c]
Bechman, 2018 [24]	Journal article	POS	REMIRA	–	1 year	Months 3, 6, 9 and 12[a]	UK	csDMARD, bDMARD, GC	Spearman's correlation with conventional DAMs, relapse[c]
Bijlsma, 2013 [25]	Conference abstract	RCT	CAMERA-II	https://isrctn.com (ISRCTN 70365169)	1 year	Baseline[a], months 1–12[a]	Netherlands	Group A: MTX + PBO; group B: MTX + GC	Spearman's correlation with conventional DAMs
Bouman, 2017 [27]	Journal article	RCT	DRESS	https://trialregister.nl (NTR3216)	18 months	Baseline[a], months 3, 6, 9, 12, 15 and 18	Netherlands	MTX, csDMARD, ADA, ETN, NSAID, GC	Spearman's correlation with conventional DAMs, predicting radiographic progression[c] and relapse[c]
Brahe, 2016 [28]	Conference abstract	RCT	OPERA	https://clinicaltrials.gov (NCT00660647)	1 year	Baseline[a], months 3[a], 6 and 12[a]	Denmark	Group A: MTX + PBO; group B: MTX + ADA	Spearman's correlation with conventional DAMs
Brahe, 2019 [14]	Journal article	RCT	OPERA	https://clinicaltrials.gov (NCT00660647)	1 year	Baseline[a], months 1, 2, 3[a], 6[a], 9 and 12	Denmark	Group A: MTX + PBO; group B: MTX + ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression and remission[c]
Genovese, 2017 [29]	Conference abstract	RCT	DARWIN 1, DARWIN 2	https://clinicaltrials.gov (NCT01888874; NCT01894516)	24 weeks	Baseline[a], week 12[a]	USA	Group A: MTX + PBO; group B: MTX + 100 mg filogitinib; group C: MTX + 200 mg filogitinib	Spearman's correlation with conventional DAMs
Hambardzumyan, 2013 [31]	Conference abstract	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	1 year	Baseline[a], year 1[a]	Sweden	MTX, other DMARD, IFX	Spearman's correlation with conventional DAMs
Hambardzumyan, 2015 [15]	Conference abstract	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	1 year	Month 3, year 1[b]	Sweden	MTX, HCQ, SSZ, IFX	Predicting radiographic progression
Hirata, 2013 [49]	Journal article	RCT	BEST	N/A	1 year	Baseline[a], year 1[a]	Netherlands, Japan	DMARD, IFX	Spearman's correlation with conventional DAMs, remission[c]
Hirata, 2015 [50]	Journal article	ROS	UOEH	–	1 year	Baseline[a], weeks 24 and 52[a]	Japan	ADA, ETN, IFX, MTX	Spearman's correlation with conventional DAMs, therapy response[c]
Hirata, 2016 [34]	Journal article	ROS	UOEH	–	7 years	Baseline[a], week 52[a]	Japan	MTX, ADA, ETN, IFX	Spearman's correlation with conventional DAMs, predicting radiographic progression[c]

(continued)

Table 1. (continued)

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Jurgens, 2020 [35]	Journal article	RCT	CAMERA-II	https://www.isrctn.com (ISRCTN 70365169)	1 year	Baseline[a], months 1, 2, 3[a], 4–12	Netherlands	MTX, GC, CsA, ADA, PBO	Spearman's correlation with conventional DAMs
Krabbe, 2017 [36]	Journal article	POS	HURRAH	–	52 weeks	Baseline[a], weeks 26 and 52[a]	Denmark	MTX, ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression[c]
Lee, 2016 [37]	Journal article	POS	BRASS	–	2 years	Baseline[a]	USA	(Massachusetts)	csDMARD, bDMARD
Spearman's correlation with conventional DAMs									
Li, 2013 [38]	Conference abstract	POS	EIRA	–	3 months	Baseline[a], month 3[a]	Sweden	MTX	Spearman's correlation with conventional DAMs, therapy response[c]
Ma, 2014 [41]	Conference abstract	POS	REMIRA	–	1 year	Baseline[a], year 1[a]	UK	N/A	Spearman's correlation with conventional DAMs
Maijer, 2013 [43]	Conference abstract	POS	Academic Medical Centre Amsterdam	–	2 years	Baseline[a]	Netherlands	N/A	Spearman's correlation with conventional DAMs
Reiss, 2016 [46]	Journal article	RCT	ACT-RAY	N/A	24 weeks	Baseline[a], weeks 4, 12 and 24[a]	USA (California)	TCZ, MTX, GC	Spearman's correlation with conventional DAMs
Roodenrijs, 2018 [47]	Journal article	POS	LUMC, UMC, HORUS	–	1 year	Baseline[a], month 6[a]	Netherlands, UK	RTX, GC	Spearman's correlation with conventional DAMs, therapy response[c]
Studies included only in the systematic review									
Boeters, 2019 [26]	Journal article	POS	LUMC	–	N/A	Annually	Netherlands	csDMARDS, bDMARDS	Relapse
Hambardzumyan, 2019 [30]	Journal article	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	3 months	months 0, 3	Sweden	MTX, HCQ, SSZ, IFX	Therapy response
He, 2020 [32]	Conference abstract	Database analysis	N/A	–	N/A	Baseline[a]	USA	DMARD	Pearson's correlation with conventional DAMs
Hirata, 2012 [33]	Conference abstract	RCT	BEST	N/A	1 year	Baseline, year 1	Netherlands	N/A	remission

(continued)

Table 1. (continued)

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Li, 2016 (48)	Journal article	POS	LUMC	–	N/A	Annually	Netherlands	csDMARD, TNFi	predicting radiographic progression
Luedders, 2020 [40]	Journal article	POS	N/A	–	16 weeks	Baseline[a], weeks 8 and 16[a]	USA (Nebraska)	MTX, FA, GC, NSAID	Pearson's correlation with conventional DAMs, remission
Ma, 2020 [42]	Journal article	POS	REMIRA	–	1 year	Baseline, months 3 and 6	UK, Singapore	csDMARDs, TNFi, GC	Remission
Markusse, 2014 [16]	Journal article	RCT	BEST	N/A	1 year	Baseline, year 1	Netherlands	csDMARD, IFX, GC	predicting and discriminating radiographic progression
Ghiti Moghadam, 2018 [48]	Journal article	RCT	POET	https://trialregister.nl (NTR3112)	1 year	Baseline, months 3, 6, 9 and 12	Netherlands	csDMARD	Relapse
Razmjou, 2020 [44]	Journal article	POS	N/A	–	12 weeks	Baseline[a], weeks 2, 6 and 12[a]	USA (California)	csDMARD, tofacitinib	Pearson's correlation with conventional DAMs
Rech, 2016 [45]	Journal article	RCT	RETRO	https://www.clinicaltrialsregister.eu (2009-015740-42)	1 year	Baseline, months 3, 6, 9 and 12	Germany	csDMARDS, bDMARDS	Relapse

[a] Time point used for calculating correlation.
[b] Time point used for calculating radiological progression.
[c] Not included in the meta-analysis.
ADA: adalimumab; CsA: ciclosporin A; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; ETN: etanercept; FA: folic acid; GC: glucocorticoid; IFX: infliximab; N/A: no data available; PBO: placebo; POS: prospective observational study; RCT: randomized clinical trial; ROS: retrospective observational study; RTX: rituximab; TCZ: tocilizumab; TNFi: TNF-α inhibitor.

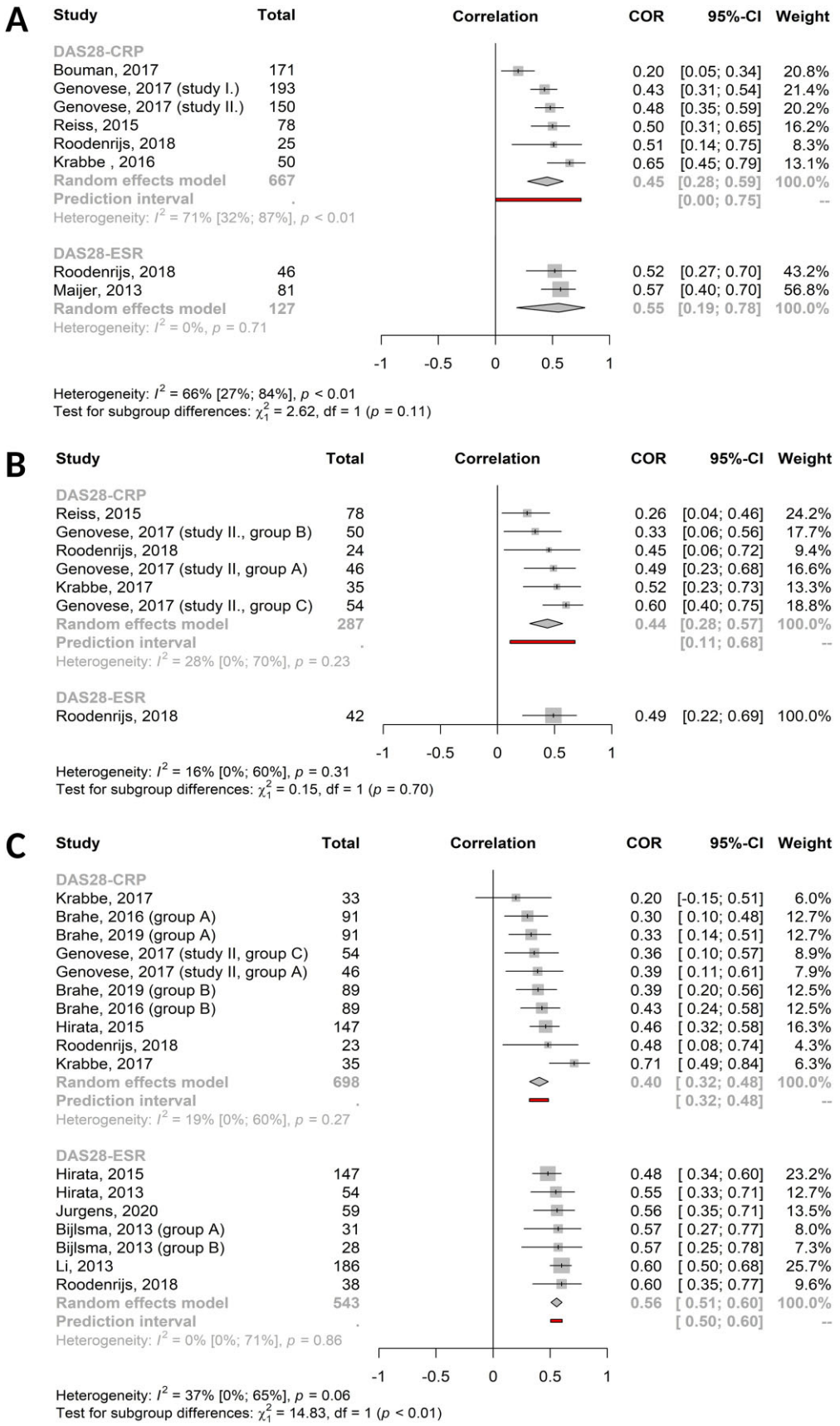

Figure 2. Forest plot for the correlation of MBDA score with DAS28-CRP/ESR. (**A**) Forest plot for the correlation of baseline MBDA score with baseline DAS28-CRP/ESR. (**B**) Forest plot for the correlation of follow-up MBDA score with follow-up DAS28-CRP/ESR. (**C**) Forest plot for the change in baseline MBDA score with the change in DAS28-CRP/ESR

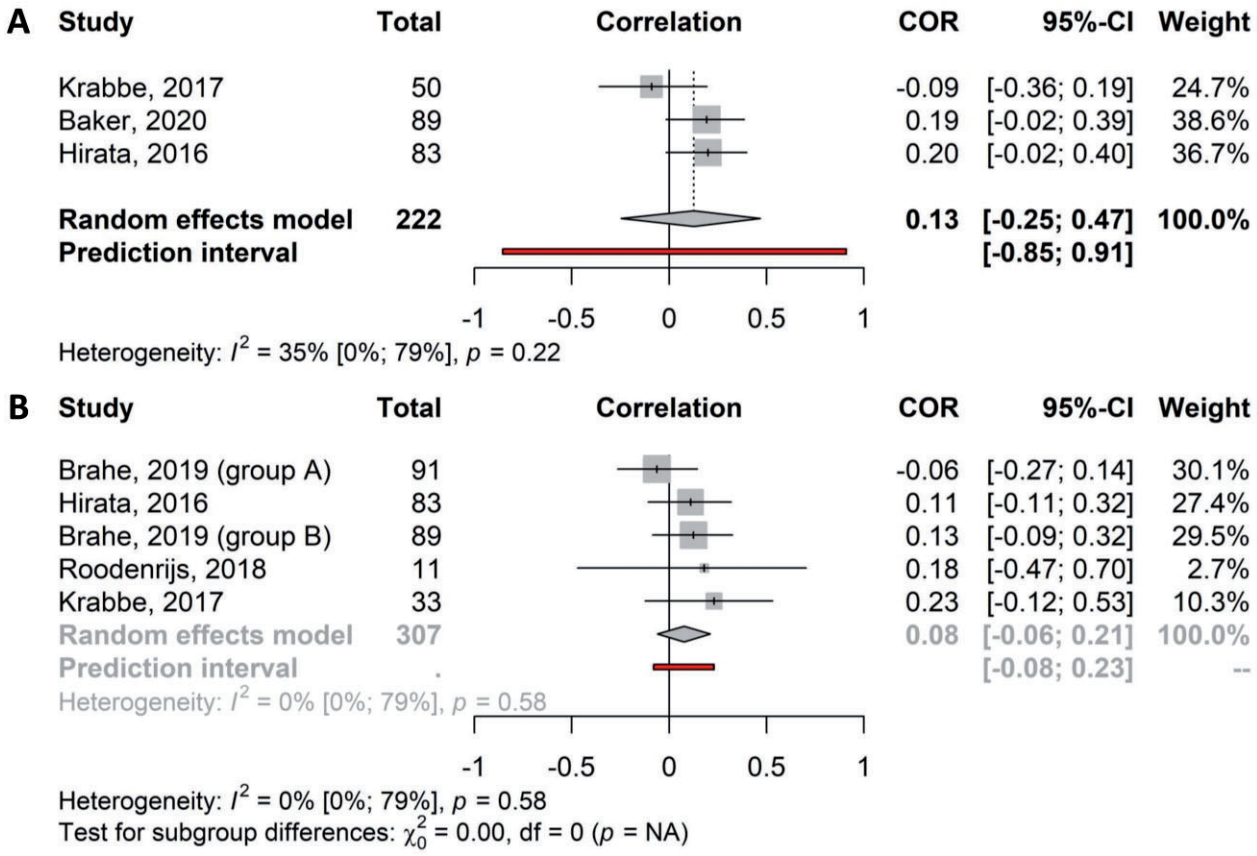

Figure 3. Forest plots for the correlations of MBDA score with SvdH score. (**A**) Forest plot for the correlation of baseline MBDA score with baseline SvdH score. (**B**) Forest plot for the correlation of the change in MBDA score with the change in SvdH score

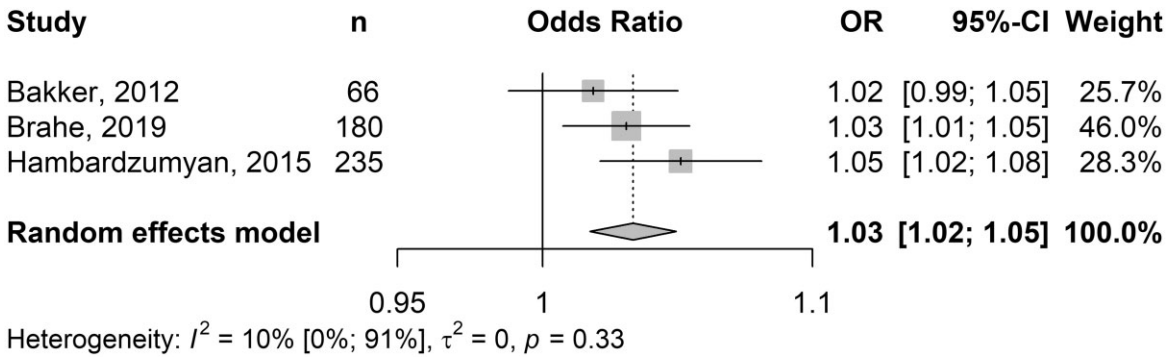

Figure 4. Forest plot of the predictive value of MBDA score for radiographic progression

for patients with a high baseline DAS28-CRP were not significantly higher than for patients with a low baseline DAS28-CRP [OR 1.12 (CI 0.91–1.37), $I^2 = 0.0\%$] (see Supplementary Fig. S9, available at *Rheumatology* online). The characteristics of the studies evaluating the predictive value of the MBDA score and DAS28-CRP for radiographic progression are detailed in Table 2.

Five additional studies evaluating the utility of the MBDA score for the assessment of radiographic progression could not be included in our quantitative synthesis [16, 27, 34, 36, 39]. Markusse *et al.* [16] found that higher MBDA scores at baseline were associated with an increased risk of radiographic progression in the subsequent year, therefore the MBDA score can be considered an independent predictor for radiographic progression. The discriminative value of the MBDA score was also assessed and the results showed that the MBDA score discriminated more between radiographic progression and no radiographic progression than the DAS at baseline and 1 year. Hirata *et al.* [34] reported that patients with moderate or high MBDA scores had a greater risk of radiographic progression than patients with low or moderate MBDA scores. Li *et al.* [39] also found that radiographic progression was not frequent when MBDA scores were low; univariate and multivariate analyses showed that high MBDA scores were strongly associated with radiographic progression. In a study by Krabbe *et al.* [36], none of the patients

Table 2. Characteristics of studies evaluating the predictive value of MBDA score and DAS28-CRP for radiographic progression

First author, year of publication	Time of evaluating RP	Definition of RP	Low MBDA score	High MBDA score	Low DAS28-CRP	High DAS28-CRP
Studies included in the meta-analysis						
Bakker, 2012 [13]	2 years	>0 units increase of SvdH score	<30	>44	≤2.7	>2.7
Brahe, 2019 [14]	1 year	>2 units increase of SvdH score	<30	>44	≤5.1	>5.1
Hambardzumyan, 2015 [15]	1 year	>5 units increase of SvdH score	<30	>44	≤2.7	>4.1
Studies included in the systematic review						
Bouman, 2017 [27]	1.5 years	>0.5 unit increase in SvdH score	<30	>44	<2.7	>4.1
Hirata, 2016 [34]	1 year	>3 unit increase in SvdH score	<30	>44	≤3.2	>5.1
Krabbe, 2017 [36]	0.5, 1 year	N/A	<30	>44	≤3.2	>5.1
Li, 2016 [39]	1 year	>3 unit increase in SvdH score	<30	>44	≤2.67	>4.09
Markusse, 2014 [16]	1 year	>0.5 unit increase in SvdH score	<30	>44	≤2.4	>3.7

N/A: no data available; RP: radiographic progression.

with radiographic progression had low MBDA scores. In contrast, Bouman *et al.* [27] found no association between baseline MBDA score and radiographic progression.

MBDA score for the assessment of therapy response, remission and relapse

We identified four studies [30, 34, 38, 47] investigating the utility of the MBDA score for the assessment of therapy response, six studies [13, 14, 33, 40, 42, 49] for remission and five studies [24, 26, 27, 45, 48] for relapse. However, these studies were not eligible for quantitative synthesis due to the widely varying outcome measures.

The change of MBDA score from baseline to 6 months was significantly associated with good or moderate EULAR response *vs* non-response at 6 months by Roodenrijs *et al.* [47]; however, the baseline MBDA score was not associated with EULAR response *vs* non-response. Similar results were recorded by Li *et al.* [38]. Although the baseline MBDA score was not associated with EULAR response at 3 months, changes in MBDA scores differentiated responders from non-responders. Hambardzumyan *et al.* [30] also reported that the MBDA score was significantly associated with treatment outcomes at 3 months. In the study of Hirata *et al.* [49], EULAR good responders were found to have significantly greater reductions in the MBDA score from baseline than EULAR moderate responders and EULAR moderate responders had significantly greater reductions than EULAR non-responders.

The MBDA score was found to be an appropriate discriminator of remission/low disease activity and moderate/high disease activity, according to two studies [13, 42]. Ma *et al.* [42] reported that the baseline MBDA score and the time-integrated MBDA score discriminated between remission and non-remission at 1 year as well. Two studies found no significant association between baseline MBDA score and remission, although, according to Brahe *et al.* [14, 40], the change in MBDA score was associated with clinical remission. Hirata *et al.* [33, 49] recorded the association of MBDA remission with clinical remission.

High baseline MBDA scores were associated with significantly greater proportions of patients experiencing relapse based on the results of Ghiti Moghadam *et al.* [48] and significantly higher MBDA scores were recorded in relapsed patients by Rech *et al.* [45]. Boeters *et al.* [26] found that high MBDA scores during DMARD treatment and before treatment reduction were associated with an increased risk of relapses in patients who reduced or stopped DMARD treatments. Bouman *et al.* [27] reported the borderline positive predictive value of baseline MBDA score for flare of patients with low disease activity at baseline. According to Bechman *et al.* [24], baseline MBDA scores were not predictive of flare. However, a sensitivity analysis limited to flares with an increase in high disease activity determined by MBDA score (> 44) did show an association between baseline MBDA value and flare risk.

Funnel plots and leave-one-out analysis

No evidence of publication bias was observed in the funnel plots for the correlations of MBDA scores with conventional DAMs (see Supplementary Figs S10–S12, available at *Rheumatology* online). The results of the leave-one-out analysis are detailed in Supplementary Tables S2–S4, available at *Rheumatology* online, showing no outlier article.

Risk of bias assessment

The majority of the outcomes of the studies included in the meta-analysis ($n = 79$) and the systematic review ($n = 37$) were rated as having a low or moderate risk of bias. The risk of bias was low in 35 outcomes of the studies included in the meta-analysis and 29 outcomes of the studies included in the systematic review, moderate in 32 outcomes of the studies included in the meta-analysis and 5 outcomes of the studies included in the systematic review and high in 12 outcomes of the studies included in the meta-analysis and 3 outcomes of the studies included in the systematic review. Common methodological limitations across studies were attrition rates, study confounding and statistical analysis and reporting. The quality assessment scores for all outcomes are shown in Supplementary Tables S5 and S6, available at *Rheumatology* online.

Discussion

Since the recommendation for the treatment of RA—the treat-to-target therapeutic approach—requires close monitoring of disease activity, the importance of objective scoring systems is indisputable. By conducting a systematic review and meta-analysis on the utility of the MBDA score to assess disease activity, radiographic progression, remission and relapse, we aim to promote decision making on the applicability of the MBDA score in clinical practice.

When analysing the correlations of MBDA score with conventional DAMs by a random-effects model, moderate correlations were recorded, similar to the meta-analysis conducted by Johnson *et al.* [17]. DAS28-CRP and DAS28-ESR, which

are considered the gold standard DAMs in RA, both showed moderate correlations with MBDA at baseline and follow-up, as well as in the change in DAS28-CRP and DAS28-ESR with the change in MBDA. Other DAMs detailed in the supplement showed weaker correlations with MBDA score, except for CRP. The correlation of the MBDA score with CRP individually was stronger than with DAS28-CRP. As the MBDA score does not contain the results of clinical assessment, its deviation from the conventional DAMs is not surprising. However, the MBDA score was designed to complement, not replace conventional DAMs, therefore its deviation from conventional DAMs can even be advantageous [51].

Since the MBDA score contains markers of cartilage and bone damage, such as MMP-3, in addition to the inflammatory markers implemented in currently used DAMs, such as CRP, it is a realistic possibility that it can outperform conventional DAMs in predicting radiological progression [52]. The results of our meta-analysis suggest that the MBDA score can be an independent predictor of radiological progression, as the odds of radiographic progression were significantly higher for patients with a high baseline MBDA score than for patients with a low baseline MBDA score, while there was no significant difference between low- and high-baseline DAS28-CRP. However, while the cut-off values for high and low MBDA scores were the same in the included studies, different cut-off values were used to define DAS28-CRP subgroups, which may influence these results and highlight the need for further investigations (see Table 2). Furthermore, the SvdH score showed a low correlation with the MBDA score at baseline and at follow-up, which suggests that these data should be interpreted with caution. These results are in line with the results of the studies included in our systematic review and also with the results of the previous meta-analysis by Curtis *et al.* [53] and the systematic review by Abdelhafiz *et al.* [54]. The limitation of both our study and the study by Curtis *et al.* [53] is the lack of included studies investigating the efficacy of DAS28-CRP for predicting radiographic progression independent of the MBDA score, potentially leading to biased results.

Based on the studies included in the systematic review, the change in MBDA score is associated with therapeutic response and seems to discriminate between therapy responders and non-responders [30, 38, 47, 49]. However, baseline MBDA scores were not predictive of therapy response [38, 47]. Similarly, while the change in MBDA score was found to be associated with remission and MBDA score discriminated remission/low disease activity and moderate/high disease activity [13, 14, 33, 42, 49], no significant associations were found between baseline MBDA scores and remission [14, 40]. In contrast, in the case of relapse, the baseline MBDA score was reported to be a predictor, although no clear conclusions can be drawn due to the heterogeneity of study designs and the potential for false positivity due to multiple testing [24, 27, 48].

There are several strengths of our study. We implemented a rigorous methodology to achieve the highest quality of evidence and provide a structured analysis of the outcomes discussed in the literature. We provide a comprehensive summary on the utility of the MBDA score for monitoring RA disease activity and also the predictive and discriminative value of the MBDA score for radiographic progression, therapy response, remission and relapse, presenting the results of quantitative analysis for both the correlation of the MBDA score with conventional DAMs and the predictive value of the MBDA score for radiographic progression.

Our main limitation is the heterogeneity of the populations. A wide range of anti-rheumatic drugs was used in the included studies, with potentially varying effects on the MBDA score: the IL-6 receptor-blocker tocilizumab may increase the serum level of IL-6 by preventing receptor binding, therefore influencing the change in MBDA score via one of the 12 included biomarkers [46]. TNF inhibitors may also influence MBDA score indirectly by decreasing the serum level of TNF-α. Hirata *et al.* [34] compared anti-TNF-α and anti-TNF-α-receptor drugs and found no significant difference between the two groups; however, further studies are needed to assess the effect of targeted therapies on the serum level of the biomarkers included in the MBDA score and therefore their effect on the change of MBDA score [34]. Furthermore, the different follow-up times used for the assessment of disease activity may also increase the heterogeneity.

By including a higher number of patients and uniformizing the follow-up time for evaluation and the cut-off values of DAS28-CRP for remission, future studies would enable further comprehensive analysis to urge implementation of the MBDA score in daily clinical practice.

Conclusion

The MBDA score can be highly valuable in RA patient care, both for monitoring disease activity and for predicting radiological progression. However, further studies are needed to better assess the utility of the MBDA score and also the potential role of individual biomarkers in disease activity monitoring.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis. The data underlying this article will be shared upon reasonable request to the corresponding author.

Authors' contributions

L.V.K. and F.A.M. were responsible for conceptualization, project administration, data curation, visualization and writing the original draft. E.G. was responsible for conceptualization, project administration, data curation and visualization. E.B. was responsible for conceptualization and data curation. F.D. was responsible for conceptualization, data curation and methodology. B.S. was responsible for methodology, formal analysis, validation and visualization. A.A. and E.L. were responsible for data curation and visualization. D.C. and P.H. were responsible for conceptualization, methodology and supervision. A.B. and G.N. were responsible for conceptualization, methodology, supervision and writing the original draft. All authors provided critical conceptual input and approved the final version of the article.

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Systematic Review

Platelet-Rich Plasma in Chronic Wound Management: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract: Background: Chronic wounds place a heavy burden on the healthcare system due to the prolonged, continuous need for human resources for wound management. Our aim was to investigate the therapeutic effects of platelet-rich plasma on the treatment of chronic wounds. Methods: The systematic literature search was performed in four databases. Randomized clinical trials reporting on patients with chronic wounds treated with platelet-rich plasma (PRP) were included, comparing PRP with conventional ulcer therapy. We pooled the data using the random effects model. Our primary outcome was the change in wound size. Results: Our systematic search provided 2688 articles, and we identified 48 eligible studies after the selection and citation search. Thirty-three study groups of 29 RCTs with a total of 2198 wounds showed that the odds for complete closure were significantly higher in the PRP group than in the control group (OR = 5.32; CI: 3.37; 8.40; I^2 = 58%). Conclusions: PRP is a safe and effective modality to enhance wound healing. By implementing it in clinical practice, platelet-rich plasma could become a widely used, valuable tool as it could not only improve patients' quality of life but also decrease the healthcare burden of wound management.

Keywords: wound healing; dressing; platelet-rich plasma

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1. Introduction

Chronic wounds are common conditions that greatly impact patients' quality of life [1]. They place a heavy burden on the healthcare system due to the high cost of dressing materials, amputation-related costs, and the prolonged, continuous need for human resources for wound management [2].

The wide range of causes underlying ulceration includes arterial and venous insufficiency, neuropathy, microangiopathy, and several additional factors [3]. Besides treating the underlying cause, the goal of ulcer management is to promote healing through professional wound care; the gold standard methods are smart dressings and compression therapy [4].

Platelet-rich plasma (PRP) is an autologous serum prepared from whole blood by centrifugation, containing high concentrations of platelets, growth factors, and cytokines, which can promote stem cell regeneration and tissue remodeling [5,6]. By potentially shortening the recovery time of ulcers, PRP, as an additional treatment modality, could improve patients' quality of life and decrease the healthcare burden of wound management.

Although the effects of PRP on wound healing are heavily investigated, the current evidence is inconclusive [7]. Our goal is to investigate the therapeutic effect of PRP on the treatment of chronic wounds by summarizing the latest data in a comprehensive manner by conducting a systematic review and meta-analysis.

2. Materials and Methods

Our study was performed according to the Cochrane Handbook's recommendations for the Systematic Reviews of Interventions, Version 6.3 [8]. The results are reported following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement [9]. The review protocol was registered on PROSPERO under registration number CRD42021287881 (see https://www.crd.york.ac.uk/prospero, accessed on 28 October 2021); no amendments to the information provided at registration were made.

The systematic literature search was performed in four databases: MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, and Web of Science from inception to 29 October 2021. The query (ulcer * OR chronic ulcer OR chronic wound OR diabetic foot) AND (platelet rich plasma OR PRP OR platelet rich plasma gel OR PRPG OR platelet rich in growth factors OR PRGF) was applied to all fields in the search engines. No language or other restrictions were imposed.

Randomized clinical trials (RCTs) reporting on patients with chronic wounds treated with PRP were included, comparing additional PRP treatment with conventional ulcer therapy alone. The following population–intervention–control–outcome (PICO) framework was used:

- P—Adult patients with chronic wounds;
- I—Platelet-rich plasma (PRP) treatment;
- C—Conventional ulcer therapy;
- O—Primary outcome: change in wound size (complete closure, reduction of wound area, healing rate); secondary outcomes: healing time, infection, pain, adverse events, amputation, recurrence, and quality of life.

EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) was used for the selection of the articles. Two independent authors (F.A.M. and K.D.K.) screened the publications separately for the title, abstract (Cohen's Kappa: 0.81), and full text (Cohen's Kappa: 0.88), and disagreements were resolved by a third author (F.D.).

Two authors (F.A.M. and K.D.K.) independently extracted the data into an Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA). We collected the following data from the eligible articles: first author, year of publication, study type, study location, number of centers included in the study, study design, demographic data, details of the received treatments, and data regarding our outcomes for statistical analysis. A third reviewer (F.D.) resolved the discrepancies. Secondary outcomes were included if three publications reporting on them were found.

The quality assessment of the outcomes was performed separately by two reviewers (F.A.M. and K.D.K.) using the revised tool for assessing the risk of bias (RoB 2) [10]. A third reviewer (F.D.) resolved any occurring disagreements. To assess the quality of the evidence, we followed the recommendation of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup [11].

The statistical analyses were made with R (R Core Team 2022, v4.2.1) [12]. For calculations and plots, we used the meta (Schwarzer 2022, v5.5.0) [13] and dmetar (Cuijpers, Furukawa, and Ebert 2022, v0.0.9000) [14] packages.

For the dichotomous outcomes, the odds ratio (OR) with a 95% confidence interval (CI) was used for the effect measure; to calculate the OR, the total number of patients in each group and those with the event of interest were extracted from each study. Raw data from the selected studies were pooled using a random effect model with the Mantel-Haenszel method [15–17]. For the pooled results, the exact Mantel–Haenszel method (no continuity correction) was used to handle zero cell counts [18]. In individual studies, the zero cell count

problem was adjusted by treatment arm continuity correction [19]. In the case of continuous outcomes, a standardized mean difference (SMD) with a 95% CI was calculated as the effect size. As different results were used from the same study, a three-level meta-analysis model was used along with estimating an additional within the study heterogeneity variance parameter. The inverse variance weighting method was used to calculate the pooled SMD. To estimate the heterogeneity variance measure, τ^2, the restricted maximum-likelihood estimator was applied with a t-distribution-based confidence interval [20].

Between-study heterogeneity was described by Higgins and Thompson's I^2 statistics [21]. As the subgroup analysis, the fixed-effects (plural) model (aka. the mixed-effects model) was used. Common τ values at the subgroup levels were assumed in the subgroup analysis, as we had a limited number of studies in some groups. A "Q" omnibus test (of all levels of the subgroup) was also calculated for comparison of the subgroup's pooled effect sizes. If the study number for the given outcome was over five, the Hartung–Knapp adjustment [22] was applied (below six studies, no adjustment was applied).

A funnel plot of the logarithm of the effect size and comparison with the standard error for each trial was used to evaluate publication bias. Publication bias was assessed with Egger's test using the Harbord method [23] to calculate the test statistic. Outlier and influence analyses were carried out following the recommendations of Harrer et al. [20] and Viechtbauer and Cheung [24].

3. Results

Our systematic search provided a total of 2688 articles; after duplicate removal, we screened 1910 duplicate-free articles. Following the title, abstract, and full-text selection, we identified 46 RCTs matching our PICO framework [25–70] and two additional articles [71,72] after the citation search. The full text of 10 articles could not be retrieved, even after contacting the authors [73–82]. The summary of the selection process is shown in Figure 1.

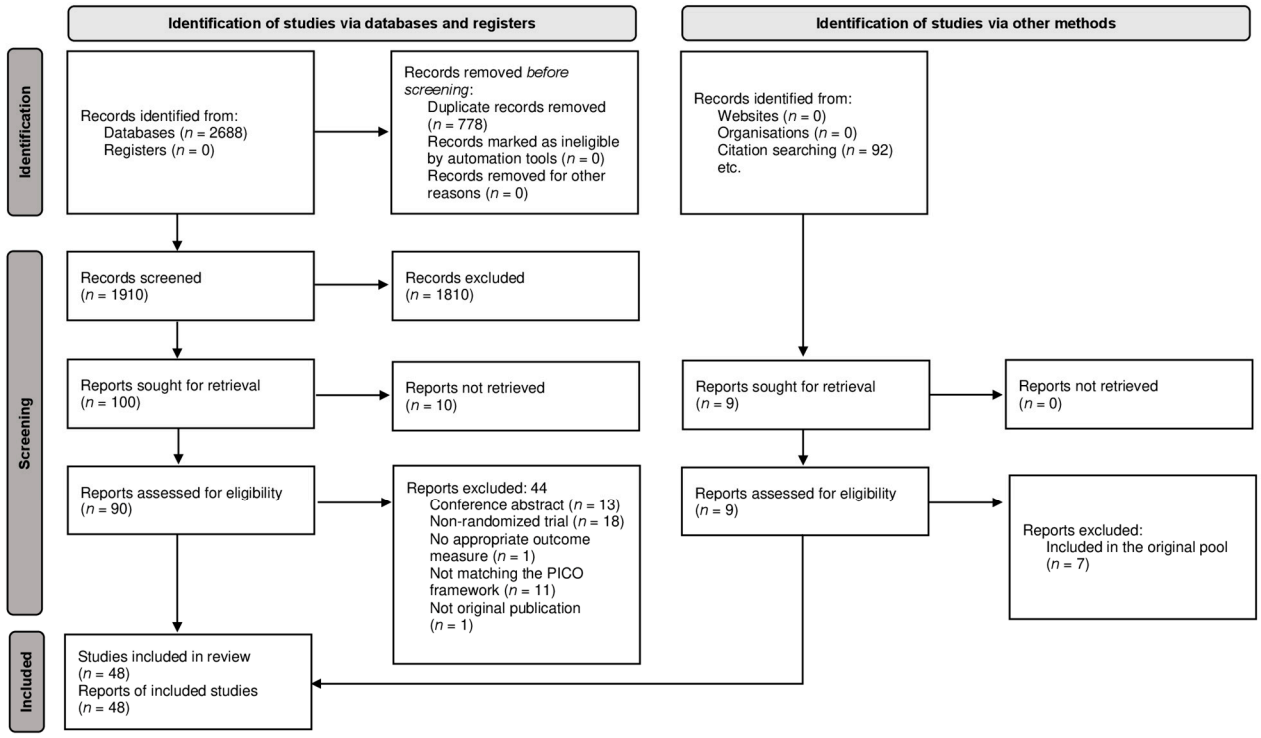

Figure 1. PRISMA Flow Diagram of the screening and selection process.

We conducted a quantitative analysis of our primary outcome, the change in wound size. The secondary outcomes are detailed in the systematic review section due to the widely varying and poorly defined outcome measures used for their assessment.

The characteristics of the identified RCTs for the systematic review and meta-analysis are detailed in Table 1.

Table 1. Characteristics of the included studies.

First Author, Year of Publication	Type of Publication	Study Type	Country	Ulcer Etiology	Outcome
Abd El-Mabood, 2018 [25]	Journal article	RCT	Egypt	Diabetic	Complete closure, healing rate, infection, and pain
Ahmed, 2017 [26]	Journal article	RCT	Egypt	Diabetic	Complete closure, healing rate, and infection
Alamdari, 2021 [27]	Journal article	RCT	Iran	Diabetic	Healing time, and amputation
Amato, 2020 [28]	Journal article	RCT	Italy	Mixed	Reduction of wound area, complete closure, infection, and pain
Anitua, 2008 [29]	Journal article	RCT	Spain	Mixed	Reduction of wound area and infection
Burgos-Alonso, 2018 [30]	Journal article	RCT	Spain	Venous	Reduction of wound area, complete closure, infection, pain, adverse events, and quality of life
Cardenosa, 2017 [31]	Journal article	RCT	Spain	Venous	Reduction of wound area, pain, and adverse events
Chandanwale, 2020 [32]	Journal article	RCT	India	Arterial	Reduction of wound area
de Oliveira, 2017 [33]	Journal article	RCT	Brazil	Venous	Reduction of wound area and infection
Driver, 2006 [34]	Journal article	RCT	US	Diabetic	Reduction of wound area, healing rate, complete closure, healing time, and adverse events
Elbarbary, 2020 [35]	Journal article	RCT	India	Venous	Reduction of wound area, complete closure, healing time, and recurrence
Elgarhy, 2020 [36]	Journal article	RCT	India	Venous	Reduction of wound area, complete closure, and healing time
Elsaid, 2020 [37]	Journal article	RCT	Egypt	Diabetic	Reduction of wound area, complete closure, and healing time
Game, 2018 [38]	Journal article	RCT	UK	Diabetic	Reduction of wound area, complete closure, healing time, infection, pain, amputation, and adverse events
Glukhov, 2017 [39]	Journal article	RCT	Russia	Venous	Complete closure, and pain
Goda, 2018 1 [41]	Journal article	RCT	Egypt	Diabetic	Healing rate, and complete closure
Goda, 2018 2 [40]	Journal article	RCT	Egypt	Venous	Reduction of wound area, and complete closure
Gude, 2019 [42]	Journal article	RCT	US	Diabetic	Complete closure, and amputation
Helmy, 2021 [43]	Journal article	RCT	Egypt	Venous	Reduction of wound area, complete closure, healing time, pain, adverse events, and recurrence
Hongying, 2020 [44]	Journal article	RCT	China	Pressure	Reduction of wound area, and complete closure
Kakagia, 2007 [71]	Journal article	RCT	Greece	Diabetic	Reduction of wound area, and complete closure
Karimi, 2016 [45]	Journal article	RCT	Iran	Diabetic	Reduction of wound area, complete closure, and amputation
Khorvash, 2017 [46]	Journal article	RCT	Iran	Diabetic	Reduction of wound area, infection, pain, and quality of life
Kulkarni, 2019 [47]	Journal article	RCT	India	N/A	Reduction of wound area, healing time, and adverse events

Table 1. *Cont.*

First Author, Year of Publication	Type of Publication	Study Type	Country	Ulcer Etiology	Outcome
Li, 2015 [48]	Journal article	RCT	China	Diabetic	Reduction of wound area, complete closure, healing time, infection, amputation, and adverse events
Milek, 2019 [49]	Journal article	RCT	Poland	Venous	Reduction of wound area and complete closure
Mohammad, 2017 [50]	Journal article	RCT	Iran	Diabetic	Reduction of wound area
Moneib, 2018 [51]	Journal article	RCT	Egypt	Venous	Reduction of wound area, complete closure, pain, and adverse events
Obolenskiy, 2014 [53]	Journal article	RCT	Russia	Mixed	Complete closure and healing time
Obolenskiy, 2017 [52]	Journal article	RCT	Russia	Mixed	Healing rate, complete closure, and healing time
Pires, 2021 [54]	Journal article	RCT	Brazil	Venous	Infection
Pu, 2019 [55]	Journal article	RCT	China	Arterial	Reduction of wound area, healing rate, and amputation
Qin, 2019 [56]	Journal article	RCT	China	Diabetic	Reduction of wound area
Rainys, 2019 [57]	Journal article	RCT	Lithuania	N/A	Reduction of wound area, complete closure, infection, and adverse events
Ramos-Torrecilla, 2015 [58]	Journal article	RCT	Spain	Pressure	Reduction of wound area, complete closure, and infection
Saad Setta, 2011 [59]	Journal article	RCT	Egypt	Diabetic	Complete closure and healing time
Saha, 2020 [60]	Journal article	RCT	India	Leprosy	Reduction of wound area, complete closure, and pain
Semenic, 2018 [61]	Journal article	RCT	Slovenia	Mixed	Reduction of wound area and adverse events
Senet, 2003 [72]	Journal article	RCT	France	Venous	Reduction of wound area, healing rate, complete closure, infection, and adverse events
Singh, 2018 [63]	Journal article	RCT	India	Diabetic	Complete closure, healing time, amputation, and adverse events
Singh, 2021 [62]	Journal article	RCT	India	Pressure	Reduction of wound area
Sokolov, 2017 [64]	Journal article	RCT	Bulgaria	Not defined	Complete closure
Somani, 2017 [65]	Journal article	RCT	India	Venous	Reduction of wound area and complete closure
Tsachiridi, 2019 [66]	Journal article	RCT	Greece	Pressure	Reduction of wound area and healing rate
Tsai, 2019 [67]	Journal article	RCT	US	Mixed	Reduction of wound area
Ucar, 2020 [68]	Journal article	RCT	Turkey	Pressure	Reduction of wound area
Yang, 2017 [69]	Journal article	RCT	China	Diabetic	Healing rate, healing time, infection, pain, and adverse events
Yuvasri, 2020 [70]	Journal article	RCT	India	Venous	Reduction of wound area and complete closure

3.1. Primary Outcome

The results of the studies assessing the change in wound size are detailed in Table S2 in the Supplementary Materials. Studies evaluating the change in wound size by measuring the baseline and post-treatment wound size or complete closure are included in our quantitative analysis.

3.1.1. Complete Closure

Thirty-three study groups of 29 RCTs with a total of 2198 wounds showed that the odds for complete closure were significantly higher in the PRP group than in the control group (OR = 5.32; CI: 3.37; 8.40; I^2 = 58%) (see Figure 2).

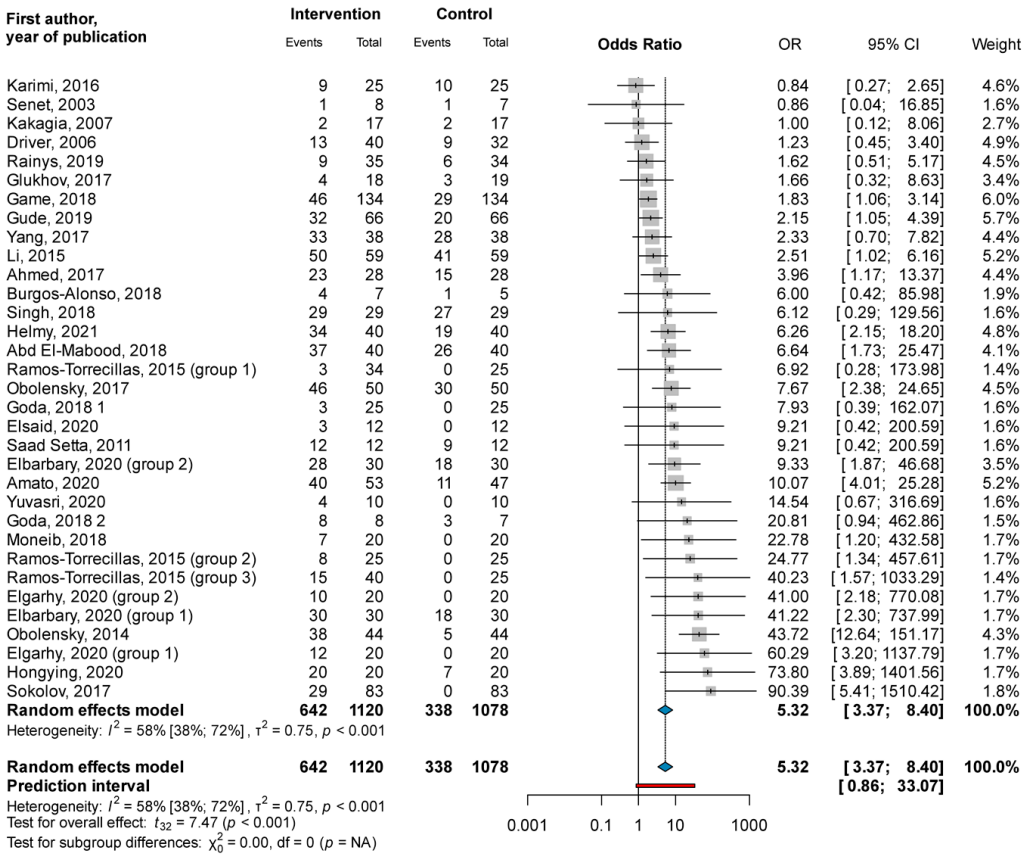

Figure 2. Forest plot for complete closure: platelet-rich plasma compared to conventional ulcer therapy [25,26,28,30,34–45,48,51–53,57–59,63,64,69–72].

When subgrouping was based on ulcer etiologies, the odds for complete closure were significantly higher in the PRP group than in the control group, both in diabetic foot ulcers (OR = 2.26; CI: 1.50; 3.41; I^2 = 12.0%) as well as venous leg ulcers (OR = 8.02; CI: 3.63; 17.71; I^2 = 10.0%). The test for the subgroup difference showed a significant difference between the two groups (χ^2 = 9.88; df = 1; p = 0.002); the odds for complete closure were significantly higher in venous ulcers than in the diabetic foot ulcers treated with PRP (see Figure S1).

Subgrouping based on the way PRP was applied showed similar results. The odds for complete closure were significantly higher both in the topically applied (OR = 4.74; CI: 2.87; 7.83; I^2 = 60%) and injected (OR = 9.42; CI: 3.32; 26.76; I^2 = 0%) PRP groups than in the control group, with no significant subgroup difference (χ^2 = 2.34; df = 1; p = 0.126) (see Figure S2).

The odds for complete closure were significantly higher in the PRP group than in the control group in the short (OR = 6.03; CI: 3.21; 11.33; I^2 = 47%), medium (OR = 3.38; CI: 1.15; 9.89; I^2 = 73%), and long (OR = 8.24; CI: 1.66; 40.87; I^2 = 0%) follow-up categories, as well with no significant subgroup differences (χ^2 = 2.50; df = 3; p = 0.476) (see Figure S3).

3.1.2. Reduction of Wound Area

The pooled SMDs from 18 study groups of 16 RCTs with a total of 1062 wounds showed a significant difference between the post-treatment wound size of the PRP and the control groups (SMD = −1.21, CI: −1.74; −0.68; I^2 = 92.5%), with the PRP group showing greater improvement (see Figure 3).

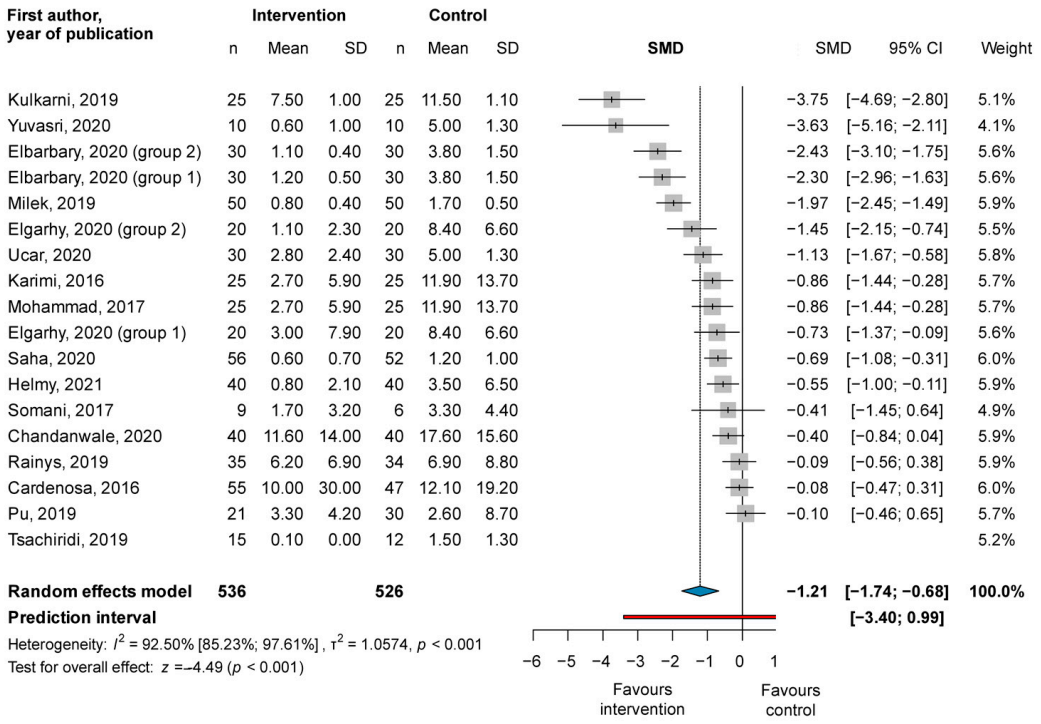

Figure 3. Forest plot for the change of wound size: platelet-rich plasma compared to conventional ulcer therapy [31,32,35,36,43,45,47,49,50,55,57,60,65,66,68,70].

Subgrouping based on ulcer etiology, the application method, and follow-up length showed similar results (see Figures S4–S6). The post-treatment wound size was significantly smaller in the PRP group than in the control group in the diabetic (SMD = −0.68, CI: −1.31; −0.06; I^2 = 93.64%), venous (SMD = −1.26, CI: −2.28; −0.24; I^2 = 90.76%), topically applied (SMD = −0.94, CI: −1.43; −0.46; I^2 = 91.26%), and injected (SMD = −1.03, CI: −1.79; −0.26; I^2 = 86.63%) subgroups, as well as in the short follow-up subgroup (SMD = −1.00, CI: −1.64; −0.35; I^2 = 89.41%). However, the difference between the PRP and the control groups was not significant in the medium (SMD = −1.38, CI: −2.96; 0.19; I^2 = 54.51%) and long (SMD = −0.63, CI: −1.64; 0.37; I^2 = 93.88%) follow-up groups. No significant subgroup differences were recorded.

3.2. Secondary Outcomes

The secondary outcomes are summarized in Table 2. Recurrence rates and quality of life are not reported, as less than three studies included them as an outcome.

Table 2. Main conclusions of the studies assessing the secondary outcomes.

First Author, Year of Publication	Main Conclusion
	Healing Time
Alamdari, 2021 [27]	Shorter healing time in the PRP group than in the control group
Driver, 2006 [34]	Shorter healing time in the PRP group than in the control group
Elbarbary, 2020 [35]	Shorter healing time in the PRP group than in the control group *
Elgarhy, 2020 [36]	Shorter healing time in the topical and injected PRP groups than in the control group *
Elsaid, 2020 [37]	Shorter healing time in the PRP group than in the control group *
Game, 2018 [38]	Shorter healing time in the PRP group than in the control group *
Helmy, 2021 [43]	Shorter healing time in the PRP group than in the control group *
Kulkarni, 2019 [47]	Shorter healing time in the PRP group than in the control group *
Li, 2015 [48]	Shorter healing time in the PRP group than in the control group *

Table 2. *Cont.*

First Author, Year of Publication	Main Conclusion
	Healing Time
Obolenskiy, 2014 [53]	Shorter healing time in the PRP group than in the control group
Obolenskiy, 2017 [52]	Shorter healing time in the PRP group than in the control group *
Saad Setta, 2011 [59]	Shorter healing time in the PRP group than in the control group *
Singh, 2018 [63]	Shorter healing time in the PRP group than in the control group *
Yang, 2017 [69]	Shorter healing time in the PRP group than in the control group *
	Infection Rates
Abd El-Mabood, 2018 [25]	More infection in the control group than in the PRP group *
Ahmed, 2017 [26]	More infection in the control group than in the PRP group *
Amato, 2020 [28]	More infection in the control group than in the PRP group *
Anitua, 2008 [29]	No statistically significant difference between the PRP and the control groups
Burgos-Alonso, 2018 [30]	No statistically significant difference between the PRP and the control groups
de Oliveira, 2017 [33]	No statistically significant difference between the PRP and the control groups
Game, 2018 [38]	No statistically significant difference between the PRP and the control groups
Khorvash, 2017 [46]	No statistically significant difference between the PRP and the control groups
Li, 2015 [48]	No statistically significant difference between the PRP and the control groups
Pires, 2021 [54]	No statistically significant differences in antimicrobial resistance between *P. aeruginosa* and *S. aureus* in the PRP and control groups. PRP decreased bacteriological growth or the microbial load and resistance profile in the case of *P. aeruginosa*
Rainys, 2019 [57]	No statistically significant difference between the PRP and the control groups
Ramos-Torrecilla, 2015 [58]	No signs of infection were recorded during the study
Senet, 2003 [72]	No statistically significant difference between the PRP and the control groups
Yang, 2017 [69]	More infection in the control group than in the PRP group *
	Pain
Abd El-Mabood, 2018 [25]	Pain occurred more frequently in the control group *
Amato, 2020 [28]	Pain occurred more frequently in the control group *
Burgos-Alonso, 2018 [30]	No statistically significant difference in pain reduction between the PRP and the control groups
Cardenosa, 2017 [31]	Pain reduction was higher in the PRP group *
Game, 2018 [38]	No statistically significant difference in pain reduction between the PRP and the control groups
Glukhov, 2017 [39]	All patients subjectively experienced pain reduction in both groups
Helmy, 2021 [43]	All patients subjectively experienced pain reduction in the PRP group
Khorvash, 2017 [46]	pain reduction was higher in the PRP group *
Moneib, 2018 [51]	All patients subjectively experienced pain reduction in both groups
Saha, 2020 [60]	Administration-related pain was reported by 10 participants in the PRP group
Yang, 2017 [69]	pain reduction was higher in the PRP group *
	Amputation Rates
Alamdari, 2021 [27]	No statistically significant difference between the PRP and the control groups
Game, 2018 [38]	No statistically significant difference between the PRP and the control group
Gude, 2019 [42]	Two amputations in the control group and no amputation in the PRP group
Karimi, 2016 [45]	No statistically significant difference between the PRP and the control groups
Li, 2015 [48]	Four amputations in the control group one amputation in the PRP group
Pu, 2019 [55]	No statistically significant difference between the PRP and the control groups
Singh, 2018 [63]	Two amputations in the control group, and no amputation in the PRP group
	Adverse Events
Burgos-Alonso, 2018 [30]	No statistically significant difference between the PRP and the control groups
Cardenosa, 2017 [31]	No adverse events recorded
Chandanwale, 2020 [32]	No adverse event in the PRP group
Driver, 2006 [34]	No administration related serious adverse event was recorded in either group; one case of Contact dermatitis in the PRP group and one case of maceration in the control group
Game, 2018 [38]	No statistically significant difference between the PRP and the control groups
Helmy, 2021 [43]	No adverse events recorded
Kulkarni, 2019 [47]	No adverse event in the PRP group

Table 2. *Cont.*

First Author, Year of Publication	Main Conclusion
	Adverse Events
Li, 2015 [48]	No adverse events were recorded in the PRP group
Moneib, 2018 [51]	No adverse events recorded
Rainys, 2019 [57]	No statistically significant difference between the PRP and the control groups, and no serious adverse event was recorded
Semenic, 2018 [61]	No adverse events recorded
Senet, 2003 [72]	No statistically significant difference between the PRP and the control groups
Singh, 2018 [63]	No adverse events recorded
Yang, 2017 [69]	No statistically significant difference between the PRP and the control groups

PRP-platelet-rich plasma; * indicates significant difference ($p < 0.05$).

3.3. Risk of Bias Assessment

The result of the assessment of the risk of bias of the studies included in the meta-analysis and systematic review are detailed in Figures S7–S18 in the Supplementary Materials. None of the studies included in the meta-analysis was at a high risk of bias. In thirty studies [26,28–30,32,34,39,42,43,47–53,56,58,59,61,62,64–72], the 'randomization process' domain, in twelve studies [28,42,44,48,50,53,56,59,63,65,68,71], the 'deviations from intended interventions' domain, in one study [29], the 'missing outcome data' domain, in five studies [44,50,56,59,71], the 'measurement of the outcome' domain, and in eight studies [26,33,42,57,58,63,65,70], the 'selection of the reported result' domain, were rated as 'some concerns' for our primary outcome.

3.4. Quality of Evidence

The quality of the evidence for our outcomes is detailed in the Summary of Findings Table (see Table S1 in the Supplementary Materials).

3.5. Publication Bias

The funnel plot assessing the publication bias can be seen in the Supplementary Materials (Figures S19 and S20). No evidence of serious publication bias can be observed in the funnel plot for complete closure; however, the funnel plot for the reduction of the wound area indicates publication bias.

4. Discussion

On the basis of our systematic review and meta-analysis, PRP is an effective add-on treatment modality to enhance wound healing. The odds for complete wound closure were significantly higher in the PRP group than in the control group, and PRP also resulted in a significantly greater reduction of the wound area compared to conventional therapy.

The subgroup analyses, which were conducted to decrease the heterogeneity, showed similar results and also highlighted differences between the ulcer etiologies and PRP application methods. Injected PRP seemed to result in greater improvement than topically applied PRP; however, due to the relatively low sample size of this subgroup, conclusions should be drawn with caution. As for ulcer etiologies, while PRP was superior to conventional therapy regarding complete closure and the reduction of the wound area in diabetic and venous ulcers as well, better results were recorded in the venous ulcer group. The reason for this phenomenon could be that diabetic ulcers are more difficult to heal; however, the fact that PRP was more frequently administered by injection in the venous ulcer group could also be a contributing factor, as we saw better results in the injected PRP subgroup discussed above. PRP was also shown to be effective after short, medium, and long follow-up times regarding complete closure.

Although we did not conduct quantitative analysis on the healing time due to the varying reporting methods of the studies, all the included studies reported shorter healing times in the PRP group than in the conventional therapy group [27,34–38,43,47,48,52,53,59,63,69].

The infection rate is another critical outcome that requires further investigation with more specific criteria for its assessment. Nine studies did not record a significant difference between the PRP and the control groups regarding infection rates [29,30,33,38,46,48,57,58,72], whereas four studies recorded a significantly lower number of infections in the PRP group [25,26,28,69], suggesting that PRP could decrease the risk of infection.

No substantial difference was recorded between the PRP and the control group regarding pain [25,28,30,31,38,39,43,46,51,60,69], amputation rates [38,42,45,48,55,63], and adverse events [30–32,34,38,43,47,48,51,57,61,63,69,72].

4.1. Strengths and Limitations

There are several strengths to our study. We summarized the latest data on PRP in wound management in a comprehensive manner, assessing the most objective outcome measure, the change in the wound area. Our results clearly support the superiority of PRP over conventional therapy alone. While previous studies only assessed the efficacy of PRP in different ulcer etiologies separately, we conducted an overall analysis; we believe, as well, that it is crucial to assess the wound-healing properties of PRP in general [7]. We only included RCTs and implemented a rigorous methodology to guarantee the highest possible quality of evidence and conducted a quantitative analysis only on the outcomes that were objectively reported to avoid drawing false conclusions based on poorly recorded secondary outcomes. Our limitations included publication bias and the diversity of the control groups, as a wide range of dressings was used as a part of the conventional therapy.

4.2. Implications for Research

Future studies should report their outcomes uniformly to enable further comprehensive analysis. As the most objective way of assessing the clinical efficacy of PRP in wound management is to record the change in wound size, the baseline and post-treatment wound area should always be reported. However, better reporting guidelines are required that entail detailed descriptive statistics, including the median and interquartile range besides the mean and standard deviation. Additionally, the varying methods used to measure wound size can also lead to further bias: chronic wounds often affect the leg, and simply photographing the wound and measuring it with software does not take into account that wounds often affect the total leg circumference. Also, assessing the wound size by only measuring its width and length can give false results due to the often asymmetrical ulcer areas. We suggest that the most applicable way of precise measurement is tracing the outline of the wound on carbon paper, which can be digitalized and available for further calculations.

In addition to the baseline and post-treatment wound area, the number of completely closed wounds is also a critical outcome measure, showing the clinical efficacy of the treatment; therefore, it should always be reported.

4.3. Implications for Practice

The importance of the early application of research results in clinical practice is undisputable [83]. Due to its wound-healing properties, platelet-rich plasma could become a widely used, valuable tool in chronic wound management. PRP can be administered topically and intralesionally, as well, and can also be applied along with the wide range of available smart dressings. These combinations enable personalized treatment strategies by providing a variety of options for treating physicians.

5. Conclusions

Platelet-rich plasma is a safe and effective modality to enhance wound healing. By implementing it in clinical practice, PRP could become a widely used, valuable tool, as it could improve patients' quality of life and decrease the healthcare burden of wound management.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11247532/s1, Table S1: Summary of findings table. Table S2: Characteristics of the studies assessing the change of wound size. Figure S1: Forest plot for complete closure, subgrouping based on ulcer etiologies. Figure S2: Forest plot for complete closure, subgrouping based on PRP application method. Figure S3: Forest plot for complete closure, subgrouping based on follow-up time. Figure S4: Forest plot for wound area reduction, subgrouping based on ulcer etiologies. Figure S5: Forest plot for wound area reduction, subgrouping based on PRP application method. Figure S6: Forest plot for wound area reduction, subgrouping based on follow-up time. Figure S7: Risk of bias assessment of the included studies assessing the change of wound size, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S8: Risk of bias assessment of the included studies assessing the change of wound size, broken down to tools, shown in percentage. Figure S9: Risk of bias assessment of the included studies assessing healing time, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S10: Risk of bias assessment of the included studies assessing healing time, broken down to tools, shown in percentage. Figure S11: Risk of bias assessment of the included studies assessing infection rates, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S12: Risk of bias assessment of the included studies assessing infection rates, broken down to tools, shown in percentage. Figure S13: Risk of bias assessment of the included studies assessing pain, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S14: Risk of bias assessment of the included studies assessing pain, broken down to tools, shown in percentage. Figure S15: Risk of bias assessment of the included studies assessing amputation rates, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S16: Risk of bias assessment of the included studies assessing amputation rates, broken down to tools, shown in percentage. Figure S17: Risk of bias assessment of the included studies assessing adverse events, using the revised tool for assessing risk of bias in randomized trials (Rob 2). Figure S18: Risk of bias assessment of the included studies assessing adverse events, broken down to tools, shown in percentage. Figure S19: Funnel plot for complete closure. Figure S20: Funnel plot for the reduction of wound area.

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Data Availability Statement: The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

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biomedicines

MDPI

Systematic Review

Platelet-Rich Plasma in Alopecia Areata—A Steroid-Free Treatment Modality: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract: Background: Alopecia areata (AA) is a chronic autoimmune condition that can lead to a serious deterioration in patients' quality of life. The first line of treatment in patchy AA is triamcinolone acetonide (TrA); however, the efficacy of the treatment varies greatly. Our aim was to investigate the therapeutic effects of platelet-rich plasma (PRP) in the treatment of AA. Method: We performed a systematic literature search in four databases. Randomized clinical trials (RCT) reporting on patients with AA treated with PRP were included, comparing PRP with TrA or a placebo. The primary outcome was the Severity of Alopecia Tool (SALT) score. Results: Our systematic search provided a total of 2747 articles. We identified four studies eligible for quantitative analysis. The pooled mean differences from the four studies did not exhibit a significant difference in the mean change in the SALT score when PRP and TrA groups were compared (MD =−2.04, CI: −4.72–0.65; I^2 = 80.4%, p = 0.14). Conclusions: PRP is a promising topical, steroid-free treatment modality in the therapy of AA. No significant difference was found between PRP and TrA treatment; however, further high-quality RCTs are needed to further assess the efficacy of PRP treatment and strengthen the quality of evidence.

Keywords: alopecia areata; patchy alopecia; platelet-rich plasma; treatment; topical

1. Introduction

Alopecia areata (AA) is an autoimmune condition characterized by inflammation-induced hair loss due to the collapse of the hair follicles' immune privilege [1]. It can affect the scalp, the beard, or even the whole body, leading to a serious deterioration in patients' quality of life [2]. In the case of AA of the scalp, three categories can be differentiated based on the extent of the disease-affected area: limited patchy AA with less than 50% scalp involvement, extensive patchy AA with more than 50% scalp involvement, and alopecia totalis, affecting the whole scalp [3].

A wide spectrum of topical and systemic agents is used in the management of AA; however, there is a lack of consensus on a standard treatment modality due to the disease's varying response to therapy [4]. The limited patchy forms of AA are usually treated with topical agents, such as corticosteroids, contact immunotherapy (1-chloro,2,4-dinitrobenzene (DNCB), squaric acid dibutylester (SADBE), and 2,3-diphenylcyclopropenone (DPCP)), and minoxidil; however, the efficacy of the latter treatments is questionable [5]. According to guidelines, the first line of treatment in limited patchy AA is triamcinolone acetonide (TrA) administered intralesionally [5,6]. Besides the frequently disputed efficacy of TrA treatment, side effects, such as skin atrophy, teleangiectasia, and hypopigmentation, frequently occur. Additionally, the use of steroids is alarming to many; a phenomenon called steroid phobia exists [7]. These provide additional reasons to look for new topical, steroid-free treatment modalities.

Platelet-rich plasma (PRP) is a relatively new, presently evolving treatment modality that is playing an increasingly important role in the field of dermatology. The efficacy of PRP varies greatly and is being investigated in numerous dermatological disorders, such as androgenic alopecia, acne scar treatment, or chronic wound management [8–10]. PRP is prepared from whole blood by a centrifugation process to achieve a product that is rich in platelets, growth factors, and cytokines. Based on the number of centrifugations, single-spin and double-spin preparation methods can be differentiated [11,12]. PRP was shown to stimulate cell proliferation in the dermal papilla (DP), increase DP cell survival through antiapoptotic effects, and stimulate hair regrowth by prolonging the anagen phase of the hair cycle [13].

The Severity of Alopecia Tool (SALT) score, the most widely used method to monitor the response to therapy, is an objective outcome measure to evaluate the severity of the disease. It is determined by visually assessing the percentage of hair loss, resulting in a score from 0 to 100 analogous to the percentage of the affected area [14]. In limited patchy AA, the SALT score is lower than 50, indicating that the scalp involvement is below 50% [3,14].

Several studies have reported promising results of PRP in the treatment of AA [15–20], but there has been no systematic evaluation of randomized trials reporting on the therapeutic effect of PRP on AA to date. Our aim was to investigate the therapeutic effects of PRP in the treatment of limited patchy AA by conducting a systematic review and meta-analysis, comparing PRP with the first line of treatment in limited patchy AA, TrA [10,13]. Our hypothesis was that PRP is as good as TrA in the treatment of AA.

2. Materials and Methods

Our systematic review and meta-analysis are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement [21]. This study was performed following the Cochrane Handbook's recommendations for Systematic Reviews of Interventions Version 6.3. [22]. The review protocol was registered on PROSPERO (York, UK) under registration number CRD42021282807 (see https://www.crd.york.ac.uk/prospero, accessed on 14 October 2021); no amendments to the information provided at registration were made.

2.1. Literature Search and Eligibility Criteria

We performed a systematic literature search in four medical databases: MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, and Web of Science, from inception to 15 October 2021. We applied the query ((alopecia areata OR patchy alopecia) AND (platelet rich plasma OR PRP OR steroid OR corticosteroid OR triamcinolone)) to all fields in the search engines. No language or other restrictions were imposed.

Randomized clinical trials (RCTs) reporting on patients with AA treated with PRP were included, comparing PRP with TrA or a placebo. The following population–intervention–control–outcome (PICO) framework was used:

P—Adult patients with patchy AA;

I—Intralesional autologous PRP injections to the AA-affected areas;

C_1—Intralesional placebo injections to the AA-affected areas;

C_2—Intralesional (TrA) injections to the AA-affected areas;

O—Primary outcome: SALT score; secondary outcomes: hair dystrophy, patient safety, cytokine expression, burning/itching sensation, Hair Regrowth Grade scale, Patient Global Assessment score, cell proliferation.

Publications without separate intervention and control groups (split scalp studies) were excluded.

2.2. Study Selection and Data Collection

We used EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for the articles' selection. Two independent authors (F.A.M. and K.I.) screened the publications separately for the title, abstract, and full text, and disagreements were resolved by a third author (F.D.).

Two authors (F.A.M. and K.D.K.) independently extracted data into a predefined Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA). The following data were collected from each eligible article: first author, year of publication, study type, study location, number of centers included in the study, study design, demographic data (sample sizes, age, and percentage of participating females), details of the received treatments, and data regarding our outcomes (baseline SALT score and SALT score after treatment, and secondary outcomes) for statistical analysis. A third reviewer (F.D.) resolved the discrepancies. Based on the baseline SALT scores and the post-treatment SALT scores reported in the included studies, we calculated the mean change in the SALT score in both the PRP and TrA groups, and the mean difference (MD) between the two groups.

2.3. Quality Assessment and Quality of Evidence

The quality assessment of the outcomes was carried out separately by two reviewers (F.A.M. and K.D.K.) using the revised tool for assessing the risk of bias (RoB 2) [23]. Disagreements were resolved by a third reviewer (F.D.). The recommendations of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup were followed to evaluate the quality of evidence [24].

2.4. Data Synthesis and Analysis

The mean baseline SALT score and SALT score after treatment were extracted for both the TrA and PRP groups. We calculated the change in the mean SALT scores for each study, and, where applicable, we also extracted the standard deviation (SD) of within-group differences. If this latter value was not published, but t-tests or ANOVA were used, we calculated the SD from the reported p values, or in the case of non-parametric tests, we obtained a conservative estimate of the SDs by adding together the reported before- and after-treatment SDs. Meta-analysis using random effects (DerSimonian and Laird) was performed following the recommendations of the Cochrane Handbook and Harrer et al. using R version 6.3 [22,25–27]. The heterogeneity of the studies was assessed with the Cochran Q test, with a significance level of 0.05 and I^2 statistic, and forest plots were constructed.

3. Results

3.1. Search and Selection

Our systematic search provided a total of 2747 articles; after duplicate removal, we screened 2002 duplicate-free articles. After the title, abstract, and full-text selection, we identified six RCTs matching our PICO framework [15–20]; of these articles, we could use four RCTs for our quantitative synthesis [15,17–19]. The results of the other two articles [16,20] and the results of two additional articles, which also included a placebo as a comparator [18,20], are discussed in the systematic review with the secondary outcomes. The summary of the selection process is shown in Figure 1.

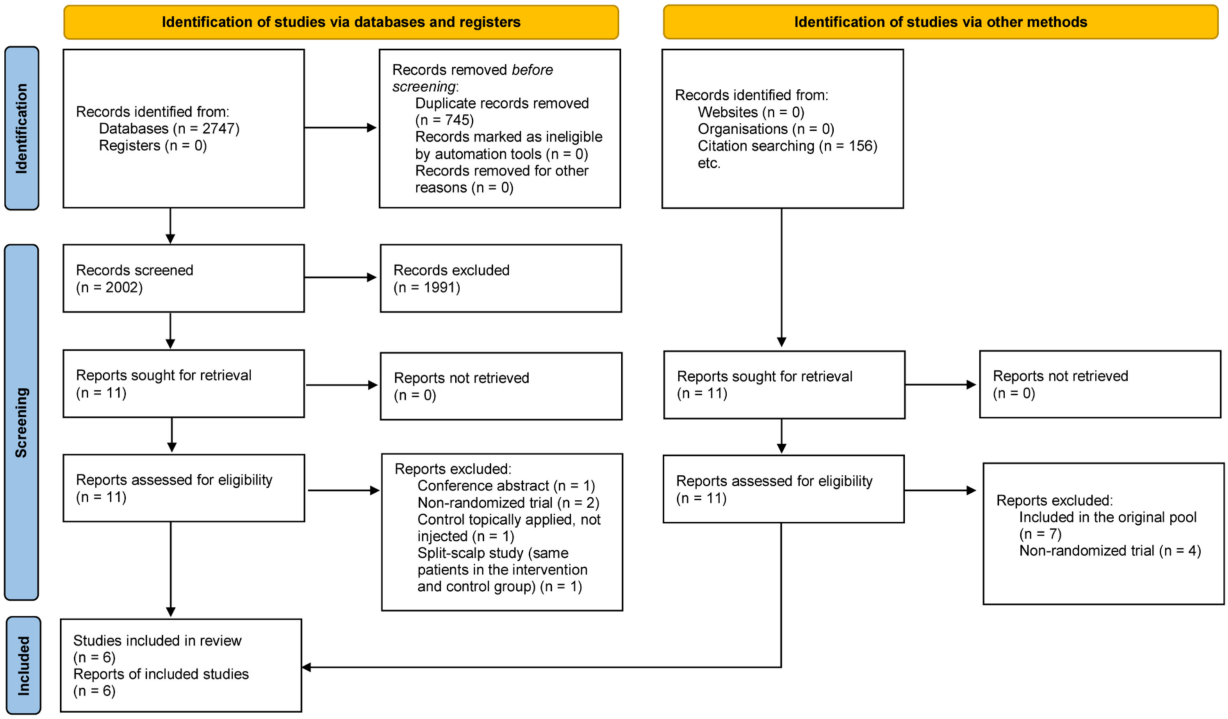

Figure 1. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines [21].

3.2. Main Characteristics of the Included Studies

The characteristics of the identified RCTs for the systematic review and meta-analysis are detailed in Tables 1 and 2.

Table 1. Main characteristics of the included studies.

First Author, Year of Publication	Country	Study Design	Number of Patients	Intervention	Control	Administration	Timepoints of Evaluation (weeks) [a]
Studies included in meta-analysis							
Albalat, 2019 [15]	Egypt	RCT	80	PRP injection (double-spin method)	TrA injection (5 mg/mL)	3–5 sessions, 2-week intervals	12
Fawzy, 2020 [17]	Egypt	RCT	31	PRP injection (single-spin method)	TrA injection (5 mg/mL)	3 sessions, 4-week intervals	12
Hegde, 2020 [18]	India	RCT	50	PRP injection (double-spin method)	TrA injection (10 mg/mL), placebo	3 sessions, 4-week intervals	16
Kapoor, 2020 [19]	India	RCT	40	PRP injection (single-spin method)	TrA injection (10 mg/mL)	4 sessions, 3-week intervals	3, 6, 9, 12 [b], 24
Studies included only in systematic review							
Balakrishnan, 2020 [16]	India	RCT	32	PRP injection (double-spin method)	TrA injection (10 mg/mL)	3 sessions, 4-week intervals	0, 4, 8, 12
Trink, 2013 [20]	Italy	RCT	30	PRP injection (single-spin method)	TrA injection (2,5 mg/mL), placebo	3 sessions, 4-week intervals	8, 24, 48

[a] weeks after the first treatment session; [b] timepoint used in our calculations. RCT: randomized clinical trial; PRP: platelet-rich plasma; TrA: triamcinolone acetonide.

Table 2. Patient characteristics of the studies included in the meta-analysis.

	Intervention (PRP) Group					Control (TrA) Group				
First Author, Year of Publication	Number of Patients	Age, Mean (SD)	Sex (Female % of Total)	Baseline SALT Score, Mean (SD)	Post-Treatment SALT Score, Mean (SD)	Numberof Patients	Age, Mean (SD)	Sex (Female % of Total)	Baseline SALT Score, Mean (SD)	Post-Treatment SALT Score, Mean (SD)
Albalat, 2019 [15]	40	30.8 (7.5)	15.0	1.7 (0.9)	0.4 (0.7)	40	36.3 (11.3)	15.0	1.7 (0.8)	0.5 (0.8)
Fawzy, 2020 [17]	17	31.4 (10.6)	23.5	5.6 (8.4)	3.8 (8.4)	14	34.2 (12.3)	28.6	4.2 (4.4)	1.4 (1.8)
Hegde, 2020 [18]	25	N/A	N/A	7.2 (3.8)	4.0 (5.3)	25	N/A	N/A	8.8 (5.8)	3.1 (5.1)
Kapoor, 2020 [19]	20	25.4 (4.9)	45.0	4.4 (2.5)	3.2 (2.0)	20	28.8 (8.6)	65.0	9.0 (1.4)	3.1 (0.8)

SD: standard deviation; N/A: data not available; PRP: platelet-rich plasma; TrA: triamcinolone acetonide; SALT score: Severity of Alopecia Tool score.

3.3. Primary Outcome (SALT score)

3.3.1. PRP Compared to Triamcinolone Acetonide

Two studies evaluated the post-treatment SALT score 12 weeks after the first treatment session [15,17], one study 16 weeks after the first treatment session [18], and one at multiple timepoints: weeks 3, 6, 9, 12, and 24 [19] (see Table 1). We used the SALT score of the 12th-week evaluation of this study for our meta-analytical calculations. The pooled MDs from four RCTs with a total of 201 subjects did not show a significant difference in the mean change in the SALT scores between the PRP and TrA groups (MD = −2.04; CI: −4.72–0.65; I^2 = 80.4%; p = 0.14) (see Figure 2).

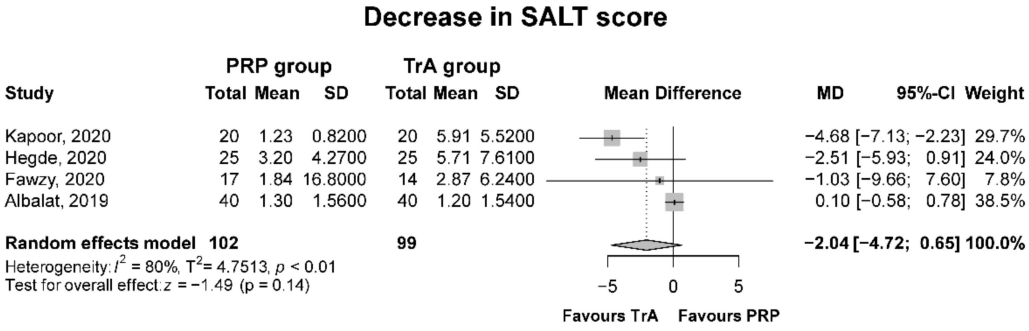

Figure 2. Forest plot for the mean decrease in the SALT score; platelet-rich plasma (PRP) compared to triamcinolone acetonide (TrA).

Due to the high heterogeneity, we performed a leave-one-out analysis; the results are detailed in Table 3.

All studies included in our systematic review and meta-analysis showed a significant decrease in the SALT scores for PRP and TrA groups [15–20].

Two of the six publications originally selected used the SALT score as a primary outcome; however, due to missing data, we could not include them in our meta-analysis.

Balakrishnan et al. found no statistically significant difference between the SALT scores of the two groups when compared at different timepoints; however, the response in the PRP group was better than that in the TrA group [16]. When the decrease in the SALT score at different timepoints was investigated, there was a significant difference in the decrease in the SALT score between the PRP group and the TrA group at the second evaluation, 4 weeks after the first treatment session (p = 0.028) [16]. After the last evaluation (12 weeks after the first treatment session), there was no statistically significant difference

between the two groups [16]. Trink et al. found that the SALT score decreased significantly in the PRP group compared with the TrA group ($p < 0.001$) [20].

Table 3. Results of leave-one-out analysis.

	Quantitative Data Synthesis					Heterogeneity	
Study	**PRP Group (*n*)**	**TrA Group (*n*)**	**Effect Size**	**95% CI**	***p* Value**	**I^2**	**T^2**
Overall Effect	102	99	−2.04	[−4.72; 0.65]	0.14	80.4%	2.24
Leave-one-out sensitivity analysis							
Albalat, 2019 [15]	62	59	−3.79	[−5.75; −1.83]	0.001	0.0%	0.04
Fawzy, 2020 [17]	85	85	−2.15	[−5.14; 0.83]	0.15	87.0%	5.57
Hegde, 2020 [18]	77	74	−1.94	[−5.62; 1.73]	0.30	85.0%	7.32
Kapoor, 2020 [19]	82	79	−0.57	[−2.54; 1.41]	0.57	9.0%	1.29

PRP: platelet-rich plasma; TrA: triamcinolone acetonide; CI: confidence interval.

The number of patients with complete hair regrowth is detailed below, since we could not conduct a meta-analysis due to the highly variable evaluation timepoints of the studies.

Trink et al., found that, 12 months after the first treatment session, complete remission was achieved in 26.6% of the patients in the TrA group and 60.0% of the patients in the PRP group [20]. Albalat et al. reported 16 patients (40.0%) in the TrA group and 18 patients (45.0%) in the PRP group with complete remission 8 weeks after the first treatment session [15]. Hegde et al. found that 10 patients (40.0%) in the TrA group and 11 patients (44.0%) in the PRP group achieved nearly complete hair regrowth 5 months after the first treatment ($p = 0.779$) [18].

Two studies also used additional categorical scales to describe the decrease in the SALT score, both referring to them as the Hair Regrowth Grade (HRG) scale [16,19]. Comparing the HRG scale between PRP and TrA treatment, Balakrishnan et al. found no statistical significance, while Kapoor et al., reported a significant difference ($p = 0.0002$): more patients from the TrA group were in the grade IV (50–74% reduction in SALT score) and grade V (>74% reduction in SALT score) categories after treatment compared with the PRP group [16,19].

3.3.2. PRP Compared to Placebo

Trink et al., found that PRP significantly increased hair regrowth in AA lesions compared with the placebo ($p < 0.001$). PRP treatment also led to increased hair regrowth when compared with the untreated side of the scalp ($p < 0.001$) [20].

Hegde et al. found that, 12 weeks after the first treatment session, PRP showed a higher percentage of regrowth than the placebo ($p = 0.0108$) [18].

3.4. Secondary Outcomes

3.4.1. Patient Safety

Adverse Effects

Balakrishnan et al., Hegde et al., and Trink et al. did not record any side effects in the enrolled patients, nor were serious side effects observed in the study by Albalat et al. [15,16,18,20]. The only side effects observed in the study by Albalat et al. were erythema and a burning sensation after treatment sessions, without significant differences between the two groups [15]. Kapoor et al. reported atrophy in five patients from the TrA group, and the difference between the PRP and TrA groups was significant ($p = 0.047$) [19].

Administration-Related Pain

Three patients in the study by Balakrishnan et al. reported severe pain during administration in the PRP group, while there was none in the TrA group. Hegde et al. and Kapoor et al. also found significant differences between the two groups regarding pain ($p < 0.05$): significantly higher visual analog scale (VAS) scores were recorded and a higher number of patients reported pain in the PRP group ($p < 0.0001$) [18,19].

Recurrence Rates

Trink et al. reported a 38% relapse in the TrA group and no relapse in the PRP group 6 months after the first treatment. Twelve months after the first treatment, 71% of the patients in the TrA group experienced a recurrence of the disease, whereas this rate was 31% of the PRP-group patients [20]. At the follow-up visit 6 months after the first treatment, two patients (5%) in the PRP group and 10 patients (25%) in the TrA group reported recurrence, according to Albalat et al. [15].

Further secondary outcomes are detailed in the Supplementary Results in the Supplementary Materials.

3.5. Risk of Bias Assessment

The results of the assessment of the risk of bias of the studies included in the meta-analysis and systematic review can be seen in Figures S1–S16 in the Supplementary Materials. None of the studies included in the meta-analysis were at high risk of bias. In three articles, the randomization process [15,17,19], and in two articles, the measurement of the outcome [18,19], were ranked as "some concerns". Deviation from the intended intervention, missing outcome data, and the selection of the reported results domains were at low risk of bias.

3.6. Quality of Evidence

The quality of evidence was low for the primary outcome (SALT score).

4. Discussion

The studies included in our systematic review and meta-analysis all showed a significant decrease in the SALT score in both the PRP and TrA groups [15–20]. The pooled MDs from the four RCTs with a total of 201 subjects did not show a significant difference in the mean change in the SALT score between the PRP and TrA groups. Although we could not conduct a meta-analysis comparing PRP with a placebo, the included studies all concluded the superiority of PRP treatment [18,20]. These results could prove the efficacy of PRP as a steroid-free treatment modality. However, several factors could have influenced these results, such as the different doses of TrA used and the length of the follow-up.

The strength of the effect of TrA can be dose-dependent: RCTs investigating the most effective dilution of TrA showed that the 10 mg/mL dose achieved the best therapeutic response; however, due to the dose-dependent increasing risk of adverse effects, it is advised to start the treatment with lower doses [28,29]. Two of the four studies included in our meta-analysis used 5 mg/mL TrA, and two studies used 10 mg/mL TrA as a comparator [19]. The decrease in the SALT score was higher in the studies using a higher dose of TrA; nevertheless, one of the latter studies registered atrophy in five cases, assumably due to the higher doses of TrA. On the contrary, PRP can be used in an unlimited number of treatment sessions without increasing the risk of adverse effects [15,16,18–20].

Complete remission and recurrence are also important factors when choosing a therapy. Only one included RCT followed up patients for more than 6 months, and they recorded a higher number of cases with complete remission and lower recurrence rates with PRP compared with TrA one year after the first treatment session [20]. Albalat et al. followed up patients for 6 months, and they also recorded lower recurrence rates in the PRP group 6 months after the first treatment session [15].

Pain is also a considerable factor that can affect the utility of a therapeutic modality. Pain related to the treatment was more frequently reported in the PRP group; however, it could possibly be decreased with the application of a pre-treatment topical lidocaine–prilocaine cream with occlusion or with a minimally invasive application technique, such as microneedling [16,18,19,30].

4.1. Strengths and Limitations

Our systematic search was conducted only 6 months before the submission of this manuscript; therefore, it includes every relevant study regarding this topic. We implemented a rigorous selection protocol and only included RCTs to obtain the highest possible quality of evidence, and it is also notable that all included studies were published recently. To our knowledge, this is the first meta-analysis to date comparing the efficacy of PRP to TrA, the first line of treatment of limited patchy AA.

The two main limitations of this study are the small sample size and high heterogeneity. Besides the small sample size, the inclusion of the study of Kapoor et al. can also be a potential reason for the high heterogeneity. Kapoor et al. used higher doses of TrA, the treatment sessions were more frequent compared with the other studies, and the baseline SALT score was also higher in the TrA group than in the PRP group. These discrepancies could explain the significantly higher mean decrease in the SALT score in the TrA group ($p < 0.0001$). The leave-one-out analysis showed that, when excluding the study of Kapoor et al., I^2 decreased to 9.0% and the confidence interval narrowed. Different preparation methods of PRP in the included studies could also lead to high heterogeneity, since the superiority of the double-spin method to the single-spin method was shown in previous studies [11,12].

4.2. Implications for Research

Our study demonstrated the efficacy of PRP in the treatment of patchy AA; however, further high-quality RCTs providing both within- and between-group detailed descriptive statistics are needed to better assess the efficacy and to strengthen the quality of evidence. The implementation of objective, comparable outcome measurements besides the SALT score could help to better assess complete remission, recurrence rates, and adverse effects. This would contribute to a better understanding of the pros and cons of each treatment modality and would also enable future systematic analysis using these parameters to further strengthen the quality of the current evidence.

Future RCTs should also focus on the comparison of PRP with different doses of TrA, since, while high doses of TrA lead to better improvement, they may also increase the risk of adverse effects [28,29]. A steroid-free treatment option, such as PRP, as a first-choice treatment could be beneficial, even if it shows slower improvement.

Follow-up protocols longer than 4 months would make it possible to see further differences between the two treatment modalities in order to better assess the complete remission and recurrence rates.

4.3. Implications for Practice

Platelet-rich plasma is a steroid-free treatment modality that can be used in a virtually unlimited number of treatment sessions without increasing the risk of steroid-specific adverse effects [15,16,18–20]. The adverse effects of TrA treatment, such as atrophy, teleangiectasia, and hypopigmentation, can be especially problematic in the facial region. Since PRP is also safely used in facial rejuvenation, it could be an optimal therapeutic choice in facially localized AA [7,31,32]. The application of PRP with microneedling or fractional carbon dioxide laser treatment could be a more convenient method of administration, particularly in the facial region and in extensive cases of AA [30].

5. Conclusions

Platelet-rich plasma is a promising topical steroid-free treatment modality in the therapy of alopecia areata. No significant difference was found between PRP and TrA treatment; however, further high-quality RCTs are needed to better assess the efficacy of PRP and to strengthen the quality of evidence. PRP can be used in a virtually unlimited number of treatment sessions without increasing the risk of steroid-specific adverse effects, and it can also be an alternative option in the treatment of facially localized AA, in extensive cases of AA, or in cases of steroid phobia.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines10081829/s1, Supplementary Results: Secondary outcomes. Figure S1: Risk of bias assessment of the SALT score outcomes of the studies included in the meta-analysis using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S2: Risk of bias assessment of the SALT score outcomes of the studies included in the meta-analysis, broken down to tools, shown as percentage. Figure S3: Risk of bias assessment of the SALT score outcomes of the studies included in the systematic review using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S4: Risk of bias assessment of the SALT score outcomes of the studies included in the systematic review, broken down to tools, shown in percentage. Figure S5: Risk of bias assessment of the adverse effect outcomes of the studies included in the systematic review using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S6: Risk of bias assessment of the adverse effect outcomes of the studies included in the systematic review, broken down to tools, shown as percentages. Figure S7: Risk of bias assessment of the administration-related pain outcomes of the studies included in the systematic review using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S8: Risk of bias assessment of the administration-related pain outcomes of the studies included in the systematic review, broken down to tools, shown as percentages. Figure S9: Risk of bias assessment of the recurrence rate outcomes of the studies included in the systematic review, using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S10: Risk of bias assessment of the recurrence rate outcomes of the studies included in the systematic review, broken down to tools, shown as percentages. Figure S11: Risk of bias assessment of the dermoscopic evaluation outcomes of the studies included in the systematic review, using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S12: Risk of bias assessment of the dermoscopic evaluation outcomes of the studies included in the systematic review, broken down to tools, shown as percentages. Figure S13: Risk of bias assessment of the Ki-67-level outcomes of the studies included in the systematic review, using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S14: Risk of bias assessment of the Ki-67-level outcomes of the studies included in the systematic review, broken down to tools, shown as percentages. Figure S15: Risk of bias assessment of the burning/itching sensation outcomes of the studies included in the systematic review, using the revised tool for assessing the risk of bias in randomized trials (Rob 2). Figure S16: Risk of bias assessment of the burning/itching sensation outcomes of the studies included in the systematic review, broken down to tools, shown as percentages.

Author Contributions: (CRediT (Contributor Roles Taxonomy) author statement) [1] F.A.M.: conceptualization, project administration, data curation, visualization, and writing—original draft. K.I.: conceptualization and data curation. F.D.: conceptualization, data curation, and methodology. P.F.: methodology, formal analysis, validation, and visualization. L.V.K.: conceptualization and methodology. K.D.K.: conceptualization and data curation. N.M.W.: conceptualization and supervision. D.C.: conceptualization, methodology, and supervision. P.H.: conceptualization, methodology, and supervision. A.B.: conceptualization, methodology, supervision, and writing—original draft. All authors provided critical conceptual input and approved the final version of the article. All authors have read and agreed to the published version of the manuscript.

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