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

Ph.D. Thesis

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

Mikhail Bulgakov, The Master and Margarita

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS 6

2. STUDENT PROFILE 9

2.1. Vision and mission statement, specific goals 9

2.2. Scientometrics 9

2.3. Future plans 9

3. SUMMARY OF THE PH.D. 10

4. GRAPHICAL ABSTRACT 11

5. INTRODUCTION 12

5.1. Overview of the topic 12

5.1.1. What is the topic? 12

5.1.2. What is the problem to solve? 12

5.1.3. What is the importance of the topic? 12

5.1.4. What would be the impact of our research results? 12

5.2. Inflammation – a key player in dermatology and rheumatology 13

5.3. The implementation of innovative disease-monitoring and modifying methods in dermatology and rheumatology 14

5.3.1. Multi-biomarker disease activity score, a novel disease monitoring system 14

5.3.2. Platelet-rich plasma, a novel disease-modifying treatment modality 16

6. OBJECTIVES 18

6.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis 18

6.2. Study II. – Investigating the efficacy of PRP in chronic wound management 18

6.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata 18

7. METHODS 19
7.1. Literature search and eligibility criteria 19
7.2. Study selection and data collection 19
7.3. Quality assessment 20
7.4. Data synthesis and analysis 20
8. RESULTS 22
8.1. Search and selection, characteristics of the included studies 22
8.1.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis 22
8.1.2. Study II. – Investigating the efficacy of PRP in chronic wound management 29
8.1.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata 37
8.2. Results of the quantitative analysis 39
8.2.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis 39
8.2.1.1. MBDA score for the assessment of disease activity 39
8.2.1.2. MBDA score for the assessment of radiographic progression 42
8.2.2. Study II. – Investigating the efficacy of PRP in chronic wound management 45
8.2.2.1. Complete closure 45
8.2.2.2. Reduction of wound area 46
8.2.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata 48
8.2.3.1. Reduction of SALT score 48
8.3. Qualitative analysis 48

8.4. Quality assessment 48

8.4.1. Study I. – Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis 48

8.4.2. Study II. – Investigating the efficacy of PRP in chronic wound management 49

8.4.3. Study III. – Investigating the efficacy of PRP in the treatment of alopecia areata..... 49

9. DISCUSSION..... 50

9.1. Summary of findings, international comparisons..... 50

9.2. Strengths..... 52

9.3. Limitations..... 53

10. CONCLUSION 54

11. IMPLEMENTATION FOR PRACTICE 55

12. IMPLEMENTATION FOR RESEARCH..... 56

13. IMPLEMENTATION FOR POLICYMAKERS 58

14. FUTURE PERSPECTIVES 59

15. REFERENCES..... 60

16. BIBLIOGRAPHY 75

16.1. Publications related to the thesis 75

16.2. Publications not related to the thesis 75

17. ACKNOWLEDGEMENTS 78

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

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.

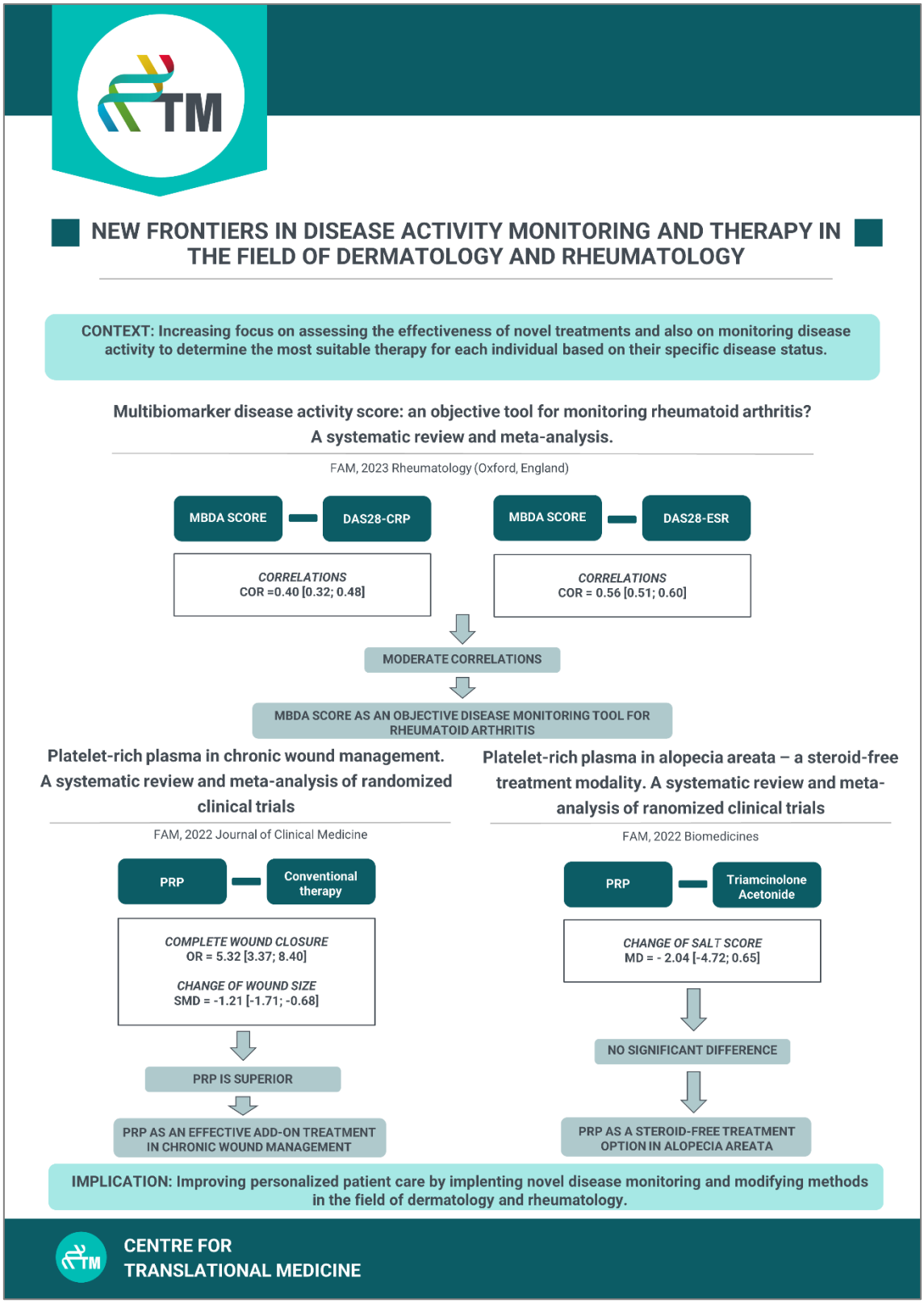
The advancements achieved in dermatology and rheumatology call for an assessment of the efficacy of novel treatments, while also highlight the importance of monitoring disease activity to facilitate personalized treatment.

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**.

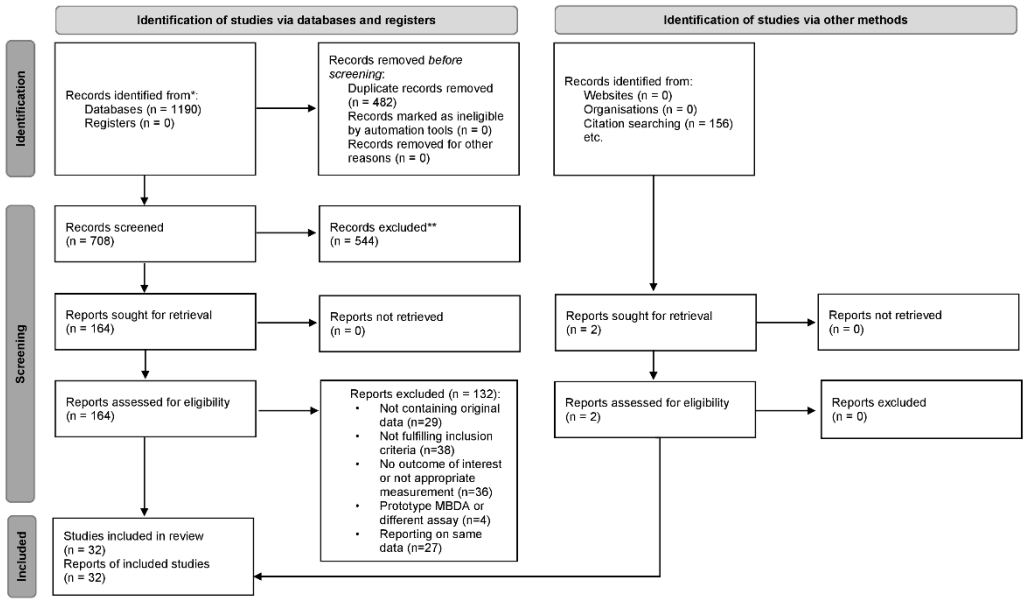


Figure 1. PRISMA Flow Diagram of the screening and selection process for Study I. (66)

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**.

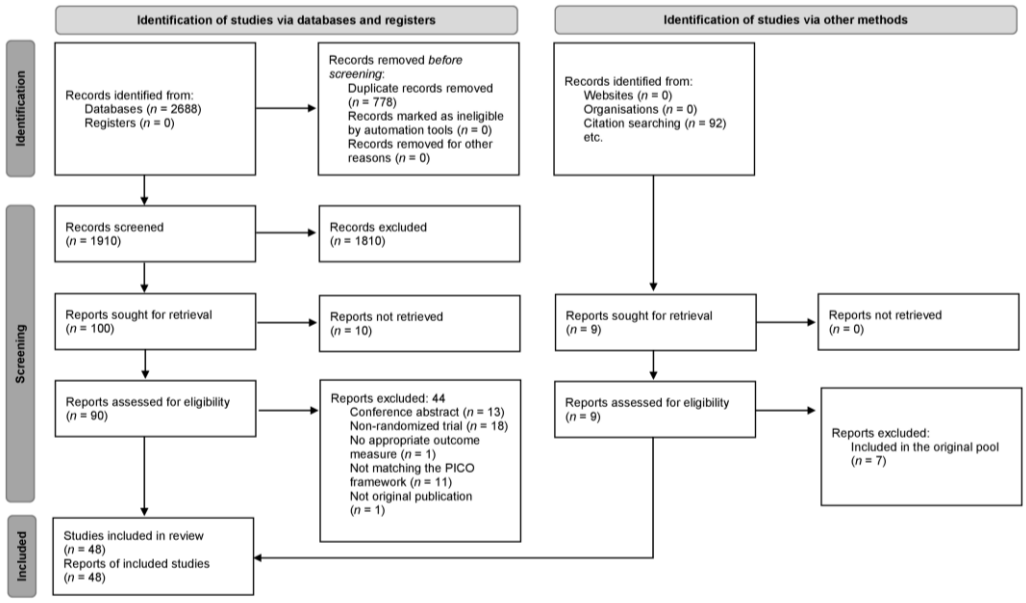


Figure 2. PRISMA Flow Diagram of the screening and selection process for Study II. (67)

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**.

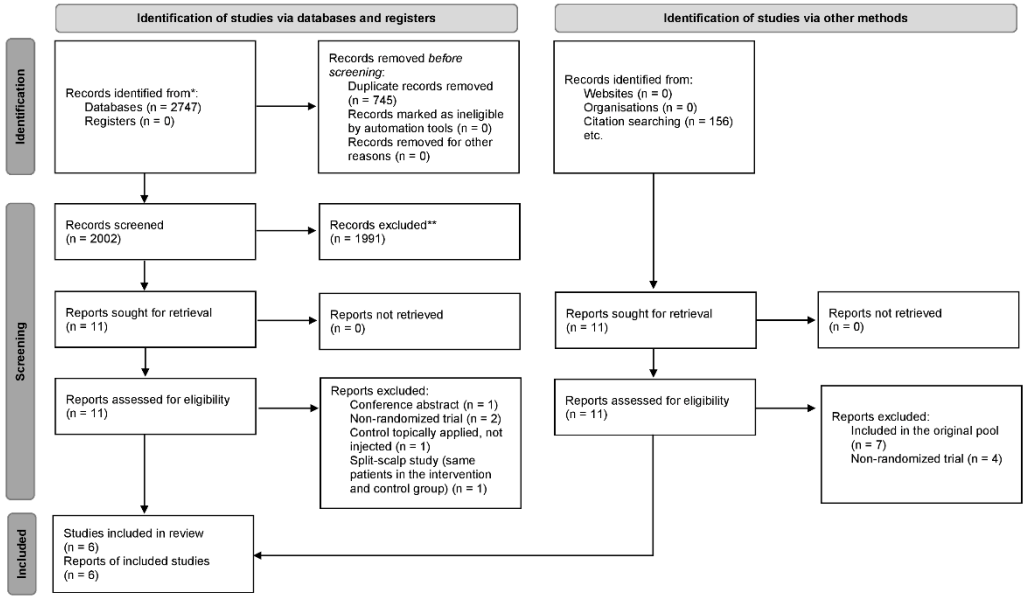


Figure 3. PRISMA Flow Diagram of the screening and selection process for Study III. (68)

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).

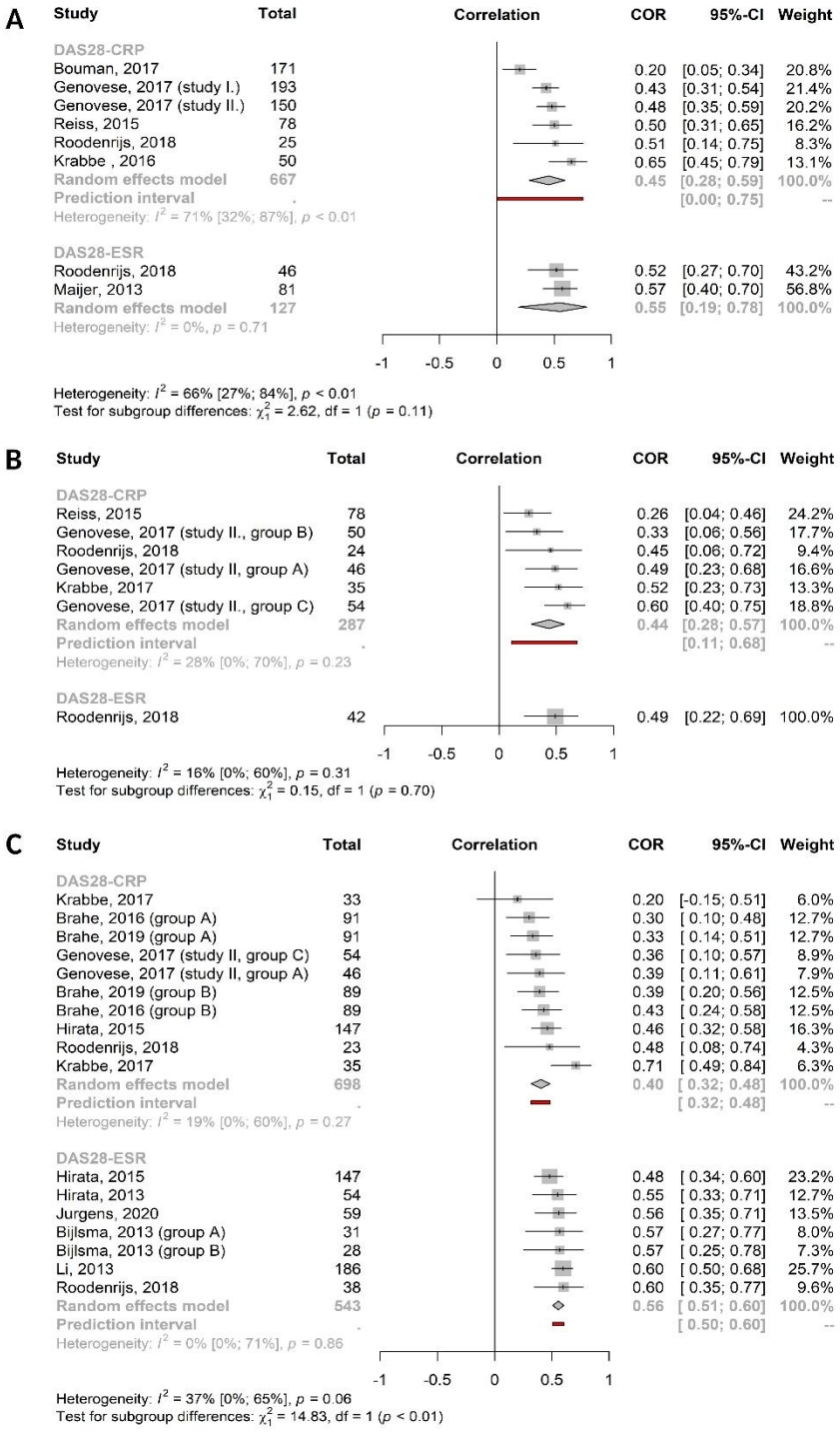


Figure 4. Forest plot for the correlation of MBDA score with DAS28-CRP/ESR **(A)** Forest plot for the correlation of baseline MBDA score with baseline DAS28-CRP/ESR **(B)** Forest plot for the correlation of follow-up MBDA score with follow-up DAS28-CRP/ESR **(C)** Forest plot for the change of baseline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

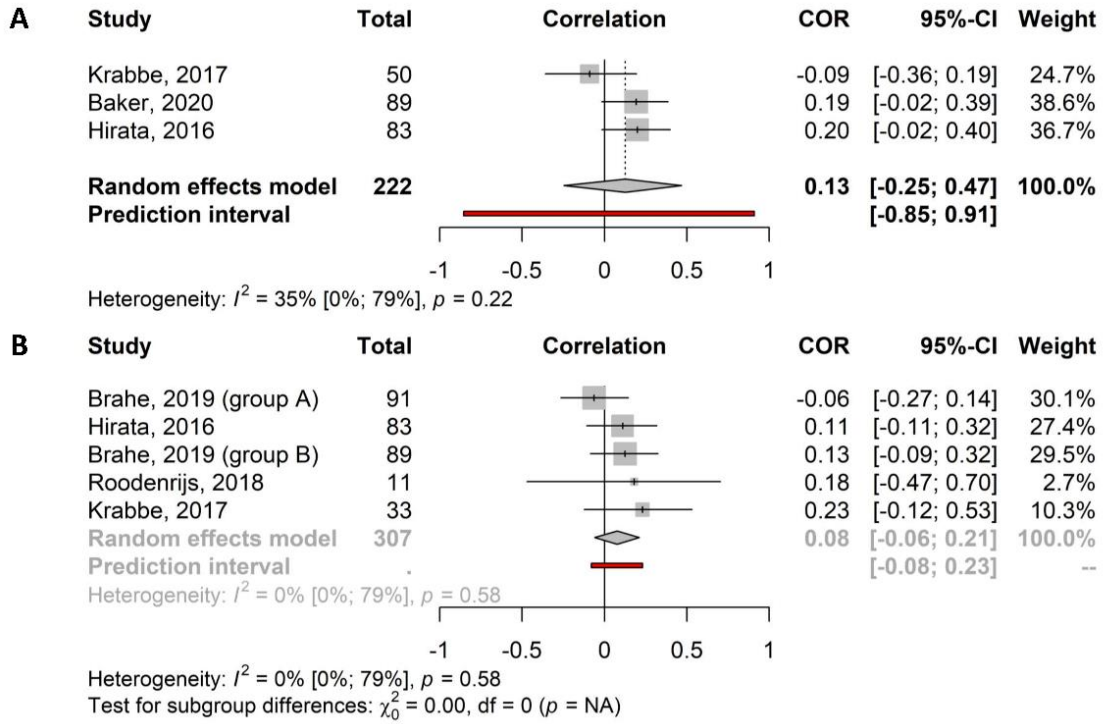


Figure 5. Forest plots for the correlations of MBDA score with SvdH score **(A)** Forest plot for the correlation of baseline MBDA score with baseline SvdH score **(B)** Forest plot for the correlation of the change of MBDA score with the change of SvdH score (66)

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).

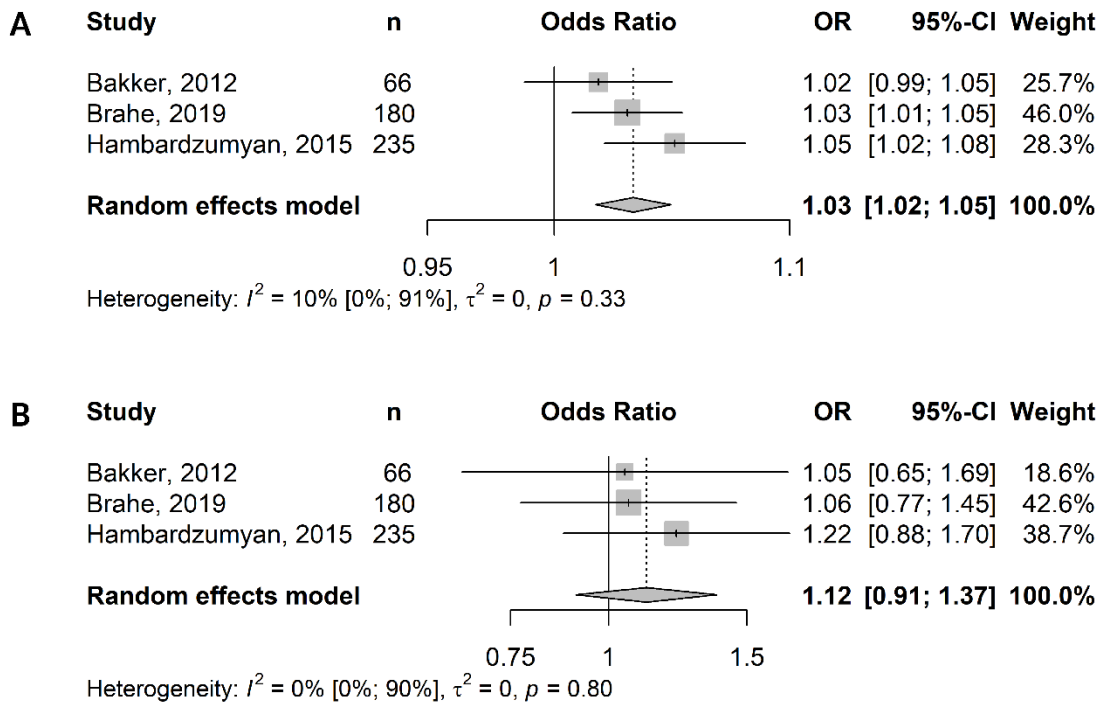


Figure 6. Forest plots for the predictive value of MBDA score and DAS28-CRP. for radiographic progression (**A**) Forest plot for the predictive value of MBDA score (**B**) Forest plot for the predictive value of DAS28-CRP (66)

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).

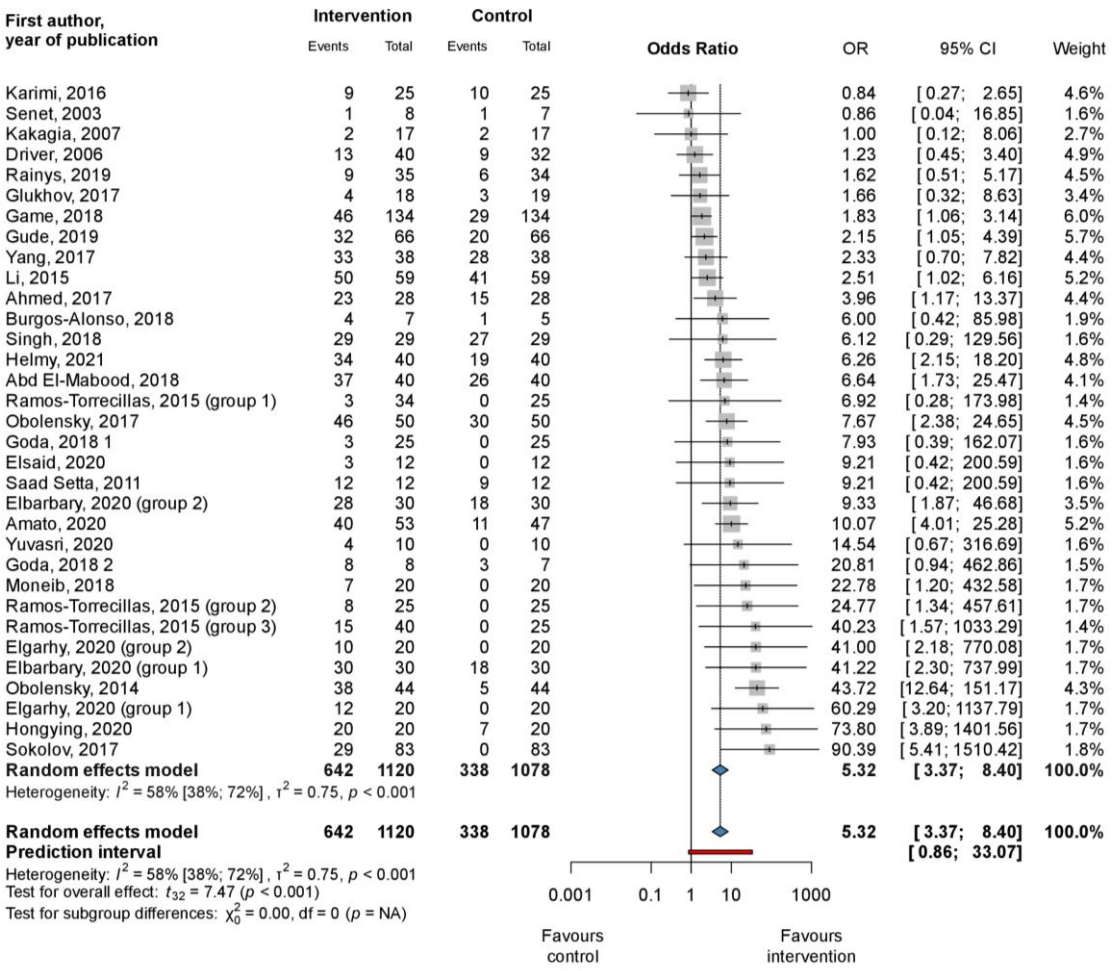


Figure 6. Forest plot for complete closure, platelet-rich plasma compared to conventional ulcer therapy (67)

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).

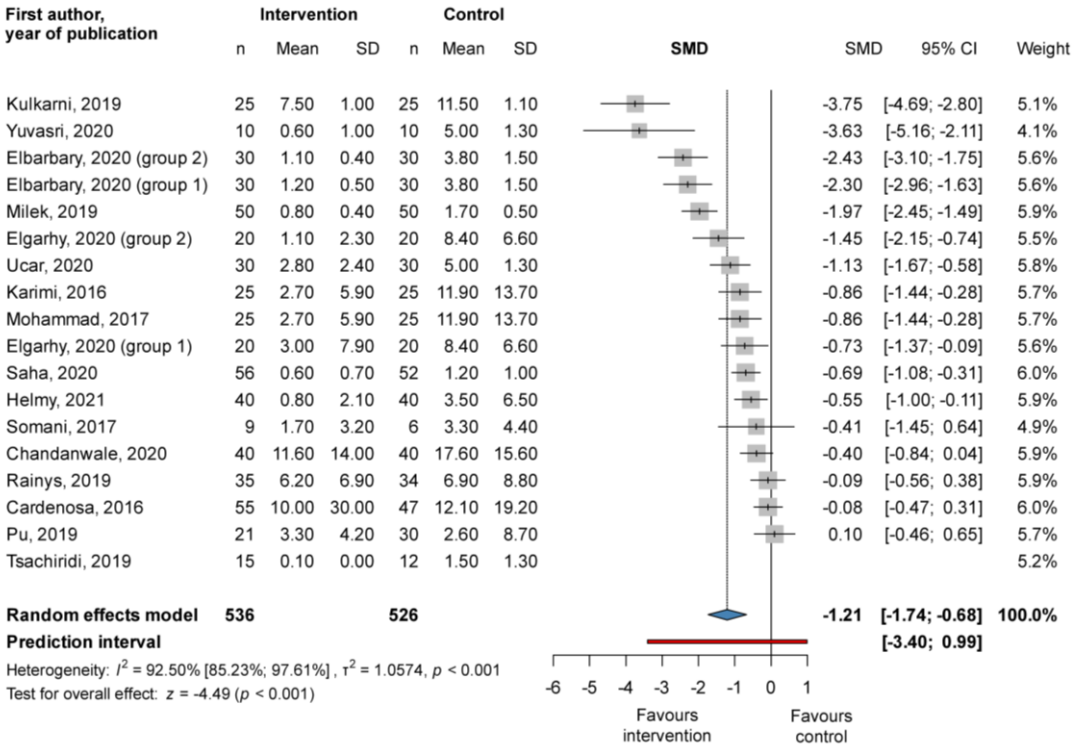


Figure 7. Forest plot for the reduction of wound area, platelet-rich plasma compared to conventional ulcer therapy (67)

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).

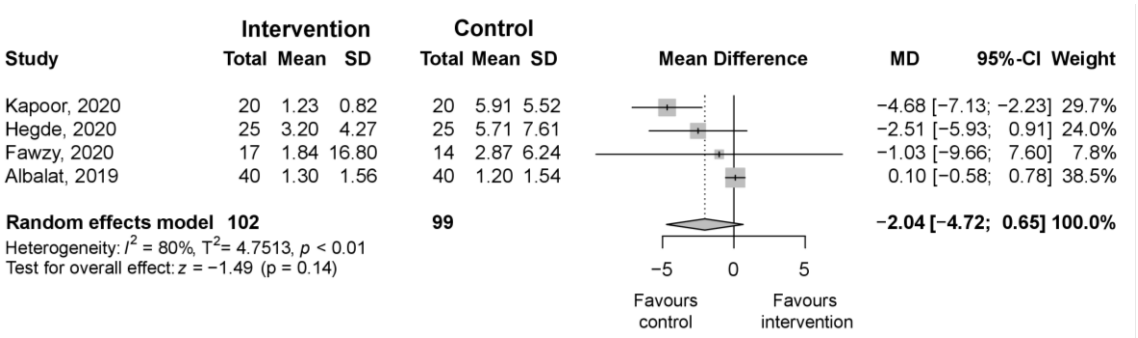


Figure 8. Forest plot for mean decrease of SALT score, platelet-rich plasma (PRP) compared to triamcinolone acetonide (TrA) (68)

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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