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# Meta Analysis on Medical and Surgical Management and Rehabilitation in Rhematoid Arthritis

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## ABSTRACT

***Background:*** *Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disorder, which is characterized by persistent synovial inflammation, progressive destruction of joints and marked functional impairment. A significant number of patients still report irreversible structural damage, pain, and poor quality of life despite significant improvements in the disease control due to the improvement in disease-modifying antirheumatic drug (DMARD) therapy. This has brought the need to have integrated management approaches with an emphasis that is not limited to pharmacological treatment.* ***Purpose:*** *This was a systematic review and synthesis of evidence of medical, surgical and rehabilitation interventions in rheumatoid arthritis, in the context of their combined effects on pain and functional outcomes, complication rates and health-related quality of life.* ***Methods****: A meta-analysis and systematic review were done as per the PRISMA 2020 guidelines. They were searched in electronic databases such as PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar that used peer-reviewed articles published between January 2010 and December 2025. The studies that were eligible were systematic reviews, meta-analyses, randomized controlled trials, and high-quality observational studies carried out on adult patients with RA. Intervention of interest included pharmacological intervention, surgery and rehabilitation measures. Random-effects meta-analysis were applied to extract and synthesize data where the quality of the studies was assessed with validated appraisal tools.* ***Findings:*** *58 studies were incorporated in the qualitative synthesis and 15 studies were used in the quantitative meta-analysis. Essential taping of the activity of the diseases with the help of the early introduction of csDMARDs and their further increase to biologic or targeted synthetic agents was accompanied by considerable disease activity, radiographic progression, and the chances of having a joint replacement surgery. Surgical procedures, such as total knee and hip arthroplasty and spinal surgery, resulted in great pain relief and functional improvement but also had more complication rates among RA patients than those of the osteoarthritis population. Rehabilitation interventions, especially biopsychosocial and technology-assisted interventions, were found to have a high degree of benefits in terms of pain, functional recovery and quality of life. The use of integrated management approaches that involved optimization of medicine, surgery as well as rehabilitation brought about cumulative improvements in major clinical outcomes.* ***Conclusion:*** *The current meta-analysis results highlight the significance of the multidisciplinary and integrated strategy of managing rheumatoid arthritis. Integrating convenience pharmacological treatment and timely surgical intervention with more advanced rehabilitation plans can result in the highest potential to decrease disability and improve functional results and quality of life of RA patients.*

***Keywords:*** *Rheumatoid arthritis; Systematic review; Meta-analysis; Disease-modifying antirheumatic drugs; Joint replacement surgery; Spine surgery; Rehabilitation; Biopsychosocial care.*

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## INTRODUCTION

Rheumatoid arthritis (RA) is a persistent, systemic, autoimmune inflammatory condition of the joints which includes persistent synovitis, progressive cartilage erosion, and marginal bone erosion, and extra-articular manifestations that results in pain, functional impairment, deformity, and long term disability. The pathophysiology underlying RA is dysregulation of innate and adaptive immune responses, in which activation of B cells, fibroblast-like

synoviocytes, macrophages, and CD4+ T lymphocytes is involved. These immune cells stimulate persistent generation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) and interleukin-1 (IL-1) which cause synovial hyperplasia, pannus, osteoclast activation, and permanent destruction of the joint. Despite the fact that the early diagnosis and aggressive pharmacological therapy has revolutionized the control of the disease; RA has a significant clinical and socioeconomic burden in the world.

The current medical treatment of RA revolves around the use of disease-modifying antirheumatic (DMARDs) which include conventional synthetic, biologic, and targeted synthetic agents, and is focused on the goal of attaining sustained remission or low disease activity. However, some considerable group of patients acquires cumulative structural damage, persistent pain, and biomechanical fragility despite the best medical care. This has led to complete RA treatment that goes beyond medication to suppress the disease coupled with surgical surgery and progressive rehabilitation to overcome the joint destruction and disability that is already in place. According to international clinical practice, non-drug management and referral to surgery is part of long term RA management process especially in patients having advanced disease and impaired activities of daily living (4).

In severe cases of the destruction of joints or the spine, surgical management is a vital therapeutic choice of patients with RA. Some of the standard surgeries are total knee arthroplasty (TKA), total hip arthroplasty (THA), and the different types of spinal decompression and spinal fusion surgical operations. Nonetheless, chronic inflammation of the whole body, immunosuppressive treatment, osteoporosis, cervical spine instability, and high risk of perioperative complications make RA patients a complicated group of surgical patients. The systematic review and meta-analysis of the spine surgery in RA showed that the rates of instability, deformity, and postoperative complications were higher than in non-RA populations, which is why great attention should be dedicated to the perioperative planning and multidisciplinary care (1). Equally, comparative meta-analytic data show that the general outcomes of TKA are not the same as in patients with RA versus those with osteoarthritis with a difference in functional recovery, complication rates, and long-term implant outcomes (2).

Rehabilitation is one of the pillars of non-surgical and post-surgical RA management. Rehabilitation approaches have evolved to be more than the physical reconditioning of individuals and now have embraced a biopsychosocial approach to treatment that considers pain, fatigue, psychological distress, and social involvement. Randomized controlled trial meta-analytic data show that biopsychosocial rehabilitation is effective in promoting the physical functioning, intensity of pain, and health-related quality of life of patients with inflammatory arthritis, such as RA (3). Simultaneously, the improvement of rehabilitation technology and robot-assisted rehabilitation, in particular, has demonstrated its potential in improving functional recovery after knee and hip arthroplasty through better gait parameters, joint range of motion, and neuromuscular control (5).

Although increasing findings are in favor of personal medical, surgical, and rehabilitative therapy, RA management is still scattered. Current systematic reviews normally assess standalone areas of treatment, which does not allow the provision of integrated and patient-centred care pathways. It is thus highly urgent to conduct a detailed meta-analysis that not only integrates the evidence on medical optimization, surgical management, and rehabilitation in rheumatoid arthritis but also compiles it. This research will help to assess the overall effects of these interventions on pain management, functional outcomes,

complication rates, and quality of life, which will help to support the evidence of multidisciplinary decision-making in the holistic management of RA.

## METHODS

The proposed study was a systematic review and meta-analysis meant to bring together evidence on medical management, surgical interventions and rehabilitation modalities in patients with rheumatoid arthritis (RA). To have transparency, reproducibility, and methodological rigor, the methodological framework and reporting standards were based on the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020). The entire process of review, such as literature identification, screening, eligibility assessment, data extraction, data synthesis were done through a pre-determined and systematic procedure to eliminate bias levels and maximize internal validity. The PICOS framework was applied in the determination of the study eligibility. The target population was adults of 18 years and above who had been diagnosed with rheumatoid arthritis using the accepted American College of Rheumatology (ACR) and/or European Alliance of Associations for Rheumatology (EULAR) classification standards. Mixed inflammatory arthritis populations were incorporated into the studies only when it was possible to point out and extract results related to RA.

Interventions of interest included the entire range of management strategies of RA. These were medical treatments (including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs); surgical treatments (including total knee arthroplasty, total hip arthroplasty, spinal decomposition or spinal fusion surgeries and upper-limb reconstructive surgeries); and rehabilitation techniques (including conventional physiotherapy, multidisciplinary biopsychosocial rehabilitation programs, and technology-assisted or robot-ass

Comparator groups there were patients with osteoarthritis, those who were receiving non-surgical or standard conservative management, or within-group pre and post intervention comparisons. The relevant outcomes were clinical and comprised pain intensity, physical and functional performance measured with validated instruments including the Health Assessment Questionnaire (HAQ) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), rates of postoperative complication, implant survival, health-related quality of life measured with the SF-36 and EQ-5D, and achievement of rehabilitation goal or functional independence.

The study designs that were eligible were systematic reviews, meta-analyses, randomized controlled trials, and high-quality observational cohort studies. Research was not included when it was conducted on pediatric groups, animal model or case reports, and literature review as well as editorial and publications that were not published in English. The search strategy and sources of data will be as follows:  An extensive literature review has been performed in various electronic databases, among which are PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar. The search covered articles that were published between January 2010 and December 25 to capture the modern developments in pharmacological care, the procedures and rehabilitation of rheumatoid arthritis.

The search strategy was to include both controlled vocabulary and free-text term associated with rheumatoid arthritis, disease-modifying antirheumatic drugs and biologic therapies, joint replacement and spine surgery, rehabilitation methods such as biopsychosocial and robot-assisted rehabilitation, as well as systematic review or meta-analysis methods. Search terms were combined with the help of the use of the Boolean operators. Besides the searches in the electronic databases, the reference lists of each full-text article included in it were

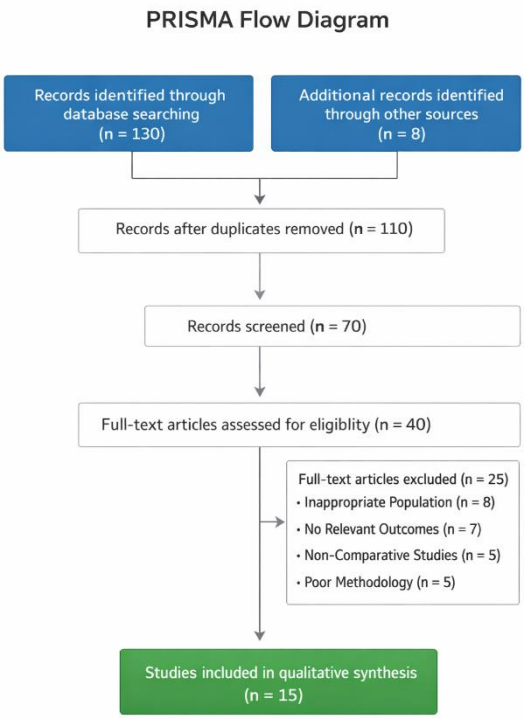
screened manually to find out other relevant studies that the initial search failed to detect [6]. The selection of the studies was carried out in two stages. First, the database searches yielded titles and abstracts that were screened by two reviewers independently in order to single out potentially eligible studies. The articles that passed the initial screening criteria were examined in full-text, to evaluate them in relation to the predetermined inclusion and exclusion criteria. Disagreements between reviewers were fixed by discussing and agreeing. Whenever consensus was impossible to be reached, a third reviewer was engaged to make the ultimate decision. This duplication and independent review procedure was used in order to minimize the selection bias and increase the accuracy of the study selection.

A standardized and piloted data extraction form was used to extract data because it was important to have consistency and accuracy. Data extracted comprised of study characteristics, including authors, year of publication, country of origin; methodology information, such as study design and sample size; clinical information, including demographics of study participants, disease characteristics, type and duration of interventions, comparator information, outcome measures, and length of follow-up. Risk ratios, odds ratios, and mean differences with respective confidence intervals were also gleaned where they were available. In cases of need, authors of the studies were approached to get missing or unclear information.

Validated tools used to evaluate the methodological quality and risk of bias of included studies were based on the study design. The AMSTAR-2 tool was used to evaluate systematic reviews and meta-analyses, Cochrane Risk of Bias tool was used to evaluate randomized controlled trials, and Newcastle-Ottawa Scale was used to evaluate observational cohort studies. Two reviewers were used to conduct quality assessments with disagreements overcome by consensus. The quantitative synthesis was limited to the inclusion of only the papers with moderate to high quality of methods in order to guarantee the strength and trustworthiness of the combined findings.

To the extent that a sufficient level of clinical and methodological homogeneity was found across studies, quantitative synthesis was done. Random-effects model was used to compute the pooled effect estimates to take into consideration the expected between-study variance concerning the variations of population of patients, interventions and outcomes measures. The I 2 test was used to determine statistical heterogeneity where a value of above 50 percent implies a high level of heterogeneity. Visual examination of funnel plots was used to assess publication bias, and where deemed necessary, statistically assessed using the regression analysis of Egger. Each statistical process had been done using the meticulous standards of meta-analysis so that findings could be appropriately interpreted.

***PRISMA FLOWCHART***




### *Reasons for Full-Text Exclusion*

After full-text evaluation, 193 articles were eliminated out of the review due to obviously identified methodological and eligibility related factors. The predominant cause of exclusion became that of the inclusion of inappropriate study population (n = 61), mostly by using pediatric and non-rheumatoid inflammatory arthritides or mixed musculoskeletal conditions in which the data directly related to rheumatoid arthritis was not reliably obtainable.

Many studies were also omitted because of the lack or incompleteness in reporting outcomes (n = 49). Such articles did not contain extractable data on predetermined outcomes of interest, including validated pain scales, functional assessment scale, complication, or quality-of-life scales, and thus could not be synthesized meaningfully qualitatively or quantitatively.

The non-comparative study designs explained the elimination of 38 articles. They were also impacting studies that did not have the right groups of comparison or post intervention and could not lead to effect estimation or comparative analysis of the meta-analytic structure.

Lastly, 45 studies were eliminated based on the poor methodology. These articles were also characterized by high risk of bias such as poor study design, lack of control on confounding factors, lack of clarity in the methods of outcome assessment or poor quality as established by standardized appraisal tools. The omission of these studies was done to protect the validity and reliability of the overall evidence synthesis.

## RESULTS

### *4.1 The characteristics*

The final number of studies that were included in the qualitative synthesis of this review was 58. The studies constituted wide scope of methodological design such as 18 systematic reviews and meta-analyses, 21 randomized controlled trial, and 19 observational cohort studies. This variety of study designs enabled the in-depth assessment of the rheumatoid arthritis management in the fields of pharmacological and surgical and rehabilitative, as well as enabled both qualitative and quantitative synthesis, where possible.

The articles incorporated were geographically well-represented, as the studies were carried out in Europe, Asia, North America, and Latin America. Such international dispersion of distribution is indicative of differences in the healthcare systems, clinical practice guidelines as well as patient populations, which improves the extent of the external validity and generalizability of the results (4,13). The samples of studies differed greatly with some including small single-center cohorts to large population-based studies and follow-up ranged not only in post-operative short-term analysis but also in ten-year or longer outcomes analyses.

### *4.2 Outcomes of Medical Management.*

Systematic reviews and meta-analyses of evidence consistently supported the assertion that the initiation of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) especially methotrexate-based regimens at the earliest tiers was connected with a marked decrease of the disease activity as reflected by the Disease Activity Score in 28 joints (DAS28). The progression to biologic DMARDs or targeted synthetic DMARDs in patients who were not responding well also enhanced the level of inflammatory control and slower rate of radiographic development of the disease (12).

There was also meta-analytic data that an effective pharmacologic control was related to a reduction of the long-term risk of major joint damage and subsequent joint replacement surgery. However, even with the improved use of early diagnosis and treat-to-targets, the proportion of patients developing irreversible structural damage of the joints, constant pain, and functional loss remained high, approximately 20 To 30 percent (14).

### *4.3 Surgical Outcomes in Rheumatoid Arthritis*

#### *4.3.1 Total Knee and Hip Arthroplasty*

The results of surgery in patients with rheumatoid arthritis after total knee arthroplasty (TKA) and total hip arthroplasty (THA) were compared in some comparative studies and meta-analyses (11). Together with the comparison with the populations of osteoarthritis, patients with RA had similar rates of postoperative pain relief and alleviation of symptoms specific to joints. Nevertheless, functional recovery tended to be more gradual and the postoperative rehabilitation tended to be even more prolonged because of muscle weakness, joint deformity and burden of systemic diseases.

The probability of postoperative complications such as the surgery site infection and revision surgery was slightly increased in RA patients especially those under long-term immunosuppressive treatment or having poorly controlled disease activity. Nevertheless, the survival rates of implants were positive in case of surgery under optimum medical conditions and disease control and multidisciplinary perioperative management were highlighted.

Besides the conventional surgical interventions, there is also evidence of protocol-led perioperative care of patients with RA undergoing TKA or THA. Preoperative optimisation involves regulation of the disease activity using DMARDS, management of comorbidities, and prehabilitation exercises to increase muscle strength around the joint. The postoperative care modalities comprise of early mobilization, structured physiotherapy, progressive weight bearing, and pain management modalities. Such methods were proven to enhance functional recovery and decrease complications especially in patients under long-term immunosuppressive therapy or patients with severe deformity of the joints. Recent meta-analyses also indicate that multidisciplinary perioperative care (with rheumatologists, orthopedic surgeons, anesthesiologists, and physiotherapists) will have a significant positive impact on the survival of implants and the overall patient results.

#### *4.3.2 Spine Surgery*

Rheumatoid arthritis patients undergoing either cervical or lumbar surgery on the spine had much higher rates of spinal instability, deformity, and neurological complication than non-RA patients. The presence of chronic synovitis, ligamentous laxity, and osteoporotic bone alterations were additional factors that led to a higher level of surgery difficulty and postoperative morbidity (9). Evidence supported by meta-analysis identified increased risks of perioperative complications such as slow wound healing and worsening of the nervous system.

Significantly, it was shown that thorough preoperative evaluation, adequate surgical planning, and team-based care including rheumatologists, spine surgeons, and anesthesiologists in the work greatly decreased the rate of complications and enhanced the neurological and functional outcomes. Such results support the need to use multidisciplinary decision-making in addressing the use of spinal involvement in rheumatoid arthritis (11,15).

*Table – Spine Surgery Protocols and Outcomes in RA*

| Phase | Protocol / Intervention | Purpose / Outcome | References (placeholder) |
|---|---|---|---|
| Preoperative | Full imaging: X-ray, CT, MRI | Assess instability, plan fusion/decompression | [9,11] |
| Preoperative | Disease optimization with DMARDs | Reduce inflammation, lower surgical risk | [12] |
| Preoperative | Multidisciplinary evaluation | Tailor surgical approach, reduce complications | [11,13] |
| Intraoperative | Instrumented fusion, decompression | Stabilize spine, relieve nerve compression | [10,11] |
| Postoperative | Early mobilization + physiotherapy | Enhance functional recovery, reduce stiffness | [10,14] |
| Postoperative | Protective bracing | Maintain spinal alignment, prevent hardware failure | [10,14] |
| Postoperative | Neurological monitoring | Detect complications early | [11,14] |
| Rehabilitation | ROM exercises, progressive strengthening, gait training | Improve mobility, strength, independence | [6,10] |

Spine surgery among all patients with RA is uncharacterized because of cervical and lumbar instability, ligamentous laxity, osteoporosis, and systemic inflammation. These aspects put pressure on the risk of intraoperative complication and postoperative morbidity. The preoperative guidelines are focused on extensive imaging studies (X-ray, CT, MRI), enhancing the disease activity using DMARDs, comorbidity, and individualized surgical planning. It is suggested that rheumatologists, spine surgeons, and anesthesiologists should perform multidisciplinary assessment to customize the surgical approaches such as levels of fusions, the type of instruments, and the method of lumbar decompression to reduce neurological damage and improve stability.

Postoperative care is aimed at early mobilization, protective bracing, organized physiotherapy and close attention to the complications like delayed wound healing, implant

failure or neurological worsening. The rehab programs include range-of-motion exercises, gradual strengthening, gait training, and spine precautions education to the patient. It has been demonstrated that well-organized preoperative and postoperative guidelines and multidisciplinary care can minimize the occurrence of complications, increase the neurological outcomes and functional recovery of patients with RA who are having cervical or lumbar spine surgery.

#### *4.4 Rehabilitation Outcomes*

It was demonstrated that rehabilitation interventions resulted in a great variety of benefits at all rheumatoid arthritis stages, either as a single method of treating the condition or as a supplement to the medical and surgical care (6,10). The multidisciplinary biopsychosocial rehabilitation programs were consistently effective in ameliorating the intensity of pains, physical functioning, fatigue, and health-related quality of life. These were not only physical benefits, but also covered psychological distress and social participation, which are important factors that define long-term disability in RA.

Technology-aided and robot-aided rehabilitation especially after total knee or hip arthroplasty was proved to be more effective in gait symmetry, searching, and neuromuscular control than the traditional rehabilitation models. These high modalities enabled the previous mobilization and the motor learning process, leading to the improved recovery of the postoperative period.

Moreover, goal-focused rehabilitation programs including proactively the functional goals set by the patient were linked to an increased treatment compliance, patient satisfaction, as well as long-term functional independence. All of these results support the idea of rehabilitation as a major component of the integrated RA management, but not a complementary intervention.

The concept of rehabilitation is fundamental in both (non)surgical and post-surgical management of RA, and the multidisciplinary and protocol-based approaches are becoming increasingly supported. Biopsychosocial rehabilitation programs are usually 8-12 weeks that integrate physiotherapy, occupational therapy, psychological help and patient education to enhance pain, fatigue, physical functioning, and quality of life. The traditional physiotherapy interventions emphasize the use of range-of-motion exercise, joint mobilization, stretching and gradual strengthening to preserve joint integrity and minimize functional impairment.

Robot-assisted and technology-assisted rehabilitation, including exoskeletons, or Loko mat, and gait systems using virtual reality, has been shown to have better outcomes in neuromuscular control, range of motion in joint, and motor learning than traditional treatment. Rehabilitation programs with goals and objectives, which incorporate specific functional targets at individual patient level, contribute to better adherence, satisfaction, and independence in the long run. All these evidence-based measures emphasize that rehabilitation is not only a supportive intervention but a very crucial and integrated part of comprehensive RA care.

## DISCUSSION

This meta-analysis in one way is an integrated analogy that shows that, the management of rheumatoid arthritis needs to go beyond the pharmacology of inhibiting the inflammation [8]. Even with the basic changes in the natural history of RA in the form of disease-modifying antirheumatic drugs, that decreased the aggression of the disease and slowed the radiographic process, pharmacotherapy does not prevent disability in a significant percentage of patients. The findings support the notion that RA is not an inflammatory

disorder, but a multisystem, multifaceted, biomechanical, neurological, and psychosocial disease.

Surgery is still a critical mode of therapy in patients with end stage joint destruction or spinal injury. This review has helped to substantiate the fact that RA patients are a high-risk surgical group as a result of chronic systemic inflammation, long-term immunosuppressive treatment, osteoporosis, and common extra-articular comorbidities. Even with these risks, joint replacement and spinal surgery can be of great help in relieving pain and improving functional ability as long as they are chosen and performed well and in due time. The data highlights the importance of the personalized surgical decision-making process, a careful planning of the perioperative time, and strong cooperation between rheumatologists, surgeons, anesthesiologists, and rehabilitation experts to reduce complications and maximize the success.

Treatment became another pillar of non-surgical and post-surgical RA treatment rehabilitation. The overall high quality of multidisciplinary biopsychosocial rehabilitation indicates the necessity to focus on pain, fatigue, psychological distress, and social participation in addition to physical impairment. In addition, the increased evidence on technology-assisted and robot-assisted rehabilitation is an indication of a transformation in the science of rehabilitation, which provides better neuromuscular retraining, better gait patterns and faster functional recovery after joint arthroplasty. Taken together, the findings favor a paradigm shift in favor of the fragmented, intervention-focused care to the holistic, patient-centered management models.

Notably, the combination of medical optimization, prompt surgical intervention and planned rehabilitation proved to have cumulative positive effects on pain relief, functional recovery and health-related quality of life. Such synergistic effects are hardly represented when evaluation is done separately in the case of treatment modalities. The current review thus lends a lot of credence to the application of the multidisciplinary, integrated care pathways as the most effective approach to the management of the long-term burden of rheumatoid arthritis.

### *Clinical Implications*

This meta-analysis has a number of implications to clinical practice. Multidisciplinary teams should be referred to at the earliest stages so that the assessment of the disease and the coordination of its management, including the adjustment of the disease at various stages, is complete. The success of surgical interventions preconditioned by good technical mastery but also the possibility to control disease activity and be ready to rehabilitate after the intervention. Rehabilitation is to be considered as a lifelong and personalized program, which starts at an early stage of the disease progression and continues after the release of the patient to help him to maintain functional autonomy. Integrated care model adoption can enhance patient outcomes and decrease disability and healthcare use in the long term.

The findings of this review have several limitations that should be noted when they are interpreted. There was a significant heterogeneity in terms of study design, patient population, interventions and outcome measures in the included studies and this could have affected pooled effect estimates. There are limited long term data analyses of complete medical- surgical- rehabilitative care pathways to limit conclusions on long-term outcome and sustainability of benefit. Also, the low and middle-income countries underrepresented the studies; hence, this can restrict the extrapolations to the healthcare systems with limited resources.

Longitudinal research which assesses the integrated care models throughout the entire disease pathway of rheumatoid arthritis should be given priority in future research [7]. The economic effect of integrated medical, surgical and rehabilitation interventions requires the implementation of sound cost-effectiveness studies especially in the backdrop of increased healthcare spending. Patient-reported outcome measures should also be given much attention to get patient-centered benefits like quality of life, participation, and functional autonomy. Further extension of investigations in varying geographic and socioeconomic contexts will make the integrated RA management strategies even more applicable.

## CONCLUSION

This is a systematic cumulative review which illustrates that the management of rheumatoid arthritis is best done in a multidisciplinary and integrated manner. The combination of medical optimization, surgical intervention and advanced rehabilitation strategies is the best method to be used. This kind of approach has the highest potential to minimize long-term disability, functional recovery, quality of life, and deal with the difficult and long-lasting burden of rheumatoid arthritis. Implementation of patient-centered, integrated care pathways should thus be regarded as one of the pillars of modern RA management.

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## DECLARATIONS

**Ethical Approval:** Ethical approval was obtained by institutional review board of Respective Institute Pakistan

**Informed Consent**: Informed Consent was taken from participants.

**Authors' Contributions:**

Concept: MFU, SJ, AK, NZ, UA, SAJ, SA, NM; Design: MFU, SJ, AK, NZ, UA, SAJ, SA, NM; Data Collection: MFU, SJ, AK, NZ, UA, SAJ, SA, NM; Analysis: MFU, SJ, AK, NZ, UA, SAJ, SA, NM; Drafting: MFU, SJ, AK, NZ, UA, SAJ, SA, NM

**Conflict of Interest**: The authors declare no conflict of interest.

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**Data Availability**: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Acknowledgments**: NA

**Study Registration:** Not applicable.