Review Article

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Rheumatoid Arthritis in Spine Surgery: A Systematic Review and Meta-Analysis

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Benjamin D. Streufert, MD[1], Chiduziem Onyedimma, MS[2], Yagiz U. Yolcu, MD[2], Abdul Karim Ghaith, MD[2], Benjamin D. Elder, MD, PhD[2], Ahmad Nassr, MD[1], Bradford Currier, MD[1], Arjun S. Sebastian, MD[1], and Mohamad Bydon, MD[2]

Abstract

Study Design: Systematic Review and Meta-analysis

Objective: The purpose of this study is to synthesize recommendations for perioperative medical management of RA patients and quantify outcomes after spine surgery when compared to patients without RA.

Methods: A search of available literature on patients with RA and spine surgery was performed. Studies were included if they provided a direct comparison of outcomes between patients undergoing spine surgery with or without RA diagnosis. Meta-analysis was performed on operative time, estimated blood loss, hospital length of stay, overall complications, implant-related complications, reoperation, infection, pseudarthrosis, and adjacent segment disease.

Results: Included in the analysis were 9 studies with 703 patients with RA undergoing spine surgery and 2569 patients without RA. In RA patients compared to non-RA patients undergoing spine surgery, the relative risk of infection was 2.29 times higher ($P = .036$), overall complications 1.61 times higher ($P < .0001$), implant-related complications 3.93 times higher ($P = .009$), and risk of reoperation 2.45 times higher ($P < .0001$). Hospital length of stay was 4.6 days longer in RA patients ($P < .0001$).

Conclusions: Treatment of spinal pathology in patients with RA carries an increased risk of infection and implant-related complications. Spine-specific guidelines for perioperative management of antirheumatic medication deserve further exploration. All RA patients should be perioperatively co-managed by a rheumatologist. This review helps identify risk profiles in RA specific to spine surgery and may guide future studies seeking to medically optimize RA patients perioperatively.

Keywords

rheumatoid arthritis, disease modifying antirheumatic drugs, steroids, biologics, spine surgery, fusion, craniovertebral junction, atlanto-occipital

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting 1–2% of the global population.[1,2] Initial treatment is medical management with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and others,[2] including novel disease modifying antirheumatic drugs (DMARDs) and biologics that directly affect the host autoimmune response. Although DMARDs and biologics have the potential to slow the progression of rheumatoid arthritis and protect the joints from permanent damage,[3,4] infectious and potentially other side effects have been attributed to use of DMARDs.[5,6]

Many patients with RA will require surgical treatment for advanced disease even with a proper use of medication regimen,[3,7,8] though this may be decreasing over time.[9] As the spine is a frequent location for RA involvement, surgical intervention may be indicated in patients with myelopathy,

[1]Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA
[2]Department of Neurological Surgery, Mayo Clinic, Rochester, MN, USA

Corresponding Author:
Benjamin D Streufert MD, Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN 55901, USA.
Email: Streufert.Benjamin@mayo.edu

radiculopathy, instability, or deformity.[7,8,10-12]The systemic inflammatory nature of this autoimmune disease as well as the subsequent medical treatments have been implicated in increasing complication rates in orthopedic and other surgery. Numerous studies have shown that RA may increase the risk of developing a variety of postoperative complications, including wound infection and instrument failure, ultimately necessitating revision after initial spine surgery,[3-7] though other reports presented no appreciable differences in surgical outcomes or complications.[8,9]

Prior studies have suggested the perioperative continuation of some DMARDs, biologics, and other antirheumatic medications may increase infection rates after surgery;[15-19] however, current evidence is varied based on type of medication, power of available studies to detect low probability events such as infection or other complications, and sometimes conflicting results.[15,16,18-22] Additional concern exists for precipitating RA disease exacerbation while off medication.[20] Although this question is studied extensively in elective hip and knee arthroplasty and other elective orthopedic procedures,[15,18,20,23,24] there is a paucity of literature on spine surgery.

Considering these knowledge gaps, the objectives of this study were to synthesize recommendations for perioperative medical management of RA patients and quantify outcomes and complications after spine surgery when compared to patients without RA.

Methods

Data Sources and Search Strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklists were used for this systematic review.[10] A certified, experienced librarian carried out an extensive search of electronic databases in PubMed, Ovid/MEDLINE, Cochrane, and Scopus for published articles for all available years. A search strategy including keywords for "spine" or "spinal" or rheumatoid or (rheumatic adj arthritis) or "inflammatory arthritis" "lumbar" or "lumbosacral" "occipital-cervical" or atlantoaxial or "atlanto-axial" or "occipitoatlantoaxial" or "occipito-atlantoaxial" or "craniovertebral junction" or "subluxation" or "vertebral" or "intervertebral" or "disc" or "discs" or "sacral" or "sacrum" or "fusion" or "fused" or "fusing" or "fixation" or "decompression' or "arthrodesis" or "reconstruct." Two authors (C.O. and Y.Y) screened the studies for eligibility after a list of articles was obtained. The senior author (M.B.) was consulted in final decision-making for any discrepancies.

Eligibility Criteria

The following inclusion criteria were used for eligibility; (i) studies that included patients with a diagnosis of rheumatoid arthritis undergoing spine surgery compared to a control group of patients without RA undergoing spine surgery. (ii) Studies that reported any complications or made an assessment regarding complications for patients with RA directly compared to patients without RA and (iii) studies in English language and with available full text. Reviews and studies that did not present specific information about spine surgery were excluded from our analysis. In addition; (i) studies that included patients with diagnosis of rheumatoid arthritis prior to spine surgery, (ii) studies that provided details regarding antirheumatic medication use prior to surgery (name, dose, timing) and (iii) studies that reported any complications or made an assessment regarding complications if no complications present were included for a separate systematic review on perioperative medication use.

Data Extraction and Processing

The following information was collected for included studies; (i) information on author name and study year, (ii) average age, gender, and follow-up (iii) number of patients specific to RA and Non-RA cohorts, (iv) location, type and specific levels of the spine surgery, (v) operative parameters including blood loss and operative time, (vi) any complications seen in patients undergoing spine surgery including wound infection, (vii) reoperation at the same level, and (viii) diagnosis of adjacent segment disease. For the systematic review of perioperative medication use, information on (i) author name and study year, (ii) study design, (iii) number of patients (total and spine-specific numbers if other procedures are included), (iv) location and specific levels of the spine surgery, (v) name and the dose of the medication used in rheumatoid arthritis treatment, (vi) whether the medication was stopped and restarted perioperatively and (vii) any complications seen in patients undergoing spine surgery were collected.

Statistical Analysis

Mean differences (MDs) were used to summarize continuous variables and the categorical outcomes were presented using risk ratios (RRs) with 95% confidence intervals (CI). The outcomes of interest were compared between patients undergoing spine surgery with and without RA diagnosis. Heterogeneity was represented with Higgins I-square (I^2). A random effects model was used when meta-analyses indicated greater than 50% heterogeneity. Pooled estimates and effect sizes were represented by forest plots. Statistical analyses were conducted using R 4.0.5. (R Foundation for Statistical Computing). P values <.05 were considered significant.

Level of Evidence

Levels of evidence were assessed by use of the Oxford Centre for Evidence-Based Medicine Levels of Evidence.[11] It was assessed by 2 authors in parallel with arbitration by a third author in cases of disagreement.

Results

Search Results and Study Characteristics

An initial search of the electronic databases revealed 2016 studies which were filtered further to 391 relevant articles.

From these, 9 full-text articles were included in the qualitative assessment. (Figure 1).[3,5,8,9,12-16] Included studies were published between 2008 and 2019 with a cumulative patient number of 703 diagnosed with RA and 2569 patients without RA. A total of 550 (78%) of all RA patients and 1259 (49%) of all Non-RA patients were female. Seven studies were retrospective cohorts, utilizing various databases comparing RA to Non-RA patients undergoing spine operations[3,5,8,9,12,13,15] 1 was a prospective cohort,[14] and the other was a case-control study.[16] The average age for RA patients was 65; for Non-RA patients, this was 63.4. The average follow-up for RA patients was 40.4 months and 42.6 months for the Non-RA group. These characteristics have been summarized further in Table 1.

Perioperative Details

In the RA and non-RA groups, operative time (95% CI: −28.78 to 17.5, P = .633, Figure 2) and estimated blood loss (95% CI: −20.43 to 137.30, P = .147, Figure 3) were not significantly different**.** Hospital length of stay was 4.62 days longer on average in the RA group (95% CI: 3.97-5.26, P < .0001, Figure 4). Due to the heterogeneity of reporting, number of operative levels and perioperative mortality in each group could not be examined or compared.

Infection and Complication Rates

Pooled analysis showed significantly more surgical site infections in the RA group than the Non-RA group, with a relative risk of 2.29 (95% CI: 1.08–4.84, P = .036**,** Figure 5**).** There were also significantly higher complication rates in the RA group, including overall complications (95% CI: 1.28–2.03, P = .001, Figure 6**)** and implant-related complications (95% CI: 1.41–10.97, P = .009, Figure 7). Reoperation occurred with a relative risk of 2.45 (95% CI: 1.69–3.55, P < .0001, Figure 8) comparing RA and non-RA groups. Pseudoarthrosis (95% CI: .75–5.40, P = .1641, Figure 9) and diagnosis of adjacent segment disease (95% CI: .43–9.01, P = .2508, Figure 10) were not statistically different between RA and non-RA groups.

Due to the varied nature or absence of reporting in the included studies, several variables of interest could not be reliably examined or compared, including: distinction between deep and superficial infection, the distinction between medical and surgical complications, and patient reported outcome measures.

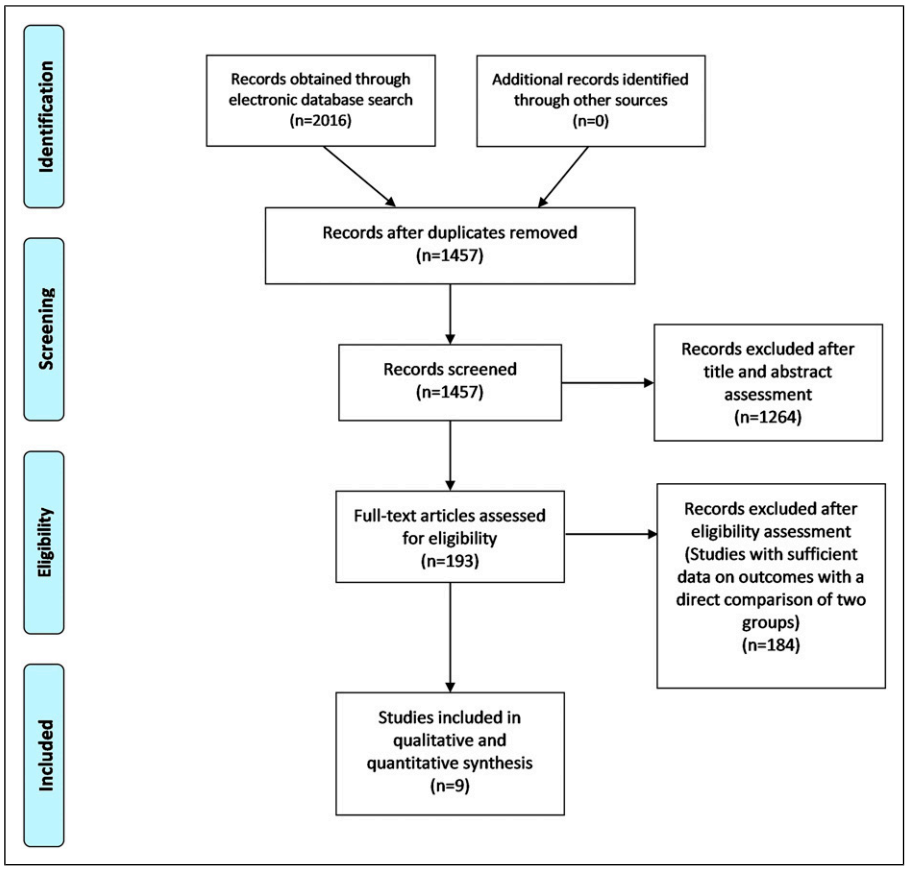

Figure 1. PRISMA flowchart for included studies.

Table 1. Baseline characteristics and surgical details for patients with and without Rheumatoid arthritis (RA).

Author, year	Number of Patients		Study Design	Age		Gender				Surgery type:(#patients)		# Levels Fused		Average Follow-up (months)		Oxford Level of Evidence
						RA		Non-RA								
	RA	Non-RA		RA	Non-RA	Male	Female	Male	Female	RA	Non-RA	RA	Non-RA	RA	Non-RA	
Takeuchi, 2006	16	15	Prospective cohort	60	52	4	12	11	4	C1–C2 posterior fusion		-	-	51	46	2b
Crawford, 2008	19	19	Retrospective cohort	64	65	2	17	1	18	Decompression and fusion		1.5	1.5	24	27	2b
Mesfin, 2015	14	14	Retrospective cohort database	66.3	67.6	1	13	2	12	PSF with Autograft		10.6	10.3	-	-	2b
Ohya, 2015	465	625	Retrospective cohort database	64.5	65.2	101	364	278	347	PSF		-	-	-	-	2b
Gulati, 2016	37	1433	Retrospective cohort database	68.2	67.7	-	28	-	675	Miscrodecompression: 20 Laminectomy:17	Miscrodecompression: 781 Laminectomy:615	lumbar single:21 2 level:16	lumbar single:816 2 level:580	12	12	2b
Kang, 2016	40	134	Retrospective cohort	64.3	65.3	1	39	17	117	PLF:40	PLF:134	3	2.9	-	-	2b
Uei, 2018	33	25	Retrospective cohort	63.6	55.6	8	25	16	9	C1-C2 intra-articular fixation				88.3	109.5	2b
Dalle, 2019	18	217	Retrospective cohort	68.1	67.7	2	-	73	-	VCR:4 PSO:14	VCR:33 PSO:184	Cervical:0 Thoracic: 5 Lumbar: 13 <10:2 >10:14	Cervical:0 Thoracic: 26 Lumbar: 189 <10:95 >10:122	30.8	21.8	2b
Xu, 2019	61	87	Case-control	65.9	64.5	9	52	10	77	PLIF		1-2level: 29 >3level:32	1-2level:41 >3level:46	-	-	3b
Total	703	2569				128	550	408	1259	-		-	-	-	-	
Average				65	63.4									40.4	42.6	

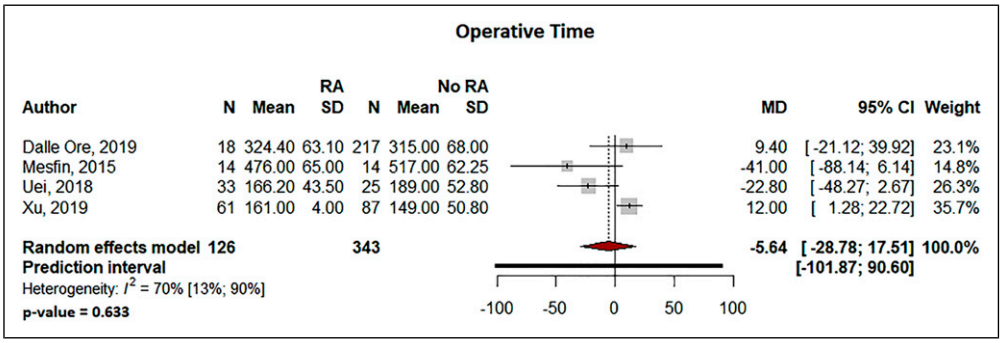

Figure 2. Forest plot comparing operative time for patients undergoing spine surgery with and without RA.

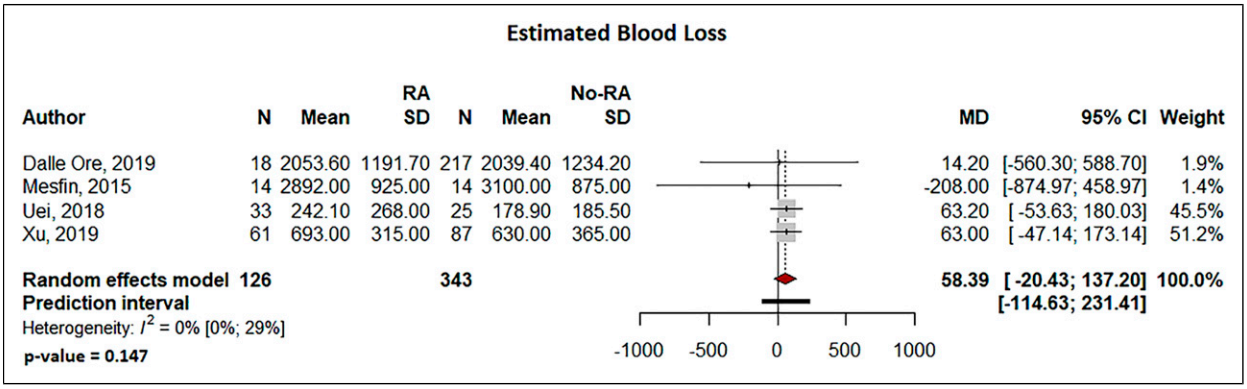

Figure 3. Forest plot comparing the estimated blood loss for patients undergoing spine surgery with and without RA.

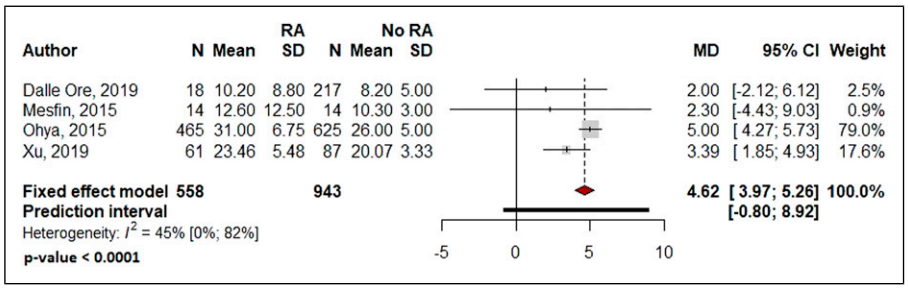

Figure 4. Forest plot comparing the hospital length of stay for patients undergoing spine surgery with and without RA.

Perioperative Antirheumatic Medication Management

After applying the inclusion/exclusion criteria, 7 full-text articles were included in qualitative assessment of management of antirheumatic medication perioperatively to spine surgery (Table 2).[17-23] Included studies were published between 2006 and 2020, all retrospective with small case series and cohorts, with a total of 226 patients undergoing spine surgery out of a total of 450. The most used RA medications were methotrexate, etanercept, and infliximab in the overall cohort. In cases where RA medications were stopped prior to surgery, time to stopping medication varied significantly, ranging from 8 days to 8.8 months. For 2 cases where postoperative medication information was available, RA medication was restarted at 4 months and 5 weeks following spine surgery. Fifteen patients were reported to experience complications following spine surgery, and 9 patients were on either methotrexate, infliximab or etanercept (60.0%). Overall, postoperative complications were mainly wound infections (both superficial and deep) and systemic infections (i.e., pneumonia and UTI). In addition, there were cases of wound dehiscence and pseudoarthrosis attributed to RA medication use.

Guidelines and Recommendations From Surgical Literature

Few studies specifically investigate perioperative RA medication management for patients undergoing spine surgery,

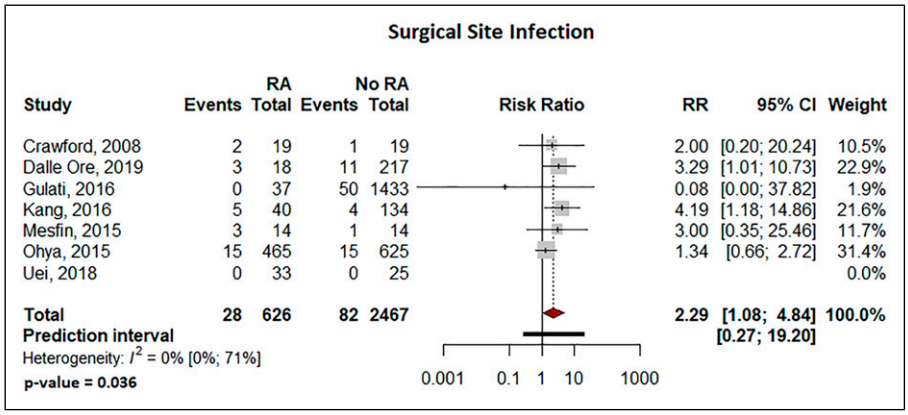

Figure 5. Forest plot comparing the surgical site related infection rates for patients undergoing spine surgery with and without RA.

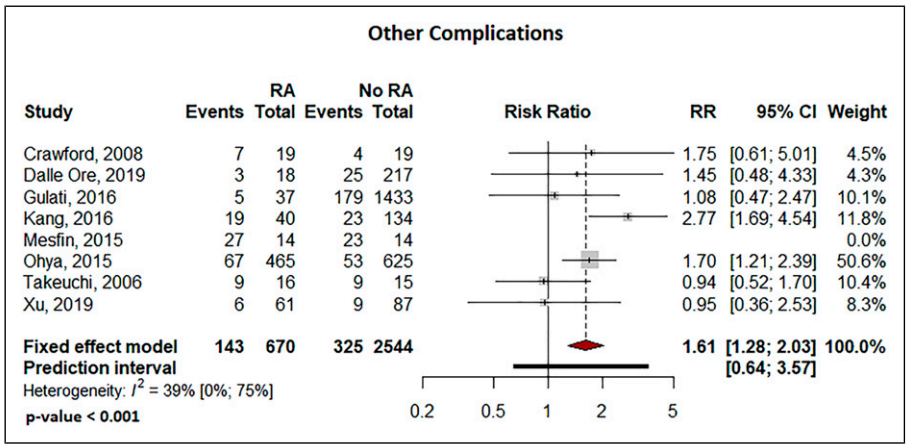

Figure 6. Forest plot comparing the overall complications for patients undergoing spine surgery with and without RA.

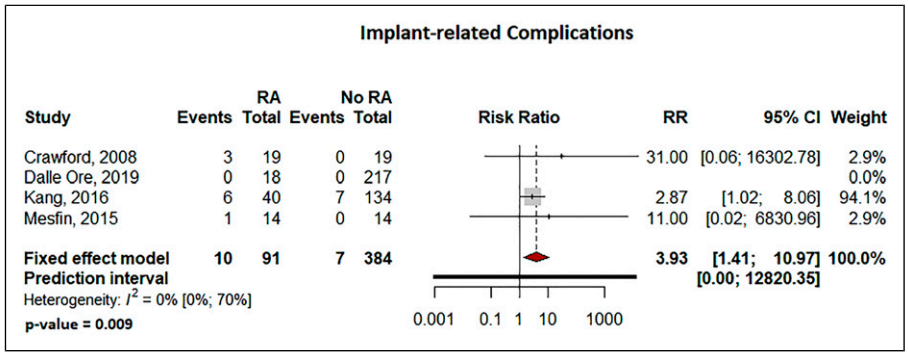

Figure 7. Forest plot comparing the implant-related complication rates for patients undergoing spine surgery with and without RA.

though there are some investigations and clinical guidelines for orthopedic surgery or other surgical fields in general. In 2011, Suzuki et al. conducted a survey of orthopedic surgeons on perioperative management of RA medications and have reported the general practice patterns regarding the use of methotrexate, tacrolimus, infliximab, etanercept, adalimumab and tocilizumab perioperatively for all procedures.[24] Time to stop these medications ranges from 9.7 days (methotrexate) to 26.4 days (infliximab). Regarding to time to restart, the earliest medications to be readministered were methotrexate (10.4 days) and tacrolimus (10.5), and the latest medication to be readministered was infliximab (24.8 days).[24]

More recently, the American College of Rheumatology and American Association of Hip and Knee Surgeons published

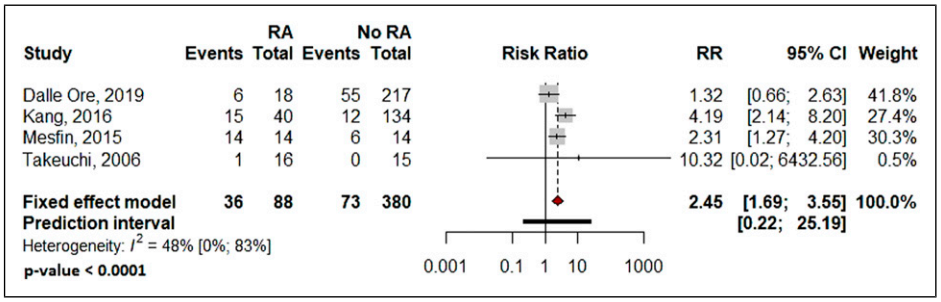

Figure 8. Forest plot comparing the reoperation rates for patients undergoing spine surgery with and without RA.

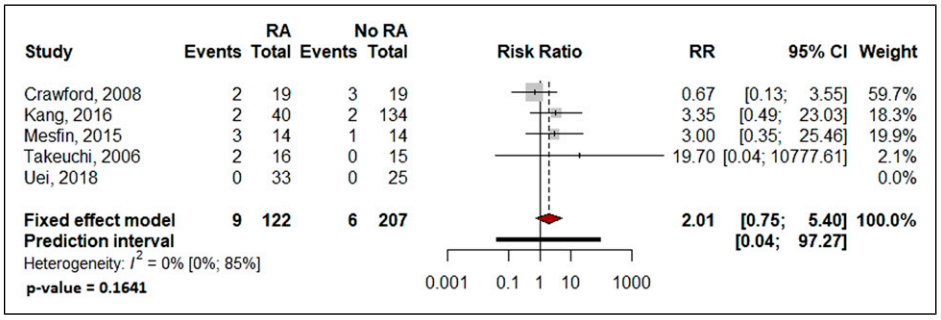

Figure 9. Forest plot comparing pseudoarthrosis for patients undergoing spine surgery with and without RA.

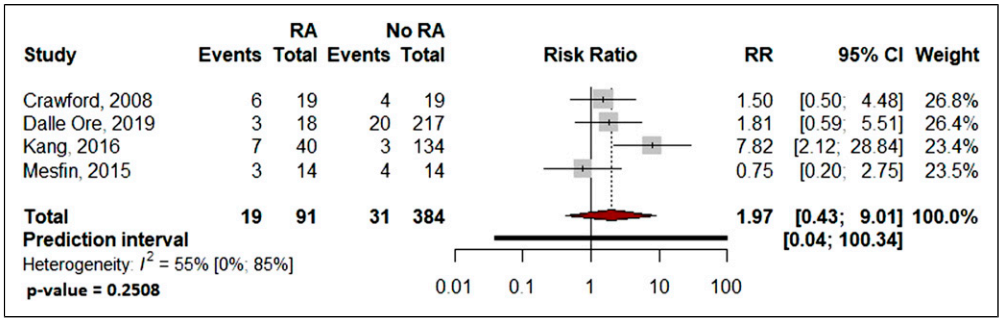

Figure 10. Forest plot comparing diagnosis of adjacent segment disease for patients undergoing spine surgery with and without RA.

guidelines for perioperative management of antirheumatic medication where medications were placed mostly in groups rather than individual assessments.[25] Commonly used RA medications (biologic and non-biologic) are listed in Table 3. Guidelines suggested that DMARDs can be continued, while biologics were recommended to be stopped prior to surgery with different timing (range: 2 days to 7 months) depending on the medication. In addition, mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus were advised to be withheld if the patient does not have severe systemic lupus erythematosus.[25]

Discussion

The primary purpose of this review was to evaluate the differences in peri- and postoperative outcomes with RA diagnosis among patients undergoing spine surgery and guide management of the medical treatments for rheumatoid arthritis in the perioperative period for spine surgery. The included studies compared RA and non-RA patients with respect to clinical outcomes, though the variable reporting of these outcomes did limit the quantitative analysis. The qualitative review of medication management revealed additional variability.

Spine surgery for patients with RA is indicated for myelopathy, radiculopathy, instability, or deformity.[26-30] Existing literature has shown differences in surgical outcomes for patients previously diagnosed with RA, often affected by the complication profile seen in RA.[3,6,31] Studies reporting on spine-specific outcomes in RA patients have shown some mixed results. In a retrospective review included in this study, Crawford et al. found no statistically significant difference in RA versus non-RA patients in complications or outcomes after

Table 2. Characteristics of RA medications, doses and subsequent complications in each study.

Study	Study Type	Number of Patients	Location	Level	RA Medication	Any Info on Dose	When was the Medication Stopped?	When was It Restarted?	Any Complications	Notes	Oxford Level of Evidence
Giles, 2006	Case control	91 orthopedic procedures, number of spine procedures unknown	Lumbar and thoracic	L4–L5 and T2–T7	Patient 4: Etanercept-MTX Patient 6:Infliximab-MTX	NA both	NA	NA	Patient 4: Paraspinal abscess Patient 6: Paraspinal abscess	Significant association between early infectious complications following orthopedic surgery and treatment with TNF inhibitors in patients with RA.	3b
Mori, 2008	Case report	One spine procedure	Lumbar	L3-L4 and L4-L5 laminectomy for spinal stenosis	Etanercept and MTX	- First–twice intravenous infusion (200 mg) of infliximab+8 mg/week of MTX: **Preop**-25 mg of etanercept subcutaneously twice a week: **Post op**-MTX (8 mg/week) added after 4 months of etanercept usage: **Post-op**	4 months before surgery	4 months later	Septic spondylodiscitis 8 months post-op	- Despite interruption of anti-TNFα therapy before surgery, patients may remain at risk of developing postoperative infections -Anti-TNF therapy was stopped due to Pneumocystis jiroveci pneumonia (PCP) and oral prednisolone was introduced (started at 25 mg/day and tapered off to 7.5 mg/day). -Recent official guidelines for prescribing anti-TNFα agents in patients with RA recommend that treatment with infliximab and etanercept be withheld for 2 to 4 weeks prior to major surgical procedures	4
Momohara, 2012	Cohort	161orthopedic procedures, 4 spine procedures	NA	NA	Tocilizumab, adalimumab, etanercept and infliximab	Tocilizumab (8 mg/kg, every 4 weeks) preoperatively and postoperatively from 1999 to 2010	23.5 days (SD = 11.2) [all patients]	NA	3 spinal surgery patients with delayed wound healing 1 spinal surgery patient with no wound healing	Tocilizumab also suppresses both surgery and infection-related acute-phase responses and thereby leads to possible difficulties in early	2b
Godot, 2013	Cohort	133 orthopedic procedures, number of spine procedures unknown	Lumbar / Lumbosacral	Patient 2: L4–L5 patient 9: L5–S1	Rituximab	NA	Patient 2: 8.8 months Patient 9: 5.1 months	NA	Patient 2: Deep nosocomial infection-pleuropneumonia and spondylodiscitis due to S aureus. Patient 9: Deep infection-Spondylodiscitis due to *Enterobacter cloacae* (positive hemocultures and urinary test)	The frequency of complications after surgery with RTX in RA seems to be in the same range as with anti-TNF. Univariate analysis revealed that spine surgery may be a risk factor of postoperative complications after RTX therapy. The rate of short-term postoperative complications in RA patients receiving a few cycles of RTX is 8.5%. The risk of complications may be more important in case of spine surgery, but does not seem linked to the time between the last RTX infusion and surgery	2b
Nishida, 2014	Case series	7 orthopedic procedures, 1 spine procedure	Lumbar	L4–L5	Abatacept	500 mg/mo	15.9 days before the surgery 8 days for the patient 3	Patient 3: Not restarted until 5 weeks post-op	Infectious spondylitis	The interval from the last abatacept infusion should be determined on a case-by-case basis, considering the type of surgery, patient-related factors, severity of the joint disease and degree of control achieved by treatment	4

(continued)

Table 2. (continued)

Study	Study Type	Number of Patients	Location	Level	RA Medication	Any Info on Dose	When was the Medication Stopped?	When was It Restarted?	Any Complications	Notes	Oxford Level of Evidence
Elia, 2020	Cohort	39 spine procedures	CVJ	Occipital-cervical or atlanto-axial	Methotrexate, leflunomide, abatacept, etanercept, sulfasalazine, hydroxychloroquine, adalimumab, mesalamine, azathioprine	NA	NA	NA	Patient 6: Occiput to C4: RA flare-up and desaturations. Patient 7: C1-C2: Long QT and transaminitis. Patient 12: Occiput to C2: Postoperative delirium. Patient 19:C1-C3: Reintubation, death secondary to pneumonia and multisystem organ failure. Patient 24: C1-C2: UTI. Patient 30: Occiput to T2: Prolonged intubation, fever. Patient 32:C1-C6: Pneumonia, dysphagia requiring g-tube, DVT with hypotension **Revision procedures:** Patient 4:C1-C3: MTX and Abatacept: ASD (C3/4) patient declined revision surgery (asymptomatic). Patient 10: Occiput-C3: Hydroxychloroquine: ASD (C3/4)/extension of fusion to T2. Patient 32: C1-C6 : Leflunomide: Wound dehiscence/debridement and closure 6 weeks post-op. Patient 33: Occiput-C5:MTX, Abatacept: Pseudoarthrosis/pending revision surgery	Overall, the implications of TNF inhibitors in the perioperative period remain mixed. Similar mixed results with respect to wound infection rates and methotrexate (MTX) use have also been observed. Continuing DMARD therapy in the perioperative period of patients undergoing surgery at the CVJ did not yield statistically significant differences with regards to re-operations, length of stay or EBL. Discontinuing DMARD therapy in the perioperative period resulted in a 10% readmission rate for RA flare-up	2b
Khanna, 2015	Cohort	20 spine procedures in 18 patients	CVJ	Occipito-cervical or atlanto-axial	Twelve of 18 (66.7%) patients were on chronic prednisone, 5 out of 18 patients (27.8%) were on methotrexate and 6 out of 18 patients (33%) were on biologics at the time of surgery	Prednisone with average daily dose of 9 mg	Not stopped	NA	Pseudoarthrosis 7 years after surgery (on 10 mg prednisone daily), basilar invagination (on 15 mg prednisone daily and biologics) and wound revision	Daily prednisone dosages of more than 7.5 mg or biologics may impact clinical outcomes	2b

Table 3. Different types of non-biologic DMARDs.

Non- Biologic DMARDs
Conventional synthetic- methotrexate, leflunomide, hydroxychloroquine sulfate, sulfasalazine
Targeted synthetic-*Janus Kinase (JAK) Inhibitors*-baricitinib, tofacitinib, upadacitinib
Biologic DMARDs
Tumor necrosis factor (TNF) inhibitors- adalimumab, certolizumab, etanercept, golimumab, infliximab
Anti-B (CD-20)- rituximab
Anti-T cell stimulation- Abatacept
Interleukin-6 (IL-6) inhibitors- Sarilumab, tocilizumab
Interleukin-1 receptor (IL-1) inhibitors- Anakinra

lumbar fusion.[8] Dalle Ore et al. reviewed major thoracolumbar deformity correction operations and compared patients with and without RA, finding no differences in overall surgical complications but an increase in wound healing complications with the use of prednisone.[12] In a similar patient population of adult scoliosis patients, Mesfin et al. noted increased complication and reoperation rates of RA compared to non-RA patients.[3] Koyama et al. retrospectively reviewed 47 RA patients undergoing spinal fusion surgery with concomitant use of biologic and non-biologic DMARDs, finding an overall 15% surgical site infection, though not correlated with the use of methotrexate, prednisone, biologic DMARDs or other operative factors.[32] Kang in a retrospective matched cohort comparison of RA and non-RA posterolateral lumbar fusion patients found higher complication rates, including infection, nonunion, implant failure, and overall reoperation in those patients with RA.[5] Horowitz performed a database review of Medicare patients with RA undergoing 1- or 2-level ACDF, finding increased medical, surgical, and infectious complications when compared to those without RA, although information on the perioperative medical treatment of these patients was unavailable.[6] Valuable details regarding perioperative medical management, such as the dosing or timing of weaning or cessation, however, were not available in any of the above studies. While some studies have shown higher rates of infection in RA patients, details of perioperative medical management are often not well reported, and the causative factors remain unclear.

Zhang et al. in a previous systematic review assessed the effect of RA on infection and complications after spine surgery, finding significantly greater rates of complications in the RA cohort.[33] However, the review included 6 studies 2 of which included information from databases and pose a risk of overlapping patients. Moreover, only complications and infections were included in the study. The present review included 9 independent studies and assessed a broader spectrum of parameters, including estimated blood loss, operative time, and implant-related complications in addition to the rates of overall complications and infection.

The increased risk of postoperative complications, including infections and wound breakdown, previously has been attributed to increased comorbidities in patients undergoing spine surgery. Several studies have found increased postoperative complication rates in patients with comorbidities including BMI, smoking, and diabetes, while others have demonstrated that increased operative times are associated with worse postoperative outcomes.[34-36] In this review, there was no significant difference in operative time between RA and non-RA patients and overall comorbid burden was unable to be compared.

In this review, implant-related complications were significantly associated with the RA group. A multicenter prospective study by Soroceanu assessed 245 patients on the incidence, risk factors, and impact of implanted related complications and quality of life measures after adult spinal deformity correction, identified nearly a third of their cohorts experienced this complication with over half of them needing reoperation after 2 years.[37] Seki investigated the differences in rates of adjacent to segment disease (ASD) and clinical outcomes in RA patients undergoing lumbar decompression. Results from this study showed a significantly increased rate of ASD in RA patients undergoing lumbar fusion.[28]

Existing literature provides some direct and indirect clues to the safety of continuing certain medications in and around the time of spine surgery. Unfortunately, some studies have produced contradictory results. There is evidence that perioperative continuation of prednisone,[12,38,39] hydroxychloroquine,[38] leflunomide,[40] and DMARDs[18,19,41,42] increase the risk of infection; however, other studies have shown no increase of infection with prednisone,[22,32] methotrexate[38] or those same or different DMARDs.[32,42,43]

Due to long-term corticosteroid use, many patients with RA may also carry increased risk of osteoporosis, present in up to 30% in some populations.[44] Theoretical risks also exist for decreased healing capacity of bone due to chronic inflammation or prednisone use.[45] Vertebral fractures and implant-related issues stemming from osteoporosis are noted in several studies.[5,46,47] Excluding infection or wound problems, other complications appear similar in some studies[8,12] but increased in RA populations in others.[3,5] Regarding clinical outcomes, most studies show that spinal surgery provides predictable improvements in outcome measures for patients with RA, similar to those patients without RA diagnosis.[5,8,12] Progression of rheumatic pathology in the spine is noted in several studies, which may affect longer-term outcomes,[5,30] including those specific to spine.[40,41]

Newer antirheumatic medications appear to be decreasing the burden of spinal disease over time[26,48]; however, medical treatments both old and new are not without risk. Terashima reported on a 10-year prospective cohort study enrolling RA patients without initial cervical instability, noting that corticosteroid use correlated with development of more severe cervical pathology.[27] Despite the high quality and long-term follow-up of this study, it is unknown whether prednisone treatment indicates a more severe disease burden or if treatment is associated with this poorer outcome.

Limitations

Several limitations exist in this systematic review. First, included studies were retrospective in nature, as a result, the influence of selection and recall biases cannot be fully withheld. Second, there was significant heterogeneity across studies. The types of operations were different, and the types of reported complications also varied greatly across studies; therefore, understanding the details surrounding individual complications was not possible. Significant heterogeneity also existed between studies for the reporting of operative parameters like EBL and length of surgery for the respective operative types. Finally, several studies reported on preoperative use of anti-RA medications, however, this was inconsistent across studies. Moreover, frequency of use and specific medications or dosing was often not reported.

Conclusion

Rheumatologic disease continues to afflict patients with spinal pathology, and patients often require surgical treatment despite recent advances in medication regimens**.** There is a dearth of current guidance on the relative risks of patients with RA undergoing spine surgery. The results from this meta-analysis suggest that patients with RA are at a significantly increased risk of postoperative complications including surgical site infections following spine surgery. Furthermore, the perioperative medication management for these patients appears to have significant variability in timing, cessation or continuance, and types of medication. All RA patients should be perioperatively co-managed by a rheumatologist. As in other areas of surgical practice, spine surgery may require further investigation in specific, patient-centered guidance on the recommendations for perioperative medication management to both optimize patients and minimize risk.

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ORCID iD

Chiduziem Onyedimma https://orcid.org/0000-0001-9210-5579

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