



SYMPOSIUM: SEX DIFFERENCES IN MUSCULOSKELETAL DISEASE AND SCIENCE

# Does Patient Sex Affect the Rate of Mortality and Complications After Spine Surgery? A Systematic Review

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#### **Abstract**

Background Available studies disagree regarding the influence of patient sex on mortality and complications after spine surgery. We sought to conduct a systematic review and pool the results of existing research to better understand this issue.

Questions/purposes We performed a systematic review to address two questions: (1) Does sex (male versus female) influence mortality after spine surgery? (2) Does sex impact the development of postoperative complications after spine surgery?

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E. N. Reamer, H. Choi Robert Wood Johnson Clinical Scholars Program, University of Michigan, Ann Arbor, MI, USA Methods This systematic review was performed through a query of PubMed using a structured search algorithm. Additional queries of Embase, SCOPUS, Web of Science, and the tables of contents of orthopaedic and neurosurgical journals were also conducted using search terms such as "sex factors", "male or female", "risk factors", and "spine surgery". Selected papers were independently abstracted by three of the authors (AJS, ENR, EIW) and pooling was performed. Our literature search returned 720 studies, of which 99 underwent full review. Of these, 50 were selected for final abstraction. The Cochrane Q test was used to assess study heterogeneity; significant study heterogeneity was present and so a random-effects model was used. A Harbord test was used to evaluate for the presence of publication bias; this analysis found no statistically significant evidence of publication bias.

Results Males were at increased odds of mortality after spine surgery (odds ratio [OR], 1.63; 95% confidence interval [CI], 1.35–1.97; p < 0.001). No differences between the sexes were identified for the odds of complications (OR, 1.04; 95% CI, 0.95–1.13; p = 0.42).

Conclusions Our results determined that males were at elevated odds of mortality but not of complications after spine surgery. These results should be used to inform preoperative discussion and decision-making at the time of surgical consent. Future work should be directed at determining the underlying factors responsible for increased

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mortality among males and prospective studies specifically designed to evaluate sex-based differences in outcomes after spine surgery.

Level of Evidence Level III, therapeutic study.

#### Introduction

Sex-based differences in the risk of postoperative morbidity between males and females are known to exist within a broad number of disciplines, including cardiothoracic and trauma surgery [56, 58]. By sex, we mean the biological character of male and female patients as opposed to gender, which reflects societal roles and expectations. Within the field of orthopaedic surgery, a patient's sex is thought to influence outcomes after total joint arthroplasty, particularly with respect to total knee arthroplasty [32]. The impact of male or female sex on the risk of mortality and complications after spine surgery is less well defined.

There are a number of hypothetical reasons that males and females might have differing mortality and complicaprofiles after spinal surgery. Variation anthropomorphic parameters, body mass indices, and comorbidity profiles may contribute to disparities in complication and mortality risks between the sexes after spine surgery. Distinct differences in tobacco and alcohol abuse as well as risk-taking behavior might also elevate the odds of postoperative death or the development of specific complications such as surgical site infection (SSI). Sexbased differences with respect to the incidence of specific spinal disorders have previously been described, including lumbar degenerative disc disease [49], lumbar radiculopathy [48], and cauda equina syndrome [45]. Furthermore, previous work [55] has identified that males are more likely than females to receive recommendations for spine surgery despite similar underlying disorders [55]. Most prior research has failed to address whether males or females may be at increased risk of morbidity or mortality after spine surgery. Furthermore, many studies that have considered this topic have come to contradictory conclusions. For example, when considering the risk of complications after spine surgery, Schoenfeld et al. [50] and Shen et al. [52] concluded that females were at increased risk, whereas Cahill and colleagues [3] claimed that males were at elevated risk of postoperative morbidity. Many of these studies are limited by small samples and statistical pooling could allow for sufficient power to reach more precise conclusions.

In this context, we sought to perform a systematic review of the literature and meta-analysis to address two questions: (1) Does sex (male versus female) influence the odds of mortality after spine surgery? (2) Does sex impact

the odds of postoperative complications after spine surgery?

# Search Strategy and Criteria

The initial literature search was performed by three independent investigators (AJS, ENR, EIW) using a structured algorithm (Appendix 1 [Supplemental materials are available with the online version of CORR®.]) that queried the published catalog in PubMed from 1966 to May 29, 2014. An additional search was performed in Embase using an Emtree algorithm comparable to the PubMed approach; supplemental queries were conducted in Web of Science and SCOPUS (AJS, ENR, EIW). A manual search of article titles in the reference lists of studies found to meet inclusion criteria was subsequently conducted to capture additionally relevant research that had not been identified in the first rounds of the systematic review. Finally, the catalogued tables of contents of Clinical Orthopaedics and Related Research®, The Spine Journal, Spine, Journal of Spinal Disorders and Techniques, Journal of Neurosurgery, Journal of Neurosurgery: Spine, European Spine Journal, and Journal of Bone and Joint Surgery (American) were searched electronically using key words to ensure that the initial search was exhaustive.

The titles and abstracts of studies identified by each query were evaluated and full-text articles were reviewed if the work appeared to meet inclusion criteria. To be included in the final review, investigations had to be published in the peer-reviewed literature and evaluate biologic sex as a risk factor for mortality or postoperative complications in adult patients (aged 18 years and older) undergoing a surgical intervention involving the cervical, thoracic, or lumbar spine. Results of eligible studies had to detail the number of patients sustaining the outcomes of interest by sex and/or evaluate their findings through statistical testing with significance reported by p value and/or effect size with 95% confidence intervals (CIs). Case reports, systematic reviews, investigations that included pediatric cases or involved spinal trauma, unpublished studies, and those in which no surgery was performed were excluded as were those with patient sample sizes less than 100 and those that involved a single sex cohort (Level IV evidence).

Determinations regarding study inclusion were made independently by three investigators (AJS, ENR, EIW) with disagreements resolved by mutual consensus. Studies included in the final review were abstracted to identify authors, year of publication, journal of publication, study quality, number of patients included in the study, number of males and females who died or sustained a complication, and statistical results regarding the influence of sex on the



risk of mortality and/or complications. Randomized prospective trials were considered Level I evidence, prospective cohort studies were considered Level II, and retrospective case-control analyses were considered Level III. Irrespective of the level of evidence applied at the time of publication, studies that performed post hoc testing for heterogeneity of treatment effects were considered Level III quality for the purposes of our review. The literature search and manner of reporting results met the criteria advocated by the Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA) statement [34].

Investigations that detailed the total number of patients and mortality and complication rates by sex were considered suitable for pooling. Study heterogeneity was assessed using the Cochran Q test with p value for significance set at 0.10 and the I<sup>2</sup> statistic. Summary measures of effect size were reported using a pooled odds ratio (OR) with 95% CI. Publication bias was assessed with Harbord's modified bias test for small-study effects [54].

The literature search identified 720 published studies (293 from PubMed, 99 in Embase, 229 from SCOPUS, 65 from Web of Science, and 34 from reference lists). No additional articles not otherwise identified in the literature search were obtained from the table of contents query of selected journals. After assessment of the title and abstract, or as duplicate citations, 621 studies were excluded, leaving 99 publications for full-text review (Fig. 1). After fulltext review, an additional 49 publications were excluded. The majority of these (n = 27) were excluded because they did not report complications or mortality by patient sex. A further 14 were excluded because they included pediatric patients. Six studies were excluded as a result of sample size less than 100, one study was excluded as a result of its being a systematic review, and one was excluded because no spine surgery was performed. Ultimately, 50 studies [1-31, 33, 35-44, 46, 47, 50-53, 57, 59] that met all inclusion criteria necessary to evaluate the influence of sex on mortality (Appendix 2 [Supplemental materials are available with the online version of CORR®.]) and complications (Appendix 3) after spine surgery were included. Five studies addressed mortality, five assessed mortality and one or more complications, and 40 dealt exclusively with one or more complications. Complications considered in the individual studies included venous thromboembolic disease, SSI, dysphagia after anterior cervical procedures, perioperative visual loss, neurological deficits, and reoperation (Appendix 3). The plurality of cohorts (n = 17[27%]) evaluated nonspecific postsurgical complications. Five studies considered dysphagia after anterior cervical spine procedures, eight reported on SSI, five documented need for reoperation, and five evaluated the development of venous thromboembolic disease. No prospective trials on sex-related differences in spine surgery were identified and

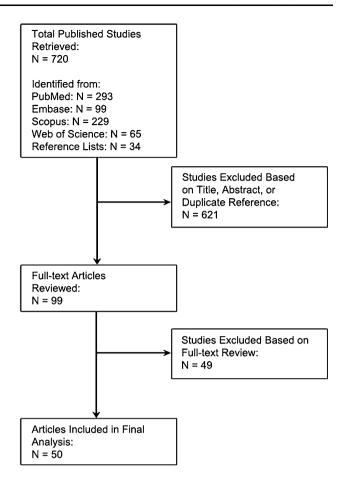


Fig. 1 Algorithm of the systematic review depicting results of the literature search and highlighting the number of articles identified and excluded at each point in the process.

none of the included investigations were specifically designed with the intent of evaluating the role of sex on the development of mortality or complications after spine surgery. All of the included investigations were graded as Level III quality because they were either retrospective case-control studies or works that performed post hoc comparisons evaluating heterogeneity of treatment effects.

Six investigations, representing 2,356,148 patients, were suited to pooling for the evaluation of mortality. For the six studies, the Q test identified significant heterogeneity (p < 0.001) and the  $I^2$  was 90%. As a result, a random-effects model was used. The Harbord test showed no statistically significant evidence of publication bias (p = 0.4).

Fifty-two cohorts, representing 4,054,451 patients, were suited to pooling in the evaluation of complications. Cochrane Q testing indicated significant heterogeneity between studies (p < 0.001) with an  $I^2$  of 94%. The Harbord test demonstrated no significant evidence of publication bias (p = 0.63).



Subset analyses were conducted for studies dedicated to dysphagia after anterior cervical procedures and SSI because of reduced between-study heterogeneity for the works considering these specific complications. Four cohorts, representing 160,575 patients, regarding dysphagia after anterior cervical procedures were suitable for pooling as were six reporting on SSI (53,223 patients). The Harbord test indicated no evidence of publication bias for either of the specific complications considered (p = 0.07 for dysphagia and p = 0.94 for SSI).

# Results

Does Sex Influence the Odds of Mortality After Spine Surgery?

Ten studies were identified that considered sex-based differences in mortality (Appendix 2). Seven of 10 reported that females were at significantly decreased risk of mortality and three maintained no significant difference between the sexes. The pooled analysis indicated that males were at increased odds of mortality (OR, 1.63; 95% CI, 1.35–1.97, p < 0.001; Fig. 2).

Does Sex Impact the Odds of Postoperative Complications After Spine Surgery?

Forty-five studies, with 64 distinct cohorts, were identified that considered sex-based differences in the development of one or more complications after spine surgery (Appendix 3). Females were identified as being at a decreased risk of complications in 25 cohorts, seven reported males to be at decreased risk, and 32 found no difference between the sexes. A random-effects model found no difference in the odds of postoperative complications based on patient sex (OR, 1.04; 95% CI, 0.95–1.13, p = 0.42). The pooled analysis demonstrated no difference in the odds of dysphagia between the sexes (OR, 0.77; 95% CI, 0.49–1.21, p = 0.25; Fig. 3) nor in terms of the odds of SSI (OR, 0.92; 95% CI, 0.56–1.49, p = 0.72; Fig. 4).

## Discussion

Biological sex has previously been found to influence outcomes after certain surgical interventions, including coronary artery bypass grafting and cardiothoracic procedures [32, 55, 58]. Less information is available with

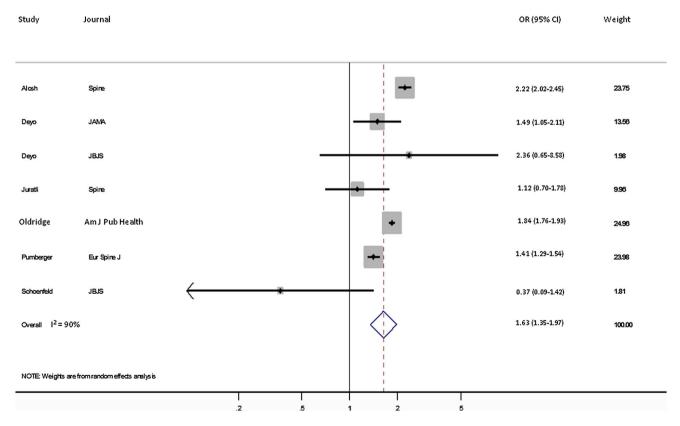


Fig. 2 Forest plot shows the ORs for mortality comparing males with females.



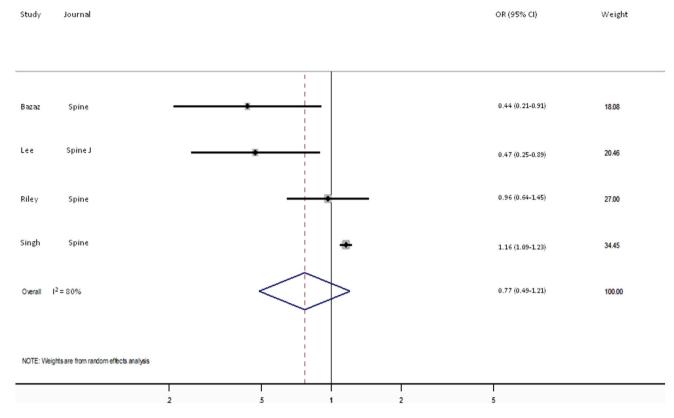


Fig. 3 Forest plot shows the ORs for dysphagia after anterior cervical spine procedures comparing males with females.

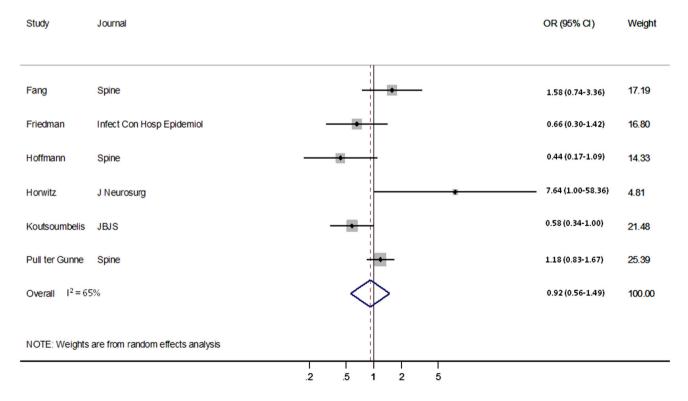


Fig. 4 Forest plot shows the ORs for SSI comparing males with females.



regard to the role that sex may play in influencing postoperative morbidity and mortality after orthopaedic interventions and this is particularly striking for the specialty of spine surgery. Relatively few studies have even included patient sex as a covariate when considering risk factors for mortality and complications. Furthermore, among those efforts that have included patient sex as a predictor variable, substantially different conclusions have been reached. Statistical pooling of the results of individual studies could be used as a technique to increase power and potentially allow for more definitive determinations. In this context, we sought to perform a systematic review of the extant literature with the goal of evaluating whether biologic sex influences the odds of mortality or complications after the performance of spine surgery.

Our findings should not be accepted, however, without appreciating limitations associated with our analysis. The lack of spine surgical literature specifically addressing this topic is clearly the main limitation. None of the studies included in the systematic review were specifically designed with the intent of identifying sex-based differences in outcomes after spine surgery. Moreover, no prospective studies or controlled trials were identified and, to ensure uniformity, we did not include unpublished work or studies solely presented in conference proceedings. Marked heterogeneity between included studies, particularly with respect to methodology, surgical intervention, sample population, and the types of complications considered, is also a shortcoming. Although we attempted to address this using a conservative random-effects model that took into account the variation between studies, the inability to assume a uniform effect of patient sex across investigations was clearly a limiting factor. As a result, outside of dysphagia and SSI, which were considered in subset analyses, it is difficult to translate our findings regarding postsurgical complications. Finally, like with any systematic review, there is the possibility that reports addressing these topics were not captured by our search algorithm. We maintain that our rigorous approach to obtaining the pertinent literature, including a manual search of reference lists and queries of tables of contents, minimized the likelihood for this to have occurred, yet its potential impact on our findings cannot truly be quantified.

Nonetheless, our results indicated that males may be at elevated odds of mortality after spine surgery. The pooled OR estimate in the meta-analysis maintained a 63% increase in postoperative odds of death for males compared with females. This may be reflective of underlying physiologic differences between the sexes as well as variation in the number and severity of medical comorbidities [45, 46, 56, 58]. Females are known to have lower rates of coronary artery disease, peripheral vascular disease, and renal dysfunction [58]. They have also been hypothesized to tolerate

shock to a greater extent and have a lower susceptibility to sepsis [55]. Seven studies in the systematic review independently identified males as having statistically elevated rates of mortality after spine surgery and similar results are apparent in other disciplines such as trauma surgery [56]. These facts, combined with the reduced between-study heterogeneity and absence of publication bias for the works included in our analysis, lend further support to our findings. Further research should be devoted to identifying the etiologies responsible for observed differences in mortality risk between the sexes as well as risk factors that may be modifiable in the perioperative period. Additionally, the findings of this systematic review should be confirmed in a scientifically rigorous, prospective analysis specifically designed to detect differences in mortality between male and female patients.

The clinical heterogeneity between studies considering postoperative morbidity substantially limits our capacity to draw firm conclusions. Although pooling failed to identify a statistically significant elevation in the odds of postsurgical complications, dysphagia, and SSI between sexes, the results could have been confounded by the sample populations, indications for surgery, and definitions of postoperative morbidity unique to the studies that were pooled. Given the deficiency of literature specifically intended to examine the effects of sex on postoperative morbidity and mortality after spine surgery, a large prospective study designed to identify sex-based differences in postoperative complications is clearly warranted. The ideal investigation would be multicentered in nature and sufficiently powered to address specific complications, including SSI, venous thromboembolic disease, reoperation, and 30-day readmission, rather than reporting results for an amalgam of nonspecific categories of perioperative morbidity (eg, one or more complications, major complications, and minor complications). Furthermore, such a study's capacity to prospectively determine sex-based differences in healthcare expenditures, environments of care, and functional outcomes in the mid- and long-term would invariably equate to best available evidence for the spine surgical field. Without question, the financial and logistic requirements for this kind of research would necessitate marshaling substantial resources within the spine surgical community, healthcare systems, insurance companies, and the US federal government.

Our results indicate that male patients may be at greater odds of mortality after spine surgery. Given that this determination was made using pooled data derived from multiple investigations, such information has value for the purposes of patient education, preoperative counseling, and prognosticating risk during the consent process. The quality of the studies included in the pooled analysis for postoperative complications causes us to interpret our



determinations with extreme caution. Future research, of the kind outlined here, should be directed at determining the underlying factors responsible for increased mortality among male patients and prospective work specifically designed to evaluate sex-based differences in outcomes after spine surgery.

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