Sex and gender determinants following spinal fusion surgery: A systematic review of clinical data

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In the last decade, numerous studies analyzed and described the surgical outcomes in male and female patients submitted to orthopedic surgery. Although this, the impact of sex/gender on spinal fusion surgery clinical outcomes is still poorly defined. This review systematically maps and synthesizes the scientific literature on sex/gender differences in postoperative outcomes for patients undergoing spinal fusion surgery. The search was performed in PubMed, Scopus, and Web of Science in the last 22 years. Clinical studies evaluating potential sex/gender differences in postoperative outcomes and/or complications, as primary or secondary aim, were included and analyzed. Out of the 1,885 records screened, 47 studies were included. These studies comprised a total of 1,158,555 patients (51.31% female; 48.69% male). About 77% of the analyzed studies reported sex/gender-related differences in postoperative outcomes. Most studies treated patients for lumbar degenerative diseases and more than 55% of them reported a worse postoperative outcome in female patients in terms of pain, disability, health-related quality of life questionnaires, and complications. Differently, a significant heterogeneity across studies on patients treated for cervical and sacral degenerative diseases as well as for spinal deformity and traumatic spinal fracture prevented the understanding of specific sex/gender differences after spinal fusion surgery. Despite this, the present review highlighted those female patients treated for lumbar degenerative spine diseases could require more clinical awareness during postoperative care. The understanding of how sex/gender differences can really affect clinical outcomes after spinal fusion surgeries is mandatory for all spinal pathological conditions to drive clinical research toward oriented and personalized protocols.

KEYWORDS
spinal fusion surgery, clinical data, systematic review, sex, gender differences

Introduction

In the last decade, sex/gender differences attracted considerable interest in several specialties, including cardiothoracic and trauma surgery (1). These differences are key issues for a personalized treatment. The National Institutes of Health (NIH) promotes investigators to design their studies in a way that allows the participants to self-
identify their sex or gender (2). By sex, we mean the biological character of male and female as opposed to gender, which reflects societal roles and expectations (2). Although, sex and gender are two different concepts, in medicine they are often linked, and, in the review, they were used as synonyms. Within orthopedic surgery, a patient’s sex/gender is thought to influence outcomes after total joint arthroplasty (manly in total knee arthroplasty), after rotator cuff repair, and after anterior shoulder surgical stabilization (3). Sex-based differences in spinal disease incidence have been previously described in several studies, such as lumbar degenerative disc disease (4), lumbar radiculopathy (5), and cauda equina syndrome (6). Nevertheless, Taylor et al. (7) highlighted that male patients generally receive more recommendations than female ones for spine surgery despite similar underlying disorders (7). The impact of male or female sex/gender on clinical outcomes in spinal fusion surgery is less well defined. This is in part because most of the studies do not consider patient sex when examining demographic trends in outcomes, reporting “sex-adjusted” statistics, or using sex-matched groups. Despite this, some data demonstrated individual differences in the postoperative outcomes between male and female patients after spinal fusion surgery. In detail, several clinical trials found a better global and functional outcome after lumbar spine fusion for males than for females. A retrospective study by Gehrchen et al. (8) reported that the female gender is an independent risk factor for nonoptimal outcomes after lumbar fusion; a randomized controlled trial (9) observed that the female gender was also associated with worse postoperative results (10). However, a prospective clinical study on 4,780 patients in the Swedish National Spine Register with lumbar degenerative disc disease and chronic low back pain showed that female patients had worse pain and function preoperatively but improved more than males after surgery (11). These conflicting results are due to the fact that several of the studies are limited to small samples size, which has insufficient power to reach accurate conclusions. Regarding complications, there are several hypothetical reasons for male and female differences after spinal surgery. Differences in anthropomorphic parameters, body mass index, and comorbidity may contribute to differences in complications and mortality risks between females and males after spine surgery (12–14). Additionally, specific differences in tobacco and alcohol use/abuse as well as in unhealthy lifestyles (malnutrition, unhealthy diet, drug abuse, etc.) might also increase the odds of postoperative death or the development of specific complications, such as surgical site infection (SSI) (15).

The number of studies suggesting that sex/gender may affect patient outcomes after a spinal fusion procedure begets the need for a comprehensive examination of these data. Thus, we performed a systematic review of the literature to better understand sex/gender-based differences in spinal fusion surgery outcomes. These aspects are of key interest for both physician and patient thus, to be informed about predictive gender and sex-related differences. This information could also have a prognostic value, playing a critical role in the decision-making process.

Methods

Eligibility criteria

The PICOS model (Population, Intervention, Comparison, Outcomes, Study design) was used to design this study: (1) studies that considered female and male patients (Population) submitted to, (2) spinal fusion surgery (Interventions), (3) with a comparison between them (female and male) (Comparisons), (4) that reported postoperative clinical and/or functional outcomes of spinal fusion surgery (Outcomes), in (5) randomized, retrospective, prospective and case series studies (Study design). Studies from May 2000 to May 2022 were included in this review if they met the PICOS criteria. We excluded studies that evaluated (1) surgeries other than the spine, (2) patients undergoing spine surgery with other severe pathological conditions (genetic and rare diseases, diffuse metastases, advanced neurodegenerative disorders), and (3) articles with incomplete outcomes or data. Additionally, we excluded reviews, case reports, letters, comments to editors, in vivo and in vitro studies, pilot studies, meta-analyses, editorials, protocols and recommendations, guidelines, and articles not written in English.

Search strategies

Our literature review involved a systematic search conducted in May 2022. We performed our review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (16). The search was carried out on three databases: PubMed, Scopus, and Web of Science Core Collection. The following combination of terms was used (spinal fusion OR spinal arthrodesis OR vertebral fusion OR vertebral arthrodesis) AND (gender differences OR sex differences OR gender-specific OR sex-specific), and for each of these terms, free words, and controlled vocabulary specific to each bibliographic database were combined using the operator “OR.” The combination of free-vocabulary and/or Medical Subject Headings (MeSH) terms for the identification of studies in PubMed, Scopus, and Web of Science Core Collection were reported in Supplementary Table S1.
Selection process

After submitting the articles to a public reference manager (Mendeley Desktop 1.19.8) to eliminate duplicates, possible relevant articles were screened using the title and abstract by three reviewers (FS, DC, and MT). Studies that did not meet the inclusion criteria were excluded from review and any disagreement was resolved through discussion until a consensus was reached, or with the involvement of a fourth reviewer (MF). Subsequently, the remaining studies were included in the final stage of data extraction.

Data collection process and synthesis methods

The data extraction and synthesis process started with cataloging the studies’ details. To increase validity and avoid omitting potentially findings for the synthesis, three authors (MT, VB, and CG) extracted and performed tables taking into consideration: the study design, female and male patients’ number and age, type of surgery (indication and operation types), presence of comorbidities, complications, main objectives related to sex/gender, follow-up, assessment measures, pre-and postoperative quantitative measures, complications, and outcomes/endpoints (specific sex/gender differences).

Assessment of methodological quality

The methodological quality of the selected studies was independently assessed by two reviewers (DC and FS), using the Cochrane risk-of-bias tool RoB for randomized trials and the Cochrane risk of bias ROBINS-I for nonrandomized studies of interventions (17). The tool for randomized trials included five domains, which assessed the possible sources of bias: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. For each domain were assigned one of three levels: low risk of bias, some concerns, or high risk of bias until an overall bias risk judgment is reached. The tool for nonrandomized trials included seven domains, which assessed the possible sources of bias: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of the outcome, and bias in the selection of the reported result. For each domain were assigned one of three levels: low risk of bias, moderate risk of bias, or high risk of bias until an overall bias risk judgment is reached. In case of disagreement, the reviewers attempted to reach a consensus by discussion; if this failed, a third reviewer (MF) was consulted to make the final decision.

Results

Study selection and characteristics

The initial literature search retrieved 1,885 studies. Of those, 798 studies were identified using PubMed, 435 using Scopus, and 652 were found in the Web of Science Core Collection. Articles were screened for title and abstract and 100 articles were selected. Subsequently, these articles were submitted to a public reference manager to eliminate duplicates. The resulting 77 complete articles were then reviewed to establish whether the publications met the inclusion criteria, and 47 studies were considered eligible for this review. Search strategy and study inclusion and exclusion criteria are detailed in Figure 1. Of these articles, 33 were retrospective studies, 12 were prospective studies, 1 was a case series, and another 1 was a randomized clinical trial (RCT).

Assessment of methodological quality

In our quality assessment, the randomized trial is judged to raise some concerns, but not to be at high risk of bias for any domain. The risk of bias was mainly about the randomization process and measurement of the outcome. The 70% of the nonrandomized studies were rated at low risk of bias for all domains, 21% were rated at moderate risk of bias, and 9% were rated at critical risk of bias. Methodological weaknesses that led to moderate or weak quality scores often included bias due to confounding, missing data, deviations from intended interventions, and bias in the measurement of the outcome. Risks of bias assessments for each randomized and nonrandomized study were reported in Supplementary Tables S2 and S3.

Studies general information, objectives, and cohort characteristics

Descriptive characteristics of each study are presented in Tables 1 and 2. The included studies involved a total of 1,158,555 patients. The overall percentages of female and male patients were 51.31% and 48.69%, respectively. Apart from five studies evaluating adolescent patients, the others consider patients operated at a mean age of 55.55 ± 7.38 years. Most studies (n = 23) examined the association between sex/gender and clinical outcomes in relation to a general clinical assessment and/or to specific scores. Eighteen studies also evaluated the association between sex/gender and
postoperative complications, such as intensive care unit (ICU) admission, superficial and deep SSI, postoperative fractures, cardiac events, heterotopic ossifications, instrumentation failure and reoperation rate, length of stay (LOS), or specific risk factors (opioid use, smoking, obesity). Furthermore, one study examined sex/gender differences in relation to recombinant human bone morphogenetic protein-2 (rhBMP2) use during spinal fusion surgery.

Examining sex/gender differences was the primary objective in 25 (52.1%) studies while the remaining evaluated the influence of several predictors and risk factors (age, smoking history, number, and location of fusion segments, plate-to-disc distances, excessive disc space distraction, kyphotic malalignment), also including sex/gender as a secondary aim. Comorbidities were assessed in 63.8% of the studies (n = 30). In two of these studies, no comorbidities were present. In the remaining 28 studies, different comorbidities were present that include diabetes (in 50% of included studies), cardiac diseases (25%) and/or hypertension (17.8%), blending disorders (14.2%), pulmonary diseases (10.7%), obesity and overweight (10.7%), osteoporosis (7.1%), dyslipidemia (7.1%), renal diseases (7.1%), osteoarthritis (7.1%), depression (7.1%), and others less common comorbidity, i.e., liver diseases, brain attack, vascular diseases,
| Reference          | Country of publication | Study design | Patients number | Sex/Age               | Diagnoses and surgery                                                                 | Comorbidities                                                                 | Main objectives related to sex/gender |
|-------------------|------------------------|--------------|----------------|-----------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------|
| Abousamra et al.  | United States          | Retrospective| 837            | F = 697
M = 140
Mean age: 15.2 ± 2.2 | AIS
Posterior fusion                                                                        | NR                                                                            | Blood loss                                                                         |
| Adogwa et al.     | United States          | Retrospective| 13,257         | F = 7,871
M = 5,386
Age > 25   | Degenerative diseases (symptomatic stenosis or spondylolisthesis)
Decompression and one, two, or three-level posterior lumbar instrumented fusion | Direct comparison revealed that female cohort had a higher prevalence of obesity, while males had greater proportions of type 2 diabetes mellitus, myocardial infarction, atrial fibrillation | Differences in opioid use                                                          |
| Alomari et al.    | United States          | Retrospective| 21,180         | Single-level group: F = 5,026, M = 6,168
Multilevel group: F = 4,953, M = 5,033 | Single- and multilevel ACDF                                                              | M: myelopathy, diabetes mellitus, hypertension, bleeding disorders                   | Peri-op outcomes after ACDF                                                  |
| Alomari et al.    | United States          | Retrospective| 44,526         | Single-level PLIF: F = 4,705, M = 4,156
Multilevel PLIF: F = 2,563, M = 2,291
Single-level PLIF/TLIF: F = 7,737, M = 7,403
Multilevel PLIF/TLIF: F = 3,481, M = 3,372
Single-level ALIF/LLIF: F = 2,281, M = 2,139
Multilevel ALIF/LLIF: F = 2,291, M = 2,107 | Degenerative diseases
Posterior lumbar fusion, posterior/transforaminal lumbar interbody fusion, anterior/lateral lumbar interbody fusion | Females were older and functionally dependent. Male were more likely to have diabetes mellitus, hypertension, and bleeding disorders | Peri-op outcomes after elective lumbar fusion spine surgery                       |
| Ayhan et al.      | Europe                 | Retrospective| 199            | F = 164
M = 35
Mean age: 51.94   | Scoliosis, thoracic kyphosis, degenerative or idiopathic deformity                      | NR                                                                            | Clinical outcomes                                                               |
| Basques et al.    | United States          | Retrospective| 20,383         | F = 10,486
M = 9,897
Age > 18   | Degenerative spine disease
ACDF                                                                                   | Male slightly older, ↑ incidence of diabetes and hypertension                    | Differences in baseline characteristics and risk factors for adverse outcomes     |
| Bumpass et al.    | United States          | Retrospective| 409            | F = 319
Mean age: 55.0
M = 90
Mean age: 58.3 | Adult spinal deformity
Primary posterior instrumented fusion ≥5 levels                                        | NR                                                                            | Complications, operative morbidity, deformity x-ray correction, HRQoL         |
| Buttermann et al. | United States          | Prospective  | 159            | 101 females
58 males
Mean age: 46.4 ± 9.7 | c20 of scoliosis or kyphosis ACDF with or without decompression                       | NR                                                                            | Clinical outcomes after ACDF                                                  |

(continued)
| Reference                  | Country of publication | Study design | Patients number | Sex/Age | Diagnoses and surgery                                                                 | Comorbidities                                                                 | Main objectives related to sex/gender                        |
|----------------------------|------------------------|--------------|-----------------|---------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Chan et al. (26)           | United States          | Retrospective| 477             | F = 159 | Grade 1 degenerative lumbar spondylolisthesis                                        | Diabetes, anxiety, coronary artery disease, osteoporosis, depression           | Patients' satisfaction                                           |
| Chaichuangchok et al. (27) | Asia                   | Retrospective| 54              | F = 19  | Degenerative cervical spondylitis, myelopathy                                        | Diabetic mellitus, hypertension, dyslipidemia                                 | Predictive factors for the outcomes after ACDF                  |
| Christian et al. (28)      | United States          | Retrospective| 536             | F = 234 | Degenerative diseases Elective spinal surgery (PCDF, ACDF, thoracic or lumbar short    | NR                                                                            | Associations between smoking and pre-op opioid consumption and   |
|                            |                        |              |                 | M = 302 | segment (≤4), and thoracic or lumbar long segment (≥5) decompression and/or fusion    |                                                                                | their impact on post-op outcomes                               |
|                            |                        |              |                 | Age ≥65 | procedures)                                                                            |                                                                                |                                                                  |
| Elsamadicy et al. (29)     | United States          | Retrospective| 4,972           | F = 3,282| Adult spine deformity                                                                  | Comorbidities: alcohol use, hypertension, diabetes mellitus, overweight/obese,| LOS and discharge disposition after elective spine fusion surgery |
|                            |                        |              |                 | M = 1,690| Elective spine fusion surgery involving ≥4 levels                                      | hyperesuglable state, heart failure, atrial fibrillation, chronic obstructive  |                                                                  |
|                            |                        |              |                 |         |                                                                                       | pulmonary disease, chronic kidney disease, peripheral vascular disease, liver  |                                                                  |
|                            |                        |              |                 |         |                                                                                       | disease                                                                      |                                                                  |
| Gulbrandsen et al. (30)    | United States          | Retrospective| 1,931           | F = 1,219| Lumbar degenerative conditions and thoracolumbar deformity                              | Comorbidities: autoimmune and gastrointestinal disorders, depression, fibromyalgia, thyroid | Recovery after spinal surgery (pain, function, complications)      |
|                            |                        |              |                 | M = 712 | Open posterior instrumented fusion                                                      | disease                                                                      |                                                                  |
|                            |                        |              |                 | Mean age: 59 ± 14.07                    | F: 1.75 ± 1.42                                                               | Females had a ↑ number of comorbidities compared to males:                  |
|                            |                        |              |                 |         | M: 1.50 ± 1.33                                                                        | F:1.75 ± 1.42                                                               |                                                                  |
|                            |                        |              |                 |         |                                                                                       | M: 1.50 ± 1.33                                                              |                                                                  |
| Helenius et al. (31)       | Europe                 | Retrospective| 60              | F = 30  | AIS                                                                                   | None                                                                         | Long-term results of operative treatment                        |
|                            |                        |              |                 | Mean age: 16.2 ± 2.6                    |                                                                                |                                                                               |
| Hermansen et al. (32)      | Europe                 | RCT          | 72              | F = 39  | Degenerative radiculopathy with or without neck pain Cervical intervertebral fusion    | NR                                                                           | Pre-op factors predicting good long-term outcomes and subgroup   |
|                            |                        |              |                 | M = 33  | cage or Cloward procedure                                                             |                                                                              | differences at the 10 year follow-up between patients with and    |
|                            |                        |              |                 | Mean age: 59 ± 8.6                      |                                                                                |                                                                                | without clinically relevant improvement                         |
| Hoyer et al. (33)          | United States          | Retrospective| 41,315          | F = 20,248| Different spine diseases                                                              | Diabetes, severe COPD, hypertension, revascularization/amputation for peripheral | 30-day complications                                            |
|                            |                        |              |                 | M = 21,067|                                                                      | vascular disease, preoperative transfusion, bleeding disorder, previous percutaneous |                                                                  |
|                            |                        |              |                 | Mean age: 57.27                         | coronary intervention, cardiac surgery                                       |                                                                  |
|                            |                        |              |                 |         |                                                                                       | Male ▲ bleeding disorder, previous percutaneous coronary intervention, cardiac surgery |                                                                  |

(continued)
| Reference          | Country of publication | Study design | Patients number | Sex/Age | Diagnoses and surgery                                                                 | Comorbidities                                                                                                                                                                                                 | Main objectives related to sex/gender                                                                                                                                 |
|--------------------|------------------------|--------------|----------------|---------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Jang et al. (34)   | East Asia              | Retrospective| 208            | F = 104 | Thoracolumbar burst fracture Posterior instrumented fusion                               | Diabetes, hypertension, heart diseases, prior brain attack                                                                                                                                                    | Risk factors and predictors for post-op recollapse                                                                                                                                                    |
|                    |                        |              |                | M = 104 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 45.9 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
| Kay et al. (35)    | United States          | Prospective  | 808            | F = 406 | Degenerative lumbar disease (herniated disc, spondylolisthesis, stenosis)              | Coronary artery disease, hypertension, previous myocardial infarction, congestive heart failure, diabetes mellitus, depression, and anxiety                                                                        | Post-op ICU admission                                                                                                                                                                                  |
|                    |                        |              |                | M = 402 | Laminitectomy with fusion                                                               |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age 58.1 ± 13.9 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
| Kaye et al. (36)   | United States          | Retrospective| 50,495         | F = 406 | Different spine diseases Single-level lumbar spine fusion (arthrodesis with posterior, posterolateral, or anterior interbody technique, including minimal disectomy, laminectomy, and/or disectomy to prepare interspace) | Diabetes mellitus, congestive heart failure, renal failure, dialysis, peripheral vascular disease, chronic obstructive pulmonary disease, hypertension                                                                 | Incidence and risk factors for adverse cardiac events                                                                                                                                                    |
|                    |                        |              |                | M = 402 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 66.75 ± 10.52 (with cardiac event) and 59.26 ± 13.58 (without cardiac event) |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
| Khechen et al. (37)| United States          | Retrospective| 169            | F = 69 females | Degenerative diseases Minimally invasive (MIS) TLIF                                      | Hypertension, cardiovascular diseases, renal diseases, pulmonary diseases, endocrine diseases, hepatic diseases                                                                                               | Post-op improvements in patient-reported outcomes after MIS TLIF                                                                                                                                      |
|                    |                        |              |                | M = 100 males | Mean age: 54.70 ± 11.36                                                               | F: 2.1 ± 1.94                                                                                      |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 54.80 ± 11.32 |                                                                                       | M: 2.10 ± 1.91                                                                                      |                                                                                                                                                                                                         |
| Kim et al. (38)    | Korea                  | Retrospective| 485            | F = 329 | Degenerative spine diseases Partial hemilaminectomy, transpedicular screw fixation, and both posterior lumbar interbody fusion with cage and posterolateral fusion | Hypertension, cardiovascular diseases, renal diseases, pulmonary diseases, endocrine diseases, hepatic diseases                                                                                               | Complications after spinal surgery                                                                                                                                            |
|                    |                        |              |                | M = 156 | Mean age: 57.5                                                                                       | F: 17.6%                                                                                          |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 58.0 ± 11.32 |                                                                                       | M: 14.7%                                                                                          |                                                                                                                                                                                                         |
| Kothari et al. (39)| United States          | Prospective  | 4,555          | F = 2,666 | Spinal fusion deformities                                                                     | Comorbidities: cardiac, pulmonary, and renal comorbidity, bleeding disorder, diabetes mellitus, Male ↑ cardiac events, bleeding disorder, diabetes mellitus                                                                 | Post-op morbidity after spinal surgery                                                                                                                                            |
|                    |                        |              |                | M = 1,894 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
| Lim et al. (40)    | Southeast Asia         | Prospective  | 296            | F = 202 | Grade 1 or 2 degenerative spondylothesis and nerve compression symptoms, radicular pain, paresthesia, or neurogenic claudication | Diabetes, ischemic heart disease, osteoarthritis, asthma, depression, hypertension, hypercholesterolemia, and renal disease                                                                                   | Functional, patient-reported outcome measures, health-related quality of life, satisfaction, and fulfillment of outcomes                                                                                   |
|                    |                        |              |                | M = 94 | Single-level MIS TLIF                                                                   | Females ↑ prevalence of osteoarthritis                                                                                                               |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 52.2 ± 3.2 |                                                                                       |                                                                                                    |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 56.1 ± 11.6 |                                                                                       |                                                                                                    |                                                                                                                                                                                                         |
| Mai et al. (41)    | Europe                 | Retrospective| 10,770         | F = 5,714 | Degenerative diseases, complex deformity corrections                                      | NR                                                                                                                                                                                                             | LOS                                                                                                                                                                                                     |
|                    |                        |              |                | M = 5,056 | Gynecal interventions with anterior or posterior fusion (+ instrumentation), thoracic/lumbar interventions with posterior decompression and/or spondylosis with rigid stabilization either with posterior and/or interbody fusion (open or mini-open/MIS) |                                                                                                                                                                                                             |                                                                                                                                                                                                         |
|                    |                        |              |                | Mean age: 62 ± 15 |                                                                                       |                                                                                                                                                                                                             |                                                                                                                                                                                                         |

(continued)
| Reference       | Country of publication | Study design | Patients number | Sex/Age | Diagnoses and surgery                          | Comorbidities                                                                 | Main objectives related to sex/gender                  |
|-----------------|------------------------|--------------|-----------------|---------|-----------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------|
| Maior et al. (42) | Romania               | Case series  | 44              | F = 17  | Mean age: 37.88 ± 13.56 M = 27 Mean age: 44.04 ± 14.28 | Single-level traumatic burst fracture in the thoracolumbar transition area (Th12-L2) | NR                                                     | Health-related quality of life and disability after a thoracolumbar burst fracture |
| Malik et al. (43)  | United States         | Retrospective| 23,615          | F = 12,805 M = 10,810 | Degenerative diseases one- to two-level posterior lumbar fusions | Diabetes mellitus, dyspnea, history of severe chronic obstructive pulmonary disease, congestive heart failure, hypertension, dialysis-dependent, bleeding disorders Females are more likely to be older and have dyspnea prior to surgery. Males were more likely to have diabetes and bleeding disorders | Early surgical outcomes after elective posterior lumbar fusions |
| Maragkos et al. (44) | United States       | Retrospective| 131             | F = 78  | M = 53 Mean age: 60 | Degenerative spinal disease (discogenic, stenosis, spondylolisthesis), Posterolateral pedicular screw fixation with or without posterior interbody fusion | Diabetes, osteoporosis | Risk factors for development of adjacent segment disease |
| Marks et al. (45)   | United States         | Prospective  | 547             | F = 449 | Mean age: 14 ± 2 M = 98 Mean age: 16 ± 2 | AIS | None | X-ray and peroperative surgical treatment outcomes of AIS |
| Nunley et al. (46)  | United States         | Prospective  | 389             | NR     | Cervical total disc replacement and cervical anterior discectomy and fusion | NR | Effects on outcomes, and risk factors for the development of heterotopic ossification after cervical total disc replacement |
| Ogihara et al. (47) | East Asia             | Prospective  | 2,184           | F = 682  | M = 1,502 Mean age: 65.9 | Degenerative diseases, spinal trauma, spinal tumor, or rheumatoid arthritis Posterior cervical instrumented fusion | Diabetes mellitus | Incidence of deep SSI development |
| Ogihara et al. (48) | East Asia             | Prospective  | 2,913           | F = 1,601 | M = 1,312 Mean age: 65.9 | Thoracic and/or lumbar degenerative diseases Posterior instrumented fusion | Diabetes mellitus | Risk factors for deep SSI |
| Park et al. (49)    | East Asia             | Prospective  | 16,927          | F = 11,054 M = 5,873 Mean age: 62.35 ± 10.43 | Degenerative lumbar disease (lumbar disc herniation, spondylolisthesis, stenosis) Single-level decompression and fusion | Diabetes, osteoporosis | Reoperation rates |
| Park et al. (50)    | East Asia             | Prospective  | 20,606          | F = 13,122 | M = 7,484 Mean age: 61.86 ± 10.97 | Degenerative lumbar diseases single-level fusion (posterolateral fusion or posterior/transforaminal lumbar interbody fusion) | Diabetes, osteoporosis | Risk factors for repeat decompression and fusions |

(continued)
| Reference                  | Country of publication | Study design | Patients number | Sex/Age          | Diagnoses and surgery                                                                 | Comorbidities                                      | Main objectives related to sex/gender |
|----------------------------|------------------------|--------------|-----------------|-----------------|--------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------|
| Parrish et al. (51)        | United States          | Retrospective| 192             | F = 77, Mean age: 53.2 ± 10.7, M = 115, Mean age: 50.6 ± 11.0 | Degenerative spine diseases (herniated nucleus pulposus, degenerative disc disease, isthmic spondylolisthesis, spondylolisthesis, foraminal stenosis) | Diabetes, diabetes mellitus                        | PROMIS-PF scores                     |
|                            |                        |              |                 |                 | Primary, one- or two-vertebral level MIS TLIF                                            |                                                    |                                     |
| Parrish et al. (52)        | United States          | Retrospective| 75              | F = 33, M = 42, Mean age: 49.9 ± 10.8 | Degenerative spine diseases, Pre-op chronic health comorbidities: the most frequent were hypertension, arthritis, diabetes |                                                    | Severity of PHQ-9 scores among patients with depressive symptoms |
|                            |                        |              |                 |                 | Primary, single-level MIS TLIF                                                          |                                                    |                                     |
| Poorman et al. (53)        | United States          | Retrospective| 803,949         | F = 410.818, M = 393.131, Mean age: 53.1 | Different spine diseases Spinal fusion, decompression of the lumbar spine (laminectomy and discectomy with fusion) | Comorbidities associated with ↑ mortality: mild and severe liver disease, congestive heart failure | Rates and risk factors associated with mortality |
|                            |                        |              |                 |                 |                                                                                       |                                                    |                                     |
| Salzmann et al. (54)       | United States          | Retrospective| 63              | Fracture: n = 21, F = 16, M = 5, Mean age: 66.4, Non-fracture: n = 42, F = 32, M = 10, Mean age: 65.3 | Sacral fractures after posterior instrumented fusion, Posterior instrumented fusion | NR                                                 | Occurrence of post-op sacral fracture after spinal surgery |
|                            |                        |              |                 |                 |                                                                                       |                                                    |                                     |
| Samuel et al. (55)         | United States          | Retrospective| 62,690          | F = 26,818, M = 35,872 | Degenerative spine diseases Single-level discectomy, or fusion | Overweight: 34.7%, Obesity class 1: 24.9%, Obesity class 2: 12.0%, Obesity class 3: 7.7% | Rate of early failures after lumbar discectomy and associated risk factors |
|                            |                        |              |                 |                 |                                                                                       |                                                    |                                     |
| Schmitt et al. (56)        | United States          | Retrospective| 172             | F = 119, M = 53, Mean age: 61.8 ± 13.4 | Long-segment fusion for adult spinal deformity correction | NR                                                 | Fusion rates using relatively low-dose eBMP-2 for adult spinal deformity surgery |
|                            |                        |              |                 |                 |                                                                                       |                                                    |                                     |
| Shabat et al. (57)         | Israel                 | Retrospective| 367             | F = 177, M = 190, Mean age: ≥65 | Degenerative spine disease (spondylolisthesis) | Obesity, depression, heart diseases, diabetes mellitus, osteoarthritis, peripheral vascular diseases | Patients' satisfaction rates in lumbar spine surgery |
|                            |                        |              |                 |                 |                                                                                       |                                                    |                                     |
| Sharma et al. (58)         | United States          | Retrospective| 191             | F = 141, M = 50, Mean age: 64.3 | Idiopathic, degenerative, or iatrogenic deformity Anterior, posterior, or circumferential lumbar and thoracolumbar fusion ≥3 levels | Obesity, diabetes II, hypertension, dyslipidemia | HRQoL                                |

(continued)
| Reference          | Country of publication | Study design | Patients number | Sex/Age | Diagnoses and surgery                                  | Comorbidities | Main objectives related to sex/gender                  |
|--------------------|-------------------------|--------------|-----------------|---------|--------------------------------------------------------|---------------|-------------------------------------------------------|
| Smorgick et al. (59) | Israel                  | Retrospective | 163             | F = 128 | AIS                                                    | None          | Clinical and radiographic characteristics after AIS    |
|                    |                         |              |                 | Mean age: 15.15 M = 35 Mean age: 16.17 |                                                      |               |                                                       |
| Triebel et al. (11) | Europe                  | Prospective  | 4,772           | F = 2,521 | Degenerative disc disease and chronic low back pain | NR           | Clinical outcomes                                     |
|                    |                         |              |                 | Mean age: 46 ± 11 M = 2,251 males Mean age: 46 ± 10 |                 |                     |                                                       |
| Ungureanu et al. (60) | Romania                 | Prospective  | 61              | F = 31  | Degenerative pathology Posterior lumbar interbody fusion | NR           | HRQoL and disability, and correlation between the two after spinal fusion for chronic low back pain |
|                    |                         |              |                 | Mean age: 48.67 ± 12.70 M = 30 Mean age: 50.93 ± 14.54 |                 |                     |                                                       |
| Wang et al. a (61)  | East Asia               | Retrospective | 36              | F = 20  | Cervical radiculopathy and myelopathy (revision surgery for symptomatic adjacent segment disease) | NR           | Incidence and risk factors                            |
|                    |                         |              |                 | M = 16  | Single-level ACDF                                      |               |                                                       |
|                    |                         |              |                 | Mean age: 48.3 |                                                      |               |                                                       |
| Wang et al. b (62)  | East Asia               | Retrospective | 153             | F = 102 | Cervical degenerative disc disease Continuous two- or three-level hybrid surgery (ACDF cervical disc replacement) for multilevel | NR           | Impact of smoking on intermediate-term outcomes       |
|                    |                         |              |                 | M = 51  |                                                                 |               |                                                       |
|                    |                         |              |                 | Mean age: 50.11 ± 7.48 |                                                      |               |                                                       |
| Xu et al. (63)      | China                   | Retrospective | 162             | F = 120 females | AIS Pedicle screw instrumentation and posterior fusion | None          | Postoperative x-ray outcomes after AIS                |
|                    |                         |              |                 | Mean age: 14.79 M = 42 Mean age: 16.79 |                                                      |               |                                                       |

M, male; f, female; NR, not reported; MIS, minimally invasive surgery; MISS, minimally invasive spine surgery; AIS, adolescent patients treated for idiopathic scoliosis; ACDF, anterior cervical discectomy and fusion; HRQoL, health-related quality of life; TLIF, transforaminal lumbar interbody fusion; LOS, length of stay; COPD, chronic obstructive pulmonary disease;SSI, surgical site infection; PROMIS-PF, Patient-Reported Outcome Measurement Information System-Physical Function.
| Ref.               | FU                        | Assessment measures                                      | Pre-op quantitative measures | Post-op quantitative measures | Complications                                                                 | Specific sex/gender differences |
|-------------------|---------------------------|----------------------------------------------------------|------------------------------|--------------------------------|--------------------------------------------------------------------------------|---------------------------------|
| Abousamra et al.  | NR                        | General health status, x-ray                            | NR                           | NR                             | Mean magnitude of main thoracic curve = 60 ± 10 degrees. Mean measured 2D T5-T12 kyphosis = 22 ± 14 degrees and mean calculated 3D T5-T12 kyphosis = 6 ± 12 degrees. | Male patients with severe thoracic lordosis (T5-T12 ≤0 degree) are the ↑ risk group for intra-op bleeding. |
| Adogwa et al.     | 1 year 2 years            | General health status                                   | NA                           | NA                             |                                                                                 | Female sex, obesity, preoperative narcotic use, and LOS associated with prolonged opioid use after index surgery |
| Aloamri et al. (20) | 30 days                   | General health status                                   | NA                           | NA                             | Peri-op blood transfusion, pulmonary embolism, deep vein thrombosis or thromboembolitis, myocardial infarction, stroke with neurological deficit, unplanned intubation, pneumonia, deep or superficial SSI, sepsis, septic shock, death | Except for an ↑ incidence of UTI in female patients and myocardial infarction in males, no significant differences in morbidity and mortality |
| Aloamri et al. (21) | 30 days                   | General health status, laboratory values                | NA                           | NA                             | Increased risk for UTI in females and myocardial infarction in males, no significant differences in morbidity and mortality between males and females |
| Ayhan et al. (22) | 1 year                    | General health status, x-ray, self-reported HRQoL measures (COMI, ODI, SF-36 MCS, SF-36 PCS, SRS-22) | MCCA = 40.85° T2-T12 kyphosis = 37.68 ODI = 40.41 SF-36 MCS = 41.48 SF-36 PCS = 35.94 SRS-22 Subtotal = 2.86 | MCCA = 20.86° T2-T12 kyphosis = 45.05 ODI = 27.92 SF-36 MCS = 45.81 SF-36 PCS = 41.87 SRS-22 Subtotal = 3.53 |                                                                                 | Gender does not have a significant effect on any of the HRQoL scores |

(continued)
| Ref. | FU | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences |
|------|----|---------------------|-----------------------------|-------------------------------|---------------|---------------------------------|
| Basques et al. (23) | 30 days | General health status | NA | NA | Pneumonia, reoperation, cardiac arrest, sepsis, unplanned intubation, ventilator for more than 48 h, death | The male gender is associated with a greater risk of any adverse event, also severe. Males with longer operative times compared to females (127 vs. 117 min) |
| Bumpass et al. (24) | 2 years | General health status, x-ray, ODI, SF-36, SRS-22r | NR | NR | NR | Males have greater mean estimated blood loss. No gender differences in operative time, transfusion, final x-ray measurements, HRQoL, incidence of complications, also controlling for age, BMI, comorbidities, and levels fused |
| Buttermann et al. (25) | >10 years | VAS, ODI, x-ray | NR | NR | NR | ACDF outcomes not related to gender |
| Chan et al. (26) | 3 months | General health status, ODI, EQ-5D, NRS-LP, NRS-BP | NR | NR | Readmission within 3 months of surgery: 9. Reoperation within 12 months: 13 | Female sex is associated with most satisfaction (58.4% vs. 38.5%) |
| Chaichuangchok et al. (27) | 6 months | JOA score | JOA score: 14.1 ± 2.7 | JOA score: 15.9 ± 1.6 | Transient hoarseness and dysphagia: n = 12 | No significant difference of surgical outcome between genders; % of improvement of male patients ↑ than female |
| Christian et al. (28) | 30 days | General health status | NA | NA | Wound infections, UTI, cases of pneumonia, myocardial infarctions, and thromboembolic events | Higher proportion of male smokers who underwent a PCDF compared to female smokers (9.93% vs. 5.98%) |
| Elsamadicy et al. (29) | At discharge | General health status | NA | NA | ↑ peri-op transfusion in female than male patients; most prevalent complication in female patients is UTI, followed by pulmonary complications, hematomas, venous thromboembolism, and myocardial infarction. Most common complication in male patients is myocardial infarction, followed by pulmonary complications, cardiac complications, UTI, venous thromboembolism | Gender was not an independent predictor of discharge disposition, but was independently associated with increased LOS (female) |
| Ref. | FU | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences |
|------|----|---------------------|-----------------------------|-----------------------------|---------------|----------------------------------|
| Gulbrandsen et al. (30) | 6 weeks, 3 months, 6 months, 1 year | VAS, ODI, x-ray | VAS: F = 6.54 vs. M= 6.14, ODI: F = 49.73 vs. M = 46.52 | VAS: 6 weeks: F = 4.36 vs. M = 3.99, 3 months, 6 months, and 1 year: no differences | NR | Females reported slightly more pain and worse function than males at the time of surgery, by 3 months no further gender differences in post-op pain or function existed |
| Helenius et al. (31) | M: mean 14.3 years, F: mean 14.1 years | X-ray, scoliosis Research Society questionnaire, spinal mobility, and non-dynamometric trunk performance tests | Mean Cobb angle of the thoracic curve: 55° (range 42–83°) in the males and 56° (range 43–80°) in the females. The lumbar curves: 33° (range 10–59°) in males and 34° (range 21–64°) in females. | Final correction of the thoracic curves: 30% (range 19%–65%) in males and 33% (range 7%–71%) in females. | None | AIS provides similar short and long-term results in males and females |
| Hermansen et al. (32) | 10 years | Clinically relevant improvement (≥30 mm improvement on VAS), CRI in neck-specific disability (≥20% improvement in Neck Disability Index (NDI)), radiological factors, EQ-5D, EQoL, VAS | Median self-efficacy scale score: M = 170.5, F = 141.5 | Median CSQ score—diverting attention: M = 9.0, F = 15.0; catastrophizing: M = 0.0, F = 8.5; praying/hoping: M = 2.0, F = 9.0; increased behavioral activity: M = 14.0, F = 17.5 | NR | Male gender was a predictor of CRI in neck-specific disability |
| Heyer et al. (33) | 30 days | General health status | NA | NA | UTI: F = 1.96%; M = 0.89%, Transfusion: F = 12.74%; M = 8.39%, Unplanned intubation: F = 0.41%; M = 0.69%, Pneumonia: F = 0.71%; M = 0.92%, Superficial SSI: F = 0.92%; M = 0.70% | Differences in complications are present between males and females. Females were at increased risk for superficial SSI, UTI, transfusions, and longer LOS; males were at increased risk of pneumonia and reintubation |
| Jang et al. (34) | 1 year | VAS, x-ray, CT, MRI, ODI | Measured body Ht.: 18.6 mm, Body Ht. loss: 35.3%, Body wedge angle: 18.9°, Sagittal Cobb angle: 18.2° | Measured body Ht.: 26.7 mm, Body Ht. loss: 8.4%, Body wedge angle: 6.9°, Sagittal Cobb angle: 4.6° | 27 cases of failure of the screw-bone interface, 4 instrument failure, 2 revision surgeries | Recollapse showed ↑ a proportion of males |
| Kay et al. (35) | 1 year | General health status, ODI | ODI% = 48.2 ± 15.0 | NA | Estimated blood loss = 12.2%, cardiac = 29.3%, respiratory = 19.5%, neurologic complications = 31.7%, other = 7.3% | Female gender, history of coronary artery disease, myocardial infarction, chronic heart failure, age, ASA grade, estimated blood loss, and LOS associated with ICU admission |
| Ref.                | FU                  | Assessment measures        | Pre-op quantitative measures | Post-op quantitative measures | Complications                                         | Specific sex/gender differences                                                                 |
|--------------------|---------------------|---------------------------|-----------------------------|------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Kaye et al. (36)   | 30 days             | General health status     | NA                          | NA                           | Myocardial infarction, sepsis, death                   | Factors associated with an increased cardiac risk after spinal fusion: age, male gender, insulin-dependent diabetes, ASA score >3, hematocrit, and smoking |
| Khechen et al. (37)| 6 weeks             | ODI                       | ODI: F = 43.77 ± 16.38; M = 36.22 ± 15.13 | ODI: −6 weeks: F = −10.62 ± 17.63; M = −7.05 ± 19.15 | Intraoperative: none                                   | Gender is not associated with surgical or clinical outcomes; it is not a predictor of outcomes following MIS TLIF |
|                    | 12 weeks            | VAS back and leg pain     | VAS back: F = 6.62 ± 2.29; M = 5.90 ± 2.58 | VAS leg: F = −18.49 ± 17.22; M = −13.53 ± 17.29 |                                                       |                                                    |
|                    | 6 months            |                           | VAS leg: F = 6.20 ± 2.73; M = 5.27 ± 2.94 | −6 months: F = −23.60 ± 17.76; M = −21.00 ± 15.98 |                                                       |                                                    |
|                    |                     |                           | VAS back: −6 weeks: F = −3.21 ± 2.94; M = −2.57 ± 3.15 | −12 weeks: F = −3.63 ± 2.81; M = −2.92 ± 2.83 |                                                       |                                                    |
|                    |                     |                           | −12 weeks: F = −3.63 ± 2.81; M = −2.92 ± 2.83 | −6 months: F = −3.67 ± 3.24; M = −3.34 ± 3.16 |                                                       |                                                    |
|                    |                     |                           | −6 months: F = −3.48 ± 3.07; M = −3.01 ± 3.36 | −12 weeks: F = −3.98 ± 2.94; M = −3.39 ± 3.12 |                                                       |                                                    |
|                    |                     |                           | −12 weeks: F = −3.98 ± 2.94; M = −3.39 ± 3.12 | −6 months: F = −4.40 ± 3.31; M = −3.32 ± 3.04 |                                                       |                                                    |
| Kim et al. (38)    | >12 months          | MacNab’s criteria         | NR                          | NR                           | None                                                  | Peri-op complications not significantly associated with gender                                    |
| Kothari et al. (39)| 30 days             | General health status     | NA                          | NA                           | Univariate analysis: F associated with ↑ intra- or post-op red blood cell transfusion, UTI, and LOS >5 days; M associated with ↑ rate of pulmonary and cardiac complications. Multivariate analysis: F predictor of any complication, intra- or post-op red blood cell transfusion, UTI, and LOS >5 days | Females are associated with ↑ overall morbidity; i.e. for UTI, transfusion, and LOS >5 days. Male associated with ↑ incidence of pulmonary and cardiac complications |

(continued)
| Ref.          | FU    | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences |
|--------------|-------|---------------------|------------------------------|------------------------------|---------------|---------------------------------|
| Lim et al. (40) | 2 years 5 years | ODI, SF-36          | ODI: M = 41.5 ± 18.0, F = 49.5 ± 17.3  
SF-36 PCS: M = 35.6 ± 10.6, F = 31.9 ± 10.3  
SF-36 MCS: M = 49.2 ± 11.7, F = 44.9 ± 12.3 | NR | Revision surgery: F = 9, M = 3  
Inadvertent durotomy: F = 4, M = 0  
Vertebral endplate perforation: F = 1 | Females are significantly younger than males at the time of surgery. At 2-year and 5-year follow-ups, no significant differences in ODI, SF-36, and pain scores between males and females |
| Mai et al. (41) | NR    | General health status, COMI | NR | NR | General medical complications and surgical complications | ↑ LOS in females than males. LOS ↑ with age in females compared to males. Female gender, age, and BMI associated with a longer LOS |
| Maior et al. (42) | 1 year | SF-36v2 ODI | NR | NR | 1 wound infection (F), 1 reinsertion of a wrongly inserted screw (M)  
Gender-related differences favoring men after surgical interventions for spinal fractures. Male patients scored ↑ in each item of the SF-36v2. Male patients had ↓ ODI score | |
| Malik et al. (43) | 30 days | General health status | NA | NA | Deep surgical site infection, superficial surgical site infection, and sepsis/septic shock. The 3 most common reoperations in men: incision and drainage hematoma/serosa/fluid collections; incision and drainage, open, of deep abscess of posterior spine; reinsertion of spinal fixation device; in female: incision and drainage, open, of deep abscess of posterior spine; incision and drainage, complex wounds; and exploration of spinal fusion  
Female gender is an independent risk factor significantly associated with a LOS longer than 3 days, occurrence of any complication within 30 days, wound complications, UTI, 30-day, 30-day readmissions, and nonhome discharge. The only adverse outcome associated with male was renal complication | |
| Maragkos et al. (44) | NR    | General health status, x-ray | NR | NR | Reoperation = 33  
Decompression of segments outside the fusion construct associated with ↑ adjacent segment disease rates, as well as female gender | (continued) |
| Ref. | FU | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences |
|------|----|---------------------|-----------------------------|-------------------------------|--------------|--------------------------------|
| Marks et al. (45) | 2 years | x-ray, pulmonary function data, SRS questionnaire | Curve magnitude: 55° ± 11° in males and 54° ± 11° in females, with flexibility of the primary curve 1° in males. % Predicted of FEV: 85% ± 18% in males versus 83% ± 16% in females; % of predicted FVC was 92% ± 20% in males versus 86% ± 16% in females. SRS scores are similar in males and females. | % correction and ratio of % correction of the primary curve to preoperative flexibility: males 57% ± 17% and 1.58, females 60% ± 18% and 1.46. ↓ correction of the primary curve at 2 years FU minimal and comparable for males and females (2° ± 6° vs. 3° ± 7°, respectively). % Predicted FEV: 4% ± 12% in males and 5% ± 13% in females; decrease in % predicted FVC: 7% ± 13% in males and 6% ± 12% in females. SRS scores are similar in males and females. | F: 5% perioperative complications, 2% major postoperative complications, 5% minor postoperative complications. M: 8% perioperative complications, 6% major postoperative complications, 2% minor postoperative complications. | X-ray and perioperative surgical treatment outcomes of AIS comparable between genders. |
| Nunley et al. (46) | 7 years | NDI VAS neck/arm pain SF-12 | NR | NR | NR | Males were ~3 times more likely to develop clinically relevant heterotopic ossification than females. |
| Ogihara et al. (47) | 1 year | General health status | NA | NA | Deep SSI | Risk factors for deep SSI: occipitocervical surgery and male gender. |
| Ogihara et al. (48) | 1 year | General health status | NA | NA | SSI | Independent risk factors: male gender, ASA score of ≥3, operation including thoracic spine. |
| Park et al. (49) | 4.5 years | General health status | NA | NA | Reoperation: > in patients with spinal stenosis than those with lumbar disc herniation. Male gender was a risk factor for reoperation. | |
| Park et al. (50) | 90 days to 4 years | General health status | NA | NA | NR | Old age, and male gender, were risk factors. |
| Parrish et al. (51) | 6 weeks 3 months 6 months 1 year | General health status PROMIS-PF scores | NR | NR | NR | No significantly different among gender in the rate of achieving minimal clinically important difference for PROMIS-PF. Females experienced significantly more improvement in post-op PROMIS-PF scores than males at the 3-month time point. |

(continued)
| Ref.                   | FU         | Assessment measures                          | Pre-op quantative measures | Post-op quantative measures | Complications                                               | Specific sex/gender differences |
|-----------------------|------------|-----------------------------------------------|-----------------------------|----------------------------|------------------------------------------------------------|--------------------------------|
| Parrish et al. (52)   | 6 weeks    | PHQ-9 scores, SF-12, VR-12                    | 38.7% mild (PHQ-9 score 5–9) | NR                        | Complications with the highest mortality rates: shock and pulmonary embolism | No significant differences between genders |
|                       | 12 weeks   |                                               | 26.6% moderate (PHQ-9 score 10–14) | NR                        |                | |
|                       | 6 months   |                                               | 34.7% moderately severe (PHQ-9 score ≥15) | NR                        |                | |
|                       | 1 year     |                                               |                             | NR                        |                | |
| Poorman et al. (53)   | NR         | General health status                         | NA                         | NA                        | Post-op fracture                                           | Increased mortality in males, black, ages 65–74, and age ≥75 |
| Salzmann et al. (54)  | >6 months  | CT                                            | NR                         | NR                        |                | BMI and female gender are risk factors for post-op sacral fractures |
| Samuel et al. (55)    | 30 days    | General health status                         | NR                         | NR                        | 22.2% reoperation within 30 days: 12% spine-related reoperations, including 0.8% revision lumbar discectomy, 0.3% irrigation and debridement of infection, 0.1% lumbar fusion | Female gender is at increased risk of readmission for pain or neurological symptoms |
| Schmitt et al. (56)   | 2 years    | X-ray                                         | NR                         | NR                        | Constipation/ileus, hypotension, arrhythmia, UTI, anemia/coagulopathy, pneumonia, transient weakness/paresthesia, superficial wound drainage/infection, urinary retention, hematoma, AKI, pseudarthrosis, instrumentation failure, proximal junctional kyphosis/adjacent segment disease, wound complication/infection with revision | Gender associated with fusion status, with 79.8% of females demonstrating fusion, compared to 60.4% of men |
| Shabat et al. (57)    | 1 year     | VAS (VAS index: basic activities of daily status) | VAS: F 8.8 ± 1.86, M 8.36 ± 2.12 | VAS: F 3.88 ± 2.56, M 3.39 ± 2.71 | n = 1 death secondary to myocardial infarction; urinary retention, exacerbation of CHF and/or COPD, and unstable angina more frequently in males; urinary tract infection and postoperative delirium more frequently in females; n = 1 depression and CVA in females. | Gender differences influence the satisfaction rate of lumbar spinal stenosis surgery, with females less satisfied than males |
|                       |            |                                               | Barthel index: F 65.82 ± 11.08, M 68.28 ± 12.38 | Barthel index: F 81.15 ± 12.24, M 84.14 ± 11.19 | Rate of complications similar among males (32%) and females (28%). More than one complication found in 30% of females and 20% of males. | |

(continued)
| Ref.             | FU     | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences                                                                                                                                 |
|-----------------|--------|---------------------|------------------------------|------------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sharma et al. (58) | 1 year | HRQoL               | NR                           | Improvement in EQ-5D scores in 98 patients (51%) | NR            | Gender interacted with obesity: obese males with at higher odds of improvement when compared to nonobese males; among females, obesity did not affect the odds of improvement |
| Smorgick et al. (59) | None   | VAS                 | NR                           | NR                           | None          | Presence of a trend toward more flexible major thoracic curves in females but no significant difference between females and males                                                                 |
| Troubl et al. (11)   | 1 year | General health status, Patient-Reported Outcome Measures, VAS for leg and back pain, ODI, HRQoL, parameter EQ-5D | NR                           | NR                           | NR            | Females with a ↑ rate of improvement from baseline to follow-up in leg pain, back pain, HRQoL, and disability. Females with better chances of clinical improvement than men for leg pain, back pain, and ODI, but improved at a slower pace in leg pain, back pain, and disability. No gender differences in HRQoL and return to work at 1-year and 2-year post-op |
| Ungureanu et al. (60) | 1 year | SF-36v2 ODI         | Female                       | Male                         | Male          | Male improved more than females in all domains of disability at the postoperative evaluation. HRQoL improved similarly in both genders. ODI score showed a strong or moderate correlation with six of the domains of the SF-36 in males, but with only three domains in females. |

Female: PCS: 27.08 ± 6.96 9.20 ± 7.05 28.32 ± 7.87 29.39 ± 6.37 46.46 ± 9.55 29.54 ± 4.76 42.06 ± 10.23 6.62 ± 0.70 47.78 ± 12.99 10.45 ± 4.70 48.52 ± 11.23 15.26 ± 9.55 29.54 ± 4.76 55.91 ± 17.6 14.79 ± 0.70 42.99 ± 1.1 ± 0.90 3.29 ± 1.13 10.86 38.29 ± 2.00 ± 1.26 3.00 ± 1.44

Male: PCS: 43.02 ± 9.76 46.05 ± 10.03 44.95 ± 9.24 50.39 ± 11.20 43.87 ± 9.83 51.93 ± 7.96 50.49 ± 0.90 50.66 ± 0.86 50.92 ± 0.67 43.39 ± 11.20 50.39 ± 0.67 50.39 ± 0.67 50.39 ± 0.67 50.39 ± 0.67 50.39 ± 0.67

MCS: 49.69 ± 10.78 53.72 ± 9.83 46.19 ± 10.78 53.22 ± 7.90 51.93 ± 7.96 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88 54.88 ± 8.88

VT: 41.36 ± 8.92 40.39 ± 11.20 40.39 ± 11.20 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80

SF: 44.95 ± 9.24 46.63 ± 9.20 46.63 ± 9.20 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80 49.39 ± 9.80

Pain intensity: 0.97 ± 0.76 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71 0.33 ± 0.71

Personal care: 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60 1.83 ± 1.60

Walking: 1.00 ± 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11 0.93 ± 1.11
| Ref.                      | FU        | Assessment measures | Pre-op quantitative measures | Post-op quantitative measures | Complications | Specific sex/gender differences |
|--------------------------|-----------|---------------------|-----------------------------|-------------------------------|---------------|---------------------------------|
|                          |           |                     | Walking: 2.68 ± 1.28         | 15.02                         | 0.30 ± 0.65   |                                  |
|                          |           |                     | Sitting: 3.35 ± 1.11         | 43.89                         | 12.62         |                                  |
| Wang et al. (61)         | 5 years   | General health status, x-ray | Standing: 3.39 ± 0.99         | 56.19                         | 1.38          | Sex life: 0.83 ± 1.50 |
|                          |           |                     | Sleeping: 1.97 ± 0.38        | 17.25                         | 0.85          | Social life: 0.90 ± 1.37       |
|                          |           |                     | Sex life: 2.22 ± 1.83        | 2.37                          | 1.25          | Traveling: 0.81 ± 0.95         |
|                          |           |                     | Social life: 2.61 ± 1.65     | 3.33                          | 1.40          |                                  |
|                          |           |                     | Traveling: 3.13 ± 1.43       | 2.93                          | 1.56          | Male gender and current smoking status are significantly associated with a 1-year fusion rate. Significant differences in the early fusion process and the 1-year fusion rate across the three smoking status groups in females |
| No gender differences    | Wang et al. (62) | General health status, JOA scale, NDI, VAS for neck and arm pain, x-ray, CT, and MRI |                         | NR              | NR              | Comparative surgical benefits between females and males |
| Xu et al. (63)           | 3 months  | X-ray               | Sized main curves: F = 51.53° vs. M = 52.45° | Sized main curves: F = 16.83 vs. M = 20.8° | None          |                                  |

NA, not applicable; CRI, Clinically relevant improvement; NDI, Neck Disability Index; ASA, American Society of Anesthesiologists physical status; COMI, Core Outcome Measures Index; PCS, physical component summary; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; MCS, mental component summary; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; LOS, length of stay; UTI, urinary tract infection; HRQoL, health-related quality of life; ODI, Oswestry Disability Index; SF-36, Short Form Health Survey 36; BMI, body mass index; VAS, visual analog scale; ACDF, anterior cervical disectomy and fusion; NRS-LP, numeric rating scale for leg pain; NRS-BP, numeric rating scale for low back pain; JOA, Japanese Orthopedic Association; PCDF, posterior cervico-decompression and fusion; ICU, intensive care unit; TLIF, transforaminal lumbar interbody fusion; SRS-22, Scoliosis Research Society-22 questionnaire; MCCA, major coronal Cobb angle; EQ5D, quality of life (QoL) parameter EQ5D; EQoL, Environmental Quality of Life; CSQ, Cognitive Style Questionnaire; FEV, forced expiratory volume; FVC, forced vital capacity; VR-12, Veterans RAND-12; SF-12, Short Form-12; AKI, acute kidney injury; CHF, chronic heart failure; CVA, Cerebrovascular accident.
asthma, and anxiety. In 12/27 studies where comorbidities were present and described gender-related differences in comorbidities distribution were also reported. The major comorbidity reported in females was obesity while in males were diabetes, cardiovascular morbidities (prevalently atrial fibrillation and hypertension), and bleeding disorders.

Qualitative and quantitative measures used for patient assessment were detailed in Table 1. The Visual Analogue Scale (VAS) score for back or leg pain was used, alone or in association with other measurements, by 21.2% of the studies, the Oswestry Disability Index (ODI) by 25.5% of studies, x-ray, to evaluate pre-and postoperative sized main curves, sagittal Cobb angle, kyphosis, by 27.6% and specific patient-reported outcomes measures and standardized measure of health-related quality of life (HRQoL) by 42.5% of studies. Other less common measures used include the numeric rating scale (NRS) scores for low back pain (NRS-BP), leg pain (NRS-LP), Japanese Orthopedic Association (JOA) scale, magnetic resonance imaging (MRI), computed tomography (CT), and laboratory values. Except for one study that evaluated sex/gender differences at discharge, all other studies performed clinical assessments from 30-day of follow-up up to 10 years.

Types of spine surgery and pathological conditions

Patients were diagnosed with different spine diseases, mainly degenerative pathological conditions such as disc herniation, stenosis, spondylolysis, radiculopathy, spondylolisthesis, myelopathy (55.3%), spinal deformities as adult scoliosis or kyphosis (12.7%), adolescent idiopathic scoliosis (10.6%), degenerative and deformity conditions together (14.8%), and traumatic pathologies such as fractures (6.3%). In detail, 235,140 patients (26 studies) were treated for degenerative diseases using anterior or posterior approaches (Table 1). Of these, 17 studies were retrospective and analyzed 188,278 patients, 8 were prospective and included 46,862 patients, and 1 study was an RCT with 72 patients. A total of five studies (four retrospective and one prospective) analyzed 1,769 adolescent patients treated for idiopathic scoliosis (AIS) using a posterior approach. Concerning adult deformities, a total of 4,714 patients were evaluated in two prospective studies and 5,752 patients in four retrospective studies, using anterior or posterior approaches. Studies that analyzed degenerative and deformity conditions together (six retrospective studies and one prospective) evaluated 910,835 patients. Finally, 315 patients (three studies) were treated for traumatic sacral or thoracolumbar fractures after posterior instrumented fusion. Of these, two studies were retrospective with 271 patients, and one study was a case series with 44 patients.

Procedures associated with spinal fusion surgery included minor, major, and complex surgeries, such as posterior lumbar interbody fusion (PLIF), hemilaminectomy, decompression, anterior cervical discectomy and fusion (ACDF), transforaminal lumbar interbody fusion (TLIF), discectomy, anterior lumbar interbody fusion (ALIF) and laminectomy (Table 1). Because the types of spine fusion surgery were not standardized across the 47 studies, it was difficult to quantify the prevalence of any single type of procedure among the studies. However, most interventions were implemented for lumbar spine procedures, through techniques such as PLIF and TLIF, followed by cervical procedures such as ACDF.

Sex/gender differences in outcomes after spinal fusion surgery

In this review, 76.6% (n = 36) of studies reported sex/gender-related differences in postoperative clinical outcomes and/or complications, while the remaining studies described comparable results between males and females (Table 2). Of these 36 studies where sex/gender differences were present, n = 21 (58.3%) were on degenerative diseases, prevalently of the lumbar spine, 13.9% were on spine deformities (1 on AIS and 4 on adult deformities), 8.4% on spine fractures, and 19.4% considered degenerative conditions and deformities together (Table 1).

Degenerative spine diseases

More than half of studies on degenerative spine diseases on the lumbar spine reported worse female experiences after spinal fusion surgery (63.8%). Kay et al. showed that the female gender was associated with an increased risk of postoperative ICU admission in patients undergoing lumbar spine surgery (35). Furthermore, Maragkos et al. also reported that female patients were 2.55 times more likely than male ones to develop adjacent segment disease requiring reoperation (44). In detail, within 30 days of follow-up female gender resulted in an independent risk factor significantly associated with a LOS longer than 3 days, occurrence of complications, including wound complications, urinary tract infection (UTI), and nonhome discharge; while the adverse outcomes associated with males were renal complication and myocardial infarction (20, 43). At the same follow-up female gender also resulted in an increased risk of readmission for pain or neurological symptoms (55). At a longer follow-up, 1 year, it was analyzed the influence that gender plays on HRQoL, disability, and the correlation between these two in patients undergoing spinal fusion for chronic low back pain (60). Results showed that male patients had higher disability scores
at the preoperative evaluation but improved more than females in all domains of disability postoperatively. HRQoL improved similarly in both genders. The ODI score showed a strong or moderate correlation with six of the domains of the Short Form Health Survey 36 (SF-36) in males, but with only three domains in females (69). At the same follow-up, it was also shown that gender differences influence the satisfaction rate of lumbar spinal stenosis surgery in elderly patients (≥65 years) with female patients that had less satisfactory results than male ones (57). After 2 years of follow-up, it was shown that the female gender was also associated with prolonged opioid use (19). Several studies reported different results. Parrish et al. reported that females experienced significantly more improvement in postoperative Patient-Reported Outcome Measurement Information System-Physical Function (PROMIS-PF) score than males at the 3-month time point (51). Chan et al. reported that at 1 year of follow-up, the female gender resulted also associated with more satisfaction than males (58.4% vs. 38.5%) (26). These results were further confirmed by Triebl et al. where it was shown that females had a high rate of improvement from baseline to follow-up (2 years) in leg pain, back pain, HRQoL, and disability, in comparison to males, but it was also reported that females improve more slowly in leg pain, back pain, and disability (11). At longer follow-up (up to 4.5 years), Park et al. showed that the male gender was a risk factor for reoperation (49, 50).

In cervical degenerative diseases at 1 year of follow-up a higher percentage of improvement was detected in male patients than in females (27). This result was also confirmed at 10 years of follow-up, where it was demonstrated a higher neck- and arm-related pain intensity, more disability, and worse psychosocial status in females than in males (32). Specifically, the male gender was a predictor of clinically relevant improvement in neck-specific disability (32). Differently, Nunley et al. (46) showed that males were ~3 times more likely to develop heterotopic ossification than females as well as they were at greater risk of any adverse event (23). Alomari et al. (21) described an increased risk for UTI in females and myocardial infarction in males. Two studies also evaluated the correlation between gender, spinal fusion surgery, and smoking. A higher proportion of male smokers who underwent posterior cervical decompression and fusion (PCDF) compared to female smokers (9.93% vs. 5.98%) was detected (28). In addition, a significant difference in the early fusion process among current smokers, former smokers, and nonsmokers was detected for male patients, but no significant differences were found at 1-year of follow-up. For female patients, statistical differences were found in both the early fusion process and the 1-year fusion rate (62).

The only study on sex/gender differences considering thoracic spine surgery was by Ogihara et al. using a multivariate analysis that showed that male gender was significantly correlated with a higher incidence of deep SSI, although it was not a significant factor in univariate analysis (48).

### Spine deformities

Of the 36 studies where sex/gender differences were evaluated, n = 4 were on adult spinal deformities. Two studies reported that female sex/gender was associated with increased postoperative morbidity compared to males; after 30 days from spinal surgery, it was observed an increased postoperative transfusion rate and complications, in particular, UTI and LOS longer than 5 days, in female patients (29, 39). Conversely, one study reported that male patients were at a greater risk for bleeding compared to females (24). Differently, from the above-mentioned studies, Schmitt et al. evaluated at 2 years of follow-up the fusion rates using relatively low-dose rhBMP-2 for the treatment of adult spinal deformity surgery, showing that gender was associated with fusion status, with 79.8% of females with a good spinal fusion compared to 60.4% of males (56).

Only one study on AIS detected gender-related differences, showing that male patients, with severe thoracic lordosis, were at a higher risk of bleeding than females (18).

### Degenerative conditions and deformities

Seven studies reported sex/gender-related differences considering patients treated for degenerative conditions and deformities together. In detail, at 30 days of follow-up, Heyer et al. (33) reported postoperative differences in complications between males and females. Females were at increased risk for superficial SSI, UTI, transfusions, and longer LOS while males were at increased risk of pneumonia and reintubation (33, 41). At the same experimental time, it was also shown that the male gender was associated with an increased risk of cardiac events (36). At a longer experimental time, 1-year follow-up, it was shown that the male gender represented a risk factor for deep SSI (47).

In a study on the mortality rates after spinal fusion surgery and on factors associated with its occurrence over a 10-year follow-up, it was shown that the male gender was a risk factor significantly associated with increased mortality rates (53). In addition to complications and risk factors related to gender, Gulbrandsen et al. (30) indicated that females reported slightly more pain and worse function than males at the time of surgery. Finally, Sharma et al. also showed that in spine surgeries gender interacted with obesity at 1 year of follow-up: obese males with at higher odds of improvement when compared to nonobese males; among females, obesity did not affect the odds of improvement (58).
Spine fractures

Of the 35 studies where sex/gender differences were present, 11 were on spine fractures after spinal fusion surgery. One study was on sacral fractures (54), and two studies were on thoracolumbar burst fractures (34, 42). Salzmann et al. observed, at a 6-month follow-up, that female gender (76.2%), advanced age (mean, 66.4 years), and obesity were risk factors for post-op sacral fractures (54). Differently, Jang et al. showed that the male gender was a risk factor for recollapse of thoracolumbar burst fractures (34). At 1-year follow-up, Maior et al. reported that male patients have better outcomes than females after thoracolumbar burst fractures; an increased score in each item of the SF-36 in male than female patients was also observed (42).

Discussion

From an epidemiological perspective, it would be critical to understand how sex/gender differences can affect clinical outcomes after spinal fusion surgery. This aspect becomes more critical from a surgical point of view since the identification of specific sex/gender differences would offer personalized approaches for patients undergoing spinal fusion procedures. Thus, the focus of this review was to analyze clinical studies aimed at evaluating sex/gender differences following spinal fusion surgery.

Our review showed that most of the analyzed studies (76.6%) report sex/gender-related differences in postoperative clinical status, outcomes, and/or complications, while the remaining described equivalent results. Furthermore, in 38.3% of the studies where comorbidities were described gender-related differences in their distribution were reported. In the female sex, obesity was the most prevalent comorbidity while in the male sex the prevalently dominant comorbidities were diabetes, cardiovascular morbidities (prevalently atrial fibrillation and hypertension), and bleeding disorders. These differences are of critical importance and could represent potential risk factors related to gender differences (both pre-op and post-op) to be analyzed in future studies, in which it will be mandatory to analyze a larger homogeneous cohort of patients, considering specific and individual spine diseases and surgical approaches. In fact, it is important to highlight that there is significant heterogeneity across the analyzed studies in terms of pathological spine diseases (degenerative, deformity, fracture), type of the spinal level treated (cervical, thoracic, lumbar, sacral), number of levels treated, and surgical approaches. In addition, it is important to underline that none of the analyzed studies evaluated specific physiological changes related to postmenopausal status in female patients submitted to spinal fusion procedures. It is known that the direct negative effects of estrogen-deficiency on bone as well as the indirect effects of altered immune status in postmenopausal women contribute to low bone mass and bone microarchitecture destruction. These bone alterations may represent a negative prognostic factor for the success of spinal fusion surgery.

In this review, most of the studies where sex/gender-related differences were present were on the patient treated for lumbar degenerative diseases (disc degeneration, disc herniation, and spondylolisthesis). Of those more than half reported a worse postoperative outcome in terms of pain, disability, HRQoL, and complications in female patients, while the remaining reported worse outcomes in terms of HRQoL and satisfaction in male patients. In studies examining pain, disability, and HRQoL differences between females and males, the complexity of evaluating these parameters which include many clinical signs and subjective outcomes must be considered. Undoubtedly, females treated for lumbar degenerative disease reported the worst postoperative scenario, but the perception and measurements of pain and disability have been debated and investigated: some studies concluded that females had lower perception thresholds and pain thresholds than males (64). This worst postoperative state in female patients is probably the reason for the prolonged postoperative opioid consumption associated with this gender (19). However, epidemiological studies have indicated that analgesic use may vary between males and females, suggesting that opioid use was higher in the female gender in general adult populations (65, 66). This systematic review found that females were also at increased risk of complications (UTI, readmission for pain or neurological symptoms, adjacent segment disease), and consequent longer LOS, following spinal fusion surgery for lumbar degenerative disease (20, 43, 44, 55). These postoperative complications may also have a link to the long-term opioid use detected in female patients. While for degenerative lumbar spine diseases a potential link between gender and clinical outcomes resulted more evident, for degenerative diseases of the cervical and thoracic spine this link is not so clear. This is probably due to the heterogeneity of the analyzed studies but also to the small number of studies found in this review. However, at 10-year to 13-year of follow-up, a prospective randomized study indicated that predictive factors of good outcome after ACDF included initial high neck-related pain intensity, nonsmoking status at the time of surgery, and male gender (32). On the contrary, other clinical studies indicated that males were more likely to develop clinically relevant heterotopic ossification than females as well as a greater risk of any adverse event, also severe (23). Similar contradictory results were also found after spinal deformity surgery, when degenerative diseases and deformities were considered and analyzed together and following spine fractures (sacral fractures and thoracolumbar...
burst fractures). Also, in these cases, the limited number of studies and the heterogeneity between studies remained critical factors that limit the interpretation of the results. For adult spinal deformities, a gender difference was founded by using relatively low-dose rhBMP-2 with the female gender demonstrating a better spinal fusion compared to male one (56). In this study, there were substantial differences between the patient’s series and those in the comparison groups. When degenerative diseases and deformities were considered and analyzed together it was also shown that gender interacted with obesity at 1 year of follow-up; obese males showed a higher odd of improvement when compared to nonobese males while among females, obesity did not affect the odds of improvement (58). Nevertheless, it should be noted that numerous studies present in the literature did not investigate and analyze spinal fusion outcomes dichotomizing by gender, thus it is difficult to establish a real conclusion and draw definitive results. As such, a true systematic review was not feasible. Furthermore, some limitations of this review warrant discussion. Most eligible studies in this review were retrospective and only one RCT on 47 analyzed studies was found and included. Additionally, many included studies had a small sample size and may be underpowered to identify significant clinical responses. Numerous studies, accounting for most patients, were prevalently published by groups in the United States; cultural discrepancies in patient-reported clinical assessment scores may differ geographically. The clinical assessment tools used to determine the postoperative outcomes are, prevalently, subjective patient-reported measures. Results were also difficult to interpret due to specific differences in spine diseases in the retrieved studies; for example, insufficient heterogenic data were retrieved for cervical and sacral degenerative diseases, spinal deformities, and traumatic spinal fractures. Furthermore, also searching for “spinal fusion” and “sex” or “gender” on the www.clinicaltrial.gov website (accessed on 22 May 2022) no clinical trials had, as a primary or secondary outcome, the analysis of sex/gender differences.

Conclusions

The review highlighted those female patients treated for lumbar degenerative spine diseases probably require more clinical awareness during postoperative care. The understanding of how sex/gender differences can really affect clinical outcomes after spinal fusion surgeries have the potential to enhance clinical decision-making and care practices and may be crucially important in the context of providing patient personalized care, a critical field of contemporary medical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

FS, DC, and MF contributed to the conceptualization of the study and to the writing—original draft preparation. FS, DC, MT, VB, and CG contributed to the methodology and data curation. FS, DC, AG, and MF contributed to the writing—review, and editing. AG and MF contributed to the supervision. MF contributed to the funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.983931/full#supplementary-material.
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