CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINES FOR PERIOPERATIVE SPINE: PREOPERATIVE NUTRITIONAL ASSESSMENT

Sponsored by: Congress of Neurological Surgeons (CNS) and the Section on Disorders of the Spine and Peripheral Nerves
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Abbreviations:
SSI: surgical site infection
MNM: multimodal nutrition management

CPR: C-reactive protein

ABSTRACT

Background: Preoperative malnutrition has been implicated in adverse events after elective surgery, potentially impacting patient outcomes.

Objective: As a potentially modifiable risk factor, we sought to determine which assessments of nutritional status, were associated with specific adverse events after spine surgery. In addition, we explored if a preoperative nutritional improvement intervention may be beneficial in lowering the rates of these adverse events.

Methods: The literature search yielded 115 abstracts relevant to the PICO (patient/population, intervention, comparison, and outcomes) questions included in this chapter. The task force selected 105 articles for full-text review, and 13 met criteria for inclusion in this systematic review.

Results: Malnutrition, assessed preoperatively by a serum albumin <3.5 g/dL or a serum prealbumin <20 mg/dL, is associated with a higher rate of surgical site infections (SSIs), other wound complications, nonunions, hospital readmissions, and other medical complications after spine surgery. A multimodal nutrition management protocol decreases albumin and electrolyte deficiencies in patients with normal preoperative nutritional status. It also improves overall complication rates but does not specifically impact SSIs.

Conclusion: It is recommended to assess nutritional status using either serum albumin or prealbumin preoperatively in patients undergoing spine surgery.

RECOMMENDATIONS

Question:

1. What preoperative serologic studies of nutritional status (and timing of these studies) are predictive of adverse event after spine surgery?

Recommendations:

Serum markers of malnutrition including low preoperative albumin, prealbumin, total protein, and albumin/globulin are associated with multiple adverse events after spine surgery. In at-risk individuals, clinicians should assess nutritional status preoperatively and counsel patients on the potential for adverse events.

Strength of Recommendation: Grade B

Question:

2. What preoperative nonserologic assessments of nutrition status (and timing of these assessments) are predictive of adverse event after spine surgery?

Recommendations:

There is insufficient evidence to make a recommendation on the impact of preoperative use of nonserologic assessments of nutrition status on adverse outcomes in patients undergoing spine surgery.

Strength of Recommendation: Grade Insufficient

Question:

3. In patients with poor nutrition, does preoperative treatment (and type of treatment) decrease the risk of postoperative adverse events?

Recommendations:

In patients with malnutrition undergoing spine surgery, there is insufficient evidence to support the use of a perioperative multimodal nutrition management protocol to decrease the risk of postoperative adverse events.
Strength of Recommendation: Grade I

INTRODUCTION

Goals and Rationale

This clinical guideline has been created to improve patient care by outlining the appropriate information gathering and decision-making processes involved in the treatment of patients with perioperative spinal disease. This guideline has been created as an educational tool to guide]physicians through a series of diagnostic and treatment decisions in an effort to improve the quality and efficiency of care.

This guideline should not be construed as including all proper methods of care or excluding methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment must be made in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Adverse events after surgery are significant drivers of both cost and quality of life, impacting the overall value of these interventions. Studies have shown that spine surgery for degenerative conditions can result in significant improvements in pain, disability, and quality of life.[1,2] However, postoperative complications, including SSI, readmission to the hospital, and nonunion, may add substantial morbidity and ultimately result in poor overall outcomes and satisfaction.[3]

There has been increased attention on identifying potentially modifiable risk factors for adverse outcomes after surgical intervention. Across surgical specialties, age, body mass index, diabetes, smoking, and nutrition[4-6] have been shown to predict adverse outcomes. Among these, few are modifiable. This chapter will provide a systematic review of the relationship of nutritional status and adverse outcomes after spine surgery to guide preoperative evaluation and intervention.

METHODS

The guidelines task force initiated a systematic review of the literature and evidence-based guideline relevant to the preoperative treatment of patients with spinal disorders. Through objective evaluation of the evidence and transparency in the process of making recommendations, this evidence-based clinical practice guideline was developed for the diagnosis and treatment of adult patients with various spinal conditions. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes. Additional information about the methods used in this systematic review is provided below.

Literature Search

The task force members identified search terms/parameters and a medical librarian implemented the literature search, consistent with the literature search protocol (see Supplemental Digital Content 1), using the National Library of Medicine/PubMed database and Embase for the period from 1946 to September 20, 2019 using the search strategies provided in Supplemental Digital Content 1.

Inclusion/Exclusion Criteria
Articles were retrieved and included only if they met specific inclusion/exclusion criteria (Supplemental Digital Content 2). These criteria were also applied to articles provided by guideline task force members who supplemented the electronic database searches with articles from their own files. To reduce bias, these criteria were specified before conducting the literature searches.

Rating Quality of Diagnostic Evidence
The guideline task force used a modified version of the North American Spine Society's (NASS) evidence-based guideline development methodology. The NASS methodology uses standardized levels of evidence (Supplemental Digital Content 3) and grades of recommendation (Supplemental Digital Content 4) to assist practitioners in easily understanding the strength of the evidence and recommendations within the guidelines. The levels of evidence range from Level I (high quality randomized controlled trial) to Level IV (case series). Grades of recommendation indicate the strength of the recommendations made in the guideline based on the quality of the literature. Levels of evidence have specific criteria and are assigned to studies before developing recommendations. Recommendations are then graded based upon the level of evidence. To better understand how levels of evidence inform the grades of recommendation and the standard nomenclature used within the recommendations, see Supplemental Digital Content 4.

Guideline recommendations were written using a standard language that indicates the strength of the recommendation. "A" recommendations indicate a test or intervention is 2 "recommended"; "B" recommendations "suggest" a test or intervention and "C" recommendations indicate a test or intervention or "is an option." "I" or "Insufficient Evidence" statements clearly indicate that "there is insufficient evidence to make a recommendation for or against" a test or intervention. Task force consensus statements clearly state that "in the absence of reliable evidence, it is the task force's opinion that" a test or intervention may be appropriate.

In evaluating studies as to levels of evidence for this guideline, the study design was interpreted as establishing only a potential level of evidence. As an example, a therapeutic study designed as a randomized controlled trial would be considered a potential Level I study. The study would then be further analyzed as to how well the study design was implemented and significant shortcomings in the execution of the study would be used to downgrade the levels of evidence for the study's conclusions (see Supplemental Digital Content 4 for additional information and criteria).

Revision Plans
In accordance with the Institute of Medicine's standards for developing clinical practice guidelines, the task force will monitor related publications after the release of this document and will revise the entire document and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations."[7] In addition, the task

force will confirm within 5 years from the date of publication that the content reflects current clinical practice and the available technologies for the evaluation and treatment for patients with perioperative spinal disease.

RESULTS

The literature search encompassed terms relevant to all chapters in this guideline series and yielded 6812 abstracts (5689 after duplicates were deleted). After a double blind review, 845 abstracts were identified as relevant to the PICO question(s). The review yielded 115 abstracts relevant to this chapter. Task force members reviewed all abstracts yielded from the literature search and identified the literature for full text review and extraction, addressing the clinical questions, in accordance with the literature search protocol (Supplemental Digital Content 1). Task force members identified the best research evidence available to answer the targeted clinical questions. When Level I, II, and or III literature was available to answer specific questions, the task force did not review Level IV studies.

The task force selected 105 articles for full text review. Of these, 92 were rejected for not meeting inclusion criteria or for being off topic. Thirteen were selected for systematic review. (Supplemental Digital Content 5-6).

DISCUSSION

Question:

1. What preoperative serologic studies of nutritional status (and timing of these studies) are predictive of adverse event after spine surgery?

Recommendations:

Serum markers of malnutrition including low preoperative albumin, prealbumin, total protein, and albumin/globulin are associated with multiple adverse events after spine surgery. In at-risk individuals, clinicians should assess nutritional status preoperatively and counsel patients on the potential for adverse events

Strength of Recommendation: Grade B

SSI AND OTHER WOUND COMPLICATIONS

Up to 1 in 6 patients having spine surgery will develop a surgical site infection,[8-10] potentially resulting in a prolongation of their hospital stay, an increased likelihood of readmission, and revision surgery. This added morbidity comes at an increased cost to both the individual and society with lost productivity and increased cost of care. [11,12]

Known risk factors for wound complications include age, sex, diabetes, body mass index, immunosuppression, and tobacco use.[4,13,14] More recently, nutritional status has been investigated as a potential risk factor for these outcomes.

Malnutrition, defined by low levels of albumin, prealbumin, and other serum rapid turnover proteins (transferrin and retinol-binding protein), is a potentially modifiable risk factor for wound complications. Four studies specifically evaluated the role of these markers.

Salvetti et al[15,16] reported on the impact of a low preoperative prealbumin level for spine surgery patients. In 2015, this group performed a case-control series, identifying 292 patients over a 3-

year period who underwent surgical wound washouts. Preoperative prealbumin levels were available on 32 patients. A control cohort of 74 patients who underwent open posterior spine surgery during the same time interval were selected. There were no differences between the groups except for the presence of nutritional deficiency ($P = .04$). Both univariate and multivariate analysis found both diabetes and preoperative prealbumin <20 mg/dL to be independent risk factors for SSI (odds ratio [OR] 2.26 [95% confidence interval {CI} 1.05-4.84], $P = .037$ and OR 2.15 [95% CI 1.05-4.44], $P = .037$)[16] (Level II). In a follow-up study,[15] this group evaluated patients undergoing posterior spinal decompression and/or fusions. For this study, the authors evaluated the impact of nutritional sufficiency on deep wound infections (according to the U.S. Centers for Disease Control and Prevention definition). Of the 387 patients included, 19% were considered nutritionally insufficient (prealbumin <20 mg/dL). After adjusting for baseline differences, those with prealbumin <20 mg/dL were 3 times as likely to experience a deep SSI (OR 3.28 [95% CI 1.19-9.09], $P = .02$) (Level II).

To investigate serum markers of possible early wound infection (SSI), Kudo, et al[17] measured total lymphocyte count, serum albumin, transferrin, prealbumin, retinol binding protein, C-reactive protein (CRP) and white blood cell count in patients undergoing spine surgery at a single institution. They defined possible SSI by an increase in CRP or lymphopenia after postoperative day 3 or 4. While a lower prealbumin was identified as significantly associated with possible SSI on univariate analysis, only operative duration was a predictor on multivariable analysis.

Focusing on revision surgeries for septic and aseptic reasons, Khanna et al[18] used the American College of Surgeons National Surgical Quality Improvement Program registry to evaluate the relationship between hypoalbuminemia and reason for revision surgery and subsequent postoperative infectious complications. More than 3000 patients undergoing revision spinal surgery were included, 11% of whom had preoperative hypoalbuminemia. Hypoalbuminemia was significantly more common in those undergoing septic revision compared with aseptic revision surgery (49.1% vs 8.5%, $P < .001$). In the patients undergoing aseptic revision, low albumin increased the risk of having an acute postoperative infection (OR 2.53, (1.17,5.49), $P = .019$) (Level II).

In addition to studies focusing on malnutrition as an independent risk factor for wound complications, several studies have sought to identify all major risk factors for these adverse events in spinal surgery. Two independent groups in China, using large cohorts of patients undergoing spine surgery, sought to identify major risk factors for SSI. Wang et al[19] retrospectively evaluated all patients from 3 major medical centers undergoing posterior lumbar surgery. With >8000 patients included, they found a prevalence of SSI in their population of 3%. In addition to multiple other factors, low preoperative total protein and albumin were independently predictive of an increase in SSI ($P = .003$ and $P = .009$, respectively) (Level III). Li et al[20] investigated patients undergoing open transforaminal lumbar interbody fusion (TLIF) procedures and found an overall incidence of SSI of 4.5%, with 55% of those patients having superficial wound infection. Independent risk factors for any SSI were thicker subcutaneous fat (OR 1.383 [95% CI 1.178-1.623], $P < .001$), higher preoperative American Society of Anesthesiologists score (OR 3.164 [95% CI 1.302-7.692], $P = .011$), lower preoperative albumin (OR 0.802 [95% CI 0.708-0.907], $P < .001$), and longer postoperative wound drainage (OR

3.745 [95% CI 1.464-9.580], *P* = .006) (Level II). These studies, while demonstrating hypoalbuminemia as an independent risk factor for SSI, are limited by their retrospective nature and their low SSI rate.

Nonunion

Nonunion or pseudarthrosis is a well-known complication of spinal fusion surgery, occurring in ≤56% of patients.[21,22] This complication is impacted by patient factors, including age, smoking status, diabetes, and surgical factors. Surgical factors include levels of surgery, surgical approach/technique, use of adjuncts, and grafts. While nonunion may be clinically asymptomatic, it may result in ≥1 readmissions or revision surgeries with resultant individual and societal costs.[23] Therefore, avoiding this complication is paramount.

In an effort to discern preoperative modifiable risk factors associated with nonunion, Inose et al[24] studied 74 consecutive patients undergoing lumbar decompression and instrumented fusion surgery (either posterior lumbar fusion, TLIF, or both) for degenerative disease. Serum bone turnover markers, procollagen type 1 amino-terminal propetide, tartrate-resistant acid phosphatase 5b, and a nutritional status marker serum albumin were assessed. Computed tomography was performed at 1 year to evaluate bony union. Preoperative albumin and bone turnover markers were independently predictive of nonunion (OR 0.028 [95% CI 0.001-0.379], *P* = .015) (Level II).

Hospital Readmissions

Adverse events often require additional interventions, prolonging hospital stays or resulting in unplanned readmissions after surgery.[25,26] Two recent articles suggest malnutrition as an independent risk factor for 30 day hospital readmission.[27,28]

Adogwa et al[27] used an institutional database to identify 145 patients undergoing elective spine surgery. All patients had preoperative albumin levels drawn with 27% having levels <3.5 g/dL. The malnourished cohort had a 3 times higher rate of unplanned readmission (27.5% vs 9.5%, *P* = .02). In addition to number of levels fused and length of surgery, measures of surgical invasiveness, preoperative albumin level was an independent predictor of 30-day readmission (*P* = .01) (Level III). In a large registry cohort, Phan et al[28] found hypoalbuminemia to confer a 2.7 times risk for unplanned readmission (OR 2.7 [95% CI 1.1-6.3], *P* = .023) (Level II).

Specific Patient Populations

With the growing elderly global population and increase in spine surgery in this potentially at-risk group, Puvanesarajah et al[29] sought to quantify the impact of poor nutritional status in the elderly on postoperative medical risk and quantify differences in length of stay and readmission rates. Using an administrative database, the authors identified patients aged 65 to 84 undergoing elective spine surgery. Poor nutrition was defined by *International Classification of Diseases, 9th revision* codes and outcomes included major medical complications, revision surgeries, wound complications, and mortality. While <1% of the cohort were malnourished, these patients had a significantly increased odds of 90-day major medical complications (OR 4.24 [95% CI 3.64-4.94], *P* < .001), 1-year mortality (OR 6.16 [95% CI 3.70-10.25], *P* < .001), postoperative infections (OR 2.27 [95% CI 1.70-3.04], *P* < .001), and wound dehiscence (OR 2.52 [95% CI 1.64-3.88], *P* < .001) (Level II).

Invasiveness of surgery has been demonstrated to be a predictor of multiple adverse events. Adult spinal deformity is often characterized by an increase in invasiveness, spanning multiple levels, combining varied surgical approaches, and involving osteotomy procedures. Phan et al[30] analyzed 2236 patients in the American College of Surgeons National Surgical Quality Improvement Program registry who were undergoing surgery for adult spinal deformity to determine the impact of nutritional insufficiency, defined by a preoperative albumin level of <3.5 g/dL, on adverse outcomes. Nutritional insufficiency, present in 8.6% of this population, was found to be an independent risk factor for multiple adverse events. It most significantly impacts mortality, with malnourished patients having a 15 times risk of mortality (Level II).

Takemoto et al[31] examined 274 patients undergoing elective thoracolumbar or lumbar surgeries and found that only 1.8% of these patients were malnourished (defined by prealbumin <15 mg/dL and transferrin <170 mg/dL). In this study, there was no association with malnutrition and postoperative complication, including wound complications. While this finding is contradictory, the chosen cutoff values for malnutrition may have been overly selective, and the potentially heterogenous patient population (did not clearly exclude tumor and trauma) may lead to bias in this study (Level III).

Question:
2. What preoperative nonserologic assessments of nutrition status (and timing of these assessments) are predictive of adverse events after spine surgery?
Recommendations:
There is insufficient evidence to make a recommendation on the impact of preoperative use of nonserologic assessments of nutrition status on adverse outcomes in patients undergoing spine surgery.
Strength of Recommendation: Grade Insufficient

The literature search did not identify any studies that specifically addressed this question and met the inclusion and exclusion criteria.

Question:
3. In patients with poor nutrition, does preoperative treatment (and type of treatment) decrease the risk of postoperative adverse events?
Recommendations:
In patients with malnutrition undergoing spine surgery, there is insufficient evidence to support the use of a perioperative multimodal nutrition management protocol to decrease the risk of postoperative adverse events.
Strength of Recommendation: Grade Insufficient

Nutritional status, a modifiable risk factor for adverse events, may be impacted by altering the diet of patients in the perioperative period. Strategies to improve the nutritional status of patients may range from the introduction of protein and carbohydrate supplements immediately preoperatively to the timed administration of enteral or parental nutrition. While this has been studied in other surgical populations, there is a paucity of literature evaluating the impact of nutrition-based interventions in spine surgery patients.

To date, there are few studies describing specific protocols to boost nutrition in this patient population. While excluded from this systematic review because of population characteristics, Hu et al[32] studied the impact of administration of total parenteral nutrition between stages of 2-stage surgery. They found that receiving total parenteral nutrition was associated with a lower risk of postoperative infectious complications. Belthur et al[33] studied the surgeon practice related to preoperative optimization for patients with cerebral palsy undergoing corrective spine surgery and found that 97% of responders identified nutrition status as a risk factor that should be optimized, yet the timing and strategy of optimization varied.

Specific to the investigated population for this systematic review, Xu et al[34] evaluated a multimodal nutritional management plan in patients undergoing lumbar instrumented fusion surgery. Patients who were not malnourished preoperatively, as defined by a preoperative albumin level ≥35 g/L, were randomized to the multimodal nutrition management (MNM) protocol (MNM group) or a control group. The MNM group received protein powder and carbohydrate powder at intervals both before and immediately after surgery as well as an early feeding protocol. Outcomes measured were the use of albumin in the immediate postoperative period, incidence of electrolyte disturbance, transfusion rate, length of stay, medical complications, wound drainage, and wound infection. One hundred eighty-seven patients were randomized. Compared with the control group, those receiving the multimodal nutrition managements received a significantly lower volume and number of transfused albumin ($P = .009$ and $P = .017$, respectively), had a lower incidence of postoperative hypokalemia ($P = .006$), hyponatremia ($P = .001$), and hypocalcemia ($P = .026$), and a shorter length of stay ($P < .001$). The groups had a similar incidence of superficial infection, 2% in the MNM group and 5% in the control group, and neither group had any patients with deep wound infections. There was a significant difference in the number of patients with wound drainage, with more than double the number of patients in the control group with this outcome ($P = .008$) (Level II).

It is important to note that the patients in this study had normal nutrition before surgery, and as such may not be representative of the patients for which we would advocate intervention. In addition, while this was a randomized controlled trial, it lacked blinding for the patients and the surgeons, introducing potential bias, particularly in the assessment of wound drainage. Overall, this study demonstrates the utility of nutritional supplementation in patients with normal nutritional status undergoing spine surgery.

Future Research

This systematic review provides evidence that malnutrition, defined by a serum albumin level <3.5 g/dL or prealbumin level <20 mg/dL, is an independent risk factor for adverse events after elective spine surgery.

Future directions include (1) ascertaining which cutoff values for preoperative albumin and prealbumin are most indicative as predictors of adverse outcomes in spine patients, (2) the investigation of nonserologic assessments of nutritional status (e.g., anthropometric measurement [arm or calf circumference, hip-waist ratio] or questionnaires [Mini Nutritional Assessment]), and their impact on outcomes after spine surgery, and (3) the development of specific nutrition

protocols and the evaluation of these protocol to (a) improve malnutrition, and (b) avoid adverse events after spine surgery.

Conclusions

In conclusion, malnutrition, as evidenced by low albumin and prealbumin, has been shown to predict SSI, nonunion, readmission rates, and overall mortality.

Conflicts of Interest

All Guideline Task Force members were required to disclose all potential COIs before beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See below for a complete list of disclosures.

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Disclaimer of Liability
This clinical, systematic, evidence-based clinical practice guideline was developed by a multi-disciplinary physician volunteer taskforce and is provided as an educational tool based on an assessment of the current scientific and clinical information regarding this guideline topic. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Supplemental Digital Content 1. Literature searches

See Chapter 1: Congress of Neurological Surgeons Systematic Review and Evidence-Based Practice Guidelines for Perioperative Spine: Preoperative Opioid Evaluation for details on full PubMed and EMBASE search terms.

Supplemental Digital Content 2. Inclusion Criteria

Articles that did not meet the following criteria, for the purposes of this evidence-based clinical practice guideline, were excluded. To be included as evidence in the guideline, an article had to be a report of a study that:

- Investigated patients with cervical spine surgery, thoracic spine surgery, and lumbar spine surgery;
- Excluded patients with tumor, trauma, or infections;
- Included patients ≥18 years of age;
- Were studies that enrolled ≥80% of cervical spine surgery, thoracic spine surgery, and lumbar spine surgery (we include studies with mixed patient populations if they report results separately for each group/patient population);
- Was a full article report of a clinical study;
- Was not a medical records review, meeting abstract, historical article, editorial, letter, or commentary;
- Appeared in a peer-reviewed publication or a registry report;
- Enrolled a minimum of 20 patients;
- Was of humans;
- Was published in or after 1946;
- Quantitatively presented results;
- Was not an in vitro study;
- Was not a biomechanical study;
- Was not performed on cadavers;
- Was published in English;
- Was not a systematic review, meta-analysis, or guideline developed by others.[1]

Systematic reviews or meta-analyses conducted by others, or guidelines developed by others were not included as evidence to support this review due to the differences in article inclusion/exclusion criteria specified compared with the criteria specified by the Guidelines Task Force. Although these articles were not included as evidence to support the review, these articles were recalled for full-text review for the Guidelines Task Force to conduct manual searches of the bibliographies.

[1]The guideline task force did not include systematic reviews, guidelines or meta-analyses conducted by others. These documents are developed using different inclusion criteria than those specified in this guideline; therefore, they may include studies that do not meet the inclusion criteria specific in this guideline. In cases where these types of documents' abstract suggested relevance to the guideline's recommendations, the task force searched their bibliographies for additional studies.

Supplemental Digital Content 3.

Criteria grading the evidence

The task force used the criteria provided below to identify the strengths and weaknesses of the studies included in this guideline. Studies containing deficiencies were downgraded 1 level (no further downgrading allowed, unless so severe that study had to be excluded). Studies with no deficiencies based on study design and contained clinical information that dramatically altered current medical perceptions of topic were upgraded.

1. Baseline study design (i.e., therapeutic, diagnostic, prognostic) determined to assign initial level of evidence.

2. Therapeutic studies reviewed for following deficiencies:
    - Failure to provide a power calculation for a randomized controlled trial (RCT);
    - High degree of variance or heterogeneity in patient populations with respect to presenting diagnosis/demographics or treatments applied;
    - Less than 80% of patient follow-up;
    - Failure to utilize validated outcomes instrument;
    - No statistical analysis of results;
    - Crossover rate between treatment groups of greater than 20%;
    - Inadequate reporting of baseline demographic data;
    - Small patient cohorts (relative to observed effects);
    - Failure to describe method of randomization;
    - Failure to provide flowchart following patients through course of study (RCT);
    - Failure to account for patients lost to follow-up;
    - Lack of independent post-treatment assessment (e.g., clinical, fusion status, etc.);
    - Utilization of inferior control group:
        - Historical controls
        - Simultaneous application of intervention and control within same patient
    - Failure to standardize surgical/intervention technique;
    - Inadequate radiographic technique to determine fusion status (e.g., static radiographs for instrumented fusion).

3. Methodology of diagnostic studies reviewed for following deficiencies:
    - Failure to determine specificity and sensitivity;
    - Failure to determine inter- and intraobserver reliability;
    - Failure to provide correlation coefficient in the form of kappa values.

4. Methodology of prognostic studies reviewed for following deficiencies:
    - High degree of variance or heterogeneity in patient populations with respect to presenting diagnosis/demographics or treatments applied;
    - Failure to appropriately define and assess independent and dependent variables (e.g., failure to use validated outcome measures when available).

Rating evidence quality. Levels of evidence for primary research question[a]

Types of Studies				
	Therapeutic studies: Investigating the results of treatment	Prognostic studies: Investigating the effect of a patient characteristic on the outcome of disease	Diagnostic studies: Investigating a diagnostic test	Economic and decision analyses: Developing an economic or decision model
Level I	High-quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals Systematic review[b] of Level I RCTs (and study results were homogeneous[c])	High-quality prospective study[d] (all patients were enrolled at the same point in their disease with ≥80% follow-up of enrolled patients) Systematic review[b] of Level I studies	Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference gold standard) Systematic review[b] of Level I studies	Sensible costs and alternatives; values obtained from many studies with multiway sensitivity analyses Systematic review[b] of Level I studies
Level II	Lesser quality RCT (e.g., <80% follow-up, no blinding, or improper randomization) Prospective[d] comparative study[e] Systematic review[b] of Level II studies or Level I studies with inconsistent results	Retrospective[f] study Untreated control subjects from an RCT Lesser quality prospective study (e.g., patients enrolled at different points in their disease or <80% follow-up) Systematic review[b] of Level II studies	Development of diagnostic criteria on consecutive patients (with universally applied reference criterion standard) Systematic review[b] of Level II studies	Sensible costs and alternatives; values obtained from limited studies with multiway sensitivity analyses Systematic review[b] of Level II studies

Level III	Case control study[g] Retrospective[f] comparative study[e] Systematic review[b] of Level III studies	Case control study[g]	Study of nonconsecutive patients without consistently applied reference criterion standard Systematic review[b] of Level III studies	Analyses based on limited alternatives and costs and poor estimates Systematic review[b] of Level III studies
Level IV	Case series[h]	Case series	Case-control study Poor reference standard	Analyses with no sensitivity analyses

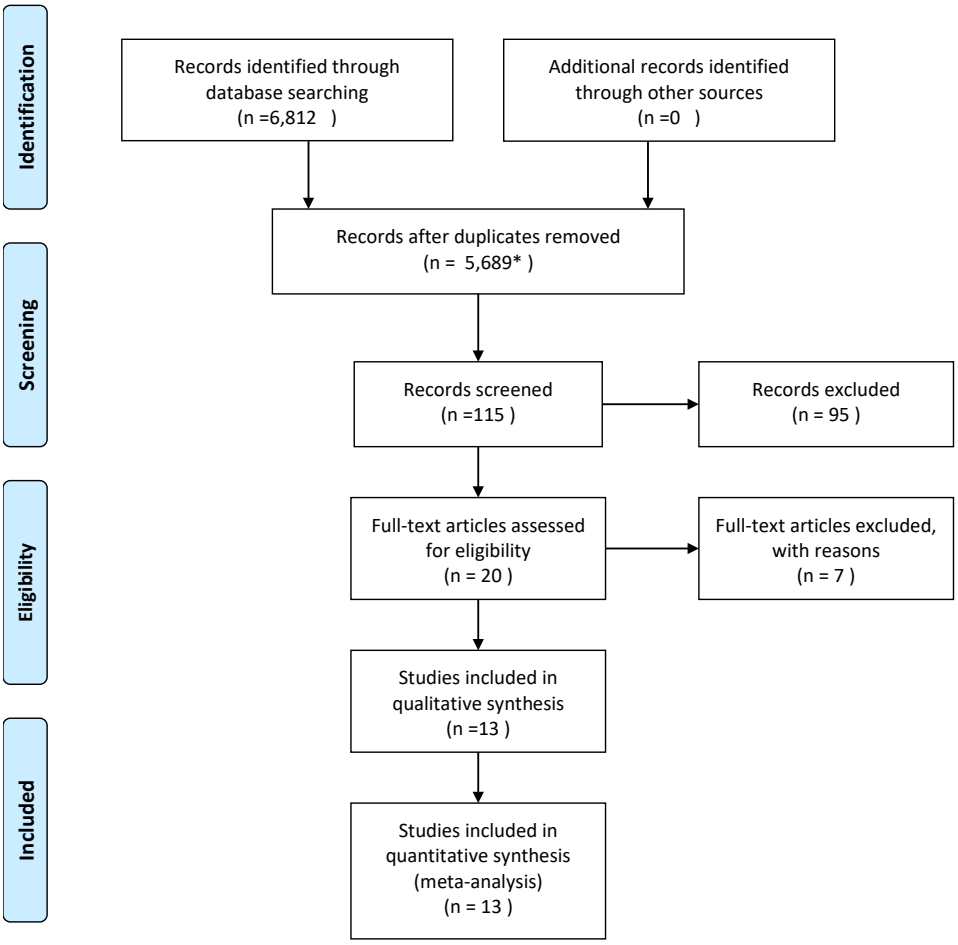
RCT, randomized controlled trial.
[a]A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
[b]A combination of results from ≥2 previous studies.
[c]Studies provided consistent results.
[d]Study was started before the first patient enrolled.
[e]Patients treated one way (e.g., instrumented arthrodesis) compared with a group of patients treated in another way (e.g., uninstrumented arthrodesis) at the same institution.
[f]Study was started after the first patient enrolled.
[g]Patients identified for the study based on their outcome, called "cases" (e.g., pseudoarthrosis) are compared with those who did not have outcome, called "controls" (e.g., successful fusion).
[h]Patients treated one way with no comparison group of patients treated in another way.

Supplemental Digital Content 4. Linking levels of evidence to grades of recommendation

Grade of Recommendation	Standard Language	Levels of Evidence	
A	Recommended	≥2 consistent Level I studies	
B	Suggested	One Level I study with additional supporting Level II or III studies	≥2 consistent Level II or III studies
C	Is an option	One Level I, II, or III study with supporting Level IV studies	≥2 consistent Level IV studies
I (insufficient or conflicting evidence)	Insufficient evidence to make recommendation for or against	A single Level I, II, III, or IV study without other supporting evidence	≥1 study with inconsistent findings*

*Note that in the presence of multiple consistent studies, and a single outlying, inconsistent study, the grade of recommendation will be based on the level of the consistent studies.

Supplemental Digital Content 5. PRISMA Flowchart



*In addition to duplicate removal, the librarian also removed strictly animal or children/adolescent studies not identified by search strategy and case reports dealing with 1 to 2 persons as encountered.

Supplemental Digital Content 6. Evidence table

PICO Question	Author, Year	Type of Evidence	Study Type	Level of Evidence	Reviewer's Conclusions
1	Adogwa et al, 2016[27]	Prognostic	Retrospective comparative	III	The study was downgraded because patient population not strictly defined—just says elective spine surgery—and is a single-center study.

					Affirms low preoperative albumin predictor of 30-day readmission
1	Inose et al, 2018[24]	Prognostic	Retrospective comparative	II	The study affirms that low preoperative albumin is an independent predictor of nonunion (multivariable analysis)
1	Khanna et al, 2018[18]	Prognostic	Retrospective comparative	II	The study affirms that hypoalbumenia associated with septic revision surgery compared with aseptic revisions AND among all revisions, hypoalbuminemia was associated with postoperative infection
1	Kudo et al, 2017[17]	Prognostic	Retrospective comparative	III	Study was downgraded because surgery was cervical, thoracic, and lumbar, and SSI was not clearly defined. This is a multivariable analysis that negates total lymphocyte count, prealbumin, and albumin. These are not associated with possible SSI
1	Li et al, 2019[20]	Prognostic	Retrospective comparative	II	This study affirms that low preoperative albumin is an independent risk factor for SSI
1	Phan et al, 2018[30]	Prognostic	Retrospective comparative	II	The study affirms nutritional insufficiency is an independent risk factor for mortality, all complications, pulmonary

					complication, renal complications, and transfusion
1	Phan et al, 2019[28]	Prognostic	Retrospective comparative	III	This was downgraded becuase there is not specific mention of excluding spine infection as the reason for surgery
1	Puvanesarajah et al, 2017[29]	Prognostic	Retrospective comparative	II	This study affirms that malnutrition was predictive of 90-day major medical complications, 1-year mortality, increased infection, wound dehiscence, and 30-day readmission (multivariate analysis)
1	Salvetti et al, 2015[15]	Prognostic	Retrospective comparative	II	The study affirms that low preoperative prealbumin is an independent risk factor for postoperative infection (multivariable)
1	Salvetti et al, 2018[16]	Prognostic	Retrospective comparative	II	The study affirms that low preoperative albumin is an independent predictor of SSI (multivariable analysis)
1	Takemoto et al, 2019[31]	Prognostic	Retrospective comparative	III	The study was downgraded because patient population is not strictly defined. The study negates low prealbumin and low transferrin, these are not associated with increased risk of complications
1	Wang et al, 2017[19]	Prognostic	Retrospective comparative	II	This study affirms low total protein, albumin, and albumin/globulin are independent

					predictors for postoperative SSI
3	Xu et al, 2019[34]	Therapeutic	Prospective RCT	II	The study was downgraded because it was not blinded. It affirms that the use of MNM protocol decreases postoperative use of albumin, electrolyte disorders, and wound drainage (also LOS)

LOS, length of stay; MNM, multimodal nutrition management; RCT, randomized controlled trial; SSI, surgical site infection.