Review Article

Optimizing health before elective thoracic surgery: systematic review of modifiable risk factors and opportunities for health services research

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Abstract: Despite progress in many different domains of surgical care, we are still striving toward practices which will consistently lead to the best care for an increasingly complex surgical population. Thoracic surgical patients, as a group, have multiple medical co-morbidities and are at increased risk for developing complications after surgical intervention. Our healthcare systems have been focused on treating complications as they occur in the hopes of minimizing their impact, as well as aiding in recovery. In recent years there has emerged a body of evidence outlining opportunities to optimize patients and likely prevent or decrease the impact of many complications. The purpose of this review article is to summarize four major domains—optimal pain control, nutritional status, functional fitness, and smoking cessation—all of which can have a substantial impact on the thoracic surgical patient's course in the hospital—as well as to describe opportunities for improvement, and areas for future research efforts.

Keywords: Thoracic surgery; preoperative risk; health services; quality improvement; outcomes; smoking cessation; pain management; nutrition; prehabilitation; exercise

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Introduction

Quality improvement efforts have accelerated over the last several decades in response to mainstream and scientific publications focusing on medical errors as well as national efforts to track and improve surgical outcomes (1,2). In particular, these initiatives have focused on patient care within the perioperative period. There have also been increased attention to using quality metrics to aid in guiding healthcare reimbursement for medical services (3). This lends additional urgency to improve surgical quality for the betterment of our patients and to protect providers. The international trends toward quality improvement reflect the long-standing physician desire to optimize practices toward better care for patients.

Despite progress in many domains of surgical care, we are still striving toward practices which reliably lead to

optimal outcomes for an increasingly complex surgical population. Thoracic surgical patients, in particular, tend to have a significant burden of pulmonary-related comorbidities (4,5). Until now, the majority of research in the area of peri-operative care has been focused on treating complications as they arise or identifying patients who carry the highest risk for these complications. Best practices on mitigation of the risk of common postoperative problems are needed to reliably improve the outcomes after thoracic surgical procedures. Such practices can be exceedingly difficult to standardize, as there are multiple viable approaches to common issues. It is important to identify, disseminate, and implement these modifiable factors which can improve the care of our patients across the world.

The purpose of this article is to analyze four major domains which have a substantial impact on the thoracic surgical patient's postoperative course in the hospital. We performed a comprehensive literature review within pain management, nutritional therapy, perioperative exercise, and smoking cessation with a focus on their impact on elective thoracic surgery patients. Our goal was to clarify current best practices within these areas and identify needs for future health services research to further improve the care provided to our patients.

Methods

A systematic review was conducted to identify major pertinent literature. PubMed, Cochrane Review, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases were queried using a combination of "thoracic surgery," "thoracic surgical procedures," "elective surgery," and the domain-specific Medical Subject Headings (MeSH) terms listed below for each domain:

- Pain control—pain management, postoperative period, analgesia, neuromuscular blockade, preanesthetic medication, anesthesia, anesthesia recovery period;
- Nutrition—nutrition therapy, diet therapy, nutritional support, enteral nutrition, parenteral nutrition, feeding methods, eating;
- Exercise/physical fitness—exercise therapy, physical therapy modalities, exercise movement techniques, rehabilitation, cardiac rehabilitation, ambulation, walking;
- Smoking cessation—smoking cessation, smoking reduction, tobacco use cessation, tobacco cessation.

The resulting abstracts were then reviewed for inclusion. Relevant literature within the last 10 years [2008–2018] was included with a focus on randomized controlled trials, meta-analyses, and systematic reviews. Literature prior to 2008 was included if referenced in identified works and was pertinent to the domain of interest. The population of interest was elective thoracic surgery patients; however, evidence relevant to all types of elective surgery was reviewed to determine best practices which may apply to the thoracic surgery population. Interventions were classified within the above four domains. Outcomes were mortality, morbidity, hospital length-of-stay (LOS), and intervention-specific metrics. Recommendations were formulated and summarized using the standardized levels of evidence. Please see *Table 1* for a summary of research questions and recommendations formulated from this review.

Perioperative pain management

Pain control following thoracic surgery is an important topic for a variety of reasons. First, thoracic incisions are considered to be among the most painful. Analgesia is necessary for patient comfort, adequate pulmonary toilet and ambulation to prevent additional complications, as well as improved psychological recovery following surgery. The pathophysiology of pain from thoracotomy incisions is multifactorial and relates to the proximity and abundance of intercostal somatic nerve fibers, pleural irritation from surgical manipulation, and planned and iatrogenic rib fracture from surgical retraction and exposure. All of these factors contribute to patient discomfort leading to immobility, shallow breathing, atelectasis, and morbid complications such as pneumonia and ventilator dependency.

Recently, pain control strategies within surgery have trended toward multi-modal approaches which feature preventive pain management, regional blockade techniques, and breakthrough medications post-operatively to help reduce the amount of pain experienced. Additionally, an under-appreciated approach to pain management is setting appropriate preoperative expectations of "pain control" versus "pain elimination." While many of these areas have been studied in thoracic surgery, there is still room for improvement to find the optimal pain management protocol for the elective thoracic surgery patient. In order to appropriately optimize a patient for the best possible pain control perioperatively, it is important to identify patients at risk for excessive opioid requirement, opioid-related in-hospital complications (respiratory depression, hypotension, urinary retention, etc.), and chronic pain syndromes. However, in thoracic surgery, all patients are at high-risk

Table 1 Research questions and recommendations within each domain

Pain control
Research questions
Does PVB have an equal effect in decreasing pneumonia following major abdominal and thoracic surgery?
Are centers across the country considering other forms of anesthesia to minimize epidural-associated complications?
What are the barriers to adoption of different, perhaps more effective, anesthetic techniques by anesthesia providers?
How many patients are being seen by dedicated anesthesia pain services during their inpatient stay?
What adjuncts are being used in pain control to pre-empt postoperative pain (i.e., non-opioid analgesics)?
What is the most cost-effective option for perioperative anesthesia?
What is the utilization of PVB versus thoracic epidural in lung resection?
Recommendations
Patients should be treated with regional anesthesia techniques at the discretion of institutional capability to minimize pain following thoracotomy and VATS (IA)
Paravertebral and intercostal blockade should be considered to be favorable over thoracic epidural anesthesia if providers skilled in these techniques are available (IA)
Prevention of chronic pain should be focused on prevention of acute pain and nerve sensitization during the perioperative period (III)
The approach to perioperative pain control should be multimodal (IA)
Exercise
Research questions
What is the national current practice for provision of pre- and post-operative exercise programs for thoracic surgery?
Do thoracic and general surgeons feel that preoperative exercise programs represent an effective intervention for reducing PPCs?
What percentage of patients would be willing to adhere to these programs if made widely available before lung cancer surgery?
Are intensive preoperative exercise programs cost-effective and scalable?
Recommendations
Patients should undergo preoperative pulmonary and exercise assessment prior to proceeding to surgical resection (IA)
Preoperative exercise programs of at least one week in duration should be offered to all patients undergoing lung surgery (IB)
Exercise programs should incorporate aerobic, resistance, and breathing exercises to appropriately prepare a patient for surgery (IA)
Recommendation for frailty assessment and pre-operative planning for those patients deemed at risk for discharge planning to a setting other than home (or pre-op assessment of home health needs/support system) (III)
Nutrition
Research questions
What is the current state of practice of preoperative nutritional optimization nationally?
Are thoracic surgery patients being appropriately evaluated for nutritional risk prior to going to the operating room?
What interventions are being pursued in patients with swallowing difficulty following surgery, and how long does it take to establish an enteral route?
What is the role of immunonutrition in well-nourished and under-nourished thoracic surgery patients?
What is the current state of nutritional support immediately following surgery?

Table 1 (*continued*)

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Recommendations
All elective thoracic surgery patients should be assessed for nutritional risk prior to scheduling for surgery (IA)
Elective thoracic surgery patients at high nutritional risk should receive at least 7–14 days of preoperative nutritional therapy to optimize preparation for surgery (IB)
Elective thoracic surgery patients at no elevated risk should receive nutritional counseling and should be considered for nutritional therapy to optimize preparation for surgery (III)
Preoperative fasting should be limited to 6 hours prior to surgery for solids and 2 hours prior to surgery for clear liquids (IA)
Immunonutrition supplementation should be considered in patients with high nutritional risk (III)
Smoking cessation
Research questions
What is the current state of smoking cessation programs in the thoracic surgical outpatient setting?
What percentage thoracic surgeons prescribe nicotine replacement therapy?
What opportunities are available in national databases which have smoking cessation data?
How often do NSQIP captured data describe smoking cessation in thoracic surgery patients?
How do smoking cessation programs alter the cardiovascular risk profile in thoracic surgical patients?
Recommendations
All elective thoracic surgery patients should be offered smoking cessation interventions prior to their surgical procedure (IIB)
Benefits of smoking cessation increase with greater length until procedure, however cessation interventions should be initiated at any time before proceeding to surgical resection (III)
Nicotine Replacement and Pharmacologic Therapies can be safely and effectively used to aid in patients quitting smoking prior to surgery (IB)
What is the current state of nutritional support immediately following surgery?

PVB, paravertebral block; VATS, video-assisted thoracoscopic surgery.

for pain issues post-operatively due to the morbid nature of possible incisions, thus we intended to explore several pain domains which have been investigated to optimize a patient's pain control in the perioperative period.

Preventive analgesia

Pain control in the perioperative period has classically been associated with treating acute postoperative pain with opioid and non-steroidal adjuncts in the days following surgery. With the focus on multi-modal pain approaches, anesthesia applied prior to surgical intervention (preemptive anesthesia) has been proposed as a method for preventing pain during the postoperative period (6,7). The philosophy behind this approach has transformed in recent years to "preventive anesthesia" which reflects a paradigm shift toward mitigating the sensitization caused by noxious stimuli rather than focusing on the timing of medication administration (6). This approach has been very successful in decreasing postoperative pain and opioid requirement across surgical subspecialties. A meta-analysis of various pain strategies including 66 studies of 3,261 participants showed that the addition of epidural analgesia, local wound infiltrations, or non-steroidal anti-inflammatory drugs (NSAIDs) had the most efficacy for decreasing the amount of additional analgesia needed after surgery as well as decreasing the amount of time to the first rescue dose (8). This meta-analysis did not investigate the effects of these therapies used in combination. Non-opioid analgesics have been effective in reducing postoperative opioid requirement following a variety in a variety of surgical disciplines (9). A recent study published in *JAMA Surgery* demonstrated potential for gabapentin as a preoperative pain adjunct to decrease opioid use following surgery (10). In this randomized controlled

trial, 410 patients were randomized to peri-operative active placebo versus gabapentin, and it was found that gabapentin had no effect on time to pain cessation, but led to increase in the rate of opioid cessation after surgery. Multimodal pain regimens focused on peripheral nerve sensitization and blockade have been reliable in controlling postoperative pain after orthopedic procedures (11). Extrapolation of these methods using preoperative administration of NSAIDs, gabapentin, and Tylenol has been used in practice by many of the authors of this review. Within thoracic surgery, there has been one randomized trial looking at pre- and post-operative administration of dextromethorphan and intercostal block in a four-arm design showing that preoperative dextromethorphan and intercostal block decreased analgesic administration over other combinations (12). There is relatively little published about multi-modal regimens, composed of preventive analgesics, regional blockade, and post-operative opioid adjuncts, while studies on regional blockade techniques is much more common.

Regional blockade

Thoracic epidural blockade has long been the gold standard for perioperative pain control. Epidural spinal analgesia has been associated with decreased pulmonary complications, better patient satisfaction, and shorter length of stay (LOS) (13-15). However, the drawbacks of epidural blocks are their association with significant complications including hypotension, nausea/vomiting, and urinary retention (13). Several other techniques have been described and utilized as alternative regional blocking techniques with debatable equivalency to thoracic epidural block.

Thoracic epidural versus paravertebral block (PVB)

Thoracic epidural anesthesia (TEA) is historically the most common regional anesthesia for thoracotomy. It is still considered to be the gold standard regional technique to mitigate postoperative pain. It is very effective in reducing postoperative pain but is associated with several common and uncommon side effects which can have morbid, and potentially fatal, consequences. Technical complications of the procedure include non-functioning epidural catheter (14–30%), accidental removal, spinal injection of anesthesia, dural puncture, high block, and local anesthetic toxicity. Rare, but severely morbid, complications include epidural hematoma and/or abscess (16). More commonly, patients experience episodes of hypotension, pulmonary/cardiac depression, and urinary retention secondary to bilateral sympathetic depression. Treatment and management of these complications, even when less severe, add hospital time, increase the likelihood of experiencing further complications, and add cost to providing care.

PVB is a technique which has been utilized in a wide range of specialties outside of thoracic surgery including breast, general, and orthopedic surgery. This involves administration of local anesthetic into the paravertebral space using a catheter or one-time injection. Proponents of PVB prefer its favorable complication profile to TEA. Moreover, the technique involves unilateral anesthesia, preserving pulmonary function on the contralateral side. It has also been shown to have less side effects when compared to TEA, including lower rates of hypotension, pulmonary complications, and urinary retention with comparable analgesic profile (17-19).

Several randomized controlled trials have directly compared PVB with TEA to examine postoperative pain relief and side effect profiles (20-26). A Cochrane Review conducted by Yeung *et al.* in 2016 synthesized the evidence of 14 trials of 698 patients and showed that PVB was equivalent to TEA for pain control. However, PVB had lower risk of minor complications such as hypotension, nausea/vomiting, pruritus, and urinary retention (16). They were unable to show differences in major complications, LOS, and 30-day mortality between the two techniques, and there were no studies that reported on costs. Chronic pain outcomes were also insufficient to measure. Another review, by Scarfe *et al.* of 23 trials of 1,120 patients came to similar conclusions. They report little difference in pain control, but PVB had significantly less hypotension, nausea/vomiting, pruritus, and urinary retention (27). Since those reviews, only a handful of randomized controlled trials (RCT) have been released. Kosiński *et al.* randomized 51 video-assisted thoracoscopic surgery (VATS) lobectomy patients to either continuous epidural block or continuous PVB and showed superior pain scores in the PVB group at 24-, 36-, and 48-hour time periods with lower side effects (28). Tamura *et al.* conducted an RCT of 36 patients per group between surgical field PVB and epidural block. They identified superior pain control by the visual analog scale (VAS) score at 2 hours after ropivacaine injection in the thoracic epidural group, however other time points were not analyzed. There was no difference in postoperative complications in their investigation (29). A recent RCT published in 2017 compared PVB to single-injection intercostal nerve blocks (INBs) in VATS procedures and

found that PVB provided superior pain control and patient satisfaction (30). In summary, the preponderance of the literature appears to slightly favor PVB over TEA for pain control following open and minimally invasive thoracic operations.

Intercostal liposomal bupivacaine blockade

In 2015, Rice *et al.* first described the use of liposomal bupivacaine as a solution to provide continuous local analgesia without the use of an indwelling catheter (31). Liposomal bupivacaine (Lipo B, Exparel, Pacira Pharmaceuticals Inc., Parsippany, NJ) was first approved by the US Food and Drug Administration in 2011, and has been shown to be effective in a variety of other surgical procedures. The technique for injection can be traced as far back as 1980, when Nunn and Slavin reported on injection of anesthetic 7 cm from the anatomic mid-line to the internal intercostal muscle, just superficial to the pleura prior to cholecystectomy (32). The same technique was used by Rice *et al.* in the patients upon which they performed a chart review comparing a propensity-matched cohort of liposomal bupivacaine (LipoB) to TEA. They found no differences in pain scores post-operatively and shorter LOS in the LipoB group, however did find that the LipoB group had increased opioid usage (31). This report demonstrated the safety and efficacy of LipoB as an alternative to regional catheter techniques. More recently, a report in *Annals of Thoracic Surgery* by Van Haren *et al.* showed the effectiveness of an enhanced recovery protocol based on the use of LipoB which showed improved postoperative outcomes (LOS, pulmonary, and cardiac comorbidities) after thoracotomy (33). Ultimately, the authors were able to show that the use of this regimen leads to similar perioperative outcomes after both open and minimally invasive approaches.

Since this initial study, there has been limited literature examining direct comparisons of LipoB with PVB or TEA. An investigation by Mehran *et al.* performed two propensity-matched analyses of 1,737 patients undergoing lung resection. The first analysis matched patients who had any surgical approach, while the second analysis matched only those who underwent thoracotomy. In both analyses, there was no difference in postoperative complications in the LipoB group, except for statistically less cardiac arrhythmias in the first analysis. LipoB patients also had a significantly shorter LOS by one day (34). One significant drawback that may contribute to poor uptake in its use is the significantly higher cost associated with LipoB despite a higher safety profile with reduced complications. The reduction in LOS associated with LipoB may negate this difference, but more studies are needed to investigate this hypothesis.

Surgical site analgesia

Local wound analgesia is the other major regional technique which has been considered as an option for postoperative pain control. This typically involves insertion of a superficial catheter for continuous administration of localized anesthesia for treatment of postoperative pain. Intercostal subcutaneous catheters have been investigated in a double-blinded RCT, but have not been shown to reduce pain scores or morphine equivalents within the hospital (35). Another potential strategy for localized wound analgesia is the ON-Q Pain Relief System (Kimberly-Clark, Roswell, GA) elastomeric pump which has proven to be effective in other surgical disciplines (36,37). There have only been a few studies examining the use of the ON-Q infiltrating catheter for post-thoracotomy analgesia. Gebhardt *et al.* retrospectively compared patients who received TEA to those who received an intra-operative ON-Q catheter supplemented with patient-controlled analgesia. They demonstrated worse pain control in the ON-Q catheter group, but earlier discharge and lower hospital cost (38). Wheatley *et al.* also examined the ON-Q catheter in a retrospective analysis of 110 patients, showing conflicting results of lower pain scores and less opioid usage in the ON-Q catheter group (39). Both of these analyses are severely limited by their retrospective design regarding the indications and choice for localized continuous infusion in some patients rather than TEA. No definitive recommendation can be made regarding using subcutaneous continuous infusions of local anesthetic as a substitute to TEA, as more compelling data needs to be collected. Moreover, localized drug administration systems have not been studied from a cost-effectiveness standpoint, which may be an area for future investigation as more technologies become available.

Chronic pain

Chronic pain following thoracic surgery is frequently encountered, with some studies reporting rates as high as 50% (40,41). Pain control in the acute period may be associated with increased risk of developing long-term chronic pain problems (42). Investigations into other

risk factors for development of chronic pain have been conducted, but there is an overall shortage of literature in this area. While it is assumed that psychosocial risk factors such as psychiatric disorders, preoperative pain disorders, and lack of social support identify populations at risk, this suggestion has not been proven by objective data (43). Surgical approach has been hypothesized as a possible factor for development of postoperative pain; however, only two studies have compared muscle-sparing to classic posterolateral thoracotomy approach without identification of any difference (44,45). As summarized by Wildgaard *et al.*, no randomized studies evaluating chronic postoperative pain syndromes have identified an advantage of one intraoperative analgesic technique over another in regard to prevention (43). All studies included had methodological concerns preventing any conclusions from being made. A recently published randomized controlled trial analyzed 300 patients divided into three groups (TEA, PVB, and INB) and identified that patients who underwent INB had significantly higher rates of chronic pain at 6 months compared to TEA and PVB. Patients who underwent TEA trended toward statistically lower rates of chronic pain, however these were not significantly different than in patients who underwent PVB (46). There have also been several other observational studies which have shown lower rates of chronic postoperative pain associated with the use of TEA (47,48). Nevertheless, larger prospective cohorts are required to adequately assess the pathophysiology, patient-reported outcomes, and factors which contribute to chronic pain in this population, as well as adequate methods of prevention.

Opportunities for research

Pain control following surgery is continuously evolving in the US due to the well-publicized opioid epidemic sweeping this country. Investigations of pain control within thoracic surgery have largely consisted of single institutional studies with heterogeneous methods of approaching postoperative pain. There are a number of unstudied factors which may contribute to a surgeon's choice of TEA versus PVB versus intercostal block, often relating to the institutional culture and anesthesia group practices. In the authors' experiences, some anesthesia providers who are less experienced in the technique of preoperative paravertebral catheter placement, thus preferring TEA due to familiarity. Partnering with anesthesiologists and dedicated anesthesia pain services to study the hospital variation in pain regimens may help to make the approach more uniform. Thoracic surgeon preferences for anesthesia are also not well characterized. As new anesthetic technologies emerge, such as LipoB, cost considerations must be considered to provide the best value care for our patients. There are several opportunities for cost-effectiveness research regarding the differences between pain strategies.

Nutrition

Nutritional therapy, or the administration of appropriate nutritional support to meet metabolic requirements, either through enteral or parenteral routes, is a well-recognized target for optimizing outcomes following elective surgery. Nutritional risk assessment, the impact of poor nutritional status, and strategies for nutritional therapy have been extensively studied in gastrointestinal surgery. Literature focusing on elective thoracic surgery is less prolific. It has been well documented that nutritional deficits in the amount of calories, particularly protein calories, has an impact on surgical outcome in the critically ill (49). Most of the data specific to thoracic surgery has focused on the assessment of nutritional risk as a prognostic factor when considering elective thoracic interventions. Surgical nutritional support for thoracic surgery is an area which warrants research focus.

Review of major guidelines

There are three major societies which have released extensive nutrition recommendations for elective surgical patients: European Society for Clinical Nutrition and Metabolism (ESPEN) (50); American Society for Parenteral and Enteral Nutrition (ASPEN) (51); and the Australasian society for parenteral and enteral nutrition (AuSPEN) (52). We encourage the readers to review these guidelines, but to summarize the primary tenants of successful surgical nutrition entail:

(I) Early feeding (within 24 hours following surgery);
(II) Enteral nutrition preferred over parenteral nutrition;
(III) Pre-operative nutritional risk assessment;
(IV) Consideration of immunonutrition supplementation in high-risk surgical patients.

Despite the importance of surgical nutrition emphasized in these guidelines, especially in high-risk cancer patients, recommendations for the preoperative assessment of patients undergoing lung surgery do not address nutritional assessment or the provision of nutritional support (53,54).

Nutritional risk assessment

"Nutritional risk" can be a difficult metric to quantify, as many scales have been proposed to assess a patient's preoperative nutritional status. International guidelines differ on their definitions of malnourishment. Patients at high nutritional risk can be summarized into the following categories:

- Underweight (BMI ≤18.5 kg/m^2) (50);
- Weight loss of >10% or >5% over 3 months of total body weight prior to surgery (50);
- Obesity (BMI ≥30 kg/m^2) (51).

Different nutritional risk scores and laboratory values have been proposed to help categorize each patient and help direct therapy. It is important to note that while obesity is often considered a "well-nourished" state, that is likely a mischaracterization of the patient's overall metabolic health. The association of obesity with a poor nutritional state is well summarized in the most recent ASPEN/Society of Critical Care Medicine (SCCM) guidelines (51).

Laboratory markers

Laboratory markers such as the acute phase reactant proteins pre-albumin, albumin, and transferrin have had extensive scrutiny as markers of short- and long-term nutritional status. In the postoperative phase, use of these laboratory markers are not recommended, as changes in levels are not normalized until the acute inflammatory and metabolic response to surgery have subsided (51). Pre-operatively, albumin has been established as a prognostic indicator for outcome following both intra-abdominal and thoracic surgeries. It is well-established that low serum albumin (<3.5 gm/dL) is a poor prognostic factor for major intra-abdominal surgery (55). This association has also been demonstrated within thoracic surgery. Inferior overall survival and recurrence-free survival was demonstrated among a cohort of 556 non-small cell lung cancer (NSCLC) patients when serum albumin was less than 4.2 g/dL (56). Two smaller studies have associated hypoalbuminemia with bronchopleural fistula and prolonged air leak after thoracic surgery (57,58).

Body mass index (BMI)

Patient weight is one of the most commonly used assessments of a patient's metabolic health. For patients with NSCLC, it has been suggested that higher BMI is associated with higher long-term survival due to decreased smoking, higher nutritional reserve, and increased statin use in this population (59). Also, BMI may simple be a surrogate of cancer-related weight loss and cachexia, which would portend poor outcomes.

BMI as a prognostic sign in lung cancer has been studied in a few analyses. A retrospective analysis of 1,311 NSCLC patients demonstrated higher 90-day mortality for underweight patients and significantly longer LOS (60). However, in a more recent study, there was no association with mortality, but underweight patients still had a significantly longer LOS (61). A review of the STS database attempting to identify risk factors for increased mortality also identified low BMI (<25) as an independent risk factor. Unfortunately, they were unable to associate low BMI with a malnourished state due to nearly 40% of the data missing albumin values (not missing at random) but did comment that the low BMI group tended to have a greater burden of comorbid disease (62). It was also shown in this analysis that obesity had a beneficial effect on survival. No studies, to our knowledge, have looked at interventions targeting the low BMI group alone. As mentioned above, this group may be at particularly high-risk due to advanced biology of disease, more numerous comorbidities, and tendency to have a higher rate of smoking.

A recent study in the *Annals of Surgical Oncology* looking specifically at skeletal muscle loss associated skeletal muscle area with poor postoperative outcomes, which lends credence to the etiology of poor outcomes in the low BMI population (63). It is reasonable to assume that nutritional interventions in this underweight group should be aggressive given the multiple etiologies of their presenting weight. Overall, BMI is not necessarily useful as a marker of malnutrition but can be used as a factor to consider when predicting a patient's postoperative clinical course.

Clinical scoring systems

Several nutritional scoring systems have been tested in the literature; however, few have been studied specifically within thoracic surgery. The Nutritional Risk Index (NRI) is a tool that was validated by the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. NRI uses serum albumin, serum prealbumin, and patient weight to calculate a risk score used to classify their malnutrition (64). Ramos *et al.* conducted a study in 219 NSCLC patients and showed NRI as an independent predictor of postoperative complications (61). A review of all the nutritional scoring systems recommended within national guidelines is beyond

the scope of this review, but it is clear that, to date, there has been inadequate attention paid to the routine use of nutritional risk assessment in thoracic surgery.

Preoperative nutrition

The most recent European guidelines do not recommend traditional preoperative fasting prior to surgery, rather limiting fasting of solid foods to six hours and clear liquids to two hours prior to the surgical procedure (50). This recommendation tends to be individualized from institution-to-institution regarding the acceptance of current practices by local anesthesia groups. There have only been a handful of studies which have formally investigated preoperative nutrition regimens prior to proceeding to lung resection. Kaya *et al.* examined the administration of an immune-modulating nutritional regimen (enriched with arginine, omega-3 fatty acids, and nucleotides) for 10 days preoperatively in a randomized design. They were able to demonstrate a lower complication rate and reduced chest tube days in the intervention group. However, the malnourished and patients with metabolic disorders were excluded (65).

Preoperative nutrition prior to esophageal cancer surgery is another special consideration. This population is notable as it consists of patients who often present with malnutrition, have adequate time before surgery for nutritional optimization due to neoadjuvant therapy, and are at particularly high nutritional risk due to their pathology. In several guideline publications, it is asserted that esophageal cancer patients should receive nutritional supplementation for at least 10–14 days before surgery (50,66). Various routes of nutritional administration have been proposed including gastrostomy, jejunostomy, and via the esophagus facilitated by esophageal stent to assist delivery (67-69). A recently published systematic review by Huddy *et al.* summarizes the available literature on these different modalities of preoperative feeding (70). The included studies within the review are primarily small, single-center, studies. No randomized, controlled trials have been conducted comparing different modalities of nutritional support therapy. Ultimately, there is a dearth of quality evidence to recommend a particular route of nutrition administration prior to surgery. As such, practices patterns vary based on institution.

Immunonutrition has shown promise in gastrointestinal surgeries and is recommended under the American College of Surgeons Strong for Surgery program. A study performed by the Surgical Care and Outcomes Assessment Program (SCOAP) in Washington state demonstrated that immunonutrition regimen per this protocol led to fewer readmissions, reduced LOS, reduced risk of infections, and reduced risk of venous thromboembolism without significant differences in cost (71). Immunonutrition in thoracic surgery appears to have promise, but with limited literature to support its benefit (65). In esophageal cancer patients, a recent, multicenter, randomized controlled study in Australia showed no difference in clinical or patient-reported outcomes following administration of an immunonutrition regimen (72).

Postoperative nutrition

Over the last decade, postoperative nutrition has evolved from intensive investigation in gastrointestinal tract surgery to the dictum of "early enteral nutrition" being the international standard of care. As summarized above, major consensus guidelines have established the benefit of initiation of nutrition within 24 hours of surgical intervention. It is recommended that initiation of nutrition be enteral over parenteral barring specific contraindications. Two meta-analyses comparing enteral versus parenteral routes of nutrition have demonstrated possible decrease in mortality (73) and complications (74), but the aggregated data are considered to be weak.

A particular thoracic surgery population deserves special mention concerning postoperative nutrition: esophageal surgery. There is ongoing debate over the best method for enteral nutrition delivery postoperatively. The main concern with immediate oral intake (postoperative day one) is the theoretical risk to the fresh surgical anastomosis, lower caloric intake, and risk of aspiration leading to pneumonia. Due to these theoretical risks, many surgeons opt for delay in resumption of postoperative nutrition or nasojejunal or surgically placed jejunostomy tubes to administer post-operative nutrition. However, there has been some prospective data supporting the adoption of early per oral feeding during the first 24 hours after surgery. Weijs *et al.* found no difference in calories administered, pneumonia rates, and anastomotic leak rates between early and delayed feeding (75). The only randomized trial investigating this question found that early feeding was non-inferior to other forms of enteral delivery (76).

Opportunities for research

There are numerous opportunities for future study within

the field of nutrition during the perioperative period around thoracic surgery. As summarized above, most of the research that has been conducted thus far relate to the use of nutritional risk scores and laboratory values to serve as prognostic indicators for patient outcomes. There remains an opportunity to look at strategies for nutritional support, especially in high-risk thoracic cancer populations.

Practice patterns for nutritional therapy in thoracic surgery are not well known. It is unclear how much perioperative nutrition is emphasized amongst thoracic surgeons nationwide, and what percentage of patients are receiving a comprehensive nutritional work-up prior to proceeding to the operating room. It is the authors' experience that nutrition has been relatively neglected on a national scale, and decisions regarding the administration of nutrition are not made until the postoperative period on the surgical ward and intensive care unit.

Finally, as noted above, the esophageal cancer patient population is a special consideration concerning perioperative nutrition. There are currently no guidelines directing thoracic surgeons on the best regimen and route of nutrition during a patient's neoadjuvant therapy prior to surgical resection, and following surgery. Investigations into different supplements and routes of feeding are needed to clarify these management strategies.

Functional fitness and exercise

National guidelines recommend extensive preoperative pulmonary evaluation prior to lung resection include assessment of lung function through forced expiratory volume (FEV_1), diffusing capacity of the lung for carbon monoxide (DLCO), and exercise testing (53,54,77). Assessment and optimization of a patient's pulmonary function are critical to prevent postoperative pulmonary complications (PPCs). PPCs have been found to be associated with higher 30-day readmission rates, longer lengths of stay, and reduced overall survival (78).

Given the high burden of comorbid disease in these patients, pulmonary rehabilitation can be a critical intervention to optimize patients for surgery. It has been described that patients undergoing resection for lung cancer tend to be less active, with more comorbid disease than the average healthy population (79). The efficacy of pulmonary rehabilitation within chronic obstructive pulmonary disease (COPD) has been well characterized (80), a disease process that is very common in the thoracic surgery population. A Cochrane review from 2017 specifically looked at the outcomes following preoperative exercise prior to lung cancer surgery. It identified five randomized studies investigating this question and found that preoperative exercise therapy reduced PPCs, length of intercostal catheter use, LOS, and improved exercise capacity and force vital capacity postoperatively (81). A systematic review conducted a year prior found the same conclusions (82). However, the number of studies available in these meta-analyses were low, thus strong recommendations could not be made based on the available evidence. There is currently an enrolling randomized controlled trial, the Precision Exercise Prescription (PEP) study for patients undergoing surgery for lung cancer (1R01CA211705-01A1), led by one of the authors of this review. It is our hope that this study will lend additional evidence to a potentially critical aspect of preparation for lung cancer surgery.

Exercise training is typically organized into three domains: aerobic exercise training, resistance training, and respiratory muscle training (81). The optimal preoperative regimen has not been clearly identified. There has also been an inability to scale these interventions across resource-limited settings as there may not be a highly skilled exercise physical therapist available.

Pre-operative exercise

Pre-operative exercise training prior to lung cancer surgery has been assessed in several randomized clinical trials (83-87). All of these studies suffer from low enrollment numbers and generalizability given the equipment and resources used in their pre-operative exercise program. Systematic reviews and meta-analyses of these trials have demonstrated reduced length of stay and lower PPCs compared to lack of preoperative exercise training (81,82). Current preoperative guidelines for physiologic assessment of resectable patients recommend preoperative and postoperative rehabilitation for patients deemed high-risk after undergoing pulmonary and exercise assessment (53). While the data support this recommendation, the ideal regimen has not been clearly delineated. Prolonged, intensive exercise training programs are not feasible prior to time-sensitive lung cancer surgery as delays may affect cancer-specific survival. The length and content of training, as well as the scalability, are all important questions to consider when recommending general preoperative pulmonary rehabilitation.

The most debated aspects of preoperative exercise training have been the length and content of exercise programs required to produce clinical results. Longer

rehabilitation intervals are more ideal for optimization of cardiorespiratory function; however, this practice leads to delays in surgery, which may have significant oncologic consequences. One of the earliest attempts at enrolling patients into a randomized controlled trial for preoperative exercise therapy had to be stopped prematurely after accruing only 9 patients over 18 months. This study initially attempted to use a 4-week exercise program (84). The primary reason for lack of accrual was patient and provider unwillingness to delay surgery. Benzo *et al.* subsequently abbreviated their study into ten exercise sessions which showed a significant decrease in chest tube days and hospital LOS in the rehab group (84). There were two other studies which used protocols of 3 and 4 weeks prior to surgery. Morano *et al.* used a 3-week program to improve several pulmonary function parameters, lower the rate of PPCs, reduce LOS, and reduce chest tube days (86). Stefanelli *et al.* used a 4-week protocol that significantly improved peak VO_2, which the authors asserted was a prognostic indicator of patient outcome undergoing thoracic surgery, thus proved a successful intervention (87). Shorter programs of one week in duration have been investigated in two randomized trials. In 2011, Pehlivan *et al.* demonstrated lower rates of PPCs and LOS in the rehab group undergoing one week of chest physiotherapy and walking exercises. More recently, Lai *et al.* proposed an intensive 7-day course focusing on exercise endurance training and inspiratory muscle training (83). After a 7-day intervention, they were able to demonstrate improved physical function, decreased PPCs, and reduced LOS. Outside of thoracic surgery, a randomized controlled trial published in *JAMA* looking at coronary bypass patients showed the effectiveness of a 2-week exercise program which reduced postoperative morbidity and LOS (88).

The appropriate content of pulmonary rehabilitation programs is a more difficult question to answer due to the heterogeneity of protocols used in published studies. In general, most studies use a combination of aerobic endurance training, resistance training, and inspiratory muscle training. The efficacy of different interventions within these domains is not well studied and may ultimately be difficult to quantify. The other concern regarding content is the ability to scale interventions. Many of the included studies used specialized equipment and had access to skilled physical therapy personnel. This may not be possible in resource-limited and rural practices where thoracic surgeons only have limited clinic and nursing staff availability.

Opportunities for research

There are many opportunities for further research in the area of pre-operative exercise interventions. The major barriers to implementation of recommended exercise interventions are provider access for the provision of these programs and patient motivation. Despite its recommendation in the guidelines, it is unclear the number of thoracic surgeons nationally who provide a formalized exercise program to patients who are at high pulmonary risk prior to lung resection. Perhaps more importantly, for those practices which cannot provide such programming, what are the financial, access, and other barriers which are preventing them from offering patients this service? Opportunities to study scalable interventions are needed to allow access to potentially complication-saving measures for patients undergoing lung surgery.

The other possible domain for potential investigation lies within patient motivation. There may be a subset of patients who will require additional intervention and motivation to undergo such a preoperative exercise regimen. Psychological studies underlying patient motivation prior to surgery may be an area ripe for additional investigation to improve compliance to these programs. These types of interventions would be valuable, not only for preoperative exercise, but for any perioperative optimization program.

Smoking cessation

The primary etiologic agent in lung cancer is smoking with an estimated 90% of lung cancer cases attributable to this behavior (77). At the time of lung cancer surgery, it is estimated that one in five patients are current smokers and 30–60% of smokers will continue to smoke after surgery (89,90). Esophageal cancer, particularly the squamous cell subtype, is also highly associated with smoking (91). It has been shown in multiple studies, that smoking is also a significant risk factor for postoperative mortality and morbidity in esophageal surgery (92-94). It is well documented that patient smoking has a significant negative impact on outcomes following elective surgical intervention, and that smoking cessation can provide both short- and long-term benefits (95,96).

The pathophysiology of the ill effects of smoking is multifactorial. It has been clearly associated with several chronic diseases such as cancer, atherosclerosis, stroke, and chronic obstructive pulmonary disease. For the thoracic surgeon, the patient population is at particularly high risk,

as smoking is a primary etiologic agent in lung carcinoma. Pertaining to surgery, the association of smoking with a greater burden of chronic disease lends itself to higher risk surgical candidates, ultimately leading to greater risk of postoperative complications 30-day mortality (95). A systematic review and meta-analysis in 2012 identified that smokers tended to have a higher incidence of healing complications in the postoperative period compared to non-smokers, and that previous smoking carried a lifetime risk of this increased risk (97). Abstinence for at least 4 weeks was emphasized to decrease surgical site infections, but had no effect on other healing complications.

Duration of smoking cessation

There has been considerable debate regarding the length of preoperative smoking cessation required to minimize postoperative complication development. A recent survey of thoracic surgeons across the United States revealed significant disagreement regarding the ideal time before surgery for a patient to quit (98). However, the majority (98%) of respondents agreed that smoking in the perioperative time period increases the risk of pulmonary complications. Thus, a preponderance of thoracic surgeons surveyed waited 2–4 weeks after smoking cessation to perform surgery. Despite this proposed length of time for smoking cessation of at least four weeks, no definitive time period has been identified (97,99,100). A recent prospective, observational study in the United Kingdom looked at 462 NSCLC patients and did not find any difference in postoperative mortality or morbidity between smokers who quit greater than 6 weeks prior to surgery versus those who quit less than 6 weeks prior to surgery. Current smokers were significantly more likely to experience complications (including pulmonary complications, hospital and ICU length of stay), but saw no differences in early mortality or long-term survival. The incidence of PPC in current smokers in this study was 22%, more than 10 times than patients who never smoked (101). A Society of Thoracic Surgeons (STS) General Thoracic Database Study identified that the incidence of PPCs declined with increasing interval to quitting smoking prior to surgery, but these differences were not found to be statistically significant. As such, no ideal interval could be recommended (100). Within esophageal cancer, the literature is even more scarce. A recent retrospective review by Yoshida *et al.* showed that smoking cessation >90 days prior to surgery lowered the patient's risk to the same level of a non-smoker (102). Follow-up investigations by the same group found that the ideal quit time for patients undergoing minimally invasive esophagectomies was 30 days, and inhaled carbon monoxide was a useful metric to predict pulmonary morbidity following surgery (103,104). To the author's knowledge, there has not been any other studies investigating the length of preoperative smoking cessation required to see maximal benefit in the esophageal cancer population.

The ideal time to quit smoking prior to surgery remains unclear, but there seems to be a dose-dependent response described by some in the literature. A meta-analysis by Mills *et al.* in 2011 demonstrated magnitude increase of 19% with each week of smoking cessation and an overall relative risk reduction of 41% (105). This analysis contained no randomized controlled trials from the thoracic surgery population, but it did include four notable observational studies within thoracic surgery (99,100,106,107). The previously mentioned studied within esophageal cancer also showed a dose-dependent relationship out to 90 days (102). Physiologically, evidence has shown that negative immune-modulating and inflammatory effects of smoking are only reversed after 6 months, however this time period is often not feasible when scheduling patients for potentially curative cancer surgery. Within esophageal cancer, quit dates exceeding 1–2 months are possible given that a significant proportion of these patients will be receiving neoadjuvant therapies prior to surgery. Larger studies to determine the ideal amount of time prior to surgery are still needed to delineate this question, however regardless of the time-frame, it is highly recommended to quit smoking at any time before surgery as the benefit is undeniable.

Pre-operative smoking cessation interventions

Knowledge of the ideal time prior to surgery for smoking cessation is important; however, implementation of a formalized program to aid in preoperative smoking cessation is necessary to translate these practices to improvement of surgical outcomes. It has been suggested that there is a unique opportunity to help patients quit smoking prior to elective surgery, and, in particular, thoracic operations utilizing the concept of a "teachable moment." (108,109).

A systematic review of smoking cessation programs across all of elective surgery only included two prospective interventions within thoracic surgical procedures. Browning *et al.* reported recruitment of surgical patients for preoperative smoking cessation at their first clinic visit and

set a quit day for 2 weeks afterwards (110). Kozower *et al.* followed patients with an expected quit date two weeks before surgery. It may be most beneficial to refer patients for smoking cessation at surgical referral to get a head-start on potential quit dates (111).

A Cochrane review in 2014 looking at smoking cessation intensity prior to surgery recommended that cessation efforts should begin 4-8 weeks prior to surgery to optimize cessation at the time of surgery, reduce postoperative morbidity, and have a better chance for long-term cessation. It was also noted that NRT could be a useful adjunct in helping patients experience short-term success (112). However, brief smoking cessation interventions were shown to have little effect on the outcomes of interest compared to more intensive methods. In one included randomized, controlled, study of elective non-cardiac surgical patients, varenicline was shown to improve long-term smoking cessation. Unfortunately, though, it had no effect on reducing postoperative complications started one week prior to surgery. The expected quit date in this study was one day prior to surgery (113). Thomsen *et al.* concludes that longer courses of NRT and varenicline are needed, within an intensive smoking cessation program to have an effect on quit rates and postoperative complications (112). The cost-savings benefits of quitting smoking prior to surgery have also been established, albeit in one cost-savings analysis using a Markov Model (114). While it is generally agreed that quitting smoking prior to surgery should be pursued, the general practice model for pursuing this reality has not been established. Additional surveys of national practice patterns regarding this opportunity for smoking cessation should be pursued.

Opportunities for research

There is still considerable debate regarding the duration of smoking cessation prior to surgery. It is clear that never smokers have significantly better outcomes than former and current smokers, however adverse effects seen in the former smoker population seem to extend back to quitting even 1 year prior to surgery. Despite this reality, the beneficial aspects of smoking cessation related to postoperative outcomes, long-term cancer survival, and overall comorbidity burden cannot be understated. There has been some literature on the current state of smoking cessation programs, however it is not known what formal tobacco cessation interventions are being provided to thoracic surgery patients in the preoperative period. Moreover, the comfort level of thoracic surgeons to provide appropriate pharmacologic interventions is not known as well as the access of many surgeons to a dedicated smoking cessation provider. Finally, while tobacco cessation in the perioperative period is important, tobacco addiction is a chronic disease, with frequent relapses requiring long-term primary care provider and smoking cessation support. Quality improvement initiatives that link patients into ongoing smoking cessation services at the time of surgical referral would help prevent tobacco-related complications and substantially relieve the health and financial burden of this costly patient behavior.

Limitations

This review has several limitations. First, due to time constraints and the scope of the selected review topics, we were unable to complete a thorough systematic review and meta-analysis within each domain. Our goal was to summarize major studies and known literature on each subject without an exhaustive review within each domain. Second, this review article represents the view of the authors in this article, however we feel that our recommendations are supported within the literature.

Nevertheless, we hope this work serves as a basis for creation of novel research interests in various domains of modifiable risk factors which can improve patient outcomes following thoracic surgery.

Conclusions

We identified several areas for further health service research which may help guide thoracic patient providers in selecting research questions. We provide an accessible summary of recent completed research which can be incorporated into current care within the selected reviewed domains.

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Footnote

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