Original Article

Thirty Days Mortality Following Lung Resection: Risk Factors, Preoperative Assessment and Improvement Program

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We conducted a systematic review of the literature to better understand how to reduce the 30-day mortality after lobectomy. Furthermore, we tried to identify the factors affecting postoperative mortality from the three stages of the perioperative period and provided corresponding countermeasures. Our review suggests that it is time to move on from considering operative risks and then patient factors as a secondary, minor consideration. At the same time, it further emphasizes the importance of preoperative assessment and co-management. Although, a few of the data in this review are dated and may be lacking in reference, the proof from multiple perspectives makes up for the deficiency in this aspect to some extent. In summary, mortality within 30 days after lobectomy is a major challenge for patients, and we should minimize postoperative mortality by optimizing perioperative management of the three stages.

Key Words: Risk factors; 30 days mortality; Morbidity; Lobectomy; Thoracic anesthesia

INTRODUCTION

Thousands of Americans die every year undergoing elective cancer surgery. A larger number of patients with postoperative complications often associated with disabilities or shortened life expectancy.¹ Most investigators concur that multiple factors including the patient, the surgery, the method of anaesthesia, and the quality of perioperative care, all influence surgical outcome.^{1,2} Lung cancer remains the second most common cancer in the United States and the leading cause of cancer death in men and women.^{3,4} Complications that occurred with surgical resection of lung cancer, the only available curative option today, are strongly associated with 30 days mortality. Clearly, not all patients are at equal risk for morbidity and mortality. It is very important to evaluate prospective morbidity and mortality rates associated with resection of lung cancer in a more careful way and minimize the perioperative risk and 30 days mortality after surgery. The purpose of this review is to identify risk factors for mortality at 30 days after lobotomy and to optimize perioperative anesthesia management during thoracic surgery.

AFFECTING FACTORS OF 30-DAY MORTALITY

In 1999, the Veterans Affairs National Surgical Quality Improvement Program (VA NSQIP) published that thirty-day morbidity and mortality were 23.8% and 4.0% for lobectomy.⁵ Although American medical technology has made great progress,

30 days mortality of pulmonary lobectomy remains about 2%.^{6,7} Therefore, it is important to identify perioperative factors associated with adverse outcomes after lobectomy. Importantly, patient factors tend to be more strongly associated with postoperative mortality than surgical and anesthetic factors.⁸ At the same time, a review suggests that the identification of preoperative risk factors may help determine the prognosis after surgical resection.⁵ Hence, this review will concentrate on risk associated with preoperative patient factors.

Preoperative factors

Trials have shown that important factors preoperatively were: male sex, prolonged operative time, low DLCO,⁶ American Society of Anaesthesiologist (ASA) physical status, plasma albumin concen-

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tration, and advanced age.^{6,8,9} Among them, male sex has been reported to be associated with an increased risk of surgery after lobectomy.^{10,11} In particular, the recently published EuroLung risk model showed that male was one of the most significant variables in the risk score for 30-day mortality.¹⁰ The increased risk of death in men may be partly due to biological factors (i.e. hormonal effects) and environmental factors (i.e. a higher proportion of smokers and people associated with smoking).⁶ The cause why the prolonged operation time affects the 30-day postoperative mortality may be related to the following reasons. First, prolonged anesthesia and surgery can lead to fluid imbalance, prolonged hypotension, "surgical shock", and hypothermia, leading to varying degrees of oxygen debt.¹² Moreover, the longer the operation, the risk of infection is greater.¹³⁻¹⁵ Finally, in lung surgery, prolonged one-lung ventilation has adverse effects on both aerated and non-aerated lungs through a variety of mechanisms:¹⁶ Lung hyperventilation, capillary lung stress failure¹⁷ Inactivation state after ventilation of inflammatory cytokines,¹⁸ low pressure/ischemia-reperfusion injury caused by pulmonary vasoconstriction. However, the advanced age factor is worth emphasizing. With the aging population, the age of patients undergoing pulmonary lobectomy is expected to increase. The medical team including surgeons, anaesthetists, and nurses looking after older patients before, during, and after surgery play a vital role in reducing postoperative mortality. A lung resection test showed that mortality increased with age, from 1.3 per cent under 60 years of age, 4.1 per cent between 60 and 69 years of age, to 7.1 per cent over 70 years of age. Age is an independent predictor of death after multivariate logic regression tests for mortality.⁵ In another NSQIP study of older patients found that thoracic surgery carried the highest risk. They found overall 30-day mortality of 8% with thoracic surgery having the highest mortality with 14% in patients aged 80 years or more vs. 6% in patients aged less than 80. However, advanced age is not only a relevant factor for mortality after lobectomy, but also has been identified as an independent relevant factor for mortality in other non-cardiac surgeries. Such as in a study of 3682 patients with unruptured intracranial aneurysm surgery from the Nationwide Inpatient Sample, increasing age and history of prior stroke were identified as independent predictors of mortality.¹⁹ It should be added that patients with Myocardial Injury After Noncardiac Surgery was significantly older.²⁰ Many studies have found that the traditional assumption that older persons generally less well from weakened immune systems, and other common diseases, recover slowly, general weakness and reduced social support is correct.²¹ Because of the increasing number of elderly patients undergoing surgery, we need to further improve the outcomes of sicker patients. The first step is to conduct a risk assessment and help the patient and his family to decide whether to perform the operation. More important is to improve postoperative care, as early as possible to rescue patients with deteriorating conditions, to avoid rescue failure and death. The rescue has two components: surveillance and intervention.²² Surveillance requires the measurement of appropriate clinical observations at appropriate intervals. Interventions need to be fully explained in terms of clinical measurements in order to provide appropriate individualized interventions for patients.⁸ A medical emergency unit (MET)²³ is an intervention where an intensive care unit doctor and nurse, at the request of the ward's medical or nursing staff, provides care for patients in the ward. Another way to improve monitoring and intervention is through co-management,²⁴ where surgeons and physicians manage patients together.

Friedman and colleagues found that patients under combined management had shorter hospitalization time, fewer postoperative complications, and shorter operation time.²⁵ These benefits are essential to reduce postoperative mortality.

An article designed to assess the elimination of wasteful parts of a process found that elimination of non-value-added steps including epidural anesthesia, arterial puncture, central venipuncture, and the use of Foley catheters can safely decrease pre-incision time without increasing patient risk in patients who undergo pulmonary lobectomy. The results showed that after all the changes were completed, the average time from entering the operating room to the incision was reduced from 64 minutes to 37 minutes. As a result, the mortality rate decreased from 3.2 percent to 0.26 percent and primary morbidity from 15.2 percent to 5.3 percent. It must be admitted that lean (the main concept of "lean" is to improve efficiency by reducing wasteful steps and improving quality, and it can be applied in health care) is a response to the focus of high-quality with low costs health care reform.²⁶ It should be noted that not all patients are suited to a lean-approach. We should not blindly pursue the low cost and reduce the operation time while ignoring whether the patients themselves meet the requirements of the scheme. For patients with complex conditions, ASAIII, high risk of bleeding or advanced age, the use of central catheters, arterial catheters and Foley catheters may be necessary.

Intra-operative factors

Compared with anesthetic methods, surgical methods may be more important for patients' postoperative effects. With the development of science and technology, increasingly complex procedures, including minimally invasive surgery (MIS) performed on patients of advanced age. Minimally invasive surgery results in decreased pain, lower incidence of perioperative complications, and a shorter median hospital length of stay (LOS). A study carried out three years ago found that after four years of VATS lobectomy, the length of hospitalization was shortened, the length of the chest tube was shortened, and the survival rate improved, compared with open lobectomy in older patients.²¹ Today, robot-assisted surgery is becoming more and more common. K.S. Kass et al. investigated whether advanced age affected peri-operative outcomes after robotic-assisted pulmonary lobectomies and concluded that younger patients²¹ had a lower risk of robotic complications during surgery and were hospitalized for a shorter period, but there was no increase in the incidence of postoperative complications or inpatient mortality in older patients compared to younger patients. Thus, technological advances play a self-evident role in improving the quality of medical care. But robotic surgery is relatively expensive, which may limit patients' options.

Perhaps the effect of anesthesia on postoperative mortality is less important than the operation itself. But good anesthesia also plays an indispensable role in the prognosis of patients. So, how to optimize thoracic anesthesia?

1) Enhanced preoperative assessment The preoperative evaluation of patients before anesthesia plays an important role in reducing the incidence of complications of any type of anaesthesia.²⁷ There are many causes of death after surgery, each of which may increase the risk of developing another factor. A complete assessment of operative risk should include evaluation of 3 components: the patient, the procedure, and the anesthetic. Importantly, patient factors often have a stronger association with postoperative mortality than surgical and anesthetic factors. Hence,

Careful preoperative physiological assessment should identify patients at increased risk of standard lung cancer resection so that patients can make informed decisions about appropriate diagnosis and treatment of lung cancer. The patient's heart, lung, liver and kidney functions should be evaluated first to determine whether the patient's physical condition can be operated on. Anesthesiologists and surgeons then help patients prepare for surgery, such as quitting smoking and drinking. Due to the numerous literature reports that preoperative smoking and alcohol abuse are associated with wound complications, general infection, pulmonary complications, neurological complications and increased risk of ICU admission, attention should be paid to smoking cessation and alcohol abuse.²⁸⁻³¹

In addition to strengthening the above systematic evaluation, benzodiazepines or α_2 -agonists can be used before anesthesia to reduce anxiety and related complications and improve patient satisfaction.

2) Optimize intraoperative management

2.1) Which Anesthesia Regimen Is Best to Reduce Morbidity and Mortality in Lung Surgery?

In order to minimize the incidence of side effects, such as postoperative nausea and vomiting, propofol is often recommended for total intravenous anesthesia. Since one-lung ventilation is primarily performed during thoracic surgery, it can lead to alveolar inflammation and the release of cytokines, the extent of which may depend on the use of anesthetics. Although numerous studies have described the use of volatile anesthetics for intraoperative protection of the heart, liver, lungs, and kidneys in the context of tissue damage caused by ischemia-reperfusion (hypoxia-reoxygenation).³²⁻³⁵ But a multicentre RCT found no significant difference between desflurane volatile anesthesia and propofol intravenous anesthesia in major complications after selective pneumonectomy. This may be related to the type of volatile anesthetic selected. However, desflurane, like sevoflurane, has a protective effect in ischemia-reperfusion (hypoxia-reoxygenation)-induced tissue damage. It could also be that thoracic surgery doesn't hurt enough to detect a way to protect against injury. In summary, this RCT shows that desflurane does not reduce the major short-term and long-term complications of standard pulmonary surgery compared to propofol.³⁶

2.2) Ventilation management

Thoracic surgery, whether it is lung surgery or surgery requiring one-lung ventilation (OLV), has one thing in common is that Anesthesiologists and surgeons compete for the same lung. The ventilation system may be damaged for a long time, which not only has multiple effects on breathing and hemodynamic physiology.³⁷

Double-lumen bronchial intubation anesthesia is the mainstream of thoracic surgery, and its most significant benefit is that it can completely separate the healthy lung from the operative lung. Double-lumen bronchial intubation can not only satisfy mechanical ventilation, but also allow patients to completely collapse the intraoperative lung, fully expose the surgical field, so that clinicians can smoothly carry out the operation, shorten the anesthesia time and operation time, and improve the operation effect. In recent years, non-endotracheal intubation VATS has been reported to be feasible and well-tolerated in the treatment of pneumothorax, sympathetic nerve resection, wedge resection of lung tumor, lung volume reduction surgery, segmentectomy, and lobectomy.³⁸⁻⁴¹ Early results of non-intubated general anesthesia include faster postoperative recovery and a lower incidence of complications compared to general anesthesia for double-lumen

bronchial intubation, which may translate into a fast-track VATS program. However, in the current situation of shortage of anesthesiologists in China, it is difficult to carry out this technique on a large scale, because non-intubation general anesthesia requires anesthesiologists to pay attention to airway management all the time and give more energy. And once massive bleeding occurs during the operation, compared with intubation general anesthesia, the former treatment will be more passive and difficult. Postoperative pulmonary complications are common complications after lung surgery and are associated with disease, mortality, length of hospital stay, and related costs. Lung protection strategies should be the focus of ERAS protocols because they reduce, minimize, and avoid further respiratory complications and acute lung injury.⁴²

Best practice recommendations for one-lung ventilation include short duration, optimization of lung compliance through post-anesthesia recruitment (i.e. vital capacity maneuvers 30–40cm H₂O for 10–40s),^{16,43} end-expiratory positive pressure (PEEP) titration, bronchodilation, and bronchial toilet. The application of low level continuous positive airway pressure (2cm H₂O) to collapsed lungs can avoid dense atelectasis and reduce intrapulmonary shunt, but will not affect surgical exposure. Protective ventilation during thoracic surgery to reduce acute lung injury tidal volume should be limited, and 4–6ml/kg of tidal volume has been shown to be protective. PEEP level is mainly dependent on individual respiratory mechanics and should be adjusted based on optimal lung compliance. Notably, permissive hypercapnia is acceptable with one - lung ventilation.

2.3) Perioperative intravenous fluid management

The concept of rapid recovery in thoracic surgery makes limited infusion become the main strategy in perioperative period of lobectomy. Reducing fluid infusion can effectively reduce the incidence of pulmonary edema and postoperative pulmonary complications. Pulmonary fluid overload has been identified as an independent risk factor for acute lung injury after lung surgery.⁴⁴⁻⁴⁷ One of the early ideas, however, was that maintaining adequate organ microcirculation was associated with reduced morbidity and mortality. The role of Goal-Directed Fluid Therapy (GDT) in thoracic surgery has been studied. They concluded that stroke volume variation (SVV)-guided fluid management did not result in fluid overload in the lungs during thoracotomy and single-lung ventilation. Although oxygenation is reduced, lung function is still within the clinically acceptable range. However, due to the limited number of participants, this conclusion needs to be carefully verified in larger, multicenter randomized controlled trials, whether to continue with restricted infusion or GDT.

2.4) How to optimize analgesia?

A clinical study by J. P. Cata et al. have reported that a trend toward significance for opioid consumption as a risk factor in stage I non-small cell lung cancer patients. Notably, lobectomy was the most common procedure performed for those patients in the study. The overall survival period (OS) is defined as the number of months from surgery to death for any reason. In addition, consumption of opioids was a risk factor for 30-day mortality in patients in the first stage, while no effects were observed in patients in the second or third stage. The findings may lead anesthesiologists to focus more on epidural or nerve block analgesia and thus reduce opioid use. At present, thoracic epidural analgesia (TEA) is recommended as the gold standard for thoracotomy analgesia. In addition to analgesic effect, perioperative TEA can increase breathing minutes and tidal

volume, reduce pulmonary vascular resistance, and reduce the incidence of atelectasis and pneumonia. Besides that, thoracic epidural also has a variety of physiological effects on cardiopulmonary and gastrointestinal systems, which may play a beneficial role in postoperative rehabilitation of thoracic surgery due to the regulation of neuroendocrine and stress response⁴⁸. Positive biological effects include improved left ventricular function, reduced cardiovascular complications, enhanced intestinal function, beneficial coagulation, postoperative immune function, and inflammation.^{48,49}

In several studies, PVB has been reported to provide analgesic effects similar to TEB, with fewer side effects, such as postoperative nausea and vomiting (PONV), hypotension and urinary retention, and fewer pulmonary complications.⁵⁰⁻⁵⁴

Insufficient analgesia directly affects the postoperative recovery of patients, so optimizing analgesia is an indispensable part of the concept of rapid recovery.

Postoperative factors

There is emerging work on quantifying Myocardial Injury After Noncardiac Surgery as a risk factor for perioperative complication and mortality as well as the need for higher level of care in hospital and after discharge from hospital. Worldwide, millions of patients die each year within 30 days of non-cardiac surgery; Myocardial ischemia is a common cause.⁵⁵ Myocardial injury after non-cardiac surgery (MINS) is defined as myocardial injury caused by ischemia that occurs during or within 30 days after surgery.⁵⁶ More and more studies have focused on the effect of MINS. A trial showed that approximately 1 in 5 patients aged 45 years or older experienced MINS following vascular surgery and MINS was independently associated with 30 days mortality.²⁰ Similarly, another study found a similar link between MINS and 30-day mortality.⁵⁶ Although, the literature available on myocardial injury after lobectomy is scarce, which needs to be further studied. It is still necessary to pay attention to myocardial protection and the detection of hsTnT during the perioperative period of lobectomy (peak postoperative hsTnT during the first 3 days after surgery was significantly associated with 30-day mortality). This will help us to detect myocardial injury early, so as to take effective measures to reduce postoperative death outcomes caused by myocardial injury. And recent research has found that second readmissions were most likely to present with heart disease after pulmonary lobectomy.⁵⁷ Therefore, we must pay attention to and prevent the occurrence of adverse cardiac events after surgery.

It should be noted that in addition to MINS, postoperative atrial fibrillation (PAF) also affects the prognosis. PAF has been shown to affect between 12 % and 17 % of patients with lobectomy, including adverse effects on short-and long-term mortality, longer hospital stays and use in intensive care units, and. Kotova et al. observed that there was a significant difference in complications between the two groups. The incidence of pneumonia, adult respiratory distress syndrome, pulmonary embolism, pneumothorax, empyema and other pulmonary complications were higher in the PAF group. In addition, the PAF group was reintubated several times more than the control group. To be clear, they have identified that age was the strongest variable associated with PAF but other variables including forced expiratory volume in 1 second (FEV1), congestive heart failure, diabetes mellitus, coronary artery disease, sex, diffusion capacity of the lung for the carbon monoxide (DLCO), surgical approach, and clinical stage, which have been reported in

the past to have a significant association with PAF were not significant.⁵⁸ It is clear from MINS and PAF that the prevention of cardiovascular adverse events after lobectomy is constructive in reducing the 30-day mortality, especially in elderly patients.

With the increase of minimally invasive thoracoscopic surgery, the morbidity and mortality after lobectomy have been significantly reduced, and surgical treatment can be considered even for patients with serious complications. Co-morbidities and complications are not only associated with 30-day mortality, some studies have shown that they are also associated with postoperative readmission within 90 days. This indicates that strengthening preoperative evaluation is significant in reducing the adverse outcomes after lobectomy. It must be emphasized that prolonged hospital stay does not reduce the risk of re-admission within 90 days after lobectomy, which supports programs to accelerate patient discharge and reduce overall health service utilization.⁵⁹

SUMMARY

Estimates of hospital mortality after inpatient surgery range from 1 to 4%, resulting in at least 2.3 million deaths worldwide each year. Patients with postoperative lung cancer have a higher chance of complications and death. Therefore, it is of great significance to strengthen the emphasis on the perioperative period of patients undergoing lobectomy. Although the surgical process is often the focus of perioperative attention, preoperative evaluation and reduction of postoperative mortality at 30 days may be more important. It is time to move on from considering operative risks and then patient factors as a secondary, minor consideration. Risk assessment and intervention where possible can reduce morbidity and mortality from lobectomy surgery. Optimizing care for these patients requires a team approach before, during, and after surgery. Minimizing complications and early rescue of those having a complication is of paramount importance. Surgeons, anesthesiologists and caregivers should work together to reduce postoperative mortality and complications.

Conflict of interest

The authors have no conflict of interest to disclose.

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