Derivation and Diagnostic Accuracy of the Surgical Lung Injury Prediction Model

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ABSTRACT

Background: Acute lung injury (ALI) is a serious postoperative complication with limited treatment options. A preoperative risk-prediction model would assist clinicians and scientists interested in ALI. The objective of this investigation was to develop a surgical lung injury prediction (SLIP) model to predict risk of postoperative ALI based on readily available preoperative risk factors.

Methods: Secondary analysis of a prospective cohort investigation including adult patients undergoing high-risk surgery. Preoperative risk factors for postoperative ALI were identified and evaluated for inclusion in the SLIP model. Multivariate logistic regression was used to develop the model. Model performance was assessed with the area under the receiver operating characteristic curve and the Hosmer-Lemeshow goodness-of-fit test.

Results: Out of 4,366 patients, 113 (2.6%) developed early postoperative ALI. Predictors of postoperative ALI in multivariate analysis that were maintained in the final SLIP model included high-risk cardiac, vascular, or thoracic surgery, diabetes mellitus, chronic obstructive pulmonary disease, gastroesophageal reflux disease, and alcohol abuse. The SLIP score distinguished patients who developed early postoperative ALI from those who did not with an area under the receiver operating characteristic curve (95% CI) of 0.82 (0.78–0.86). The model was well calibrated (Hosmer-Lemeshow, $P = 0.55$). Internal validation using 10-fold cross-validation noted minimal loss of diagnostic accuracy with a mean ± SD area under the receiver operating characteristic curve of 0.79 ± 0.08.

Conclusions: Using readily available preoperative risk factors, we developed the SLIP scoring system to predict risk of early postoperative ALI.

What We Already Know about This Topic

- Acute lung injury is the most common cause of postoperative respiratory failure and is responsible for important postoperative morbidity and mortality. The ability to predict patients' risk of acute lung injury remains elusive.

What This Article Tells Us That Is New

- The surgical lung injury prediction model presented here includes the following variables: high-risk cardiac, vascular, or thoracic surgery; diabetes mellitus; chronic pulmonary obstructive disease; gastroesophageal reflux disease; and alcohol abuse.
- The surgical lung injury prediction model enabled stratification of patients (n = 4,366) into low (0.5%), intermediate (2.6%), and high (12.2%) risk of acute lung injury.

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POSTOPERATIVE respiratory complications are important causes of perioperative morbidity and mortality.[1–3] Postoperative acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), are particularly severe pulmonary complications with an estimated mortality exceeding 45% in certain surgical populations.[4,5] ALI has recently been identified as the most common cause of postoperative respiratory failure.[6] Although appropriate ventilator[7] and fluid strategies[8] may improve outcomes, morbidity and mortality remain unacceptably high.

Mechanistically, postoperative ALI results from injury to the alveolar epithelium and capillary endothelium with associated alterations in the innate immune system,[9] activation of the coagulation cascade,[10] and generation of reactive oxygen species.[11] The resulting influx of alveolar fluid leads to a severe impairment in gas exchange with hypoxemia and respiratory failure requiring ventilatory support. Surgical insults and various perioperative healthcare delivery factors (*e.g.*, ventilator management, fluid and transfusion strategies) may impact all three of the major pathways involved in ALI pathogenesis. It is noteworthy that patient comorbidities, medications, and other pertinent exposures can potentially impact the host response to these perioperative events as well.

In contrast to the numerous investigations of ALI treatment, surprisingly little emphasis has been placed on ALI prevention. This paucity of research on prevention strategies is likely because studies evaluating ALI are typically performed in the intensive care unit and enroll patients with established lung injury who are beyond the therapeutic window of potential prevention or early treatment strategies. The perioperative period is an attractive alternative environment for studying ALI mechanisms and for testing prevention and early treatment strategies because the timing of the intraoperative insults that contribute to postoperative ALI are predictable. This allows enrollment of subjects before ALI and before major intraoperative insults that portend risk of ALI. However, at the onset of surgical procedures, we cannot currently predict who is at risk of this serious postoperative complication. This limitation precludes the enrollment of appropriate at-risk populations into prevention studies and prevents the full and appropriate study of ALI mechanisms in a clinical setting. Furthermore, with an incidence estimated at 3%,[6] testing prevention strategies in unselected patient populations is both inefficient and prohibitively expensive.

Previous studies using administrative data have identified certain demographic and surgical factors associated with high risk of postoperative respiratory failure, but neither the incidence of ALI nor specific risk factors for this postoperative respiratory complication were reported.[1,12,13] Recent clinical studies attempted to identify patients at high risk of ALI in nonselected (medical and surgical) high-risk patients,[14,15] but no model exists for the preoperative prediction of postoperative ALI. The objective of this study was to develop a surgical lung injury prediction (SLIP) model for predicting risk of postoperative ALI/ARDS based on readily available preoperative patient and procedural factors.

Materials and Methods

Study Design

After receiving approval from the Mayo Clinic Institutional Review Board (Rochester, Minnesota), a secondary analysis of a prospective cohort study was used to identify risk factors associated with early postoperative ALI/ARDS. These variables were then used to construct a SLIP score to estimate risk of developing postoperative ALI/ARDS. The Standards for Reporting of Diagnostic Accuracy guidelines were used for reporting our study results.[16]

Study Population

Participants were identified from a previous prospectively collected database of consecutive patients undergoing elective surgery at Mayo Clinic from November 2005 to August 2006. The objective of this initial investigation was to determine the incidence and survival of ALI-associated postoperative respiratory failure and its association with intraoperative ventilator settings, specifically tidal volume. Details of the study population have been previously described.[6] In brief, participants were included if mechanically ventilated for more than 3 h during general anesthesia for the following procedures: (1) all cardiac and aortic vascular surgeries, (2) noncardiac thoracic surgeries, including esophageal and pulmonary surgeries, (3) all major abdominal surgeries, including laparoscopic procedures (excluding appendectomy and other lower abdominal procedures such as hernia repairs) and laparoscopic gastric bypass, (4) spine surgeries (performed by either orthopedic surgeons or neurosurgeons), (5) surgical procedures on the hips and knees, (6) cystectomies, (7) neurosurgical procedures (excluding ventriculoperitoneal shunts and stereotactic and peripheral nerve surgeries) and (8) head and neck surgeries.

Patients were excluded if: (1) they denied permission to use their health information for research, (2) they were younger than 18 yr, or (3) they had prevalent major risk factors for lung injury or respiratory failure or they previously required mechanical ventilation, including the following: (a) mechanically ventilated before surgery, (b) trauma, sepsis, aspiration, shock, acute congestive heart failure, idiopathic interstitial pneumonia with diffuse bilateral infiltrates on chest radiography, pneumonia or respiratory failure at any point before surgery during the hospitalization associated with the surgical procedure of interest, (c) underwent emergency surgery, (d) had previous high-risk surgery during the study period (no patient was included more than once), (e) had a history of sleep apnea or neuromuscular disease requiring continuous positive airway pressure for postoperative respiratory failure, or (f) required reintubation or need for mechanical ventilation for reoperation. The exclusion of patients with prevalent risk factors for ALI was performed to

limit confounding factors and to facilitate an evaluation of the association of interest (intraoperative tidal volume and ALI) in the initial investigation.

Predictor Variables

Preoperative baseline characteristics, comorbidities, and clinical variables were extracted from electronic medical records. Potential ALI risk factors were identified *a priori* and included: procedural factors such as surgical specialty (cardiac, aortic vascular, thoracic, abdominal, orthopedic, neurologic, urologic, otolaryngology), current and past smoking,[6,17,18] alcohol abuse,[6,17,19–21] body mass index (BMI),[22] recent chemotherapy (within 6 months of surgical procedure),[20,23] diabetes mellitus,[6,24–26] chronic obstructive pulmonary disease (COPD),[6,27] restrictive lung disease,[23,28,29] cirrhosis, gastroesophageal reflux disease (GERD), and use of amiodarone,[30,31] statins,[32] angiotensin-converting enzyme inhibitors,[33] or angiotensin II receptor blockers.[34] Smoking was defined as never, former, or active. Former smoking was defined as more than 1 yr since last tobacco use. Alcohol abuse was defined as any one of the following: (1) more than 14 alcohol-containing drinks per week (more than 2 drinks per day),[12] (2) a score of 1 or more on the CAGE questionnaire,[35,36] or (3) presence of an alcohol-related medical diagnosis such as alcohol-related cirrhosis, alcohol-related pancreatitis, or alcohol withdrawal. The CAGE questionnaire is a simple 4-question test (Have you ever felt the need to *cut* down on your drinking? Have people *annoyed* you by criticizing your drinking? Have you ever felt *guilty* about drinking? Have you ever had a drink first thing in the morning—*eye-opener*—to steady your nerves or to get rid of a hangover?) that has been recognized as a useful tool for alcohol abuse screening.[35,36] BMI was calculated from the most recent height and weight documented before the surgical procedure. If there was no documented weight in the 6 months before the surgical procedure, BMI was not calculated. Chemotherapy was considered present if administered at any time during the 6-month interval preceding surgery. We included both type 1 and type 2 diabetes mellitus in the definition. A history of gestational diabetes mellitus was not sufficient. COPD was defined as a history of emphysema or chronic bronchitis. Both interstitial lung diseases and extrinsic disorders such as spinal deformity and morbid obesity were included in the definition of restrictive lung disease. For the latter category (extrinsic disorders), formal documentation of "restrictive lung disease" in the medical record and/or confirmation with pulmonary function tests was required. Cirrhosis was defined as the documentation of "end-stage liver disease" or "cirrhosis" in the electronic medical record. GERD was defined as the documentation of "GERD," "gastroesophageal reflux," "esophageal reflux," or "heartburn" in the electronic medical record. Because of the large proportion of patients referred from outside facilities and the retrospective nature of this investigation, documentation of formal diagnostic criteria for the comorbidities of interest was not required. Rather, comorbidities (diabetes mellitus, COPD, restrictive lung disease, cirrhosis, GERD) were considered present if a physician documented the diagnosis in the electronic medical record before the surgical procedure. Medications (amiodarone, statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers) were considered present if documented in the list of current medications for the patient at the time of hospital admission. The majority of these risk factors were chosen because each had been previously noted to have an association with ALI. GERD and cirrhosis were included in light of our preliminary data suggesting an association with early postoperative ALI.

Data were collected from two primary sources. The first source was the original database from which our population was identified.[6] These data were collected prospectively by a single research coordinator who was blinded to the assessment of outcomes. The following variables were identified using this data set: age at surgery, sex, BMI, surgical specialty, smoking status, and alcohol history. Because of the inconsistent nature of reporting social history, a second patient-provided data source was interrogated as well. This data source arises from a questionnaire administered to all patients receiving care at Mayo Clinic. In addition to questions regarding medical history, social history is evaluated with multiple questions specifically relating to smoking and alcohol status. Review of the responses to these questionnaires was performed by a single physician investigator (D.J.K.). When discrepancies were identified between the two data sources, the prospectively collected database determined the allocation of smoking and alcohol status. Study participants with no documentation regarding smoking (85 [1.94%]) and/or alcohol status (38 [0.87%]) were left classified as "missing" and were not included in any of the analyses that evaluated the associations between smoking and alcohol with early postoperative ALI.

The second source of data were patients' electronic medical records. These data were collected using a Web-based query tool. This tool is used to extract pertinent data with high reliability from various source databases that contain clinical notes, laboratory tests, diagnostic findings, and related clinical information. The variables extracted using this technique included diabetes mellitus, COPD, restrictive lung disease, GERD, cirrhosis, recent chemotherapy, amiodarone, statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. For comorbidities, all clinical notes in the 5-yr interval before surgery were evaluated for the diagnoses of interest. For medications, all clinical notes in the 3-month interval (6 months for chemotherapy) before surgery were interrogated. When medications were identified with the query tool, the medical record was manually reviewed to confirm active administration of the medication at the time of surgery. All electronic queries were performed by one of two physician investigators (D.J.K., A.A.).

To ensure the validity of the data obtained using this Web-based tool, we compared the performance of the auto-

mated data-extraction strategies with manual data extraction in a subset of 249 patients. Using Landis and Koch Cohen κ statistic magnitude guidelines,[37] agreement between manual and automatic electronic data-collection strategies were almost perfect for four variables (COPD, restrictive lung disease, diabetes mellitus, cirrhosis), substantial for one variable (statin therapy), and moderate for four variables (GERD, chemotherapy, immunosuppressive therapy, and amiodarone). To better define the validity of the Web-based queries, we also performed an independent exhaustive review of the medical record for the 249-patient subgroup. This evaluation served as a "gold standard" for comparing the initial manual data extraction with automated data collection. In this evaluation, automated data-extraction strategies were noted to have greater sensitivity than manual data extraction for all variables evaluated except statin therapy. The specificities were uniformly high for all variables with both data extraction strategies. The Web-based data-collection strategies for angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers had been previously validated in random sample of this study population (1,629 and 690 patients, respectively). The sensitivities for the electronic searches were noted to be 97.6% and 94.2% with specificities of 92.4% and 98.7%, respectively.

Details regarding the surgical procedure were manually extracted from the electronic medical record of all patients by two physician investigators (D.J.K., A.A.). Hypothesizing that specific procedural characteristics would influence the frequency of ALI within high-risk specialties such as cardiac, vascular, and thoracic surgery, subgroup analyses evaluating surgical details in these three populations were planned *a priori*. Specifically, we evaluated the frequency of ALI in patients undergoing major categories of cardiac procedures including coronary artery bypass grafting, valve replacement, valve repair, pericardial resection, ascending aortic/aortic arch repair, atrial septal defect/ventricular septal defect repair, myectomy, and other less invasive procedures such as sternal wound revision and pacemaker lead extraction. In a similar fashion, aortic vascular surgery was stratified into descending thoracic or thoracoabdominal aortic repairs and abdominal aortic repairs. Further consideration was given to an open *versus* endovascular approach. Thoracic surgery was stratified into video-assisted thoracoscopic surgery, fundoplication procedures, open lung biopsy, lung resection involving wedge resection or segmentectomy, lung resection involving multiple segments or lobectomy, lung resection involving multiple lobe resections, pneumonectomy, esophagectomy, lung decortication, and other miscellaneous procedures. Finally, the impact of revision surgery *versus* an initial/primary surgical procedure was considered as well. Procedures were then grouped into low- or high-risk categories to characterize more accurately the procedure-related risk of ALI/ARDS. Effect estimates were used to assist in establishing these categories, but statistical significance was not required because of the limited number of ALI outcomes in many of the subgroups analyzed. The classification of procedures into low *versus* high risk for ALI/ARDS are presented in table 1.

Primary Outcome

ALI/ARDS was defined according to the standard American-European consensus conference definition as acute, bilateral pulmonary infiltrates and hypoxemia (ALI, PaO_2/FIO_2

Table 1. Classification of Cardiac, Aortic Vascular, and Thoracic Procedures into Low- and High-risk for ALI/ARDS

Low-risk Surgery		
Cardiac	Aortic	Thoracic
Single valve repair	Primary abdominal aortic aneurysm repair	Video-assisted thoracoscopic surgery
ASD/VSD closure	Endovascular repair	Fundoplication surgery
Myectomy		Open Lung biopsy
Sternal wound revision		Wedge lung resection
Pacemaker lead/device removal		Segmental lung resection
High-risk Surgery		
Cardiac	Aortic	Thoracic
CABG	Descending thoracic aortic surgery	Multiple segmental lung resections
Valve replacement	Thoracoabdominal aortic surgery	Lobectomy
Multiple valve repair	Any revision aortic surgery	Multilobectomy
Pericardial resection		Pneumonectomy
Ascending aortic/aortic arch repair		Esophagectomy
Congenital heart repair		Lung decortication
Cardiac transplantation		
Cardiac reoperation		

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ASD = atrial septal defect; CABG = coronary artery bypass grafting; VSD = ventricular septal defect.

<300; ARDS, PaO_2/FIO_2 <200) in the absence of clinical signs of left atrial hypertension as the main explanation for pulmonary edema.[38] Postoperative ALI/ARDS was defined as occurring within the first 5 postoperative days. The outcome assessment was restricted to this time interval because ALI occurring after this period is unlikely to have resulted from insults encountered during the surgical course.[21] In addition, we believed the inclusion of these later cases would negatively impact the performance of the predictive model. It is noteworthy that our recent work[6] and the work of Licker *et al.*[21] both confirm that the vast majority of postoperative ALI cases occur within this early window. The outcome assessment was performed during the initial prospective investigation by an investigator (E.R.F.) who underwent a structured ALI/ARDS tutorial before reviewing patients' medical records.[6]

Statistical Analysis

Assuming an ALI incidence of 3% from our preliminary data, we calculated that a sample size of 4,000 patients would allow us to determine the sensitivity and specificity as well as the positive and negative predictive values of the model to predict ALI within 95% CI of approximately ± 0.07. Dichotomous variables are presented as counts with percentages. Continuous data are presented as median with 25–75% interquartile ranges. For univariate analyses, comparisons between the two groups were performed with a Pearson's chi-square test or Fisher exact test as appropriate for categorical variables. Continuous variables were tested with the Mann–Whitney rank-sum test.

The primary analysis consisted of determining the predictive validity of the SLIP model. Model derivation began with univariate analyses evaluating the associations between each risk factor and postoperative ALI/ARDS. Variables associated with postoperative ALI/ARDS ($P \leq 0.1$) in these univariate analyses were included in a multivariate logistic regression model. Variables with biologic plausibility and multiple existing reports suggesting a strong relationship with postoperative ALI/ARDS were also considered for inclusion in the initial multivariate model, irrespective of their statistical association with ALI/ARDS. Risk factors with significant associations with postoperative ALI in the initial multivariate analysis ($P \leq 0.05$) were included in a second and final multivariate model and were assigned SLIP points. Vascular, cardiac, and thoracic procedures were classified as low *versus* high risk based on univariate analysis as described above before inclusion of procedural characteristics into the model. SLIP points were then assigned to each predictor in the final model by multiplying the predictor's parameter estimate by a factor of 10 and rounding to the nearest integer. Recognizing that a combination of low exposure frequency and a moderate number of ALI/ARDS outcomes can reduce the likelihood of identifying significant associations with ALI/ARDS, a second model was also created including variables with existing literature supporting an association with ALI/ARDS and moderate or large effect estimates (odds ratio [OR] ≥1.5) in the initial multivariate analysis (irrespective of the presence of statistical significance). These procedures (inclusion of variables with biologic plausibility and moderate to large effect estimates, despite a lack of statistically significant association) were performed to improve the external validity and reproducibility of the scoring system.

Model discrimination was assessed by calculating the area under the receiver operating characteristic curve (AUC). Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test statistic. The threshold score, which maximizes the Youden index, [sensitivity + (specificity − 1)],[39] was determined and the corresponding positive and negative predictive values, positive and negative likelihood ratios, and their 95% CIs at this optimal cut off were calculated. To improve the functionality of the prediction model, a sensitivity analysis was performed to determine the model performance at two additional cut-off points. The first point was chosen to assist in identifying patients at risk of ALI with greater sensitivity and to improve the negative likelihood ratio. The second point was chosen to assist with the identification of patients at high risk of ALI with greater specificity and to improve the positive likelihood ratio. Using these cut points, we also developed three stratum of risk for postoperative acute lung injury: low, intermediate, and high.

Because of the absence of an external data set for model validation, a 10-fold cross-validation procedure was performed. The AUC was estimated in 10 test samples to provide an estimate of what the AUC would be if the model were used for prediction in an independent external validation sample. The AUC was estimated in place of the misclassification error rate as the anticipated future use of the model is as a prediction score rather than a dichotomous classification. The SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC) PROC LOGISTIC was used with a backwards elimination variable selection procedure in the 10-fold cross-validation. All variables with statistically significant associations with ALI in univariate analyses were considered potential predictors, but only those that had a *P* value less than 0.05 were retained in the final 10 learning models. Thus, 10 learning models were developed and applied to the 10-test samples with the AUC calculated in each test sample. This process was repeated 50 times, yielding 500 estimates of the AUC in samples that were not used to fit the model.

Results

Between November 2005 and August 2006, a total of 4,366 patients undergoing high-risk surgery were identified for inclusion in this study. Fifty-four patients were excluded from the initial study of Fernández-Pérez *et al.* (n = 4,420).[6] Thirty-two patients had rescinded research authorization for the use of their medical record in the interval between the initial study and the current investigation. Twenty-two patients were excluded due to a duration of anesthesia less than 3 h (a predefined exclusion criteria). One-hundred thirteen (2.6%;

Table 2. Baseline Characteristics and Predisposing Factors

Predictor	ALI (n = 113)	No ALI (n = 4,253)	*P* Value
Demographics			
Age, median (IQR), yr	69 (61–77)	67 (54–75)	0.01
Age >75 yr	35 (31.0)	933 (21.9)	0.02
Sex, male	74 (65.5)	2,410 (56.7)	0.06
Procedural factors			
Cardiac surgery	68 (60.2)	1,297 (30.5)	<0.01
High risk	67 (59.3)	1,121 (26.4)	<0.01
Low risk	1 (0.9)	176 (4.1)	0.09
Aortic vascular surgery	9 (8.0)	137 (3.2)	<0.01
High risk	6 (5.3)	21 (0.5)	<0.01
Low risk	3 (2.7)	116 (2.7)	1.0
Thoracic surgery	19 (16.8)	627 (14.7)	0.54
High risk	14 (12.4)	228 (5.4)	<0.01
Low risk	5 (4.4)	399 (9.4)	0.07
Abdominal	4 (3.5)	373 (8.8)	0.05
Spine	2 (1.8)	437 (10.3)	<0.01
Orthopedic	2 (1.8)	210 (4.9)	0.18
Neurologic	2 (1.8)	335 (7.9)	0.02
Other	7 (6.2)	835 (19.6)	<0.01
Comorbidities			
Diabetes mellitus	34 (30.1)	703 (16.5)	<0.01
COPD	24 (21.2)	317 (7.5)	<0.01
Restrictive lung disease	9 (8.0)	173 (4.1)	0.04
GERD	62 (54.9)	1,578 (37.1)	<0.01
Cirrhosis	4 (3.5)	86 (2.0)	0.30
Modifying factors			
Smoking*			
Never	35 (31.0)	1,761 (42.3)	0.02
Former	56 (49.6)	1,862 (44.7)	0.30
Active	22 (19.5)	545 (13.1)	0.05
Alcohol abuse*	43 (38.4)	534 (12.7)	<0.01
BMI, median (IQR)	28 (25–33)	28 (25–32)	0.75
Obesity*	21 (33.9)	1,015 (36.5)	0.68
Recent chemotherapy†	5 (4.4)	48 (1.1)	0.01
Amiodarone	17 (15.0)	179 (4.2)	<0.01
Statins	59 (52.2)	1,484 (34.9)	<0.01
ACE-I/ARB	50 (44.3)	1,625 (38.2)	0.19

All data presented as No. (%) unless otherwise specified.

* Total sample size as follows: smoking, n= 4,281 (ALI = 113, No ALI = 4,168); alcohol abuse, n = 4,328 (ALI = 112, No ALI = 4,216); obesity (BMI >30 kg/m^2), n = 2,847 (ALI = 62, No ALI = 2,785). † Within 6 months of the surgical procedure; only in patients undergoing esophagectomy or lung resection for cancer.

ACE-I = angiotensin-converting enzyme inhibitor; ALI = acute lung injury; ARB = angiotensin II receptor blocker; BMI = body mass index; COPD = chronic obstructive lung disease; GERD = gastroesophageal reflux disease; IQR = interquartile range (25–75%).

95% CI, 2.2–3.1%) patients had early postoperative ALI, of whom 55 met criteria for ARDS. Mortality was significantly higher among those who had ALI/ARDS when compared with those without ALI/ARDS (14.2 *vs.* 1.2%; OR 13.5; 95% CI, 7.48–24.7; $P < 0.01$) as was the median length of hospital stay (11 days [25–75% interquartile range, 7–20 days] *vs.* 5 days [25–75% interquartile range, 4–8 days]; $P < 0.01$). Baseline characteristics and ALI predictors are presented in table 2.

Numerous baseline characteristics and ALI predisposing conditions differed in univariate analyses among those who did *versus* those who did not have early postoperative ALI/ARDS. Specifically, patients with ALI/ARDS were older and more likely to undergo high-risk cardiac, vascular, or thoracic surgery. In contrast, abdominal, spine, orthopedic (hip and knee replacements), and neurologic procedures were associated with a lower incidence of early postoperative ALI/ARDS. The frequency of ALI/ARDS by surgical procedure is listed in figure 1. High-risk vascular surgery was associated with the greatest risk of ALI/ARDS (22%; 95% CI, 11–41%), whereas spine surgery was associated with a much lower frequency of postoperative ALI/ARDS (0.5%; 95% CI, 0.1–1.6%). Patients who developed ALI were also more likely to have diagnoses of diabetes mellitus, COPD, restrictive lung disease, and GERD. Smoking status, alcohol abuse, recent chemotherapy, and preoperative amiodarone and/or statin therapy were also significant predictors of postoperative ALI/ARDS. Cirrhosis, BMI, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker therapy were not significantly associated with ALI/ARDS.

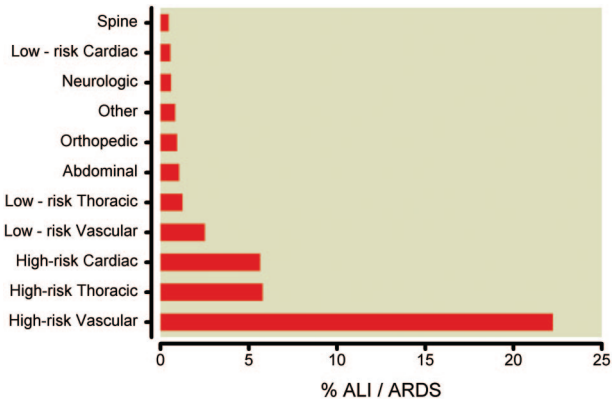

Fig. 1. Frequency of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) by surgical procedure.

Table 4. SLIP Scoring Criteria (n = 4,328)

Predictor Variables	Parameter Estimate	SLIP Points
High-risk surgical procedure		
Cardiac	1.88	19
Vascular	3.21	32
Thoracic	1.60	16
Comorbidities		
Diabetes mellitus	0.62	6
COPD	0.95	10
GERD	0.72	7
Modifying conditions		
Alcohol abuse	1.13	11

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; SLIP = surgical lung injury prediction.

SLIP points were determined based on the coefficients from multivariate logistic regression analysis as described above. The logistic regression parameter estimates and ORs for ALI risk factors included in the initial multivariate analysis are shown in table 3. The logistic regression parameter estimates and corresponding SLIP points for predictors included in the final scoring system are shown in table 4. Age, sex, low-risk vascular surgery, restrictive lung disease, tobacco use, recent chemotherapy in patients undergoing lung or esophageal resection for cancer, and preoperative amiodarone and/or statin therapy were not assigned SLIP points in the final model as there was insufficient evidence ($P > 0.05$) for an association with early postoperative ALI/ARDS in the initial multivariate logistic regression analysis. Age was evaluated in the multivariate model as a continuous variable and then separately as a dichotomous variable with a cut off of 75 years. It was not associated with postoperative ALI in either model. Low-risk vascular surgery, restrictive lung disease, recent chemotherapy in patients undergoing lung or esophageal resection for cancer, and active smoking had moderate to large effect estimates (OR ≥1.5) and have existing literature suggesting an association with postoperative ALI. Therefore, these variables were included in the secondary SLIP model (see table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A746).

SLIP scores ranged from 0 to 60 (median 7). The SLIP model distinguished patients who developed early postoper-

Table 3. Parameter Estimates for ALI Risk Predictors in a Multivariate Logistic Regression Analysis (n = 4,280)

Risk Predictor	Parameter Estimate	Odds Ratio (95% CI)	*P* Value
Demographics			
Age*	0.010	1.01 (0.99–1.03)	0.25
Sex, male	−0.071	0.93 (0.61–1.45)	0.75
Procedural factors			
High-risk cardiac	1.854	6.39 (3.87–10.87)	<0.01
High-risk vascular	3.276	26.46 (8.52–73.63)	<0.01
Low-risk vascular	0.542	1.72 (0.39–5.23)	0.39
High-risk thoracic	1.486	4.42 (1.86–9.67)	<0.01
Comorbidities			
Diabetes mellitus	0.588	1.80 (1.13–2.80)	0.01
COPD	0.761	2.14 (1.22–3.63)	<0.01
Restrictive lung disease	0.510	1.66 (0.73–3.40)	0.19
GERD	0.619	1.86 (1.23–2.82)	<0.01
Modifying conditions			
Tobacco use			
Former	0.063	1.07 (0.66–1.73)	0.79
Active	0.473	1.60 (0.86–2.95)	0.13
Alcohol abuse	1.050	2.86 (1.85–4.38)	<0.01
Recent chemotherapy†	0.667	1.95 (0.55–6.25)	0.27
Amiodarone	0.312	1.37 (0.73–2.44)	0.31
Statins	0.154	1.17 (0.77–1.78)	0.47

* Age, for each additional year. † Within 6 months of the surgical procedure; only in patients undergoing esophagectomy or lung resection for cancer.

ALI = acute lung injury; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.

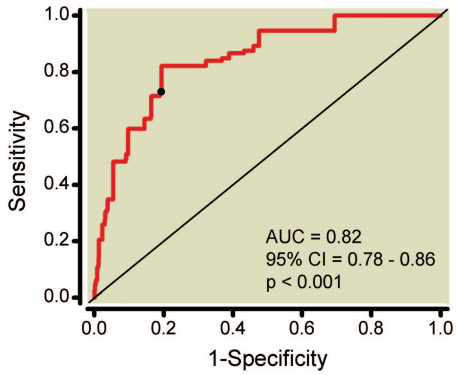

Fig. 2. Receiver operating characteristic curve for predicting early postoperative acute lung injury/acute respiratory distress syndrome with the surgical lung injury prediction model. AUC = area under the receiver operating characteristic curve. *Dot* on curve represents the optimal cut-off point that maximizes the Youden index.

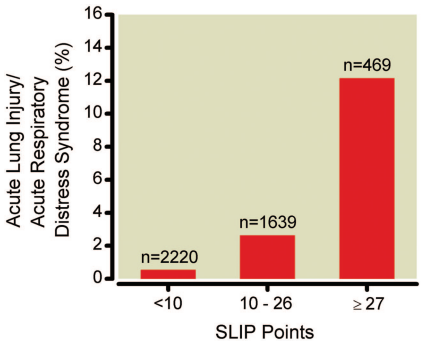

Fig. 3. Frequency of acute lung injury/acute respiratory distress syndrome based on surgical lung injury prediction (SLIP) points.

ative ALI/ARDS from those who did not with an AUC (95% CI) of 0.82 (0.78–0.86; fig. 2). The model was well calibrated with a Hosmer-Lemeshow goodness-of-fit chi-square value of 4.95 ($P = 0.55$). In the internal validation procedure, the mean ± SD AUC in the 500 learning and test samples were 0.82 ± 0.01 and 0.79 ± 0.08, respectively. Receiver operating characteristic curve analysis determined the optimal cut off for maximizing the Youden index to be 22. At this level, the positive likelihood ratio (95% CI) was determined as 3.81 (3.34, 4.34) with a negative likelihood ratio (95% CI) of 0.34 (0.25, 0.46). The associated sensitivity and specificity (both 95% CI) were 72% (63–80%) and 81% (80–82%), respectively. The sensitivity analysis evaluating the sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios at the two additional SLIP cut points are shown in table 5.

Using the two SLIP cut-point scores identified in the sensitivity analysis, we defined three groups of patients: low risk (<10 points), moderate risk (10–26 points), and high risk for postoperative ALI/ARDS (≥27 points). This scale resulted in the assignment of 51.3% of patients to the low-risk group, with an associated frequency of ALI of 0.54%; 37.9% were in the moderate-risk group, with an associated ALI frequency of 2.62%; and 10.8% of patients were in the high-risk group, with an associated ALI frequency of 12.2% (figure 3).

Discussion

In this single-center, retrospective cohort evaluation, we developed a scoring system for predicting risk of early postoperative ALI/ARDS based solely on preoperative patient characteristics and procedural factors. Using readily available data, the SLIP score identified patients at risk of early postoperative ALI before undergoing their surgical procedure. It is noteworthy that identification of patients who are at high risk for postoperative ALI before surgical procedures may afford an opportunity for the implementation of timely interventions to prevent this complication. Moreover, it could facilitate the enrollment of participants into meaningful mechanistic, prevention, and early treatment trials.

Although a number of risk-prediction models for postoperative respiratory failure have been described, all have important limitations when attempting to determine risk of ALI before a surgical procedure. Most are not specific to ALI/ARDS[1,12,13,40,41] and those looking at ALI/ARDS are isolated to specific surgical populations such as lung resection surgery[5,21,42–46] or cardiopulmonary bypass[47–49] (table 6). In addition, most have emphasized the importance of a variety of intraoperative and postoperative variables. Our predic-

Table 5. Sensitivity Analysis: SLIP Score Performance at Different Cut-off Points

	SLIP Cut-off Points		
SLIP Performance	≥10	≥22*	≥27
Prevalence of ALI/ARDS	0.03 (0.02, 0.03)	0.03 (0.02, 0.03)	0.03 (0.02, 0.03)
Sensitivity	0.89 (0.82, 0.94)	0.72 (0.63, 0.80)	0.51 (0.41, 0.60)
Specificity	0.52 (0.51, 0.54)	0.81 (0.80, 0.82)	0.90 (0.89, 0.91)
Negative predictive value	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	0.99 (0.98, 0.99)
Positive predictive value	0.05 (0.04, 0.06)	0.09 (0.07, 0.11)	0.12 (0.09, 0.16)
Positive likelihood ratio	1.87 (1.75, 2.01)	3.81 (3.34, 4.34)	5.21 (4.25, 6.38)
Negative likelihood ratio	0.20 (0.12, 0.35)	0.34 (0.25, 0.46)	0.54 (0.45, 0.66)

Data are expressed as value (95% confidence interval).

* Optimal cut-off based on the area under the receiver operating characteristic curve analysis.

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; SLIP = surgical lung injury prediction.

Table 6. Previous Studies Evaluating Incidence and Risk Factors for Postoperative ALI/ARDS

Authors, Year (Reference No.)	Surgical Population	Sample Size (% ALI)	Risk Factors
Messent *et al.*, 1992 (47)	Cardiopulmonary bypass	840 (1.3)	High intraoperative and postoperative intervention score, total volume of blood pumped during bypass (greater than 300 l), age >60 yr
Christenson *et al.*, 1996 (48)	Cardiopulmonary bypass	3,848 (1.0*)	Combined cardiac surgery, diffuse coronary artery disease, preoperative hypertension, current smoking, emergency surgery, CHF, left ventricular ejection fraction <40%, postoperative hypotension, postoperative gastrointestinal complication (*e.g.*, ischemia)
Kutlu *et al.*, 2000 (5)	Pulmonary resection	1,139 (3.9)	Age >60 yr, male, resection for cancer, extent of resection
Ruffini *et al.*, 2001 (4)	Pulmonary resection	1,221 (2.2)	Extent of resection, laterality (right > left),
Tandon *et al.*, 2001 (18)	Esophagectomy	168 (14.5)	Low BMI, history of smoking, intraoperative cardiorespiratory instability, positive fluid balance, postoperative anastomotic leak
Milot *et al.*, 2001 (49)	Cardiopulmonary bypass	3,278 (0.4*)	Previous cardiac surgery, increasing blood product administration, hemodynamic compromise
Licker *et al.*, 2003 (21)	Pulmonary resection	879 (4.2)	High intraoperative ventilatory pressure index, excessive fluid infusion, pneumonectomy, preoperative alcohol abuse, intercurrent complications
Algar *et al.*, 2003 (27)	Pneumonectomy	242 (2.5)	Predicted postoperative FEV_1, cardiac disease, COPD. operative time, laterality (right > left)
Fernández-Pérez *et al.*, 2006 (43)	Pneumonectomy	170 (8.8)	Larger intraoperative tidal volume, increasing fluid administration
Alam *et al.*, 2007 (44)	Pulmonary resection	1,428 (3.1)	Decreasing postoperative predicted lung function, increasing perioperative fluid administration
Fernández-Pérez *et al.*, 2009 (6)	Elective high-risk surgery	4,420 (3.0)	Smoking, COPD, diabetes mellitus, duration of surgery, hypotension, transfusion, positive fluid balance, peak airway pressure
Sen *et al.*, 2010 (46)	Pulmonary resection	143 (7.5)	Alcohol abuse, ASA score, resection type, fresh frozen plasma

* Acute respiratory distress syndrome (ARDS) only.

ALI = acute lung injury; ASA = American Society of Anesthesiologists Physical Status Classification System; BMI = body mass index; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second.

tion model is specifically restricted to factors identifiable preoperatively and it allows clinicians to identify patients at high risk for postoperative ALI before surgical procedures.

Existing literature supports associations between high-risk surgical procedures such as cardiac, vascular, and thoracic surgery[6,15,21,43] as well as alcohol abuse[6,17,19–21] with ALI/ARDS. In addition to these previously identified associations, we have also confirmed and/or identified a number of less well-described predictors of postoperative ALI. Specifically, we noted COPD, diabetes mellitus, and GERD to be associated with early postoperative ALI. These associations remained significant after multivariate adjustment (table 3). Although previous investigations have recognized COPD as a risk factor for ALI after lung resection surgery,[27] its association with ALI in more diverse surgical populations is a novel finding. In contrast with much of the published literature,[6,24–26] we also noted diabetes mellitus as being associated with risk for ALI. It is noteworthy that the evidence suggesting a protective role for diabetes mellitus in patients at risk of ALI appears most significant in the setting of sepsis.[20,26,50] Moreover, a suggestion of increased risk of early postoperative ALI in patients with diabetes mellitus has been previously described.[21] To our knowledge, the association between GERD and postoperative ALI has not been well described. Although we hypothesize that this increased risk may be the result perioperative microaspiration, our study was not designed to address this issue and thus cannot definitively characterize this association.

In contrast, we did not confirm previous reports of associations between active smoking,[6,17,18] recent chemotherapy in patients undergoing lung resection or esophagectomy for cancer,[20,23] restrictive lung disease,[23,28,29] or amiodarone[30,31] with ALI. Considering the relatively infrequent occurrence of these variables (1.5–13%), we believe the lack of an association between these variables and postoperative ALI is largely the result of inadequate power. As an example, 567

patients were actively smoking at the time of their surgical procedures. To identify an OR of 1.5 when assessing the association between active smoking and postoperative ALI (assuming an ALI frequency of 2.6% in nonsmoking group), a sample of 1,661 active smokers and 12,783 nonsmokers would be required to obtain a β level of 0.20 (two-sided α of 0.05). Recognizing the potential importance of these previously identified risk factors, a second SLIP model was generated (see table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A746). The performance of this secondary model was similar to the more parsimonious primary model with an AUC (95% CI) of 0.82 (0.79–0.86) and a Hosmer-Lemeshow goodness-of-fit chi-square value of 3.63 ($P = 0.73$). Regarding statins, our univariate evaluation suggested risk for early postoperative ALI with statin therapy. However, this association was lost when adjusting for additional, potentially confounding factors (table 3). Currently, the evidence addressing this potential association is conflicting.[32,51]

Although the modest overall performance of the SLIP score may limit its usefulness in clinical practice, its potential utility in identifying high-risk patients for participation in prospective investigations of ALI/ARDS prevention persists, particularly if the higher cut-off value is chosen. Moreover, it may still be clinically useful for future low-cost, low-risk ALI/ARDS-prevention interventions. The addition of intraoperative and early postoperative variables such as transfusion, ventilator management, and duration of cardiopulmonary bypass or aortic cross clamp placement would likely increase the accuracy of the prediction model. However, the primary aim of the proposed scoring system was to identify patients at risk of ALI before their surgical procedure for potential inclusion in prospective mechanistic, prevention, and early treatment trials. By identifying patients at higher risk, the SLIP score can greatly enhance the feasibility of such future investigations. As an example, the sample size requirements for a clinical trial of postoperative ALI/ARDS prevention for an effective intervention that was shown in preclinical studies to halve the risk of ALI/ARDS development is much lower when using the SLIP score with a cut off of 27 points (830 total, 415 per group) than it would be without the SLIP score (3,662 total, 1,831 per group).

In addition to the usual limitations of a retrospective study, such as the potential for bias and confounding, this study has other important limitations as well. The limited number of ALI/ARDS cases (n = 113) and the low frequency of some potentially important risk factors may have masked important associations with ALI/ARDS. Specific examples include chemotherapy, restrictive lung disease, amiodarone, and smoking. We attempted to mitigate this possibility by performing a secondary analysis including factors with existing evidence for an association with postoperative ALI/ARDS and moderate to large effect estimates in the current study (ORs $\geq$1.5), despite a lack of significance in the initial multivariate model. It should be emphasized that additional predictors of ALI may still have been missed despite this secondary analysis.

An additional limitation is the heterogeneity of the study population. This heterogeneity is at least partially responsible for the study's suboptimal sensitivity (72%; 95% CI, 63–80%) and specificity (81%; 95% CI, 80–82%) at the optimal cut point of the SLIP model. Improved model performance may be seen in more homogeneous surgical populations or with more specific characterization of the surgical procedures. Indeed, previous investigations have focused on specific surgical specialties such as cardiac[47–49] or thoracic[4,5,18,21,27,44,46] surgery. However, restricting the study to a specific surgical population would necessarily preclude the screening of high-risk patients undergoing other types of surgery. Because it is important to identify patients at high risk for ALI in these surgical populations as well, we aimed to develop a risk-scoring system that would be more broadly applicable. We further recognize that the discriminative power of the SLIP score might be improved with additional variables and more complex modeling strategies. However, our primary aim was to create a model that could be used for the preoperative identification of high-risk participants for future ALI prevention and mechanistic studies. Well-designed investigations in these time-sensitive studies require very efficient risk-prediction strategies. As complex scoring systems entail time-consuming calculations, we elected to focus on creating a more parsimonious risk-prediction model. In addition, the utility of increasing the granularity of procedural detail beyond what has been described is unclear and would not appear to be supported with our moderate number of ALI/ARDS outcomes. We also acknowledge the selection bias that results from our exclusion of patients undergoing lower risk procedures lasting less than 3 h. As a result of their exclusion, we cannot be sure that our model will generalize to these low-risk populations.

A third limitation is our lack of consideration for intraoperative and postoperative variables that may be associated with risk for postoperative ALI. Factors such as infection,[52] ventilator management,[43,53] fluid[21,54] and transfusion strategies,[55] and choice of volatile anesthetic[56] may potentially impact the development and/or progression of ALI in the postoperative period. Although the addition of such variables would be expected to improve the overall performance of our prediction model, their inclusion would preclude the use of this model as intended (preoperative risk assessment), prohibiting the identification of patients at high risk of ALI before surgical procedures. In turn, we believe this delayed recognition could lead to missed opportunities for ALI prevention strategies and adequately detailed studies of ALI mechanisms.

Another limitation of this study is the single-center, tertiary care nature of the institution providing care to the study population. This limitation raises concern for referral and institution-specific bias as well as overall generalizability.

The final and most important limitation of this investigation is the lack of a validation cohort. To address this limitation, we performed an internal validation of the SLIP model using the 10-fold cross-validation technique. Only slight shrinkage in model performance was noted in this validation procedure with a mean ± SD AUC of 0.79 ± 0.08.

In conclusion, we have developed a SLIP score to predict risk of early postoperative ALI/ARDS before operative procedures. If validated in an external data set, this score will assist clinicians in estimating surgical patients' risk of early postoperative ALI/ARDS. Moreover, by identifying patients who are at high risk of ALI before their surgical procedures, the SLIP model may facilitate the performance of prospective investigations of postoperative ALI pathogenesis, prevention, and early treatment.

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