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Early Identification of Patients at Risk of Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a Multicenter Cohort Study

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ABSTRACT

Rationale: Accurate, early identification of patients at risk for developing acute lung injury (ALI) provides the opportunity to test and implement secondary prevention strategies.

Objectives: To determine the frequency and outcome of ALI development in patients at risk and validate a lung injury prediction score (LIPS).

Methods: In this prospective multicenter observational cohort study, predisposing conditions and risk modifiers predictive of ALI development were identified from routine clinical data available during initial evaluation. The discrimination of the model was assessed with area under receiver operating curve (AUC). The risk of death from ALI was determined after adjustment for severity of illness and predisposing conditions.

Measurements and Main results: Twenty-two hospitals enrolled 5584 patients at risk. ALI developed a median of 2 (interquartile range 1-4) days after initial evaluation in 377 (6.8%; 148 ALI-only, 229 ARDS) patients. The frequency of ALI varied according to predisposing conditions (from 3% in pancreatitis to 26% after smoke inhalation). LIPS discriminated patients who developed ALI from those who did not with an AUC of 0.80 (95%CI 0.78 to 0.82). When adjusted for severity of illness and predisposing conditions, development of ALI increased the risk of in-hospital death (OR 4.1, 95% CI 2.9-5.7).

Conclusion: ALI occurrence varies according to predisposing conditions and carries an independently poor prognosis. Using routinely available clinical data, LIPS identifies patients at high risk for ALI early in the course of their illness. This model will alert clinicians about the risk of ALI and facilitate testing and implementation of ALI prevention strategies.

INTRODUCTION

Investigations of therapeutic interventions in Acute Lung Injury (ALI) and its more severe form, Acute Respiratory Distress Syndrome (ARDS) have concentrated on patients with established disease. Proven and effective treatments at that point are limited. Indeed many treatments targeting the mechanisms identified in promising preclinical studies have failed to improve patient outcomes. Failed trials likely result, in part, from delayed recognition of patients at risk and the subsequent development of the full-blown syndrome.(1-5) Preventing the development of ALI may be more effective in improving outcomes. Unfortunately, delivering preventative ALI therapies to at-risk individuals has received little attention. Given that there are over 200,000 cases of ALI in the United States each year, any intervention decreasing the incidence of ALI will significantly impact the mortality, morbidity, and intensive care unit (ICU) utilization associated with this syndrome.(6)

A major obstacle to any early intervention or preventive studies is our inability to anticipate which patients are likely to develop ALI. Epidemiologic data suggest that ALI is rarely present at the time of initial Emergency Department (ED) evaluation or hospital admission for high risk elective surgery, but develops over a period of hours to days in a subset of at risk patients.(7-17) Recent Spanish study reported that the vast majority of patients with predisposing conditions never develop ALI making the enrollment of unselected patients into ALI prevention studies neither feasible nor efficient.(10) Moreover, a large number of patients who ultimately would not develop ALI would be subjected to the risk and expense of a prevention strategy. Recent studies have identified several “risk modifiers” which may alter the likelihood of ALI development in patients

with predisposing conditions. These include alcohol abuse,(18-21), hypoalbuminemia,(22, 23) tachypnea,(14, 20) oxygen supplementation,(24) chemotherapy,(20, 25) obesity,(26) and diabetes mellitus,(14, 27) although whether these factors are independent of one another is unclear. The lack of a validated risk model that confirms and consolidates these risk modifiers prevents the systematic determination of a population at high risk for developing ALI and is a major limitation to studies aimed at prevention or early intervention in ALI.

A recent single center observational study(28) reported an ALI prediction model, the Lung Injury Prediction Score (LIPS), incorporating the risk factors and risk modifiers present at the time of hospital admission, before ALI onset. Our aim was to validate and refine the LIPS model in at risk patients identified early in the course of their illness, and to determine the contemporary attributable mortality of this important complication. We believe that our results will facilitate the design and conduct of future ALI prevention strategies**.** Some of the results of these studies have been previously reported in the form of an abstract(29).

Materials and Methods:

Study Design

The multi-center observational cohort study was approved by the Institutional Review Board at each participating institution. Patients were enrolled prospectively in 19 hospitals and retrospectively (after hospital discharge) in 3 hospitals over a 6-month period, beginning in March 2009).

Study Patients

Consecutive adult patients admitted to academic and community acute care hospitals were eligible for the study if they presented with one or more study defined ALI risk factors including sepsis, shock, pancreatitis, pneumonia, aspiration, high risk trauma or high risk surgery. Patients were excluded if ALI criteria were present at the time of the initial assessment, if they were transferred from an outside hospital, died in the ED, or were admitted for comfort or hospice care. Hospital readmissions during the study period were also excluded.

Data Collection

Baseline characteristics, including sociodemographics, comorbidities, and clinical variables, were collected during the first 6 hours after initial ED evaluation or preoperatively at the time of hospital admission for high risk elective surgery . Predisposing conditions and ALI risk modifiers were identified *a priori* and were incorporated into the LIPS model predicting ALI development. Predisposing conditions included: high risk trauma,(14-16) high risk surgery,(11, 19, 30, 31) aspiration,(11, 14, 16, 32) sepsis,(10, 11, 15, 16) shock,(10, 33-35) pneumonia,(10, 11, 22, 36) and pancreatitis(10, 37-42). ALI risk modifiers included: alcohol abuse,(18-21), hypoalbuminemia,(22, 23), acidosis, (22) tachypnea,(14, 20) oxygen supplementation,(24) obesity,(26) chemotherapy,(20, 25) and diabetes mellitus(14, 27).

De-identified subject information was entered at each center into the secure, password-protected NIH supported web form (REDCap http://www.project-redcap.org). Electronic range checks and validation rules were utilized to eliminate erroneous data entry and artifacts in numeric values. Hospital admission logs were reviewed to minimize the possibility that patients with predisposing condition were missed. Investigators and study

coordinators at each site reviewed structured online training for the ALI assessment and the definitions of each risk factor (see electronic data supplement) prior to study initiation. Primary investigators from each site provided a written statement stating the responsibility for the quality control of data collection and entry. In the 3 hospitals that enrolled retrospectively the investigators followed the same protocol and definitions but data were collected after patient discharge.

Outcomes

The primary outcome was the development of ALI during the hospital stay. ALI was defined according to the standard American-European Consensus Conference (AECC) definition(43) as the development of acute, bilateral pulmonary infiltrates and hypoxemia (PaO_2/FIO_2 <300 - ALI, PaO_2/FIO_2 <200 - ARDS) in the absence of clinical signs of left atrial hypertension as the main explanation for pulmonary edema. Secondary outcomes included ICU and hospital mortality, and ICU and hospital length of stay.

Data analysis

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines(44) were followed in the design and reporting of this observational study. Analyses were performed by data coordinating center at the Mayo Clinic. Data were summarized as number (%) and median (IQR). Frequency of ALI was calculated per number of patients presenting with predisposing condition at the time of hospital admission. Sample size was determined prior to beginning of the study; 300 outcomes (ALI cases) were required to determine a proportion of the model (i.e. sensitivity) of 0.80 with a precision of +/- 0.04 (95%CI 0.76 to 0.84), requiring ~ 300 patients per center to reach the enrollment goal.

The primary analysis consisted of a validation of the predictive ability of the LIPS model that was previously developed and validated in a single-center population-based cohort (28), see electronic data supplement. LIPS weighting points were adjusted based on logistic regression analysis results from a training data set (a random sample of 2500 patients from the cohort). The score was derived by doubling of parameter estimates rounded to the closest 0.5 taking into consideration results from previous studies and the number of patients exposed (to prevent 'data fitting' and increase the likelihood of replicability). The scores corresponding to very high parameter estimates derived from a small number of exposures (i.e. near-drowning) were adjusted downwards. The scores corresponding to parameter estimates that grossly deviated from previously published studies (10-28) were also adjusted (for example in the derivation cohort pancreatitis was observed as "protective" but the corresponding score was neutral). The model was subsequently independently validated in the remaining patients. Model discrimination was assessed by calculating the area under the Receiver Operating Characteristic curve (AUC). Model calibration was assessed using the Hosmer and Lemeshow test statistic. The threshold score providing the best combination of sensitivity and specificity was determined by AUC analysis, and corresponding positive and negative predictive values, positive and negative likelihood ratios, and their 95% confidence intervals were calculated. A sensitivity analysis was performed to determine the model performance at different cut off points.

In secondary analyses, we compared hospital mortality and length of stay between patients at risk who developed ALI and those who did not. To determine the mortality burden due to the development of ALI, we performed a logistic regression analysis

adjusted for the propensity for ALI development (LIPS) and baseline severity of illness (Acute Physiology and Chronic Health Evaluation-APACHE II score) (45).

Additional post-hoc analyses evaluating LIPS performance in patient subgroups are presented in the electronic data supplement. These include the exclusion of patients from the 3 centers which enrolled retrospectively, restricting the analysis to patients who were admitted to the ICU and mortality prediction.

RESULTS

Between March 2009 and August 2009, twenty-two hospitals screened 5992 patients at risk for ALI; 5,584 were enrolled in the study (Figure 1), of whom 377 (6.8%) developed ALI a median of 2 days (interquartile range 1-4) after admission to the hospital. Among patients who developed ALI, a subset of 229 met ARDS criteria. The follow up to hospital discharge was complete in all patients.

The frequency of ALI varied according to predisposing condition (Figure 2) with the highest rate of ALI occurring after smoke inhalation (26%) and the lowest rate occurring in pancreatitis (3%). Baseline characteristics and predisposing conditions and ALI risk modifiers (Table 1) differed between patients who did and those who did not develop ALI. The vast majority of patients had all measurements available at the time of hospital admission except for serum albumin (n=2423) and arterial pH (n=1499). As these tests are usually ordered based on clinical suspicion, missing data were considered normal (i.e. if serum albumin or arterial pH were not measured, hypoalbuminemia and acidosis were coded as absent), similarly to APACHE score calculation (45).

The weighting of LIPS points was adjusted based on the multivariate logistic regression analysis in the derivation cohort of 2500 randomly selected patients (Table 2),

and validated in the remaining (3084) patients. LIPS model calculation worksheet and the examples how to use it are presented in the Table 3. LIPS model discriminated patients who developed ALI from those who did not with an AUC of 0.80 in the derivation cohort (95%CI 0.76 to 0.83), the validation cohort (95%CI 0.77 to 0.84), and in a combined data set (95%CI 0.78 to 0.82) composed of all study patients. The model was well calibrated in both training and testing datasets (Table E1, electronic data supplement). Once validated, remaining analyses were performed in a combined data set. LIPS scores ranged from 0 to 15.5 (median 2.5). Figure 3 plots the frequency of ALI development across the range of the score. At the cutoff point of 4 determined by ROC analysis, positive and negative likelihood ratios (95%CI) for development of ALI were 3.1 (2.9 to 3.4) and 0.4 (0.3 to 0.5), respectively, with a sensitivity of 0.69 (0.64 to 0.74), specificity of 0.78 (0.77 to 0.79).. Table 4 describes the performance of LIPS model at different cut off points in a sensitivity analysis. When comparing prognostic accuracy, LIPS outperformed the APACHE II score calculated at the time of hospital admission (AUC 0.70, 95%CI 0.66 to 0.74; p=0.01, Figure E1 electronic data supplement).

Outcome data for the study cohort are shown in Table 5. Two thirds of the entire cohort and 91% of patients with ALI were treated in the ICU. Similarly, 40% of the entire cohort and 95% of patients with ALI were mechanically ventilated. Compared to at-risk patients who did not develop ALI, those who developed lung injury had increased mortality (23% vs 4%), and increased resource utilization as reflected in longer ICU (8 vs 2 days) and hospital (15 vs 6 days) lengths of stay. When adjusted for severity of illness using APACHE II score, and predisposing conditions (LIPS), the development of ALI

markedly increased the risk of in-hospital death (OR 4.1, 95%CI 2.9-5.7) (Table E2 electronic data supplement).

Figure 4 provides a histogram of ALI/ARDS development during the entire hospital stay. The majority of patients who developed ALI/ARDS did so within the first 5 days after hospital admission. The ability of LIPS model to predict ALI/ARDS development in patients at risk was similar irrespective of the timing of ALI/ARDS onset (Figure 4, Table E3 electronic data supplement)

DISCUSSION

In this multicenter cohort study, we refined and validated a prediction model to identify patients at high risk for ALI at the time of hospital admission. The strengths of this study include the large sample size from a geographically diverse population of patients at both academic and community hospitals. Using routinely available clinical data, the LIPS identified patients at high risk for ALI early in the course of their illness and before ICU admission. The early identification and subsequent intervention to prevent or minimize secondary injury may affect disease progression and further clinical deterioration. Importantly, this model will facilitate enrollment of patients into future mechanistic studies and ALI prevention trials.

The frequency of ALI for many known risk factors such as shock, pneumonia, and sepsis found in this study is lower than rates reported in prior studies.(11, 14, 16) This is likely because the study population was assessed at the time of hospital admission as opposed to ICU admission and patients with ALI within 6 hours of admission were excluded.(10) In a recent Spanish study by Ferguson at al(10) only 7% of hospitalized patients with sepsis, 2% of patients with pancreatitis, 10% of patients with pneumonia and

15% of patients with witnessed aspiration developed ALI.(10) Indeed, the majority of patients with predisposing conditions never develop ALI and are not admitted to the ICU(10), prompting the development of LIPS model. Clinical risk prediction models are being increasingly used in both clinical practice and research to identify high-risk patients who may benefit from specific interventions.(46-53) Until now no such model has existed to predict the development of ALI.

The LIPS model has several strengths and it is both unique and easy to perform. First, it includes clinical information strongly associated with ALI in multiple studies and readily available at the time of the admission. It uses information that is clearly defined and routinely available in the medical record and as part of usual care. Second, the model identifies at risk patients early in the course of illness and before ICU admission. Finally, the model also includes a previously understudied group of patients at high risk of ALI who undergo high risk elective (cardiothoracic) surgery. In clinical practice the LIPS model may potentially be used to alert the providers to patients at risk of ALI. While no specific intervention has been shown to prevent ALI in patients at risk, applying a model such as LIPS to identify high risk patients may alert physicians to avoid specific "second hit" hospital exposures such as blood product transfusions, amiodarone, high tidal volume mechanical ventilation, and aspiration. In fact, single center studies have shown a significant decrease in the incidence of ALI in association with changes in health care delivery (17). Given the high mortality associated with the development of ALI and the significant functional and cognitive impairment experienced by survivors of ALI, prevention of ALI may improve survival and long term functional outcomes better than interventions aimed at reducing mortality after development of ALI.

While ALI development markedly increased the risk of death, the observed mortality rate of 23% is lower then previously reported. The exclusion of patients with established ALI transferred from outside facilities, the inclusion of patients who did not require invasive mechanical ventilation and secular trends in ALI prognosis provide potential explanations for the observed findings.

Our study shares the limitations inherent to clinical research studies in ALI such as reliability of portable chest X-ray interpretation (particularly in obese patients) or the consistency in exclusion of left atrial hypertension as the principal cause of pulmonary edema. Mandatory structured training in ALI assessment and the site PIs responsibility for quality control to some extent mitigate these concerns. The vast majority of patients was enrolled prospectively ensuring close follow-up for ALI development and reducing the risk of misclassification from medical record review. When the data from three centers enrolling retrospectively were excluded, the performance of LIPS model was similar (AUC 0.81)

Modest overall performance of the LIPS model with relatively low positive predictive value satisfies the requirements for clinical trial enrollment but limits its usefulness in clinical practice. A negative predictive value of LIPS model is excellent, efficiently excluding patients with risk factors who do not have high risk of ALI. With a relatively low positive predictive value the model may still be clinically useful if the preventive interventions are low-cost and low-risk (for example, limiting blood transfusions, limiting alveolar stretch). Depending on specific therapeutic decisions, clinicians may decide to use higher thresholds of the score (Figure 3). The model could be further improved by the use of novel analytic methods such as neural network, adding additional variables,(54)

measuring specific risk modifiers in all patients (serum albumin, pH), or using specifically designed questionnaires (for example, to precisely ascertain alcohol abuse). Unfortunately, adding sophisticated technology or additional data collection might also complicate the simplicity of using this tool in real practice environments, particularly in the ED. Addition of health care delivery factors such as fluid and transfusion management, duration of cardiopulmonary bypass, or mechanical ventilation would certainly increase the accuracy of the prediction model. However, the principal purpose of the proposed scoring system is to identify patients as early as possible so that the health care delivery factors could be modified with an ultimate goal of ALI prevention. Pre planned ancillary studies are ongoing to explore potential differences in development of ALI in different institutions. Our inclusion criteria required the presence of at least one ALI risk factor at the time of hospital admission, potentially missing the patients who develop a risk factor later in the hospital stay. However, in a recent population-based study <1% of patients admitted to the hospital without any of ALI risk factors actually develop ALI (28). Finally, the screening was performed daily, precluding timing ALI onset more precisely. It is possible that a minority of the patients identified at high risk were already on the way to developing full-blown ALI at the time of enrollment. We do believe however that earlier identification of such patients can limit the progression of ALI and improve patient outcomes by alerting providers to limit second-hit exposures.

Despite these limitations, the LIPS model discriminates efficiently between those patients who have a low risk of developing ALI while maintaining an appropriate sensitivity for a screening tool (negative predictive value of 0.97). By identifying the patients at higher risk of ALI the LIPS score may greatly enhance the feasibility of

mechanistic studies and ALI prevention trials. For example the sample size requirements for a clinical trial of ALI/ARDS prevention of an effective intervention that was shown in preclinical studies to halve the risk of ALI/ARDS development (relative risk reduction of 50%) is much higher without (1778 total, 889 per group) than with (564 total, 282 per group) selecting high risk patients based on LIPS model.

In conclusion, our study is one of the largest available multicenter studies examining the clinical predictors for development of ALI in a diverse group of patients. This allowed us to develop and validate a simple tool to screen for patients at risk for ALI at the time of initial Emergency Department assessment or hospital admission for high-risk elective surgery. Given the fact that the majority of patients with predisposing conditions never develop ALI and are never admitted to the ICU, utilizing our prediction model will facilitate the identification of patients who can benefit from interventions to prevent disease progression, and also aid the timely and efficient enrollment of patients into future ALI prevention trials.

REFERENCES

1. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. The ARDS Network. *JAMA.* 2000;283(15):1995-2002.

2. Jepsen S, Herlevsen P, Knudsen P, Bud MI, Klausen NO. Antioxidant treatment with n-acetylcyesteine during adult respiratory distress syndrome: a prospective randomized placebo controlled study. *Crit Care Med.* 1992;20(7):819-923.

3. Meade MO, Jacka MJ, Cook DJ, Dodek P, Griffith L, Guyatt GH. Survey of interventions for the prevention and treatment of acute respiratory distress syndrome. *Crit Care Med.* 2004;32(4):946-954.

4. The ARDS Clinical Trials Network. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. *Crit Care Med.* 2002;30(1):1-6.

5. Zeiher BG, Artigas A, Vincent JL, et al. Neutrophil elastase inhibition in acute lung injury: Results of the STRIVE study. *Crit Care Med.* 2004;32(8):1695-1702.

6. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29(7):1303-1310.

7. Fernandez-Perez ER, Yilmaz M, Jenad H, et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. *Chest.* 2008;133(5):1113-1119.

8. Gajic O, Moore SB. Transfusion-related acute lung injury. *Mayo Clin Proc.* 2005;80(6):766-770.

9. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med.* 2007;176(9):886-91.

10. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. *Crit Care.* 2007;11(5):R96.

11. Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med.* 1983;98(5 Pt 1):593-597.

12. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med.* 2004;32(9):1817-1824.

13. Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? *Crit Care Med.* 2006;34(5 Suppl):S170-173.

14. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005;33(6):1191-1198.

15. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;151(2 Pt 1):293-301.

16. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg.* 1982;144(1):124-130.

17. Yilmaz M, Keegan MT, Iscimen R, et al. Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med.* 2007;35(7):1660-1666.

18. Moss M, Bucher B, Moore FA, Moore EE, Parsons PE. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA.* 1996;275(1):50-54.

19. Fernández-Pérez ER, Sprung J, Afessa B, et al. Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case-control study. *Thorax.* 2009;64(2):121-127.

20. Iscimen R, Cartin-Ceba R, Yilmaz M, et al. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. *Crit Care Med.* 2008;36(5):1518-1522.

21. Iribarren C, Jacobs DR Jr, Sidney S, Gross MD, Eisner MD. Cigarette smoking, alcohol consumption, and risk of ARDS: A 15-year cohort study in a managed care setting. *Chest.* 2000;117(1):163-168.

22. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005;33(6):1191-1198.

23. Mangialardi RJ, Martin GS, Bernard GR, et al. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med.* 2000;28(9):3137-3145.

24. Levitt JE, Bedi H, Calfee CS, Gould MK, Matthay MA. Identification of early acute lung injury at initial evaluation in an acute care setting prior to the onset of respiratory failure. *Chest.* 2009;135(4):936-943.

25. Naito Y, Tsuchiya S, Ishihara S, et al. Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. *Am J Clin Oncol.* 2008;31(4):340-344.

26. Gong MN, Bajwa E, Thompson BT, Christiani DC. Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax.* 2010;65(1):44-50.

27. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. *Crit Care Med.* 2000;28(7):2187-2192.

28. Trillo Alvarez C, Cartin-Ceba R, Kojicic M et al. Acute Lung Injury Prediction Score: Derivation and Validation in a Population Based Sample. *Eur Respir J* 2010

29. Gajic O, Dabbagh, PK Park et al. Towards Prevention of Acute Lung Injury: Identification of Patients at Risk at the Time of Hospital Admission. *Am J Respir Crit Care Med 2010; A1101*

30. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Ann Surg.* 2000;232(2):242-253.

31. Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med.* 2001;135(10):847-857.

32. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med.* 2001;344(9):665-671.

33. Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27-28 April 2006. *Intensive Care Med.* 2007;33(4):575-590.

34. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.

35. Gutierrez G, Reines HD, Wulf-Gutierrez ME. Clinical review: hemorrhagic shock. *Crit Care.* 2004;8(5):373-381.

36. Hudson LD, Steinberg KP. Epidemiology of acute lung injury and ARDS. *Chest.* 1999;116(1 Suppl):74S-82S.

37. Napolitano LM. Pulmonary consequences of acute pancreatitis: critical role of the neutrophil. *Crit Care Med.* 2002;30(9):2158-2159.

38. Pastor CM, Matthay MA, Frossard JL. Pancreatitis-associated acute lung injury: new insights. *Chest.* 2003;124(6):2341-2351.

39. Matthay MA, Zimmerman GA, Esmon C, et al. Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. *Am J Respir Crit Care Med.* 2003;167(7):1027-1035.

40. Lankisch PG, Rahlf G, Koop H. Pulmonary complications in fatal acute hemorrhagic pancreatitis. *Dig Dis Sci.* 1983;28(2):110-116.

41. Renner IG, Savage WT 3rd, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci.* 1985;30(10):1005-1018.

42. Steer ML. Relationship between pancreatitis and lung diseases. *Respir Physiol.* 2001;128(1):13-16.

43. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* Mar 1994;149(3 Pt 1):818-824.

44. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med.* 2007;147(8):573-577.

45. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med.* 1985;13(10):818-829.

46. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997;336(4):243-250.

47. Buising KL, Thursky KA, Black JF, et al. A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. *Thorax.* 2006;61(5):419-424.

48. Buising KL, Thursky KA, Black JF, et al. Identifying severe community-acquired pneumonia in the emergency department: a simple clinical prediction tool. *Emerg Med Australas.* 2007;19(5):418-426.

49. España PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med.* 2006;174(11):1249-1256.

50. Espana Yandiola PP, Capelastegui A, Quintana JM, et al. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. *Chest.* 2009;135(6):1572-1579.

51. Ewig S, de Roux A, Bauer T, et al. Validation of predictive rules and indices of severity for community acquired pneumonia. *Thorax.* 2004;59(5):421-427.

52. Leroy O, Georges H, Beuscart C, et al. Severe community-acquired pneumonia in ICUs: prospective validation of a prognostic score. *Intensive Care Med.* 1996;22(12):1307-1314.

53. Liapikou A, Ferrer M, Polverino E, et al. Severe community-acquired pneumonia: validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to predict an intensive care unit admission. *Clin Infect Dis.* 2009;48(4):377-385.

54. Zhai R, Sheu CC, Su L, et al. Serum bilirubin levels on ICU admission are associated with ARDS development and mortality in sepsis. *Thorax.* 2009;64(9):784-790.

Figure legends:

Figure 1. Outline of the screening protocol and case ascertainment

ED emergency department; ALI acute lung injury; ARDS acute respiratory distress syndrome

Figure 2. Frequency of ALI/ARDS development according to predisposing conditions.

The figure depicts the frequency of ALI/ARDS development in subsets of patients with different risk factors. Since the risk factors are not mutually exclusive, the patients who presented with more than one risk factor maybe counted more than once. ALI – acute lung injury; ARDS – acute respiratory distress syndrome

Figure 3. Frequency of ALI/ARDS development according to LIPS value.

The figure depicts the frequency of ALI/ARDS development with different LIPS values. N denotes number of patients in the study who had particular LIPS value. ALI – acute lung injury; ARDS – acute respiratory distress syndrome; LIPS – lung injury prediction score

Figure 4. Timing of ALI/ARDS development during hospital stay.

LIPS performance was similar in different subgroup analyses: i.e. exclusion of patients who developed ALI/ARDS during the first 24 hours (6-24 hours) or after 5 days were excluded (full lines); exclusion of patients who developed ALI/ARDS during the first 48 hours (dashed line). The day of admission is marked as “day 0” and the second day as “day 1”. The dashed line is at the end of “day1” (48hours).

Table 1. Patient Demographics and Predisposing Conditions

Variable	Total (n=5584)	No ALI (n=5207)	ALI (n=377)	p-value
Demographics				
Median age (Q1, Q3)	57.0 (43.0, 70.0)	57.0 (43.0, 70.0)	57.0 (43.0, 69.0)	0.30
Male, no. (%)	3152 (57%)	2912 (56%)	240 (65%)	0.001
Caucasian, no. (%), n=5426	3419 (63%)	3197 (63%)	222 (60%)	0.20
Admission source, no. (%) n=5512				<0.001
Home	4447 (81%)	4128 (82%)	258 (71%)	
Nursing facility	346 (6%)	320 (6%)	17 (5%)	
Outside ED	476 (9%)	414 (8%)	48 (13%)	
other	243 (4%)	199 (4%)	42 (12%)	
APACHE II (Q1, Q3)	9 (5 to 14)	8 (5 to 13)	13 (8 to 18)	<0.001
Predisposing conditions				
Shock	403 (7%)	331 (6%)	72 (19%)	<0.001
Aspiration	212 (4%)	177 (3%)	35 (9%)	<0.001
Sepsis	1815 (33%)	1691 (32%)	124 (33%)	0.87
Pancreatitis	325 (6%)	316 (6%)	9 (2%)	0.003
Pneumonia	1234 (22%)	1132 (22%)	102 (27%)	0.016
High risk surgery				
Thoracic (noncardiac)	175 (3%)	168 (3%)	7 (2%)	0.14
Orthopedic spine	486 (9%)	470 (9%)	16 (4%)	0.001
Acute abdomen	295 (5%)	268 (5%)	27 (7%)	0.09
Cardiac surgery	541 (10%)	486 (9%)	55 (15%)	<0.001
Aortic vascular	127 (2%)	106 (2%)	21 (6%)	<0.001
High risk trauma				
Traumatic brain injury	495 (9%)	450 (9%)	45 (12%)	0.030
Smoke inhalation	27 (0%)	20 (0%)	7 (1%)	<0.001
Near drowning	3 (0%)	2 (0%)	1 (0%)	0.19
Lung contusion	190 (3%)	163 (3%)	27 (7%)	<0.001
Multiple fractures	332 (6%)	306 (6%)	26 (7%)	0.42
Risk Modifiers				
Alcohol abuse (n=4827)	471 (10%)	289 (7%)	44 (9%)	0.028
Obesity (n=4686)	1408 (30%)	1284 (30%)	124 (37%)	0.003
Chemotherapy	173 (3%)	159 (3%)	14 (4%)	0.48
Diabetes mellitus	1295 (23%)	1221 (23%)	74 (20%)	0.13
Smoking (n=5194)				0.07
None	2606 (50%)	2447 (50%)	159 (46%)	
Former	1252 (24%)	1172 (24%)	80 (23%)	
Active	1337 (26%)	1239 (25%)	107 (31%)	
Emergency surgery	339 (6%)	282 (5%)	57 (15%)	<0.001
Respiratory rate (n=5239), median (Q1,Q3)	20.0 (18.0, 22.0)	20.0 (18.0, 22.0)	22.0 (18.0, 26.0)	<0.001
Tachypnea (RR >30/min, n=5239), no. (%)	324 (6%)	269 (5%)	55 (16%)	<0.001
SpO_2 (n=5406), median (Q1, Q3)	97.0 (95.0, 99.0)	97.0 (95.0, 99.0)	96.0 (92.0, 98.0)	<0.001
FiO_2 (n=4796), median (Q1, Q3)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.4 (0.2, 1.0)	<0.001
FiO_2 >0.35 (n=4796), no. (%)	1084 (23%)	899 (20%)	185 (54%)	<0.001
Albumin (n=2423), median (Q1, Q3)	3.6 (3.0, 4.1)	3.6 (3.1, 4.1)	3.3 (2.5, 3.9)	<0.001
Hypoalbuminemia (n=2423), no. (%)	1027 (18%)	914 (18%)	113 (30%)	<0.001
pH (n=1499), median (Q1, Q3)	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	7.3 (7.3, 7.4)	<0.001
Acidosis (pH <7.35), no. (%)	622 (11%)	491 (9%)	131 (35%)	<0.001

Table 2. Predictors of ALI Development: Parameter Estimates from a Multivariate Analysis in a Training Set, all Patients were Included in the Analyses with Missing Data Considered as Normal. To simplify the calculation non-significant variables with minimal or no effect size were removed (gender, smoking and pancreatitis)

	Logistic regression coefficient	(95% CI)		p-value
Predisposing Conditions				
Shock	0.77	0.19	1.32	0.008
Aspiration	0.79	0.07	1.45	0.024
Sepsis	0.37	-0.13	0.87	0.139
Pancreatitis	-1.07	-3.96	0.51	0.299
Pneumonia	0.83	0.33	1.34	0.001
High risk surgery*				
Thoracic (noncardiac)	-0.14	-2.00	1.15	0.896
Orthopedic spine	0.75	-0.11	1.53	0.071
Acute abdomen	0.93	0.06	1.72	0.028
Cardiac	1.32	0.67	1.96	<.001
Aortic vascular	1.78	0.93	2.56	<.001
High risk trauma				
Traumatic brain injury	1.29	0.67	1.91	<.001
Smoke inhalation	0.93	-0.21	1.41	0.438
Near drowning	1.68	-2.74	6.00	0.498
Lung contusion	0.40	-0.48	1.21	0.355
Multiple fractures	0.64	-0.21	1.41	0.117
Risk modifiers				
Male gender	0.02	-0.34	0.39	0.905
Alcohol abuse	0.51	-0.08	1.07	0.080
Obesity (BMI >30)	0.56	0.18	0.93	0.004
Chemotherapy	0.46	-0.54	1.29	0.314
Diabetes mellitus*	-0.59	-1.40	0.15	0.135
Smoking	0.06	-0.29	0.40	0.403
Emergency surgery	1.13	0.47	1.77	<0.01
Tachypnea (RR >30/min)	0.69	0.11	1.25	0.017
SpO2 <95%	0.35	-0.04	0.73	0.078
FiO_2 >0.35 (>4 L/min)	1.02	0.62	1.41	<.001
Hypoalbuminemia	0.46	0.04	0.87	0.029
Acidosis (pH <7.35)	0.55	0.09	1.00	0.017

*Only if sepsis

Table 3 LIPS Score calculation worksheet

Predisposing Conditions	**LIPS Points**	**Examples**
Shock	2	i. Patient with history of alcohol abuse with septic shock from pneumonia requiring FIO2>0.35 in the emergency room:
Aspiration	2	
Sepsis	1	
Pneumonia	1.5	
High risk surgery*		Sepsis + shock + pneumonia + alcohol abuse + FIO2>0.35
Orthopedic spine	1	
Acute abdomen	2	
Cardiac	2.5	1 + 2 + 1.5 + 1 + 2 = 7.5
Aortic vascular	3.5	
High risk trauma		ii. Motor vehicle accident with traumatic brain injury, lung contusion and shock requiring FiO_2 >0.35
Traumatic brain injury	2	
Smoke inhalation	2	
Near drowning	2	
Lung contusion	1.5	
Multiple fractures	1.5	Traumatic brain injury + lung contusion + shock + FiO_2 >0.35
Risk modifiers		2 + 1.5 + 2 + 2 = 7.5
Alcohol abuse	1	
Obesity (BMI >30)	1	iii. Patient with history of diabetes mellitus and urosepsis with shock
Hypoalbuminemia	1	
Chemotherapy	1	
FiO_2 >0.35 (>4 L/min)	2	Sepsis + shock + Diabetes
Tachypnea (RR >30)	1.5	
SpO2 <95%	1	1 + 2 - 1 = 2
Acidosis (pH <7.35)	1.5	
Diabetes mellitus**	-1	

*Add 1.5 points if emergency surgery.
**Only if sepsis.

Table 4. Sensitivity analysis: LIPS performance at different cut off points

	LIPS Cut Off Points		
LIPS Performance	>4*	>3	>5
Prevalence of ALI/ARDS (95% CI)	0.07 (0.06 to 0.07)	0.07 (0.06 to 0.07)	0.07 (0.06 to 0.07)
Sensitivity (95% CI)	0.69 (0.64 to 0.74)	0.83 (0.79 to 0.87)	0.53 (0.48 to 0.58)
Specificity (95% CI)	0.78 (0.77 to 0.79)	0.62 (0.61 to 0.64)	0.87 (0.86 to 0.88)
Negative predictive value	0.97 (0.97 to 0.98)	0.98 (0.98 to 0.99)	0.96 (0.96 to 0.97)
Positive predictive value	0.18 (0.16 to 0.20)	0.14 (0.13 to 0.15)	0.23 (0.20 to 0.26)
Likelihood ratio (+)(95% CI)	3.10 (2.85 to 3.37)	2.22 (2.09 to 2.35)	4.12 (3.66 to 4.64)
Likelihood ratio (-)(95% CI)	0.40 (0.34 to 0.46)	0.27 (0.21 to 0.34)	0.54 (0.48 to 0.60)

*Optimal cut point based on the AUC analysis.
AUC - Area under the curve.
LIPS - Lung injury prediction score.
ALI/ARDS - Acute lung injury/acute respiratory distress syndrome.

Table 5. Hospital Course and Outcome.

Variable	Total (n=5584)	No ALI (n=5207)	ALI (n=377)	p-value
Hospital Course and Outcome				
ICU admission, no. (%)	3262 (58%)	2918 (56%)	344 (91%)	<0.001
ICU length of stay, median (Q1, Q3)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	8.0 (4.0, 16.0)	<0.001
Mechanical ventilation	2171 (40%)	1814 (36%)	357 (95%)	<0.001
Invasive, no. (%)	1856 (34%)	1519 (30%)	337 (90%)	<0.001
Non-invasive, no. (%)	534 (10%)	433 (9%)	101 (29%)	<0.001
Both, no. (%)	219 (4%)	134 (3%	81 (25%)	<0.001
Duration of mechanical ventilation				
Invasive, median (Q1, Q3)	1.0 (1.0, 4.0)	1.0 (1.0, 3.0)	6.0 (2.0, 14.0)	<0.001
Non-invasive, median (Q1, Q3)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	3.0 (1.0, 6.0)	0.15
Vasopressors use, no. (%)	1061 (19%)	909 (17%)	152 (40%)	<0.001
Acute hemodialysis, no. (%)	172 (3%)	135 (3%)	37 (10%)	<0.001
Hospital length of stay, median (Q1, Q3)	6.0 (4.0, 10.0)	6.0 (3.0, 9.0)	15.0 (8.0, 24.0)	<0.001
ICU mortality, no. (%)	207 (4%)	130 (2%)	77 (20%)	<0.001
Hospital mortality, no. (%)	286 (5%)	199 (4%)	87 (23%)	<0.001

Figure 1. Outline of the screening protocol and case ascertainment.

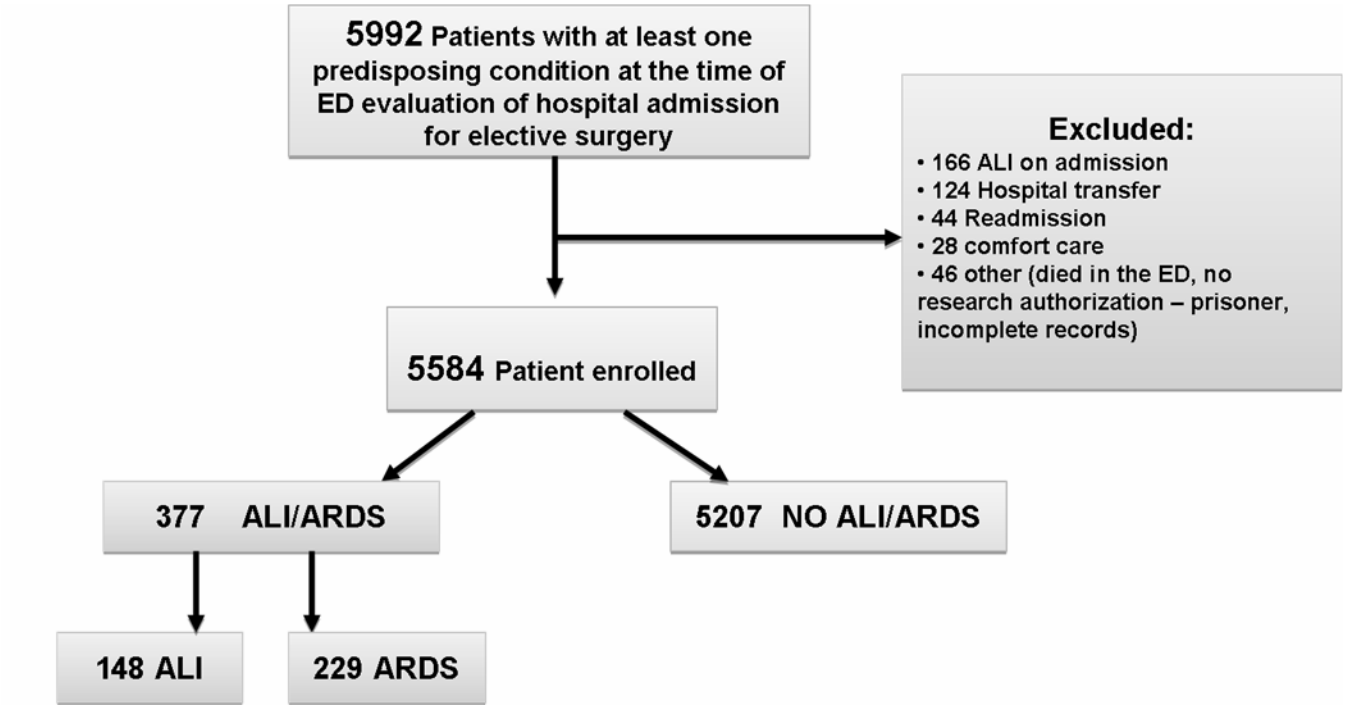


Figure 2. Frequency of ALI/ARDS development according to predisposing conditions.

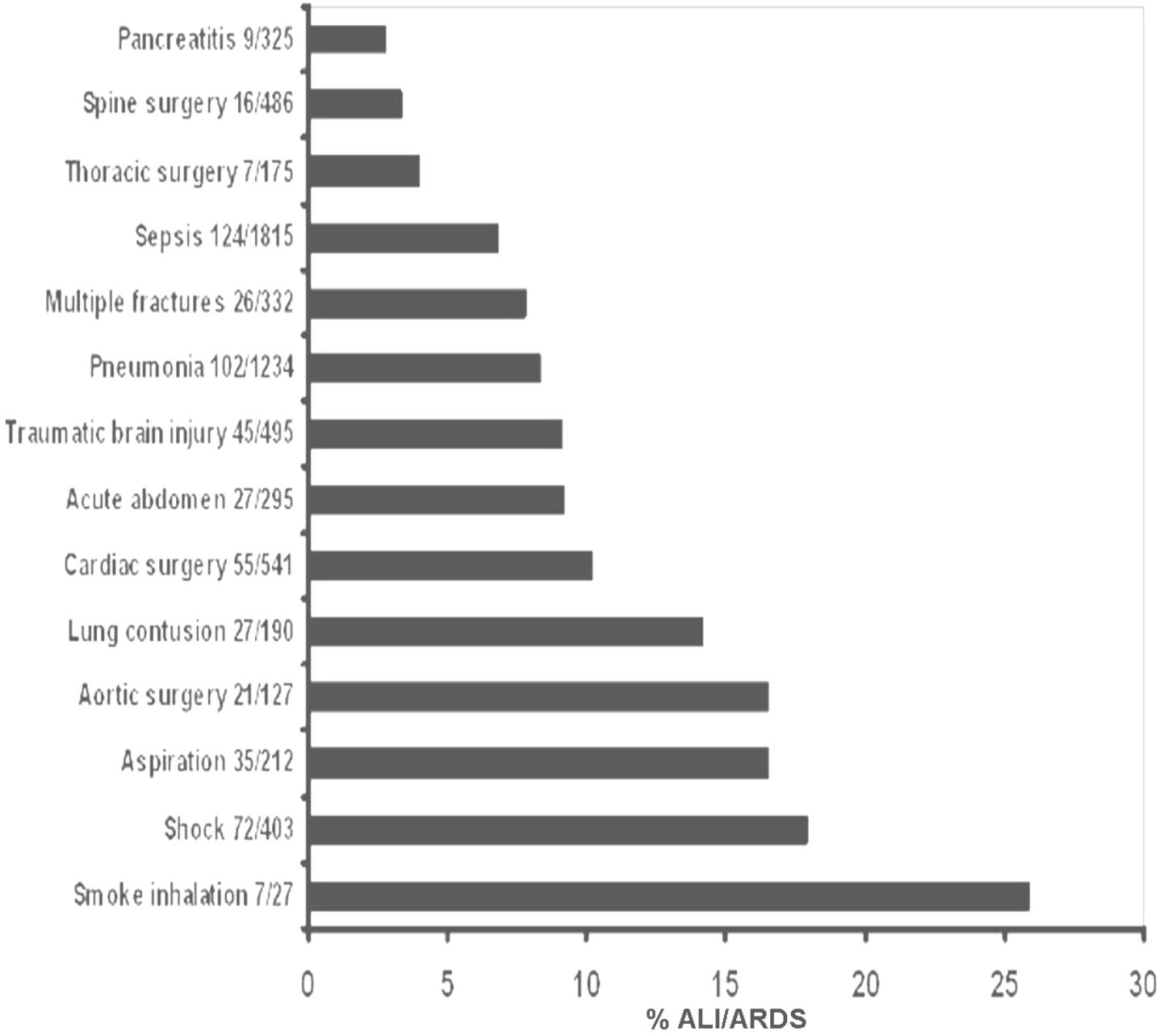


Figure 3. Frequency of ALI/ARDS development according to LIPS value

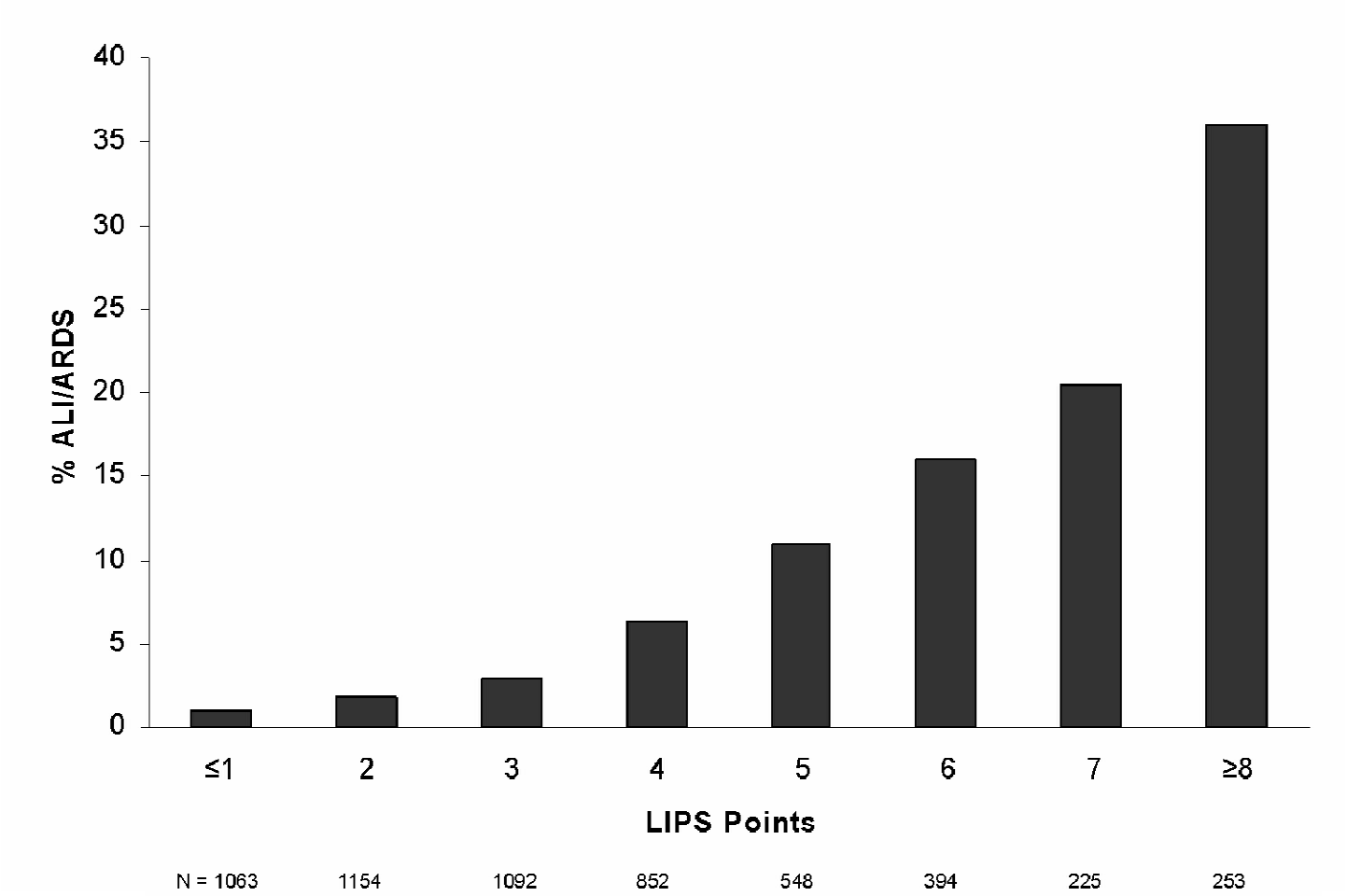
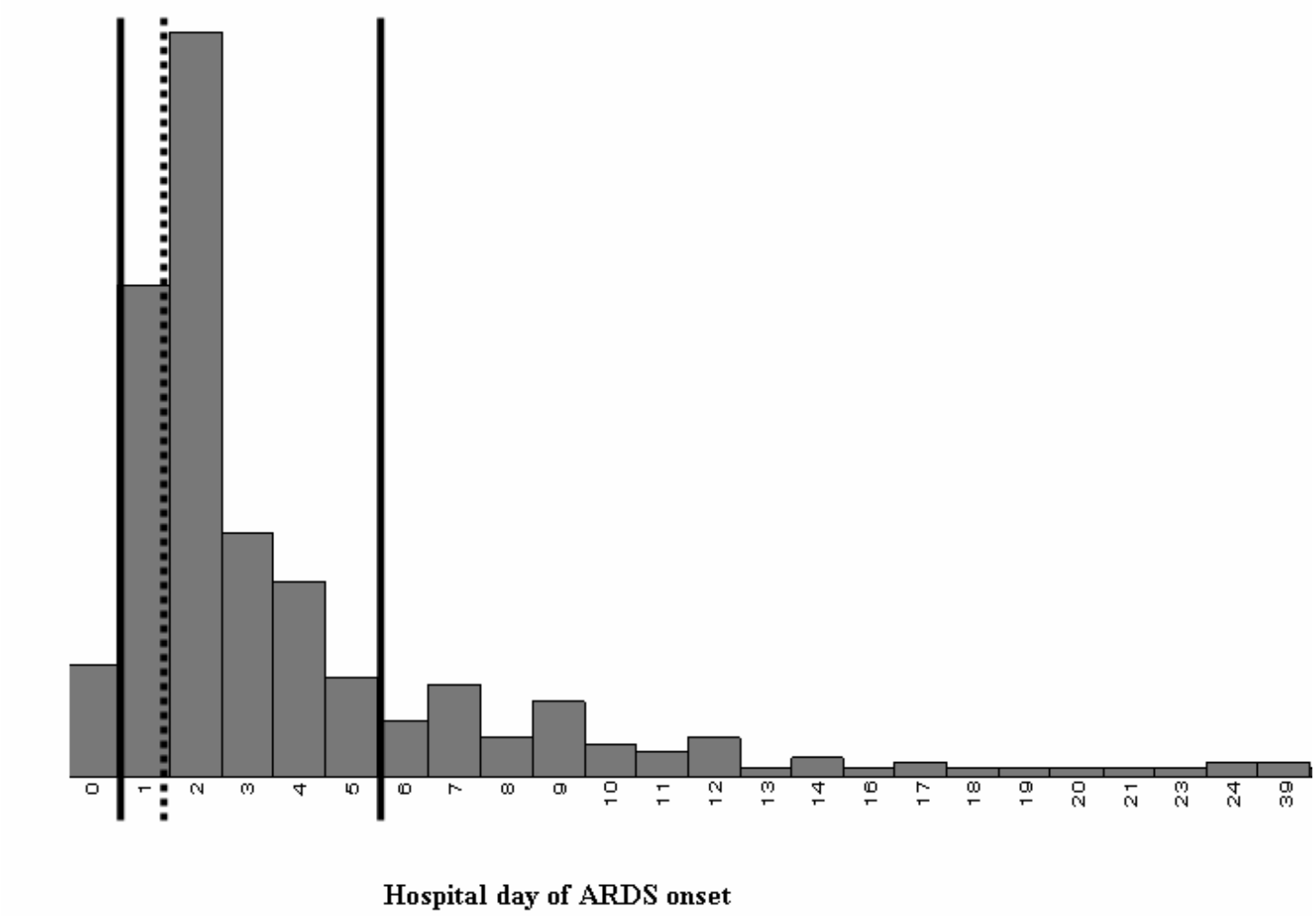


Figure 4. Timing of ALI/ARDS development during hospital stay



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