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Acute Lung Injury Prediction Score: Derivation and Validation in a Population Based Sample

Cesar Trillo-Alvarez, M.D.[1], Rodrigo Cartin-Ceba, M.D[1]., Daryl J Kor M.D.[2], Marija Kojicic M.D.[1], Rahul Kashyap, M.B.B.S.[1], Sweta Thakur, M.B.B.S.[1], Lokendra Thakur, M.B.B.S.[1], Vitaly Herasevich, M.D. Ph.D.[1], Michael Malinchoc, M.S. [3], Ognjen Gajic, M.D. M.Sc.[1]

From the Departments of: [1]Internal Medicine, [2]Anesthesiology and the Multidisciplinary Epidemiology and Translational Research in Intensive Care (M.E.T.R.I.C.) Program and [3]Health Sciences Research

Mayo Clinic College of Medicine, Rochester, Minnesota, USA

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The study was performed at Mayo Clinic Rochester, MN.

Address correspondence requests to:

Ognjen Gajic, M.D. MSc.

Mayo Clinic

200 First Street SW

Rochester, MN 55905

Telephone: 507-255-6051

E-mail: Gajic.Ognjen@mayo.edu

ABSTRACT

Early recognition of patients at high risk of acute lung injury (ALI) is critical for successful enrollment of patients in prevention strategies for this devastating syndrome. We aimed to develop and prospectively validate an acute lung injury prediction score in a population-based sample of patients at risk.

In a retrospective derivation cohort, predisposing conditions for ALI were identified at the time of hospital admission. The score was calculated based on the results of logistic regression analysis. Prospective validation was performed in an independent cohort of patients at risk identified at the time of hospital admission.

In a derivation cohort of 409 patients with ALI risk factors the lung injury prediction score discriminated patients who develop ALI from those who did not with an AUC of 0.84 (95%CI 0.80-0.89; Hosmer Lemeshow, p=0.60). The performance was similar in a prospective validation cohort of 463 patients at risk of ALI (AUC 0.84, 95%CI 0.77-0.91; Hosmer Lemeshow, p=0.88).

Acute lung injury prediction score identifies patients at high risk for ALI before ICU admission. If externally validated, this model will serve to define the population of patients at high risk for ALI in whom future mechanistic studies and ALI prevention trials will be conducted.

Introduction:

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are examples of critical care syndromes with limited treatment options once the condition is fully established. Preclinical studies support a "two hit" model of ALI/ARDS development whereby exposure to pertinent risk factors modify the development and expression of ALI/ARDS in an already susceptible host with predisposing conditions[1]. The condition usually develops in patients with underlying risk factor (pneumonia, severe sepsis, trauma and aspiration) [2, 3] but is modified by different patients characteristics including genetic predisposition [4], as well as certain medical interventions (adverse ventilator settings, transfusion of alloimunized plasma) [5, 6]. Animal models provide compelling evidence in support of oxidative stress, lung deformation, loss of compartmentalization of inflammation, and intravascular coagulation as the pathogenic mechanisms involved in the development of ALI/ARDS [7-14]. However, many treatments targeting these mechanisms have failed to improve patient outcomes despite compelling preclinical data. It is likely that inadequate or delayed recognition and treatment of patients at risk of the full-blown syndrome have obscured the therapeutic window [15-19]. The recent National Institute of Health workshop [20] prioritized the development of strategies to perform ALI/ARDS prevention trials.

Importantly, epidemiologic data suggest that ALI/ARDS is rarely present at the time of hospital admission. Rather, ALI/ARDS appears to develop over a period of hours to days in this subset of patients at risk [21-23]. Unfortunately, clinical studies are usually performed in the ICU setting, enrolling patients with established ALI/ARDS who are

beyond the therapeutic window of potential prevention strategies. This delayed enrollment prevents adequate study of patients at risk.

A significant challenge with early enrollment of patients at risk of ALI/ARDS into prevention trials is the fact that the majority of patients with predisposing conditions never develop ALI/ARDS and are never admitted to the ICU. This makes the enrollment of unselected patients into ALI/ARDS prevention studies neither feasible nor efficient [21]. The likelihood of ALI development depends not only on specific risk factor (from 5% with elective cardiopulmonary bypass [24] to 40% in patients with septic shock [25]), but also on the presence of specific risk modifiers. These include alcohol abuse [24-27], smoking [24, 27], hypoalbuminemia [28, 29], tachypnea [25, 28], oxygen supplementation [30], chemotherapy [25, 31], and diabetes mellitus [28, 32].

To facilitate the enrollment of patients into future mechanistic and outcome studies, we aimed to develop and validate an ALI/ARDS prediction model which incorporates risk factors and risk modifiers that are present at the time of hospital admission, before the development of ALI. This model will serve to define populations of patients at high risk of ALI, guide the interpretation of results and the satisfactory enrolment of patients into specific groupings for putative therapeutic interventions.

Materials and Methods:

This was an observational cohort study designed to develop and validate a numerical index which accurately estimates the probability of developing ALI/ARDS. The study was approved by the Institutional Review Board and all patients provided consent to the use of their medical records for research. The retrospective derivation cohort included Olmsted County residents admitted to an adult ICU in Rochester, MN from January to December of 2006. Exclusion criteria included age less than 18 years,

pregnancy, and a previous hospital admission during the study period. The prospective validation cohort included Olmsted County residents with risk factors (see below) for ALI/ARDS at the time of hospital admission admitted from November 2008 to May 2009. Exclusion criteria for the validation cohort included age less than 18 years, pregnancy, and a previous admission during the study period. All patients were cared for at a single academic medical center as it is the only hospital system with advanced ICU capabilities in this geographical area. Trained investigators abstracted data from the electronic medical records of patients from both cohorts and confirmed presence of specific ALI/ARDS risk factor according to standardized definitions.

Outcome variable

The primary outcome of interest in this study was the development of ALI/ARDS during the hospital stay. Standard American-European consensus conference [33] criteria were used for determination of ALI/ARDS occurrence. Patients with possible ALI/ARDS were first identified with an electronic alert system (”ALI sniffer”). This system utilizes a Microsoft SQL-based integrative database, ICU datamart, where data are populated within one hour of entry into the electronic medical record (EMR). An automatic alert was created if a patient had both the qualifying PaO2/FIO2 ratio on arterial blood gas analysis and a qualifying chest radiograph report (trigger words include [“bilateral” AND “infiltrate”] OR “edema”). This system has been validated in previous publications and has excellent sensitivity for identifying ALI/ARDS [34]. Records of alerted patients were independently reviewed by two trained investigators who underwent a structured ALI/ARDS tutorial prior to reviewing the EMR in orderd to confirm presence of ALI/ARDS. Interobserver agreement was measured using Kappa values with disagreements solved by consensus.

Predictor variables

For model derivation, risk factors independently associated with development or prevention of ALI/ARDS in previously published studies were evaluated. These variables had to be recorded during the first six hours of admission to the hospital to be considered present. Standardized definitions were used to identify risk factors (high risk trauma [28, 35-37], high risk surgery [24, 38-40], aspiration [28, 35, 38, 41], sepsis [21, 35, 36, 38], shock [21, 42-44], pneumonia [21, 28, 38, 45], and pancreatitis [1, 21, 46-50]) and risk modifiers (alcohol abuse [24-27], smoking [24, 27], hypoalbuminemia [28, 29], tachypnea [25, 28], oxygen supplementation [30], chemotherapy [25, 31], diabetes mellitus [28, 32]). The validation cohort included 467 Olmsted County, MN patients who were admitted to hospital wards (ICU and non-ICU), excluding one day surgical procedures, cardiac observation, pediatric and maternity wards. Participants had to have at least one predisposing condition to be included in this validation cohort. The variables needed to generate the LIPS score were collected prospectively by trained study coordinators from the data recorded in electronic medical records during the first 6 hours of admission.

Statistical Analyses

Fourteen previously reported independent predictors of ALI/ARDS were included in the model derivation. Seven of these predictors were considered predisposing conditions (high risk trauma, high risk surgery, sepsis, shock, pneumonia, aspiration, pancreatitis). The 7 remaining predictors were considered modifier conditions (respiratory rate > 30, alcohol abuse, hypoalbuminemia, oxygen supplementation, chemotherapy, diabetes mellitus, smoking history). The relative weight assigned to each LIPS covariate was quantified according to the beta coefficients from logistic regression

analysis in the derivation cohort. Consideration was given to the magnitude of effects reported in previous studies showing an independent association between a specific factor and ALI/ARDS as well. In order to assess the discriminatory power of our rule, the area under the receiver-operating curve (AUC) of the prediction scale was determined. The threshold score providing the best combination of sensitivity and specificity was determined by AUC analysis of the retrospective cohort. We evaluated the model for lack of fit with the Hosmer-Lemeshow statistic.

Results:

The characteristics of both retrospective (ICU) and prospective (hospital) cohorts are presented in Table 1.

Retrospective derivation cohort

Of 409 patients with at least one predisposing condition at the time of hospital admission (out of 1707 Olmsted County admissions who required ICU care during the study period), 68 (17%) developed ALI/ARDS. Tables 2 and 3 provide univariate and multivariate comparisons of specific risk factors and risk modifiers in the derivation cohort. Corresponding LIPS points are shown in Table 3 as well.

The LIPS model discriminated well between patients who did and did not develop ALI (AUC of 0.84, 95%CI 0.80 to 0.89) and was well calibrated (Hosmer-Lemeshow p=0.60) (Figure 1A).

Prospective validation cohort

The validation cohort included 467 patients with at least one predisposing condition for ALI/ARDS identified at the time of hospital admission (out of 2600 Olmsted County admissions screened during the study period). The incidence of

ALI/ARDS was 7%. Performance of the LIPS was similar to what was observed in the retrospective derivation cohort with an AUC of 0.84 (0.77 to 0.91). The model was well calibrated (Hosmer-Lemeshow p=0.88) (Figure 1B).

Table 4 describes the performance of the score in both cohorts. Despite similar characteristics, positive predictive value was lower in the validation cohort, due to a lower incidence of ALI/ARDS in a hospital (rather than ICU) based cohort, respectively.

Discussion:

In this population-based cohort, we developed a prediction model for identifying patients at high risk of ALI/ARDS at the time of hospital admission. The model showed good discrimination and calibration in both the derivation and validation cohorts.

Importantly, when comparing the validation cohort (hospitalized patients regardless of ICU disposition at the time of admission) to the derivation cohort (only ICU patients), the proportion of patients with risk factors who developed ALI was markedly reduced. Similar results were recently published by Ferguson at al [21] where only 7% of hospitalized patients with sepsis, 2% with pancreatitis, 10% of patients with pneumonia and 15% of patients with witnessed aspiration developed ALI [21]. Indeed, the majority of patients with predisposing conditions never develop ALI/ARDS and are never admitted to the ICU [21]. This makes the enrollment of unselected patients into ALI/ARDS prevention studies neither feasible nor efficient without a method for identifying those who are at high risk. The failure to take into account multiple triggers that influence ALI/ARDS development has likely led to the discarding of a number of potentially important therapeutic advances in ARDS that may prove to be effective in

specific and highly characterized groups of patients, particularly if applied early in the course of illness.

Our study have confirmed many but not all of the previously published ALI risk factors. In spite of striking increase of incidence of ALI/ARDS in the elderly in study by Rubenfield et al [3] age did not predict ALI/ARDS development in our derivation cohort and therefore was not taken into account in the final model.

While some previous studies reported the increased risk of ALI/ARDS in the elderly [5, 27, 51], other studies did not confirm this association [52, 53, 54]. It could be argued that elderly patients seem to have an increased incidence of ALI/ARDS as they tend to have more sepsis, pneumonia, aspiration, and require more medical interventions. However, in patients admitted to the hospital with a risk factor (pneumonia, sepsis), age does not seem to increase the risk of ALI/ARDS development. Indeed, recent work implies that incidence of ALI/ARDS due to community-acquired pneumonia is lower in patients age ≥85yrs [52].

Risk prediction models have been increasingly used to identify high-risk patients who may benefit from specific interventions. While their accuracy and precision are often limited, the models developed for severe pneumonia [55, 56] and perioperative cardiovascular complications [57] have been extensively used in both clinical practice and research. This study is the first attempt to develop a similar risk prediction tool for the development of ALI/ARDS in patients at risk.

The overall performance of the LIPS tool is modest and it is likely the model could be refined by 1) separating specific predisposing conditions (refining the high risk surgery according to a surgery type: cardiovascular, thoracic, acute abdomen) 2) utilizing sophisticated analytic methods such as neural network analysis and recursive partitioning,

and 3) adding additional pertinent variables as their association with ALI/ARDS are described.

Nonetheless, the LIPS model discriminates efficiently the patients that have a small chance of developing ALI/ARDS (good specificity), while maintaining an appropriate sensitivity for a screening tool. Through the early and accurate identification of patients with high risk of ALI/ARDS at the time of hospitalization, the model will allow timely and efficient enrollment of patients into future ALI/ARDS mechanistic studies and prevention trials. If externally validated, this tool may also be used in clinical practice to alert providers of patients who are at particular risk of ALI/ARDS.

The LIPS model utilizes variables that are clearly defined and routinely available in the medical record. It does not require testing beyond the standard of care and is not restricted to an ICU population. It identifies patients early, at the time of hospital admission, and is validated for hospitalized patients irrespective of their required intensity of care at the time of admission. The population-based sample increases generalizability by avoiding the referral bias often found in tertiary academic medical centers. However, the most important limitation of our study is the fact that, although population-based, both cohorts come from a single institution, with specific practice patterns, in addition to a suburban homogenous population. The small sample size poses a significant potential for overfitting the logistic regression model**,** and further refinement and validation is needed prior to clinical use of this tool. The US Critical Illness and Injury Trials Group is currently testing the external validity of the LIPS (NCT00889772).

In conclusion, we have developed and validated an efficient and effective prediction tool for evaluating risk of ALI/ARDS at the time of hospital admission. As the majority of patients with predisposing conditions never develop ALI and are never

admitted to the ICU, our prediction model can facilitate the timely and efficient enrollment of patients into mechanistic and outcome studies as well as future ALI prevention trials. Since ALI patients represent etiologically diverse group a focus should be on defining subgroups that could benefit from particular target therapies. Nevertheless, multicenter validation is required before large-scale screening projects are performed.

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Table 1 Baseline characteristics of both cohorts

Patient Characteristics*	Retrospective derivation cohort (ICU, n=409)		Prospective validation cohort (hospital, n=467)	
Demographics				
Age, Median (IQR)	68.0	(57.0, 78.0)	68.0	(51, 84)
Female gender, No. (%)	186	(45)	243	(52)
Predisposing conditions				
Sepsis, No. (%)	47	(11)	257	(55)
Trauma, No. (%)	18	(4)	27	(6)
Shock, No. (%)	164	(40)	135	(29)
Pneumonia, No. (%)	55	(13)	214	(46)
Aspiration, No. (%)	19	(5)	44	(9)
Pancreatitis, No. (%)	4	(1)	41	(9)
High risk surgery, No. (%)				
. None	308	(75)	419	(90)
. Elective	31	(8)	16	(3)
. Emergent	70	(17)	32	(7)
Risk modifiers				
Alcohol, No. (%)	26	(6)	36	(8)
Smoking, No. (%)	175	(43)	198	(42)

Hypoalbuminemia, No. (%)	13	(3)	58	(12)
Diabetes, No. (%)	87	(21)	116	(25)
Chemotherapy, No. (%)	2	(0)	31	(7)
Oxygen supplementation >0.35 FiO2 (>4L/min nasal cannula), No. (%)	194	(47)	126	(27)
Tachypnea (respiratory rate 30 per minute), No. (%)	51	(12)	47	(10)

* Missing data: smoking (83% complete), alcohol (93% complete) and serum albumin (7% complete). Missing data were considered as negative.

Table 2 Comparison of ALI risk factors and risk modifiers between patients who did and did not develop ALI in a derivation cohort

Patient Characteristics*	**ALI (N=68)**		**No ALI (N=341)**		**P value**
Demographics					
Age, Median (IQR)	68.0	(19.0, 96.0)	68.0	(18.0, 97.0)	0.69
Female gender, No. (%)	32	(47)	154	(45)	0.77
Predisposing conditions					
Sepsis, No. (%)	14	(21)	33	(10)	0.01
Shock	44	(65)	120	(35)	<0.001
Trauma, No. (%)	5	(7)	13	(4)	0.19
Pneumonia, No. (%)	9	(13)	46	(13)	0.96
Aspiration, No. (%)	7	(10)	12	(4)	0.015
Pancreatitis, No. (%)	1	(1)	3	(1)	0.65
High risk surgery, No. (%)					
. Elective	8	(12)	23	(7)	0.15
. Emergent	25	(37)	52	(15)	<0.001
Risk modifiers					
Alcohol, No. (%)	12	(18)	14	(4)	<0.001
Smoking, No. (%)	36	(53)	139	(41)	0.06

Hypoalbuminemia, No. (%)	7	(10)	6	(2)	<0.001
Diabetes, No. (%)	13	(19)	74	(22)	0.63
No sepsis	10	(19)	56	(18)	0.95
Sepsis	3	(21)	18	(55)	0.05
Chemotherapy, No. (%)	1	(1)	1	(0)	0.20
Oxygen supplementation >0.35 (>4L nasal cannula), No. (%)	46	(68)	148	(43)	<0.001
Tachypnea (respiratory rate >30 per minute), No. (%)	18	(26)	33	(10)	<0.001

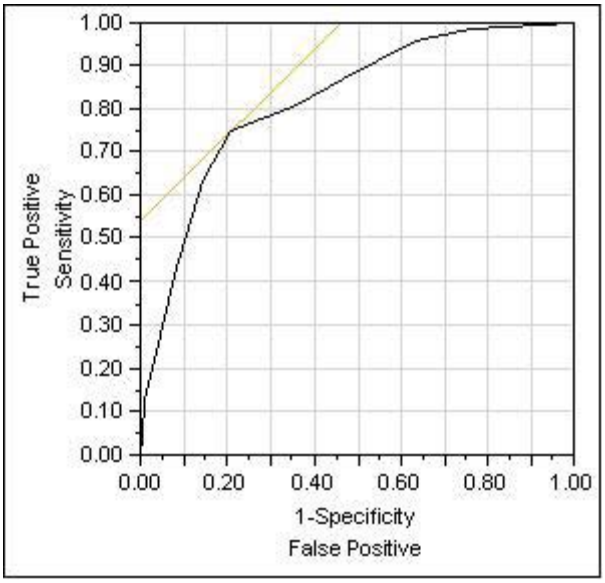
Table 3 Predictors of ALI development in the derivation cohort of 409 patients at risk for ALI/ARDS: parameter estimates from a multivariate analysis, and corresponding LIPS points

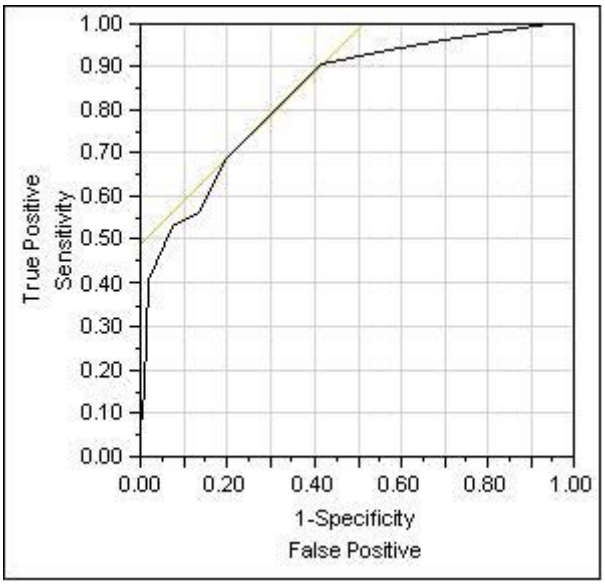
	Estimate	*(95% CI)*		*p-value*	Points Assigned *(if positive finding)*
Predisposing conditions					
Sepsis	2.14	0.97	3.35	<.001	1.5
Shock	1.12	0.42	1.84	0.002	1.5
Trauma	0.33	-1.08	1.64	0.63	0.5
Pneumonia	0.53	-0.66	1.66	0.37	0.5
Aspiration	1.87	0.54	3.18	0.005	1.5
Pancreatitis	1.75	-1.40	4.08	0.17	1.5
Elective surgery	1.70	0.60	2.77	0.002	1.5
Emergency surgery	2.19	1.36	3.07	<.001	2
Risk modifiers					
Alcohol	1.17	0.12	2.21	0.027	1
Smoking	0.32	-0.34	0.99	0.33	0.5
Hypoalbuminemia	2.06	0.53	3.65	0.009	2
Diabetes mellitus	-1.83	-3.64	-0.26	0.031	-1.5
Chemotherapy	3.54	0.10	7.00	0.025	2
FiO2 >0.35	1.11	0.42	1.85	0.002	1
Tachypnea	1.11	0.25	1.97	0.011	1

Table 4. Performance of LIPS in the two cohorts

	Retrospective derivation cohort (ICU)	Prospective validation cohort (hospital)
Incidence of ALI/ARDS	0.17 (68/409)	0.07 (32/463)
AUC (95%CI)	0.84 (95%CI 0.80-0.89)	0.84 (0.76 to 0.92)
Sensitivity (95%CI), LIPS>3	0.41 (0.32 to 0.50)	0.69 (0.53 to 0.82)
Specificity (95%CI), LIPS>3	0.90 (0.89 to 0.92)	0.84 (0.83 to 0.85)
Positive predictive value (95%CI), LIPS>3	0.46 (0.36 to 0.56)	0.24 (0.18 to 0.28)
Likelihood ratio (+)(95%CI), LIPS>3	4.26 (2.77 to 6.41)	4.27 (3.03 to 5.39)
Likelihood ratio (-)(95%CI), LIPS>3	0.65 (0.54 to 0.77)	0.37 (0.22 to 0.56)

Figure 1A and B


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
True Positive
Sensitivity
0.00
0.20
0.40
0.60
0.80
1.00
1-Specificity
False Positive


1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
True Positive
Sensitivity
0.00
0.20
0.40
0.60
0.80
1.00
1-Specificity
False Positive