CHEST Online Supplement

Decision Support Tool for Early Differential Diagnosis of Acute Lung Injury and Cardiogenic Pulmonary Edema in Medical Critically Ill Patients

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e-Appendix 1. ***Definitions for data collection of predictor variables***

Predictor Variable	Definition	Coding
General Information		
Age (at T0)	Calculated as difference between date of birth and time of ALI sniffer alert	value
Gender	As documented in EMR	0 = male 1 = female
Body Mass Index (at T0)	Calculated from weight and height available in the EMR closest to time of ALI sniffer alert	value
Risk Factors for Cardiogenic Pulmonary Edema		
History (>3 days before T0) of **Heart Failure**	Diagnosed or suggested in EMR, or Suggested by Echo findings (EF<54% or diastolic relaxation abnormalities of at least grade II)	0 = no 1 = yes
History (>3 days before T0) **of Coronary Artery Disease**	Diagnosed (as CAD or ischemic Cardiomyopathy) in EMR, or Suggested by heart catheterization report, or Previous ischemic event like myocardial infarction, known Angina, etc	0 = no 1 = yes
History (>3days before T0) **of Valvular Disease**	At least moderate stenosis or regurgitation of any valve (mitral, aortic, tricuspid or pulmonary) **Not:** if successfully repaired	0 = no 1 = yes
ST Changes	New ST Segment deviation of >/ 1mm in two consecutive leads, or	0 = no / NA 1 = yes

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(within 12h before till 6h after T0)	New Left Bundle Branch Block **Not:** "secondary ST changes" (e.g. RBBB) or "unspecific ST abnormalities"	
Risk Factors for Acute Lung Injury		
Sepsis (within 24 h before T0)	I. Suspected or documented infection + II. Systemic Inflammatory Response Syndrome SIRS (=at least two out of the following four are prevalent) a) Temperature >38° or <36° C b) Heart rate (HR) > 90/min c) >20 respirations/min or PaCO2<32mmHg d) Leucocytes <4,000/mm³ or >12,000/mm³	0 = no 1 = yes
Shock (within the 12 h before till T0)	I. Hypotension, defined by either a), b) or c) a) Systolic blood Pressure (SBP) <90mmHg or decreased >40mmHg from baseline b) Shock Index (HR/SBP) >1 c) Mean arterial blood pressure <65mmHg + II. Evidence of inadequate tissue perfusion: altered mental status only explainable by hemodynamic status and urine output <0.5ml/Kg/min, or	0 = no 1 = yes
	in absence of hypotension: I. Shock suggested by history and physical exam + II. at least 1 marker of inadequate perfusion: a) ScvO2 or SvO2 <70% b) Lactate >4mmol/L (in absence of liver disease) c) Base excess <-4 d) Blood pH <7.32, or	
	Any Vasopressors used (**not:** Dobutamine)	
Pneumonia (within the 5 days prior to T0)	I. New or progressive radiographic infiltrate + II. High clinical suspicion of pneumonia: a) or b) a) New cough, sputum, fever or WBC>12,000/mm³ b) Suggested or diagnosed in EMR (not only DD, should be at least treated), or	0 = no 1 = yes
	I. NEW Abnormal chest radiograph of uncertain cause + II, Microbiological or serological evidence of definite or probable pneumonia (result available till 6h after SnifferTime!) +	

	III. Low or moderate clinical suspicion of pneumonia	
Aspiration (within 48 hours before T0)	Witnessed or suggestive history of aspiration	0 = no 1 = yes
Pancreatitis (within 24 hours before T0)	Two or more out of the following three: a) Abdominal pain characteristic of acute pancreatitis b) Serum amylase and/or lipase >/ 3 times the upper limit of normal c) Characteristic findings of acute pancreatitis on CT	0 = no 1 = yes
Severe Trauma (within 24 hours before T0)	Any of the below: a) Lung contusion - blunt, penetrating trauma to thorax that results in new infiltrates in x- ray b) Polytrauma with at least 2 fractures (#) of long bones (tibia plus fibula # count as 1 long bone #) Traumatic brain injury - closed or open head injury with one more associated condition like fracture	0 = no 1 = yes
High Risk Surgery (within the 5 days before T0)	Any of the below: a) All cardiac and aortic vascular procedures b) Noncardiac thoracic surgery including esophageal and pulmonary c) Acute abdomen d) Orthopedic spine surgeries Liver transplant	0 = no 1 = yes
Smoke inhalation (within 3 days before T0)	reported in EMR	0 = no 1 = yes
Near drowning (within 3 days before T0)	reported in EMR	0 = no 1 = yes
Laboratory and Vital Sign Measurements		
Body Temperature (within 12h before till 6h after T0)	Highest value in EMR	value
Troponin T (within 12h before till 6h after T0)	Highest value in EMR	value

Brain Natriuretic Peptide (within 12h before till 6h after T0)	Highest value in EMR	value
Bicarbonate (within 12h before till 6h after T0)	Lowest Value in EMR	value
Lactate (within 12h before till 6h after T0)	Highest value in EMR	value
Leucocytes (within 12h before till 6h after T0)	Highest value in EMR	value
Creatinine (within 12h before till 6h after T0)	Highest value in EMR	value
FiO2 at 6 (/5h)	Closest value before 6h after T0	value
SpO2 at 6h (/5h)	The value within 30 minutes before till 30 minutes after 6h after T0 ([T0+6h-30min;T0+6h+30min[ ) closest to this exact time If NA, use T0 plus 5h as alternative time point (change FiO2 accordingly)	value
Risk Modifiers		
Chemotherapy	Currently taken or within the six months before T0 as of documentation in EMR	0 = no 1 = yes
Alcohol Abuse	>2drinks per day (any alcoholic beverage), or if previous alcoholic, sober for <1 year	0 = no 1 = yes
Smoking	Actively, or >20 pack years	0 = no 1 = yes
Diabetes mellitus	Diabetes Type I or II according to EMR	0 = no 1 = yes
Interstitial Lung Disease	Diagnosed or suggested in EMR	0 = no 1 = yes
Transfusions		

Platelets (within 48h before T0)	According to EMR	Number of units
Red Blood Cells (within 48h before T0)	According to EMR	Number of units
Fresh Frozen Plasma (within 48h before T0)	According to EMR	Number of units

Abbreviations: T0 = time of the "Sniffer Alert", EMR = Electronic Medical Record,

Under the assumption that the results were similar before onset of acute respiratory failure, laboratory Tests and EKGs were considered till 6hours after "T0" to minimize missing data. "Smoke Inhalation" and "Near Drowning" were assessed, but were not prevalent in the cohort and thus not further considered in the analysis. High risk surgery and severe trauma were originally collected as ALI risk factors for model inclusion, but were later used as exclusion criteria (details see manuscript). General information, laboratory results, vital sign measurements and transfusion data was electronically pulled from our intensive care database *datamart* [Herasevich V. et al. (2010). "Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness." Mayo Clin Proc 85(3): 247-254.] the remainder was obtained by manual chart review.

e-Appendix 2. Details on post-hoc expert review (gold standard)

A. Development Cohort (DC)

All Olmsted County residents admitted to any ICU in 2006 were reviewed at or after hospital discharge by one of two critical care specialists (one attending physician and one senior critical care fellow) blinded to the results of the decision support tool. Patients were classified as *acute lung injury* (*ALI*), *cardiogenic pulmonary edema* (*CPE*), *Both* (i.e. ALI+CPE) or as *Other*. All patients that were screened positive by the ALI-Sniffer as well as (very few) sniffer-negative patients who were marked as *ALI*, *CPE* or *Both* by the one expert were reviewed (blinded to each other) by both experts. Cases of disagreement were resolved by consensus. Thus, 1707 patients were reviewed yielding excellent agreement (kappa 0.86). Agreement between experts was similar in cases with (33%) vs cases without (67%) echocardiographic reports available (kappa 0.86 vs 0.85).

Patients enrolled in the years 2007-2009 were reviewed by experienced research fellows who underwent same structured training for the assessment of ALI/CPE as all expert reviewers. Critical care attending physicians re-reviewed all cases, in which the primary reviewers had doubts regarding final diagnosis or selected *Both* (ALI+CPE). Given the good kappa value in the 2006 subset duplicate evaluation in the remaining part of the development cohort (as well as in the VC) was omitted.

Rather than just looking for a "PAOP >18 mmHg or clinical evidence of left atrial hypertension" (Bernard et al. *Am J Respir Crit Care Med.* 1994) the post-hoc review followed a more formal determination of the role of left atrial hypertension (LAH) according to a previously published algorithm (Gajic et al. *Crit Care Med*. 2006): LAH was excluded by echocardiographic findings (E/E' <15), brain natriuretic peptide levels (BNP <250 pg/ml in the

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absence of renal failure) and venous filling pressures (PAOP <18 mmHg or CVP <12 mmHg in the absence of pulmonary hypertension). A brisk response (i.e. resolution of respiratory failure within 24 hours of onset) to appropriate therapy (preload/afterload reduction, treatment of ischemia or inotropic agents) was used as an indicator of hydrostatic edema (CPE).

B. Validation cohort (VC)

Expert reviewers consisted of a mix of 4 critical care fellows and 2 attending physicians who followed the same formal approach in evaluating patients as in the development cohort.

References:

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.* 1994;149:818-824.

Gajic O, Gropper MA, Hubmayr RD. Pulmonary edema after transfusion: how to differentiate transfusion-associated circulatory overload from transfusion-related acute lung injury. *Crit Care Med.* 2006;34:S109-113.

e-Appendix 3.

Calculator for predicted probability of Acute Lung Injury (ALI) vs Cardiogenic Pulmonary Edema (CPE)

DEMOGRAPHIC	
Age <45 years	
CPE RISK FACTORS	
History of Heart Failure	
History of CAD	
New ST changes/ LBBB	
ALI RISK FACTORS	
Sepsis or Pancreatitis	
Pneumonia	
Aspiration	
ALI RISK MODIFIER ("yes" only if any of above ALI RF present)	
Alcohol Abuse*	
MISCELLANEOUS	
Chemotherapy*	
Persistent Hypoxemia: SpO2/FiO2-ratio at 6h* <235	
Score sum	####
Predicted Probability (%) for:	
ALI	####
CPE	####

Instructions:

Enter in each blank field "Yes" or "No". Once all fields are filled the probability for ALI vs CPE (and vice versa) will be displayed.

Legend:

Abbreviations: CAD=Coronary Artery Disease, LBBB=Left Bundle Branch Block; *Definitions: *SpO2/FiO2-ratio at 6 hours* after onset of acute pulmonary edema, *Alcohol Abuse* is more than 2 drinks per day or known alcoholic sober for less than 1 year, *Chemotherapy* for malignancy within past 6 months;

Disclaimer:

This prediction score is for research use and MUST NOT be used in patient care. It has been developed in a population-based cohort and may not be applicable to other settings. There has been NO external validation. This calculator is part of the paper by Schmickl et al. "Prediction of ALI vs CPE" and should only be appreciated in this context.

Available under www.lipsgroup.org/alicpe/

e-Table 1. ***Candidate variables for model development and their potential contribution to the prediction of ALI/ALI+CPE versus CPE (univariate analysis)***

Predictor (N=332, otherwise shown)	**n (%)**	**OR (95%-CI) for ALI**
General Information		
Age, <45 years	20 (6)	11.4 (3.2 to 72.1)*
Female Sex	174 (52)	0.69 (0.44 to 1.06)
Risk Factors for Acute Lung Injury		
Sepsis or Pancreatitis †	108 (33)	6.4 (3.8 to 10.9)*
Shock	89 (27)	2.13 (1.30 to 3.52)*
Pneumonia	109 (33)	2.54 (1.60 to 4.1)*
Aspiration	34 (10)	2.24 (1.09 to 4.84)*
Platelet Transfusion	8 (2)	3.5 (0.79 to 24.0)
Risk Factors for Cardiogenic Pulmonary Edema		
Hx of Heart Failure	103 (31)	0.38 (0.23 to 0.62)*
Hx of Coronary Artery Disease	136 (41)	0.40 (0.25 to 0.63)*
ST Changes/ LBBB, N=235	52 (22)	0.39 (0.19 to 0.75)*
Hx of Valvular Disease	50 (15)	0.72 (0.38 to 1.31)
Laboratory Results and Vital Sign Measurements		
SpO2/FiO2-ratio at 6h <235‡, N=324	186 (57)	2.62 (1.67 to 4.16)*
Brain Natriuretic Peptide, <250pg/ml, N=74	18 (24)	1.81 (0.62 to 5.58)
Bicarbonate, <22mmol/L, N=317	114 (36)	1.70 (1.07 to 2.71)*
Creatinine, >1.1mg/dl, N=312	154 (49)	0.81 (0.52 to 1.27)
Lactate, >2.3mmol/L, N=142	51 (36)	1.09 (0.55 to 2.18)
Leucocytes, <4 or >12/nl, N=311	176 (57)	1.34 (0.85 to 2.10)
Temperature, <36 or >38° Celsus, N=268	79 (30)	1.74 (1.03 to 2.98)*
Troponin T, >0.03ng/ml, N=213	113 (53)	0.59 (0.34 to 1.02)
Risk Modifiers and Miscellaneous		
(Alcohol Abuse x ALI RF§)	20 (6)	11.4 (3.2 to 72.1)*
Chemotherapy	18 (5)	9.9 (2.8 to 63.5)*
Smoking, current or >20 pack years	149 (45)	1.10 (0.72 to 1.70)
Diabetes mellitus	91 (27)	0.66 (0.40 to 1.07)

Abbreviations: OR=Odds Ratio, 95%-CI=95%-Confidence Interval, Hx=History, LBBB=left bundle branch block;

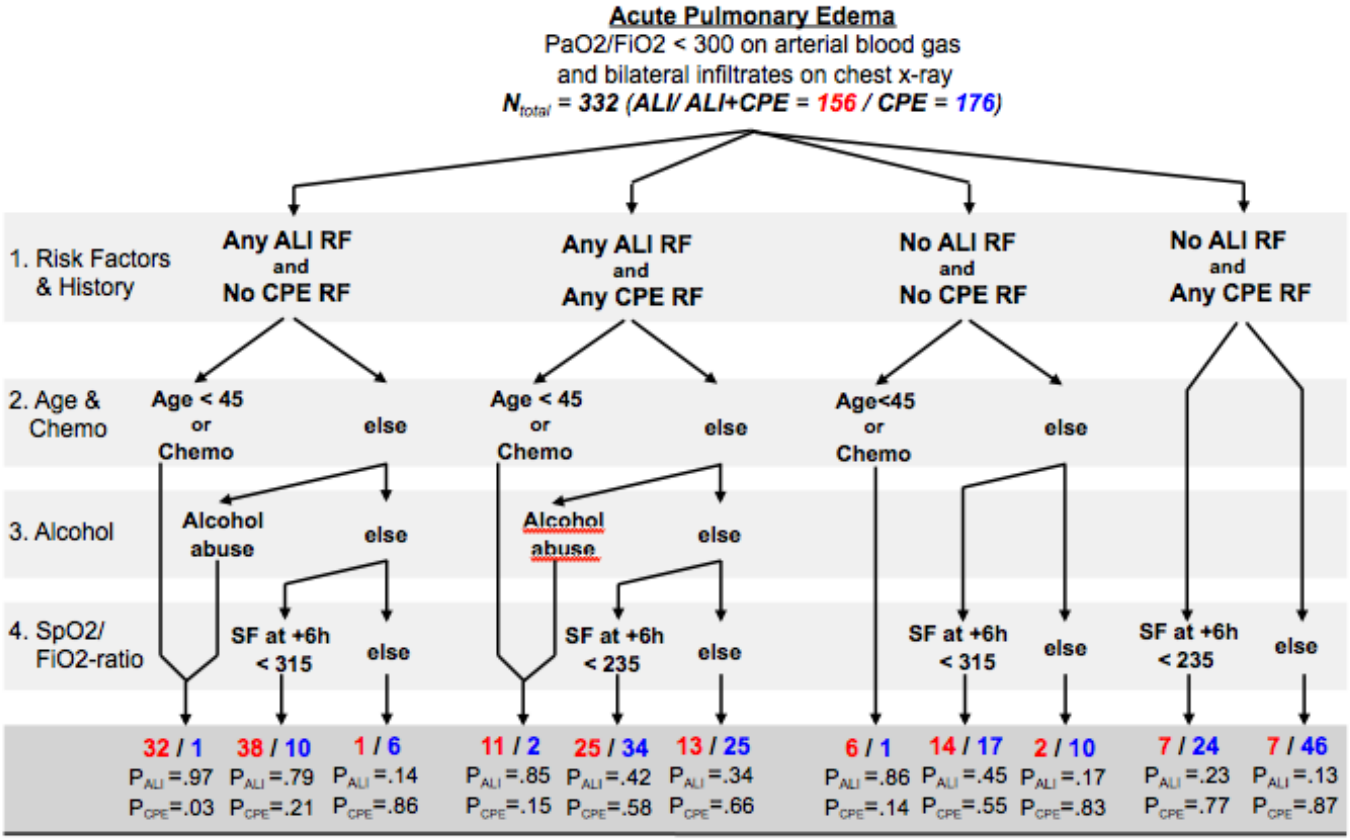
* statistically significant;

† Variables were combined since pancreatitis had a small event rate and pathophysiological mechanism causing acute lung injury is similar to that of sepsis;

‡ SpO2/FiO2-ratio at 6 hours after onset of acute pulmonary edema;

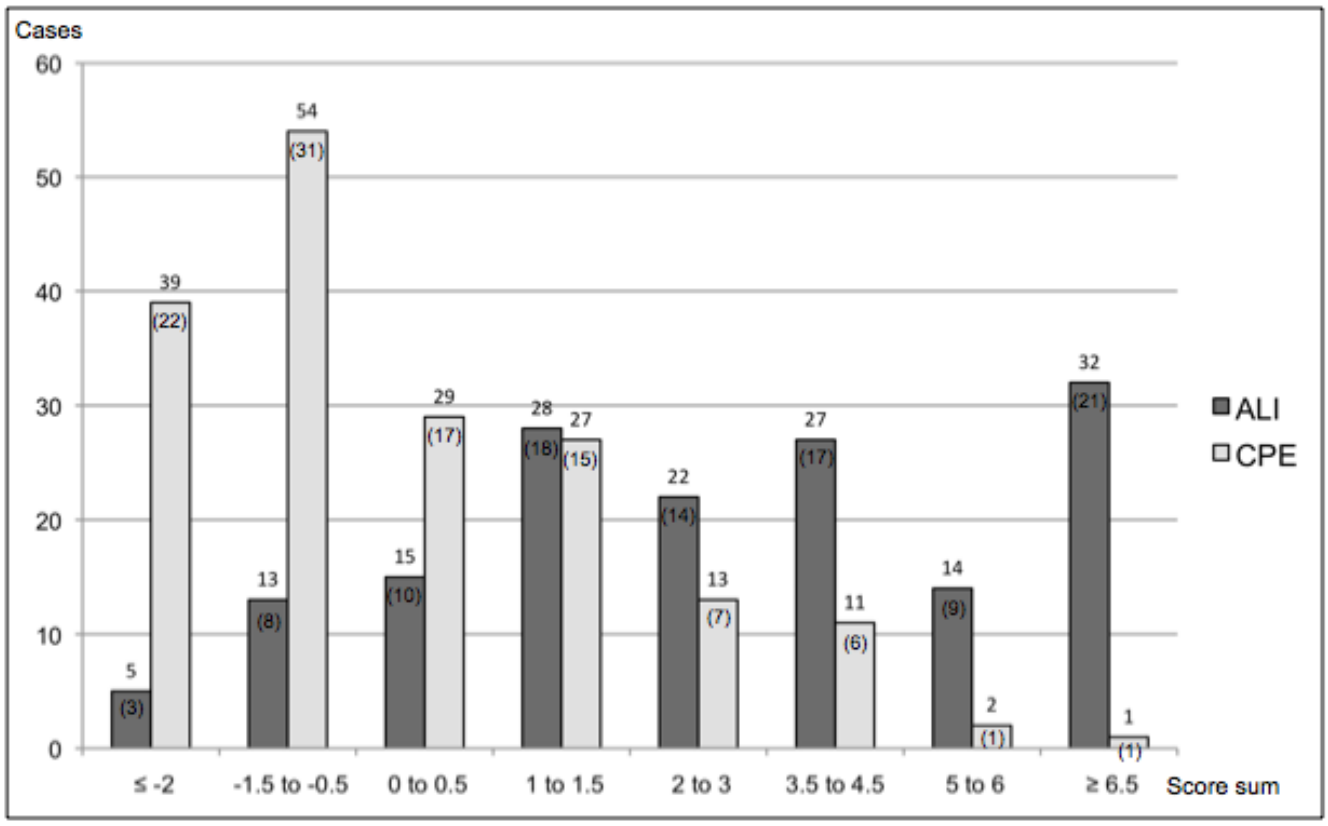
§ ALI RF=ALI risk factor (coded 1 if patient had any of the following: Sepsis, Pancreatitis, Pneumonia, Aspiration; else 0);

The chosen cut-off values for continuous variables reflect standard thresholds. Odds ratios were calculated using univariate logistic regression. Higher odds ratio indicates a higher risk of ALI/ALI+CPE vs CPE.



Explanations: RF=risk factor; ALI=acute lung injury, CPE=cardiogenic pulmonary edema, P_{ALI} or P_{CPE} are the probability for a patient with the characteristics of a certain branch to have ALI or CPE, respectively; **ALI RF:** Sepsis, Pancreatitis, Shock, Pneumonia, Aspiration; **CPE RF:** History of coronary artery disease, History of heart failure (clinical or by Echo) or New ST segment changes (>1mm in 2 consecutive leads) or left bundle branch block; **Alcohol abuse:** >2 alcoholic beverages per day; **Chemo**: Chemotherapy for malignancy in past 6 months; **SF at +6h:** SpO2/FiO2-ratio at 6 hours after the onset of acute pulmonary edema;

e-Figure 1. Recursive partitioning model



e-Figure 2. Distribution of score sums among ALI/ALI+CPE and CPE patients, respectively. Above each column is the absolute number of cases shown, the number in parentheses denotes the percentage of cases with respect to each group. 61% (95/156) of ALI patients had a score sum of equal or greater than 2. Conversely, 69% (122/176) of CPE patients had a score sum of equal or less than 0.5.

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