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ORIGINAL ARTICLE

Predicting Persistent Acute Respiratory Failure in Acute Pancreatitis: The Accuracy of Two Lung Injury Indices

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Abstract

Background/Aims Early and accurate identification of patients with acute pancreatitis (AP) at high risk of persistent acute respiratory failure (PARF) is crucial. We sought to determine the accuracy of simplified Lung Injury Prediction Score (sLIPS) and simplified Early Acute Lung Injury (sEALI) for predicting PARF in ward AP patients.

Methods Consecutive AP patients in a training cohort from West China Hospital of Sichuan University (n = 912) and a validation cohort from The First Affiliated Hospital of Nanchang University (n = 1033) were analyzed. PARF was defined as oxygen in arterial blood/fraction of inspired oxygen < 300 mmHg that lasts for > 48 h. The sLIPS was composed by shock (predisposing condition), alcohol abuse, obesity, high respiratory rate, low oxygen saturation, high oxygen requirement, hypoalbuminemia, and acidosis (risk modifiers). The sEALI was calculated from oxygen 2 to 6 L/min, oxygen > 6 L/min, and high respiratory rate. Both indices were calculated on admission.

Results PARF developed in 16% (145/912) and 22% (228/1033) (22%) of the training and validation cohorts, respectively. In these patients, sLIPS and sEALI were significantly increased. sLIPS ≥ 2 predicted PARF in the training (AUROC 0.87, 95% CI 0.84–0.89) and validation (AUROC 0.81, 95% CI 0.78–0.83) cohorts. sLIPS was significantly more accurate than sEALI and current clinical scoring systems in both cohorts (all $P < 0.05$).

Conclusions Using routinely available clinical data, the sLIPS can accurately predict PARF in ward AP patients and outperforms the sEALI and current existing clinical scoring systems.

Keywords Acute pancreatitis · Persistent acute respiratory failure · Early prediction · Simplified Lung Injury Prediction Score · Simplified early acute lung injury

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Introduction

Acute pancreatitis (AP) is one of the most common acute gastrointestinal diseases and there is no effective pharmacological therapy [1]. Severe acute pancreatitis (SAP), characterized by respiratory, circulatory, and renal systems alone or in combination that persist for at least 48 h, is associated with significant mortality (> 30%) [2–4]. Early identification of patients at high risk for developing a severe course of the disease is therefore crucial. There are more than 20 scoring systems designed to predict major clinical outcomes for AP patients [5] including recent developed web-applied nomogram [6] and EASY-APP [7]. However, none of these has been specific for predicting persistent acute respiratory failure (PARF), the most common type of organ failure in SAP [8–10].

The diagnosis of PARF is based on the degree and duration of hypoxemia (oxygen in arterial blood/fraction of inspired oxygen, $PaO_2/FiO_2 < 300$ mmHg lasting for > 48 h) [11, 12]. A previous study from our group has shown that the mortality from AP was 0% (0/44), 9.4% (6/64), and 15.8% (3/19) in patients with PaO_2/FiO_2 ratio > 200 to ≤ 300, > 100 to ≤ 200, and < 100 mmHg, respectively [13]. Recent studies have shown that PARF occurs early in the clinical course of SAP and accounts for approximately 60% of early mortality [14–18]. Early and accurate identification of AP patients at high risk of PARF is crucial for triage, optimizing fluid therapy to avoid fluid overload [19–21], and initiating respiratory intervention(s) especially for trial entries [22, 23].

Recently, the United States Critical Illness and Investigation group derived and validated the Lung Injury Prediction Score (LIPS) to accurately predict patients at an increased risk for developing acute respiratory distress syndrome (ARDS) from all causes [24–27]. Another approach is the Early Acute Lung Injury (EALI) which identifies patients with early ARDS. Because EALI only comprises 3 components (oxygen requirement, respiratory rate, and immune suppression) it is easy to use at the bedside [28–30]. These two indices were designed and validated in deteriorating patients in the Emergency Department (ED), intensive care unit (ICU), or hospital ward settings (Table 1) [24–30].

PARF/ARDS occurs and progresses in spontaneously breathing patients and usually in the pre-ICU settings, with up to half of these patients being treated in hospital wards [31–35]. Many of these PARF/ARDS patients, including those with SAP, do not meet the criteria for mechanical ventilation and/or admission to ICU. Extrapolation of the LIPS and EALI in AP population may help to develop a respiratory failure-specific, multivariable predictive model. However, complicated and varied predisposing conditions (including high-risk trauma, high-risk surgery, aspiration, sepsis, and pneumonia, Table 2) [36–38] and risk modifiers (use of chemotherapy currently or within 6 months of the hospital admission [39, 40], Table 2) for ARDS from all causes do not always exist in ward patients of AP centers. Therefore, these indices may need to be simplified before the extrapolation.

This study aimed to investigate and validate the accuracy of a simplified LIPS (sLIPS) and a simplified EALI (sEALI) in predicting PARF in AP patients managed in the ward setting.

Materials and Methods

Study Design and Participants

The current study complied with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [41]. Data were obtained from 2 prospective databases of consecutive AP patients admitted to West China Hospital of Sichuan University in Chengdu [19, 21] and the First Affiliated Hospital of Nanchang University in Nanchang [42]. Both institutions obtained ethical approval (Chengdu: 2015[247]; Nanchang: 2011[001]). Both institutions used the Revised Atlanta Criteria for AP diagnosis [11] and only included patients with symptoms ≤ 48 h prior to hospital ward admission. Exclusion criteria are presented in Supplementary Materials and Methods. The patient selection process has been published in full [19, 42].

Study Variables and Data Collection

Demographic characteristics, comorbidities, physiologic, laboratory variables, and current clinical scoring systems [43], including systemic inflammatory response syndrome (SIRS), Glasgow, Acute Physiology and Chronic Health Evaluation II (APACHE-II), and Sequential Organ Failure Assessment (SOFA). The LIPS has two indexes (predisposing conditions and risk modifiers) including 21 categories which ranges from -1 to 36. Among these categories, aspiration, sepsis, pneumonia, traumatic brain injury, smoke inhalation, near-drowning, lung contusion, multiple fractures, high-risk surgery, emergency surgery, and chemotherapy were removed because there was no number of cases (patients included in this study are those triaged into two AP centers and treated in general wards). Diabetes mellitus was removed because protective effect of diabetes only applies to septic patients [36]. Then, a total of 8 variables remained in the sLIPS (ranging from 0 to 11): predisposing condition included shock [32, 44, 45], risk modifiers included: alcohol abuse [40, 46], obesity [47], high respiratory rate [37, 40], low oxygen saturation

Table 1 Characteristics of Studies Using LIPS and EALI to Predict ARDS/ALI

Author	Year	Scoring Tool	Setting	Patient Number	Study Design	Patient Population	ARDS/ALI predisposing conditions
Gajic et al. [1]	2011	LIPS	Tertiary (MC), USA	5584	Prospective, observational	Patients with ALI risk factors in academic and community acute care hospitals	Sepsis (33%), high-risk surgery (29%), pneumonia (22%), trauma (18%), shock (7%), AP (6%), aspiration (4%)
Trillo-Alvarez et al [2]	2011	LIPS	Tertiary (SC), USA	409	Retrospective, observational (derivation)	Patients in ICU	Shock (40%), high-risk surgery (25%), pneumonia (13%), sepsis (11%), aspiration (5%), trauma (4%), AP (1%)
				463	Prospective, observational (validation)	Patients with ALI/ARDS risk factors at the time of hospital admission	Sepsis (55%), pneumonia (46%), shock (29%), high-risk surgery (10%), AP (9%), aspiration (9%), trauma (6%)
Mikkelsen et al [3]	2013	LIPS	Tertiary (MC), USA	778	Retrospective, observational	Patients with severe sepsis presenting to the ED	Etiology of sepsis: pneumonia (27%), urosepsis (21%), gastrointestinal (15%) bacteremia (14%)
Soto et al [4]	2016	LIPS	Tertiary (MC), USA	500	Retrospective, observational	Non-ED hospitalized patients with ARDS risk factors at the time of critical care	Sepsis (55%), pneumonia (39%), shock (29%), aspiration (13%), high-risk surgery (10%), AP (6%)
Xu et al [5]	2018	LIPS	Tertiary (SC), China	158	Prospective, observational	Patients with ARDS risk factors in respiratory and emergency ICUs	Pneumonia (76%), sepsis (36%), trauma (23%), shock (8%), high-risk surgery (3%), AP (4%)
Levitt et al [6]	2014	EALI	Tertiary (SC), USA	256	Prospective observational	Patients with bilateral opacities on chest radiograph on admission	Pneumonia (62%), sepsis (22%), aspiration (5%), trauma (3%), others (9%)

LIPS Lung Injury Prediction Score, *EALI* Early Acute Lung Injury, *ARDS* acute respiratory distress syndrome/acute lung injury, *ALI* acute Lung Injury, *MC* multicenter, *USA* United States of America, *AP* acute pancreatitis, *SC* single center, *ICU* Intensive Care Unit, *ED* emergency department.

Table 2 The Calculation Worksheet of the sLIPS and sEALI

LIPS Components	sLIPS Components	Points assigned	Examples
Predisposing condition	*Predisposing condition*		
Shock	Shock[a]	2	Obesity patient with history of alcohol abuse with shock requiring $FiO_2 > 0.35$: shock + obesity + alcohol abuse + $FiO_2 > 35\%$: 2 + 1 + 1 + 2 = 6
Aspiration	-		
Sepsis	-		
Pneumonia	-		
Pancreatitis	Pancreatitis	0	
Traumatic brain injury	-		
Smoke inhalation	-		
Near-drowning	-		
Lung contusion	-		
Multiple fractures	-		
High-risk surgery	-		
Risk modifiers			
Emergency surgery	-		
Alcohol abuse	Alcohol abuse[b]	1	
Obesity	Obesity (body mass index > 30 kg/m^2)	1	Patients with high respiratory rate and hypoalbuminemia: 1.5 + 1 = 2.5
Chemotherapy	-		
Diabetes mellitus	-		
High respiratory rate	High respiratory rate (> 30 bpm)	1.5	
Low oxygen saturation	Low oxygen saturation ($SpO_2 < 95\%$)	1	
High oxygen requirement	High oxygen requirement ($FiO_2 > 35\%$ or oxygen > 4L/min)	2	
Hypoalbuminemia	Hypoalbuminemia (< 3.5 g/dL)	1	
Acidosis	Acidosis (pH < 7.35 arterial or < 7.32 venous)	1.5	
EALI Components	*sEALI Components*		
Immune suppression	-		Patients requiring oxygen > 6 L/min with high respiratory rate: 2 + 1 = 3
Oxygen 2 to 6 L/min	Oxygen 2 to 6 L/min	1	
Oxygen > 6 L/min	Oxygen > 6 L/min	2	
High respiratory rate	High respiratory rate (> 30 bpm)	1	

sLIPS simplified Lung Injury Prediction Score, *sEALI* simplified Early Acute Lung Injury, *LIPS* Lung Injury Prediction Score, *FiO_2* fraction of inspired oxygen, *SpO_2* oxygen saturation

[a]Definition of shock: use of vasopressors (epinephrine, phenylephrine, dopamine, noradrenaline, or vasopressin) OR Both of 1–2 below: 1. Any of the following: mean arterial pressure < 65 mmHg, systolic blood pressure < 90 mmHg, systolic blood pressuredecrease ≥ 40 mmHg from baseline; 2. AND inadequate tissue perfusion (any of the following): on physical examination, altered mental status not explained by other causes other than the hemodynamic status, urine output < 0.5 ml/ kg / hour (disregard first urine output measure), central venous oxygen saturation single draw or continuous monitoring (< 70%), lactate > 4 mmol/L without known acute or chronic liver disease, arterial pH < 7.32;

[b]Definition of alcohol abuse: known diagnosis ever in the patient's lifetime of chronic alcoholism; OR a previous admission for alcohol detoxification or alcohol withdrawal; OR trauma related to alcohol use; OR alcohol consumption of > 14 drinks a week for males or > 7 drinks a week for females; or binges consisting of > 5 drinks

[29], high oxygen requirement [29], hypoalbuminemia [37, 48], and acidosis [37]. EALI has 3 categories which ranges from 0 to 4. None of the patients in the study has immune suppression [49] on admission, then the sEALI contains 2 components (oxygen requirement, respiratory rate), which ranges from 0 to 3. Standardized definitions were used to characterize these variables, as previously described, and these two scores were calculated on admission. The original LIPS, original EALI, the calculation worksheet of sLIPS, sEALI, and the examples of how to use them are presented in Table 2. More details of these study variables are described in Supplementary Materials and Methods.

Management of AP

AP patients were managed based on the International Association of Pancreatology and American Pancreatic Association Guidelines [50] and this did not overtly differ between the two centers.

Management of Respiratory Dysfunction

Once AP patients admitted to wards, patients have continuation of oxygen requirement evaluation and titration. Level of supplemental oxygen was guided by maintaining a peripheral oxygen saturation ≥ 95%. For patients whose peripheral oxygen saturation was consistently ≥ 95% while receiving less than 6 L/min, nurses went to the bedside three times daily to titrate down the level of supplemental oxygen to maintain a minimum oxygen requirement. For safety reasons, patients already receiving > 6 L/min, facemask oxygen, or non-invasive positive-pressure ventilation were not titrated. Indications for non-invasive positive-pressure ventilation were described in our previous published studies [19]. Indications for invasive mechanic ventilation are mastered by experienced critical care medicine specialists in both centers, based on current guidelines [51].

Clinical Outcomes

Patients were followed up until hospital discharge or death. The primary outcome was progression to PARF as defined by the modified Marshall scoring system in the revised Atlanta criteria ($PaO_2/FiO_2 < 300$ mmHg lasted ≥ 48 h) [11, 52]. Secondary outcomes included multiple organ dysfunction syndrome (MODS) [53], admission to Highly Dependent Unit (HDU)/ICU, invasive mechanical ventilation (IMV), local pancreatic complications, necrosectomy, length of hospital stay (LOHS), and overall mortality followed up to 3 months after hospital discharge. Other definitions for etiologies, comorbidities, and other study variables are shown in Supplementary Material and Methods.

Statistical Analysis

Categorical data are expressed as number and percentage and compared by χ^2 test (or Fisher's exact test). Continuous data are presented as median with 25th-75th percentile and compared using Mann–Whitney *U* test if distribution was skewed. Baseline variables were compared between groups using univariate analysis. Risk factors with a *P* value < 0.2 were then entered into a multivariate model [54]. Discrimination and calibration of the sLIPS for identifying patients who progressed to PARF were compared to the sEALI and existing clinical scoring systems by the area under the receiver-operator characteristic curve (AUROC). We also calculated the net reclassification index (NRI) [43]. A two-sided $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS® 26.0 (IBM, Armonk, New York).

Results

Characteristics of Patients

The training cohort of 912 AP patients from Chengdu, 16% (145/912) developed PARF of whom 18.6% (27/145) died. The validation cohort of 1033 AP patients from Nanchang [42] met the eligibility criteria (Supplementary Fig. 1), 22% (228/1033) developed PARF of whom 19.7% (45/228) died. Compared with the training cohort, patients in the validation cohort had a higher severity of illness (Supplementary Table 1a) and a worse clinical outcome (after adjusting baseline variables from the univariate analysis with $P < 0.2$; Supplementary Table 1b). In both cohorts, AP patients with PARF were older and had increased body mass index, tertiary referral rates, severity (all $P < 0.05$), and worse secondary outcomes (including single persistent organ failure, MODS, HDU/ICU admission, need for IMV, acute necrotic collection, necrosectomy, and overall mortality, all $P < 0.05$) (Table 3).

Admission sLIPS and sEALI Scores

At the time of admission, patients with PARF had significantly higher incidence of shock, high respiratory rate, low oxygen saturation, hypoalbuminemia, acidosis, and higher oxygen requirement (all $P < 0.05$; Table 4) as well as higher median sLIPS (2 vs 0, $P < 0.001$; Table 4) and sEALI (1 vs 1, $P < 0.001$; Table 4). Patient distributions for each category and admission scores of the sLIPS and sEALI scores in the PARF and non-PARF groups in both cohorts are shown in Supplementary Table 2, Figs. 2 and 3 respectively.

Prediction of PARF

Performance of the sLIPS

In the training cohort, the sLIPS (range 0 to 7) had an AUROC of 0.87 (95% CI 0.84–0.89) for PARF development, a sLIPS ≥ 2 (recommended cut-off and best performance in this cohort) had a 74% sensitivity (26% of PARF cases were missed), 89% specificity, 56% PPV (6 in 10 patients selected would subsequently be classed as PARF), 95% NPV, and 56% positive post-test probability (in contrast to 16% pre-test probability) (Fig. 1a and Supplementary Table 3).

In the validation cohort, the sLIPS (range 0–7.5) had an AUROC of 0.81 (95% CI 0.78–0.83) for PARF development, a sLIPS ≥ 2 had a 66% sensitivity, 86% specificity, 57% PPV, 90% NPV, and 57% positive post-test probability

Table 3 Baseline Characteristics and Clinical Outcomes of Patients with and Without PARF in Training Cohort and Validation Cohort

	Training cohort ($n=912$)			Validation cohort ($n=1033$)		
	No PARF ($n=767$)	PARF ($n=145$)	P value[a]	No PARF ($n=805$)	PARF ($n=228$)	P value[a]
Demographics						
Age, years, median (25th-75th percentile)	45 (37, 51)	46 (41, 52)	**0.009**	48 (37, 62)	53 (41, 65)	**0.001**
Gender, male, %	522 (68.1)	98 (67.6)	0.923	502 (62.4)	130 (57.0)	0.145
Body mass index, kg/m^2 median (25th-75th percentile)	25.0 (22.9, 27.5)	26.3 (24.0, 28.4)	**< 0.001**	23.5 (21.3, 26.0)	24.2 (20.0, 26.3)	**0.021**
Etiology						
Biliary	175 (22.8)	36 (24.8)	0.593	401 (49.8)	103 (45.2)	0.230
Hypertriglyceridemia	276 (36.0)	59 (40.7)	0.302	280 (34.8)	91 (40.0)	0.213
Alcoholics	57 (7.4)	14 (9.7)	0.397	59 (7.3)	20 (8.8)	0.052
Others	259 (33.8)	36 (24.8)	**0.042**	65 (8.1)	14 (6.1)	0.398
Referral[b], %	384 (50.0)	120 (82.7)	**< 0.001**	330 (41.0)	118 (51.8)	**0.013**
Clinical scoring systems						
SIRS, median (25th-75th percentile)	1 (1, 2)	3 (2, 3)	**< 0.001**	1 (1, 2)	2 (2, 3)	**< 0.001**
Glasgow, median (25th-75th percentile)	1 (0, 2)	2 (2, 3)	**< 0.001**	1 (1, 2)	3 (2, 4)	**< 0.001**
APACHE II, median (25th-75th percentile)	4 (2, 5)	7 (5, 10)	**< 0.001**	7 (4, 9)	10 (7, 14)	**< 0.001**
SOFA, median (25th-75th percentile)	0 (0, 1)	2 (0, 3)	**< 0.001**	1 (1, 2)	2 (1, 3)	**< 0.001**
Clinical outcomes						
Single persistent organ failure						
Respiratory, %	0	145 (100)	**< 0.001**	0	228 (100)	**< 0.001**
Circulatory, %	0	10 (6.9)	**< 0.001**	1	6 (2.6)	**0.001**
Renal, %	3 (0.4)	19 (13.1)	**< 0.001**	6 (0.1)	47 (20.6)	**< 0.001**
MODS, %	0	22 (15.2)	**< 0.001**	0	49 (21.5)	**< 0.001**
HDU/ICU admission[c], %	36 (4.7)	121 (83.4)	**< 0.001**	153 (19.0)	182 (79.8)	**< 0.001**
IMV, %	0	33 (22.8)	**< 0.001**	0	102 (44.7)	**< 0.001**
ANC, %	129 (16.8)	58 (40.0)	**< 0.001**	93 (11.6)	115 (50.4)	**< 0.001**
Necrosectomy, %	20 (2.6)	23 (15.9)	**< 0.001**	12 (0.1)	32 (14.0)	**< 0.001**
Mortality, %	0	27 (18.6)	**< 0.001**	0	46 (20.2)	**< 0.001**

PARF persistent acute respiratory failure, *SIRS* Systemic Inflammatory Response Syndrome, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *MODS* multiple organ dysfunction syndrome, *HDU* Highly Dependent Unit, *ICU* Intensive Care Unit, *IMV* invasive mechanic ventilation, *ANC* acute necrotic collection

[a]Indicates χ^2 (or Fisher's exact test) for qualitative data and Mann–Whitney U test for quantitative data

[b]These are two tertiary referrals from other hospitals

[c]Some predicted severe acute pancreatitis patients were monitored and managed in HDU, but they were confirmed as no PARF eventually

(in contrast to 22% pre-test probability) (Fig. 1b and Supplementary Table 3).

Performance of the sEALI

The sEALI had an AUROC of 0.77 (95% CI 0.74–0.80) for PARF development in the training cohort and an AUROC of 0.74 (95% CI 0.71–0.77) in the validation cohort (Fig. 1 and Supplementary Table 3). A mEALI ≥ 2 had 50% sensitivity, 98% specificity in the training cohort and 46% sensitivity, 98% specificity in the validation cohort (Supplementary Table 3).

Comparing sLIPS, sEALI, and Other Clinical Scoring Systems

In the training cohort, the sLIPS outperformed the sEALI and 3 of the 4 existing clinical scoring systems (SIRS, APACHE II, and SOFA, all $P < 0.05$), and was comparable with Glasgow ($P = 0.09$). In the validation cohorts, the sLIPS outperformed the sEALI and all the 4 existing clinical scoring systems in predicting PARF (all $P < 0.05$; Fig. 1 and Supplementary Table 3). The validation cohort indicated inferior discrimination when compared with the training cohort ($P = 0.023$).

Table 4 Details of the sLIPS Score of Acute Pancreatitis Patients With and Without PARF in Training and Validation Cohorts

Parameters	Training cohort ($n=912$)			Validation cohort ($n=1033$)		
	No PARF ($n=767$)	PARF ($n=145$)	P value[a]	No PARF ($n=805$)	PARF ($n=228$)	P value[a]
Predisposing conditions						
Shock	4 (0.5)	5 (3.4)	**0.007**	7 (0.9)	7 (3.1)	**0.019**
Risk modifiers						
Alcohol abuse %	183 (23.9)	44 (30.3)	0.117	119 (14.8)	42 (18.4)	0.180
Obesity (body mass index > 30 kg/m^2)	62 (8.1)	24 (16.6)	**0.003**	52 (6.5)	22 (9.6)	0.109
Respiratory rate, beats/min, median (25th-75th percentile)	20 (20, 21)	24 (21, 28)	**< 0.001**	20 (20, 21)	24 (20, 32)	**< 0.001**
High respiratory rate (> 30 bpm) %	8 (1.0)	26 (17.9)	**< 0.001**	25 (3.1)	59 (24.6)	**< 0.001**
Low oxygen saturation (SpO_2 < 95%)	24 (3.1)	13 (9.0)	**0.004**	25 (3.0)	37 (16.2)	**< 0.001**
SpO_2, %, median (25th-75th percentile)	99 (98, 99)	98 (96, 99)	**0.004**	97 (96, 98)	97 (96, 98)	**0.001**
High oxygen requirement (FiO_2 > 4L O_2)	16 (2.1)	68 (46.9)	**< 0.001**	17 (2.0)	89 (39.0)	**< 0.001**
FiO_2, %, median (25th-75th percentile)	25 (21, 25)	40 (25, 50)	**< 0.001**	25 (21, 25)	29 (25, 41)	**< 0.001**
Hypoalbuminemia (< 3.5 g/dL)	46 (6.0)	62 (42.8)	**< 0.001**	171 (21.2)	106 (46.5)	**< 0.001**
Albumin, g/dL, median (25th-75th percentile)	44 (40, 46)	37 (32, 42)	**< 0.001**	39 (36, 42)	36 (31, 40)	**< 0.001**
Acidosis (pH < 7.35 arterial) %	28 (3.7)	48 (33.1)	**< 0.001**	46 (5.7)	43 (18.9)	**< 0.001**
Arterial pH, median (25th-75th percentile)	7.43 (7.40, 7.45)	7.38 (7.32, 7.42)	**< 0.001**	7.41 (7.39, 7.43)	7.40 (7.35, 7.44)	**0.001**
sLIPS, median (25th-75th percentile)	0 (0, 1)	2 (1, 4)	**< 0.001**	0 (0, 1)	2 (1, 4)	**< 0.001**

sLIPS simplified Lung Injury Prediction Score, *PARF* persistent acute respiratory failure, *SpO_2* oxygen saturation, *FiO_2* fraction of inspired oxygen

[a]Indicates χ^2 (or Fisher's exact test) for qualitative data and Mann–Whitney U test for quantitative data

In both cohorts, the sEALI was inferior to the sLIPS, but sEALI was comparable with current clinical scoring systems (SIRS, Glasgow, APACHE II, and SOFA) for predicting PARF (Fig. 1 and Supplementary Table 3). The validation cohort indicated similar discrimination when compared with the training cohort ($P=0.336$).

Subgroup Analyses

Subgroup analyses were performed for sLIPS and sEALI in predicting PARF in both training and validation cohorts (Supplementary Tables 4a-e and Supplementary Figs. 4a-e). It was found that restricting the analysis to those admitted with symptoms for less than 24 h, those without organ failure on admission, those with organ failure on admission, those with predicted SAP (Glasgow > 2) [43], those not transferred from another hospital did not significantly change the performance of sLIPS or sEALI in the training or validation cohorts (assessed by AUROC comparison, all $P > 0.05$). In addition, the predictive values of sLIPS and sEALI did not significantly change when restricting to hypertriglyceridemia-associated or biliary AP (data not shown).

Net Reclassification Index of the sLIPS and the sEALI

As assessed by the net reclassification index [5], a sLIPS ≥ 2 and a sEALI ≥ 2 had significant improvement in reclassification compared with existing clinical scoring systems at the current recommended threshold (Supplementary Table 5).

Multivariate Regression Analyses of the sLIPS and the sEALI for Predicting PARF

Each point increase in the sLIPS was associated with increased likelihood of PARF in the training cohort (OR 3.0, 95% CI 2.4–3.8) and validation cohort (OR 2.3, 95%, CI 2.0–2.6). Each point increase in the sEALI was associated with increased likelihood of PARF in the training cohort (OR 4.0, 95% CI 2.8–5.9) and validation cohort (OR 3.7, 95% CI 2.9–4.8) (Table 5). Further, PARF development significantly increased with increasing sLIPS and sEALI (Supplementary Fig. 5).

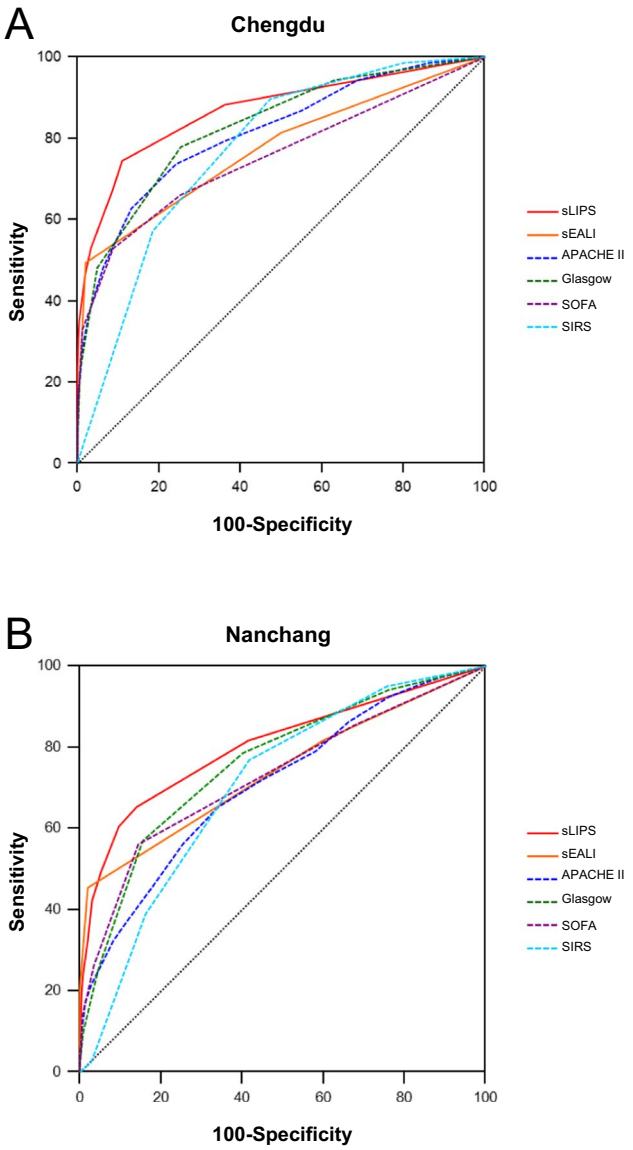

Fig. 1 **A** Receiver operating characteristic curve for persistent acute respiratory failure (PARF) development in the training cohort (West China Hospital of Sichuan University in Chengdu). The area under the receiver operating characteristic curve (AUROC) of simplified Lung Injury Prediction Score (sLIPS) was 0.87 (95% CI 0.84–0.89), which was outperformed Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome scores, and was comparable with Glasgow. The AUROC of simplified Early Acute Lung Injury (sEALI) was 0.77 (95% CI 0.74–0.80), which was comparable with these four existing clinical scoring systems. **B** Receiver operating characteristic curve for PARF development in the validation cohort (First Affiliated Hospital of Nanchang University in Nanchang). The AUROC of sLIPS was 0.81 (95% CI 0.78–0.83), which was outperformed sEALI and the existing clinical scoring systems. The AUROC of sEALI was 0.74 (95% CI 0.71–0.77), which was comparable with the existing clinical scoring systems

Discussion

This study investigated and validated the performance of two simplified lung injury scoring tools for predicting PARF ($PaO_2/FiO_2 < 300$ mmHg for > 48 h) in ward AP patients [24–30]. The key findings of this study were that sLIPS and sEALI scores were both significantly increased on admission in PARF patients and sLIPS (≥ 2) was significantly more accurate in predicting PARF than sEALI and existing clinical scoring systems (all $P < 0.05$).

PARF is the most common organ dysfunction/failure in patients with AP [17] and develop ARDS that is indistinguishable from other causes. Some patients are admitted with PARF but most develop it during the first few days of illness. The overall incidence of PARF in this study was 19% which only included patients with pain for less than 48 h. The primary and secondary clinical outcomes were significantly worse in AP patients with PARF. While non-invasive oxygen therapy for PARF is required for many ward patients [19, 21], admission to the ICU for IMV is frequently required. It was found that more than 50% of ICU patients were transferred from the wards rather than admitted from the ED [31–35] Through the early and accurate identification of patients at high risk of early PARF at the time of ED or ward admission, the sLIPS will facilitate the identification of patients who can benefit from interventions to prevent disease progression and aid the timely and efficient enrollment of patients into future PARF prevention trials. It was found that a sLIPS ≥ 2 on admission was the most accurate predictor of PARF and outperformed a sEALI ≥ 2 and other existing clinical scoring systems.

The accurate prediction of patients who will develop PARF is an important objective. Data suggest that physiologic markers of developing PARF/ARDS may not be apparent at time of initial ED admission, but develop over a period of hours to days [55, 56]. Thus, having a single prediction score validated for both ED and non-ICU ward patients should allow earlier identification and initiation treatment as well as significantly increase enrollment into PARF/ARDS prevention trials. In clinical practice, identifying patients at high risk of PARF alerts physicians to avoid specific ''second-hit'' hospital exposures, such as aggressive fluid resuscitation, blood product transfusions, and high tidal volume IMV [24, 28] which will increase the likelihood of developing PARF. Given the limited strategies to improve mortality once PARF develops, early and accurate identification of AP patients who are at high risk of PARF is crucial.

Clinical severity prediction models are being increasingly used in both clinical practice and research in many disease settings [57–59], but a specifically designed tool

Table 5 Details of the sEALI Score of Acute Pancreatitis Patients with and without PARF in Training and Validation Cohorts

Parameters	Training cohort ($n=912$)			Validation cohort ($n=1033$)		
	No PARF ($n=767$)	PARF ($n=145$)	P value*	No PARF ($n=805$)	PARF ($n=228$)	P value*
High respiratory rate (> 30 bpm)	8 (1.0)	26 (17.9)	**< 0.001**	25 (3.1)	59 (24.6)	**< 0.001**
High oxygen requirement						
2–6 L/min	364 (47.5)	47 (32.4)	**0.001**	469 (58.3)	103 (45.2)	**0.001**
> 6 L/min	14 (1.8)	66 (45.5)	**< 0.001**	11 (1.4)	88 (38.6)	**< 0.001**
sEALI, median (25th-75th percentile)	1 (0, 1)	1 (1, 2)	**< 0.001**	1 (0, 1)	1 (1, 2)	**< 0.001**

sEALI simplified Early Acute Lung Injury, *PARF* persistent acute respiratory failure

*Indicates χ^2 (or Fisher's exact test) for qualitative data and Mann–Whitney U test for quantitative data

to predict the development of PARF in AP patients is not available. Thus, developing a respiratory failure-specific, multivariable predictive model that is easy to use is a priority. The criteria for respiratory failure in mechanically ventilated patients are usually based on the SpO_2/FiO_2 ratio [52, 60]. Recently, studies show that the degree of oxygenation impairment by the level of supplemental oxygen required to maintain an oxygen saturation ≥ 90% strongly predicts the progression to early respiratory failure [30]. Thus, oxygen saturation, levels of oxygen requirement, and respiratory rate can be used as pre-defined criteria [29]. In this study, the level of supplemental oxygen was guided by the goal of maintaining a peripheral oxygen saturation ≥ 95%, and not 90%. The reason for this was that there is no direct evidence to support the immediate implementation of permissive hypoxemia [61].

Other risk modifiers included obesity [47], alcohol abuse [40, 46], hypoalbuminemia [37, 48], and acidosis [37]. Obesity is a widely accepted risk factor associated with severity of AP [1, 62]. Alcohol abuse is one of the leading causes of AP [1, 63] and synergistically worsens local pancreas damage with smoking [64]. Hypoalbuminemia is significantly correlated with fluid retention, development of ARDS, and poor respiratory outcome in patients with sepsis [48]. Study shows hypoalbuminemia represents an independent risk factor for severity and mortality in AP, and it shows a dose-dependent relationship with local complications, organ failure, and length of stay [65]. Arterial pH at presentation is useful early marker for predicting adverse outcome in AP [66–68].

Nearly six in ten patients with sLIPS ≥ 2 will develop PARF during the hospitalization. Increasing sLIPS and sEALI scores were significantly associated with the development of PARF, similar to other studies [24, 25, 30, 36]. Our findings are also consistent with earlier studies that used the LIPS to predict ARDS in the ward critical care, ED and ICU (AUROC range 0.70 to 0.84) [24–26]. This study presented significantly more specific (89% vs 37%) but less sensitive (74% vs 97%) (Table 6). It was notable that sLIPS ≥ 2 performed better in the present study (PPV 57%) in predicting PARF than the other studies: hospital ward LIPS study (17%) [36], ED LIPS study (18%) [24], and ICU LIPS study (46% or 24%) [25]. In regard the prediction performance of the sEALI, this study showed relatively unsatisfactory discrimination (AUROC 0.85) and being less sensitive (50% vs 89%), but more specific (98% vs 75%), when compared with early studies [30]. When restricted to patients who admitted less than 24 h after symptoms onset, patients with organ failure on admission, patients without organ failure on admission, predicted SAP patients, non-transferred patients, or different etiologies, the performance of the sLIPS and the sEALI did not significantly change compared with the full cohorts. These results may help to extrapolate our findings to these subgroup populations.

When compared with the training cohort, the validation cohort indicated similar discrimination in the sEALI, but inferior discrimination in the sLIPS. Differences of the sLIPS in these two study cohorts may account for the differences in the accuracies of the predictive rules: in particular, the prevalence of PARF was significantly different between the 2 cohorts (16% vs 22%; $P=0.001$), as was the proportion of male (68% vs 61%; $P=0.002$) and transferred patients (55% vs 43%; $P<0.001$).

The sLIPS and sEALI scores have several strengths, which were reasons. Firstly, they have both been validated in different clinical settings and have been strongly associated with PARF/ARDS [30, 36]. Secondly, they are easy to use in clinical practice [30, 36]. Thirdly, they are derived from readily available data on admission which are clearly defined. Fourthly, they both identify at risk patients very early in the course of illness (on admission).

There are several limitations to this study. Other environmental factors include smoking was not included in the sLIPS and sEALI [64]. Further, generalize our findings

Table 6 Univariate and Multivariate Regression Analyses of sLIPS and sEALI in Predicting PARF in Both Cohorts

Variables	Training cohort ($n=912$)				Validation cohort ($n=1033$)			
	Univariable	Multivariable			Univariable	Multivariable		
	P value	OR	95% CI	*P* value	*P* value	OR	95% CI	*P* value
Age, year[a]	**0.009**	1.0	0.9–1.0	0.694	**0.001**	1.0	1.0–1.0	0.488
Gender[b]	0.923				0.145	0.7	0.5–1.1	0.117
Time to admission, hour[a]	**< 0.001**	1.0	0.9–1.0	0.408	0.325			
Etiology[b]	0.084	0.9	0.7–1.1	0.497	0.237			
Referral[b]	**< 0.001**	1.7	0.9–3.1	0.110	**0.013**	1.3	0.9–1.8	0.157
APACHE II[a]	**< 0.001**	1.4	1.2–1.5	**< 0.001**	**< 0.001**	1.1	1.0–1.2	**< 0.001**
sLIPS[a]	**< 0.001**	3.0	2.4–3.8	**< 0.001**	**< 0.001**	2.3	2.0–2.6	**< 0.001**
sEALI[a]	**< 0.001**	4.0	2.8–5.9	**< 0.001**	**< 0.001**	3.7	2.9–4.8	**< 0.001**

sLIPS simplified Lung Injury Prediction Score, *sEALI* simplified Early Acute Lung Injury, *PARF* persistent acute respiratory failure, *OR* odds ratio, *CI* confidence interval, *APACHE II* Acute Physiology and Chronic Health Evaluation II

[a]Continuous variable

[b]Categorical variable

to non-tertiary hospital practice may be difficult because data from patients admitted first to these hospitals have not been included. Up to 30% of patients with respiratory failure may have concomitant volume overload [69], patients with suspected left atrial hypertension should be excluded [70], we did not show N-terminal pro-B-type natriuretic peptide data, but we excluded patients who had coexisted congestive heart failure. Evidence regarding the effects of the sLIPS and sEALI on patient outcomes needs to be further studied [5].

In conclusion, this is the first study to confirm that sLIPS and sEALI can be used in patients admitted with AP to identify those at risk of developing PARF. This will prove useful in clinical practice and in future trials designed to reduce the risk of PARF.

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Declarations

Conflict of interest None.

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