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Immature granulocytes: A novel biomarker of acute respiratory distress syndrome in patients with acute pancreatitis

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ABSTRACT

Purpose: To investigate the relationship between immature granulocyte percentage (IG%) and acute respiratory distress syndrome (ARDS) in patients with acute pancreatitis (AP).
Materials and methods: A cohort of 2289 patients with AP was screened; 1933 were enrolled in this prospective multicenter study. Blood samples for IG% analysis were collected on admission and processed using a hematology analyzer. Demographic, radiological, and clinical laboratory data were prospectively collected and reviewed retrospectively.
Results: Increased IG% reflected significant upward tendency of ARDS incidence and severity. Multivariable logistic regression revealed that Acute Physiology and Chronic Health Evaluation (APACHE) II, CT severity index, C-reactive protein, white blood cells, granulocytes, lymphocytes, and IG% (OR 1.297 [95% CI 1.230–1.368]) were independent factors predicting ARDS onset in patients with AP. Receiver operating characteristic curve analysis revealed that area under the curve for APACHE II and IG% were 0.837 (95% CI 0.798–0.876) and 0.821 (95% CI 0.794–0.849), respectively. The combination of APACHE II score and IG% demonstrated excellent predictive power for ARDS incidence.
Conclusions: IG% is a new type of biomarker for ARDS in patients with AP, which may promote timely and efficient identification of individuals at high risk for ARDS in the early stages of disease.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a syndrome of pulmonary edema and inflammation associated with high mortality and morbidity [1-4]. ARDS is characterized by acute bilateral pulmonary infiltrates and impaired oxygenation, and can develop quickly after various pathogenic conditions, such as pulmonary disease, as well as other extra-pulmonary conditions such as severe sepsis and acute pancreatitis (AP) [5]. AP has been established as one of common precipitating factors for the incidence of ARDS. In fact, ARDS remains a major challenge in the clinical management of AP. Epidemiological evidence reveals that ARDS, to a certain degree, is preventable, and interventions delivered in early course of ARDS may improve clinical outcomes [6-8]. Many studies have also suggested that some degree of ARDS is preventable [6,8-10]. However, the major challenge is how to easily and quickly identify individuals at high risk for ARDS.

Great efforts have been made to characterize potential biomarkers capable of screening out patients at high risk for ARDS in the early stage(s) of disease or even at admission, which may greatly promote ARDS prevention and clinical management of AP. These biomarkers,

Abbreviations: AP, acute pancreatitis; ARDS, acute respiratory distress syndrome; IG, immature granulocytes; APACHE II, acute physiology and chronic health evaluation scoring system; AUC, area under the receiver-operating curve; CTSI, CT severity index; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; MOF, multiorgan failure; ICU, intensive care unit; IQR, interquartile range; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; Ang-2, angiopoietin-2; IL-6, interleukin-6; IL-8, interleukin-8; sICAM-1, soluble intercellular adhesion molecule-1; VEGF, vascular endothelial growth receptor; LIPS, lung injury prediction study score.

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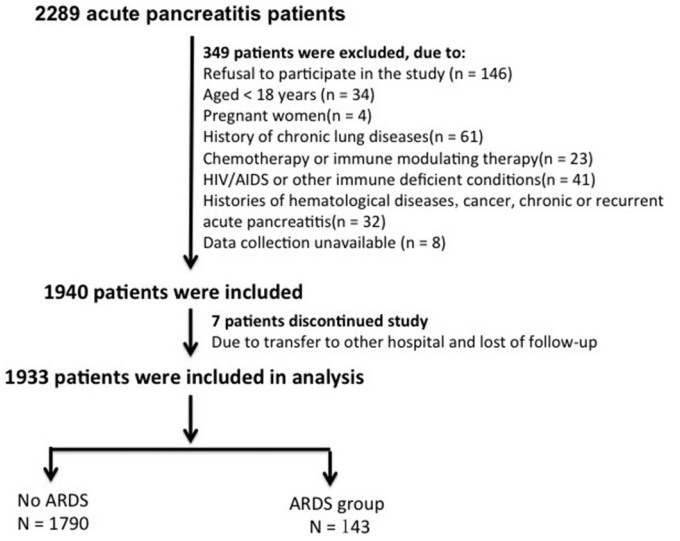

Fig. 1. Patient enrollment flow diagram

including angiopoietin-2 (Ang-2), interleukin-6, interleukin-8, soluble intercellular adhesion molecule-1, vascular endothelial growth receptor and lung injury prediction study (LIPS) score for ARDS diagnosis are, however, far from perfect [9,11-14]. For example, LIPS score and Ang-2 are believed to be currently the most promising ARDS biomarkers; however, the area under the receiver operating characteristic curves of these two biomarkers ranges only between 0.74 and 0.82 [13,15-17]. The discovery of novel biomarkers for easy and early prediction of ARDS onset, therefore, remains a pressing need.

Extensive research has revealed that neutrophils play critical roles in ARDS development in AP patients through release of granular enzymes, and production of reactive oxygen metabolites and cytokines [18-22]. Immature granulocytes (IGs) are neutrophils in the maturation period from progenitor cells in the bone marrow. IGs including promyelocytes, myelocytes and metamyelocytes, usually are not released or detected in peripheral blood in healthy individuals. However, in response to infection, inflammation or other stimuli, IGs can enter the peripheral blood. The early response of IGs make it a candidate indicator of severity of the early innate immune response and inflammation, which may be more accurate than neutrophil counts. Benefiting from quick and accurate detection using cell analysis instruments, evaluation of IG count and percentage (i.e., IG%) has been reported to be a promising option for sepsis prediction, such as mortality in neonatal sepsis and infected patients in the intensive care unit (ICU) [22-25].

However, to date, the link between IG and ARDS has never been addressed in any patient population. Because ARDS could be caused under various pathogenic conditions, the investigation of ARDS during pathogenesis of a specific disease would simplify the question [26]. Considering the dominant role of neutrophils in ARDS and pathogenesis of AP, it is reasonable to speculate that IG could be a novel biomarker of ARDS to screen AP patients at high risk for ARDS. In the present study, we investigated the relationship between IG% and ARDS development in patients with AP, which may improve clinical outcomes in both ARDS and AP.

2. Methods

2.1. Study design and setting

A cohort of 2289 patients that presented with AP was screened from the Hunan Provincial Hospital and the third Xiangya Hospital of Central South University (Changsha, China) between March 2013 and October 2017 (Fig. 1). All AP patients were diagnosed and treated according to the Chinese Guidelines for Management of AP [27]. Exclusion criteria were as follows: age < 18 years; pregnancy; history of chronic lung disease; previous chemotherapy or immune modulating therapy; HIV/AIDS or presence of other immune-deficiency conditions; and medical histories of hematological diseases, cancer, chronic or recurrent AP. Demographic, radiological and clinical laboratory data were prospectively collected and reviewed retrospectively. Informed consent was obtained from each patient before enrollment in the study, which was approved by the Ethics Committee of the Hunan Provincial Hospital the third Xiangya Hospital of Central South University.

2.1.1. Characteristics of the subjects and data collection

The primary outcome measure of the present study was the development of ARDS during the hospital stay. Blood samples for complete blood count with differential (CBC + DIFF) blood routine analysis were obtained on admission and tested immediately using hematology analyzers (XN-9000 and XE-2100, Sysmex, Kobe, Japan). IG count and IG% were included in the CBC + DIFF routine analysis, using the following formula: IG% = IG count/white blood cells. The Acute Physiology and Chronic Health Evaluation (APACHE) scoring system and CT severity index (CTSI) scores were calculated with blinded view by experienced physicians or radiologists within the first 24 h after admission. CTSI score was calculated from contrast-enhanced CT scan results according to the reference grading system described by Balthazar et al. [28]. ARDS was defined according to the Berlin definition [29]. Circulatory failure, pulmonary failure, and renal failure were defined according to revision of the Atlanta classification and definitions [30]. Persistent multi-organ failure (MOF) was defined as failure of ≥2 organs and lasting >48 h.

2.2. Statistical analysis

Continuous variables are expressed as means ± standard deviations, or medians with interquartile ranges, as appropriate. Differences in continuous variables between patients with and without ARDS were tested using the Student's *t*-test or Mann-Whitney *U* test, depending on variable distribution. Categorical variables are expressed as frequencies and percentages. Differences in categorical variables between patients with and without ARDS were tested using Pearson's chi-squared test or Fisher's exact test, as appropriate. To assess the association between IG% and ARDS, a multivariable logistic regression analysis was

Table 1
Demographics and clinical characteristics of ARDS in prospective acute pancreatitis cohort ($n = 1933$).

Variables	NO ARDS	ARDS	*P*
N	$N = 1790$	$N = 143$	
Median age, years (IQR)	49 (40–60)	49 (42–60)	0.74
Male sex, N (%)	1059 (58.6%)	87 (60.8%)	0.66
APACHE II	5.00 (3.00–7.00)	9.00 (7.00–13.00)	<0.001
CTSI	4.00 (3.00–5.00)	6.00 (4.00–8.00)	<0.001
Etiology			0.06
Biliary, N (%)	812 (45.3%)	65 (45.5%)	
Alcohol, N (%)	102 (5.7%)	7 (4.9%)	
Hypertriglyceridemia, N (%)	742 (41.5%)	69 (48.2%)	
Others, N (%)	134 (7.5%)	2 (1.4%)	
ICU need, N (%)	99 (5.5%)	112 (78.3%)	<0.001
Median ICU stay (days, IQR)	0 (0.0–0.0)	5.0 (1.0–11.0)	<0.001
Pancreatic necrosis (N, %)	189 (10.6%)	127 (88.8%)	<0.001
Mortality, N (%)	12 (0.7%)	29 (20.3%)	<0.001
Persistent MOF (N, %)	196 (10.9%)	139 (97.2%)	<0.001
CRP(mg/L)	0.80 (0.80–25.75)	161.00 (0.80–239.00)	<0.001
PCT(ug/L)	0.10 (0.10–0.10)	0.69 (0.10–4.27)	<0.001
White blood cell($x10^9$/L)	11.90 ± 5.17	14.54 ± 7.12	<0.001
Granulocyte($x10^9$/L)	9.70 ± 5.07	12.35 ± 6.98	<0.001
Lymphocyte($x10^9$/L)	0.50 (0.30–1.20)	2.00 (1.00–5.50)	<0.001
IG%	0.50 (0.30–1.20)	2.00 (1.00–5.50)	<0.001

IQR: interquartile range; APACHE II: acute physiology and chronic health evaluation scoring system; CTSI: CT severity index; ICU, intensive care unit; SAP: severe acute pancreatitis; MOF, multiorgan failure; ARDS: acute respiratory distress syndrome; CRP: C reactive protein; PCT: procalcitonin; IG%: immature granulocyte percentage.

performed. For discrimination of the prediction according to IG%, receiver operating characteristic (ROC) curves were generated; a two-sided $P < .05$ was considered to be statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient demographics and clinical characteristics

Between March 2013 and October 2017, 2289 patients with AP from the Hunan Provincial Hospital and the third Xiangya Hospital of Central South University were subjected to ARDS risk screening in the authors' hospital. A total of 1933 patients were enrolled in the study (Fig. 1), and 143 (7.4%) developed ARDS at a median of 2.5 days after admission. Demographic information and clinical characteristics of the patients are summarized in Table 1. There were no significant differences in age ($p = .74$), etiology ($P = 0.06$), or male sex ($P = .66$) between the non-ARDS and the ARDS groups. Compared with the non-ARDS group, patients with ARDS had higher ICU requirements (78.3% versus [vs] 5.5%; $P < .001$), median ICU stay (5.0 vs 0.0; $P < .001$), pancreatic necrosis (88.8% vs 10.6%; $P < .001$), mortality (20.3% vs 0.7%; $P < .001$), persistent MOF (97.2% vs 10.9%; $P < .001$). Compared with non-ARDS group, the levels of APACHE II, CTSI, C-reactive protein (CRP), procalcitonin (PCT), white blood cells, granulocytes, lymphocytes and IG% were significantly increased in the ARDS group (all $P < .05$) (Table 1).

3.1.1. Biomarkers and ARDS severity

Based on the Berlin definition, 143 ARDS patients were divided into a mild group ($n = 67$ [46.9%]), moderate group ($n = 36$ [25.2%]), and severe group ($n = 40$ [28.0%]). The IG% level in the severe group was significantly higher than in the moderate group (8.00 vs 2.90; $P < .001$) and the mild group (8.00 vs 1.10; $P < .001$) (Fig. 2A). Furthermore, according to the normal upper limit (0.5%) and the levels of IG%, all patients were divided into five groups (Fig. 2B). According to IG%, all 1933 AP patients were divided into a < 0.5% group ($n = 779$, [one case of ARDS (0.1%)]), a 0.5–1% group ($n = 542$ [38 ARDS cases (7.0%)]), a 1–2% group ($n = 280$ [36 ARDS cases (12.9%)]), a 2–5% group ($n = 176$ [32 ARDS cases (18.2%)]), and a > 5% group ($n = 136$ [36 ARDS cases (26.5%)]). As shown in Fig. 2B, a significant upward tendency of ARDS incidence was observed with increased IG%. There were no significant differences in age ($P = .30$), etiology ($P = .736$), male sex ($P = .672$), median ICU

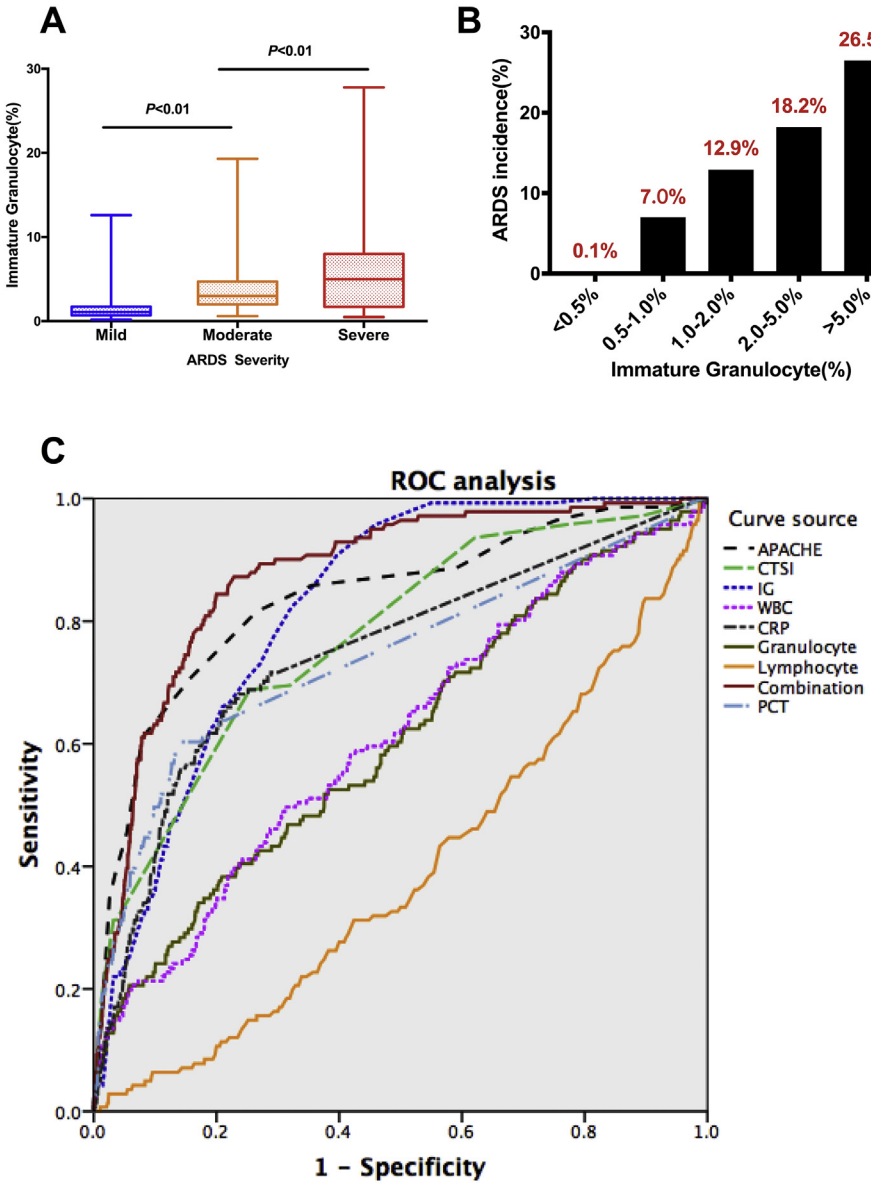

Fig. 2. Immature granulocytes(%) and ARDS

Table 2
Demographics and clinical characteristics of mortality in ARDS cohort (n = 143).

Variables	ARDS survivor	ARDS non-survivor	*P*
N	*N* = 114	*N* = 29	
Median age, years (IQR)	48 (41.0–58.0)	52 (47.0–65.0)	0.30
Male sex, N (%)	68 (59.6%)	19 (65.5)	0.672
APACHE II	9.00 (7.00–12.00)	10.00 (8.00–16.0)	0.05
CTSI	5.00 (0.00–11.00)	6.00 (4.00–8.00)	0.732
Etiology			0.736
Biliary, N (%)	52 (45.6%)	13 (44.8%)	
Alcohol, N (%)	6 (5.3%)	1 (3.4%)	
Hypertriglyceridemia, N (%)	54 (47.4%)	15 (51.8%)	
Others, N (%)	2 (1.8%)	0 (0.00%)	
ICU need, N (%)	84 (73.7%)	28(96.6%)	<0.001
Median ICU stay (days, IQR)	5.00(0.00–11.00)	5.00 (3.00–13.00)	0.304
Pancreatic necrosis (N, %)	101 (88.6%)	26 (89.7%)	1.00
Persistent MOF (N, %)	110 (96.5%)	29 (100.0%)	0.582
CRP(mg/L)	163.0 (0.80–237.00)	108.0 (0.80–291.0)	0.74
PCT(ug/L)	0.61 (0.10–3.50)	1.15 (0.10–19.68)	0.26
White blood cell($x10^9$/L)	14.94 ± 7.37	12.92 ± 5.87	0.17
Granulocyte($x10^9$/L)	12.61 ± 6.80	11.29 ± 7.69	0.86
Lymphocyte($x10^9$/L)	0.89 (0.66–1.23)	0.75 (0.45–1.34)	0.28
IG%	2.00 (1.00–5.00)	5.00 (1.30–8.00)	0.07

IQR, interquartile range; APACHE II: acute physiology and chronic health evaluation scoring system; CTSI: CT severity index; ICU, intensive care unit; SAP: severe acute pancreatitis; MOF, multiorgan failure; ARDS: acute respiratory distress syndrome; CRP: C reactive protein. PCT: procalcitonin. IG%: immature granulocyte percentage.

stay ($P = .304$), pancreatic necrosis ($P = 1.00$) or persistent MOF ($P = .582$) between the ARDS survivor group and the ARDS non-survivor group (Table 2). Compared with the non-ARDS group, there were no significant difference in APACHE II, CTSI, CRP, PCT, white blood cells, granulocytes, lymphocytes and IG% of the ARDS group (all $P > .05$) (Table 2). No statistically significant associations between IG% and mortality were detected.

3.1.2. ROC analysis

Multivariable logistic regression revealed that APACHE II (adjusted OR 1.459 [95% CI 1.380–1.542]), CTSI (adjusted OR 1.714 [95% CI 1.568–1.872]), CRP (adjusted OR 1.008 [95% CI 1.007–1.010]), white blood cells (adjusted OR 1.079 [95% CI 1.050–1.110]), granulocytes (adjusted OR 1.083 [95% CI 1.053–1.114]), lymphocytes (adjusted OR 0.486 [95% CI 0.335–0.706]), and IG% (adjusted OR 1.297 [95% CI 1.230–1.368]) were independent factors for predicting ARDS onset in patients with AP (Table 3).

Moreover, ROC analysis demonstrated that areas under the curve (AUC) of APACHE II and IG% for predicting ARDS were 0.837 (95% CI 0.798–0.876) and 0.821 (95% CI 0.794–0.849), respectively (Table 4, Fig. 2C). ROC curve analysis demonstrated that the AUC of IG% was greater than those of CTSI, CRP, white blood cells, granulocytes, and lymphocytes. Furthermore, ROC analysis also revealed that the AUC of IG% to predict ARDS was, in part, comparable with APACHE II scores. In addition, the APACHE and IG% had the largest AUC values, which were selected for combination. The combination of APACHE and IG% demonstrated excellent predictive power for ARDS incidence in AP patients, which was higher than any of these biomarkers alone (Fig. 2C).

Table 3
Prognostic factors for predicting ARDS in AP patients.

Variables	OR (95%CI)	*P* value	Adjust OR* (95%CI)	*P* value
APACHE II	1.428 (1.356–1.503)	<0.001	1.459 (1.380–1.542)	<0.001
CTSI	1.720 (1.575–1.878)	<0.001	1.714 (1.568–1.872)	<0.001
Pancreatic necrosis	67.238 (39.310–115.537)	<0.001	73.873 (42.507–128.386)	<0.001
CRP (mg/L)	1.008 (1.006–1.008)	<0.001	1.008 (1.007–1.010)	<0.001
PCT (μg/L)	1.008 (1.000–1.016)	0.05	1.008 (1.000–1.016)	0.054
WBC ($\times10^9$/L)	1.080 (1.051–1.110)	<0.001	1.079 (1.050–1.110)	<0.001
Granulocyte ($\times10^9$/L)	1.080 (1.051–1.110)	<0.001	1.083 (1.053–1.114)	<0.001
Lymphocyte ($\times10^9$/L)	0.520 (0.363–0.744)	<0.001	0.486 (0.335–0.706)	<0.001
IG%	1.293 (1.227–1.362)	<0.001	1.297 (1.230–1.368)	<0.001

* Adjust OR: Adjusted for possible confounding factors as well as age, gender and etiology; APACHE II: acute physiology and chronic health evaluation scoring system; CTSI: CT severity index; ARDS: acute respiratory distress syndrome; OR: odds ratio; CRP: C reactive protein; PCT: procalcitonin; WBC: white blood cell; IG%: immature granulocyte percentage;

4. Discussion

To the best of our knowledge, this was the first and largest multicenter prospective investigation focusing on the association between IG% and ARDS. We found a clear upward tendency of ARDS with increases in IG% on admission in patients with AP. More importantly, we also demonstrated that IG% could discriminate between AP patients with and without risk for ARDS. The addition of IG% to the panel of clinical predictors would provide better discriminative ability in stratifying patients with high risk for ARDS.

ARDS is a clinical syndrome with a variety of pathophysiological processes, and could develop rapidly after various pathogenic conditions such as pneumonia, severe sepsis, trauma, aspiration, and AP. In this study, we investigated predictors for ARDS development in subphenotypes of AP patients, which would improve efficiency in early prediction and diagnosis of ARDS. Early recognition of patients at high risk for ARDS is critical for improving clinical management and outcomes [8,15,31-33]. The challenge is how to rapidly identify patient populations at high risk for ARDS in the early stages of disease. In previous studies, numerous protein biomarkers, including inflammatory cytokines, endothelial proteins, among others, have been investigated as candidates for ARDS prediction [9,11,13,14,16,32,34]. However, to date, no marker has demonstrated the ability to supplant current clinical criteria for ARDS diagnosis and management.

IG counts have been traditionally determined using manual smear examination, with low accuracy and poor reproducibility. Benefiting from advances in modern technology, however, IG% can be provided by current automatic hematology analyzers within minutes and with high accuracy. This means that IG% can be a potential practical biomarker. The majority of previous research investigating IG% has focused on early and rapid diagnosis of bacterial infections and sepsis. To date, there has been only one report addressing the possibility of IG% as an independent biomarker for early prognosis of severe AP [34]. However, conclusions from that study were quite limited because only 12 severe AP patients were included [35]. Furthermore, the predictive value of IG% for ARDS associated with AP was not investigated in this report. To date, the relationship between IG% with ARDS associated with AP remains unknown.

Compared with previously studied protein biomarkers, IG% is a new type of biomarker. In the present study, IG% demonstrated the ability to predict ARDS risk and development. Additionally, IG% was independently associated with the occurrence of ARDS in patients with AP. Our ROC analysis revealed that IG% is a potential indicator of ARDS incidence, which has predictive power similar or partially greater than other biomarkers such as Ang-2, interleukin-8, LIPS score and vascular endothelial growth receptor [13,14,26,32]. CRP, APACHE II, and CTSI scores are classical predictive indicators that have been widely applied in AP, and have demonstrated good correlations with clinical courses and AP outcomes. In the present study, our ROC analysis revealed that IG% was similar or partially greater than these biomarkers for the prediction of ARDS. More importantly, IG% tests are included in the CBC + DIFF routine analysis, which can be available within minutes. This suggests that IG% could serve as one of the most simple and practical biomarkers for prediction of ARDS without additional cost. Moreover, it also suggests that IG% could facilitate accurate identification of AP patients at high risk for ARDS at admission, which could greatly promote timely enrollment of this patient population for the study of ARDS mechanisms and prevention development.

Table 4
The receiver operating characteristic curves for ARDS prediction.

Variables	AUC (95% CI)	P^* Value	Cut-off	Sensitivity	Specificity
APACHE II	0.837 (0.798–0.876)	0.000	6.50	81.6%	73.5%
CTSI	0.772 (0.731–0.814)	0.000	4.50	69.5%	68.0%
WBC ($\times 10^9$/L)	0.611 (0.561–0.662)	0.000	10.00	73.8%	39.6%
CRP (mg/L)	0.747 (0.700–0.794)	0.000	3.46	71.6%	71.1%
PCT (μg/L)	0.740 (0.690–0.791)	0.000	0.13	63.1%	79.7%
Granulocyte ($\times 10^9$/L)	0.606 (0.556–0.657)	0.000	5.89	85.8%	24.2%
Lymphocyte ($\times 10^9$/L)	0.393 (0.345–0.441)	0.000	0.54	83.7%	10.1%
IG%	0.821 (0.794–0.849)	0.000	0.65	90.8%	60.4%
Combination	0.876 (0.848–0.905)	0.000	8.77	87.2%	77.1%

* The p value obtained by comparing AUC with 0.5. APACHE II: acute physiology and chronic health evaluation scoring system; CTSI: CT severity index; ARDS: acute respiratory distress syndrome; OR: odds ratio; CRP: C reactive protein; PCT: procalcitonin; WBC: white blood cell; IG%: immature granulocyte percentage; Combination: APACHE II and IG% combination.

In addition, ARDS is a systemic syndrome involving various biochemical and cellular processes. Combination of multiple biomarkers to diagnose ARDS could provide slightly higher sensitivity and specificity than any individual biomarker. In the present study, the combination of APACHE II score and IG% was found to be the most optimal method for predicting ARDS among patients with AP. It also suggested that IG% could be a good substitute and supplementary biomarker for ARDS diagnosis and clinical management.

The present investigation had one particular strength. This was a multicenter prospective cohort study involving a large sample size from a diverse patient population from both academic and regional hospitals. Furthermore, IG% results were made available within minutes without additional cost, indicating that IG% could be used to identify patients at high risk for ARDS in the early stage, usually before ICU admission. Early identification and subsequent intervention to prevent or minimize secondary injury could greatly affect disease progression and deterioration in clinics. More importantly, IG% could also help effectively facilitate enrollment of patients for future mechanistic studies and ARDS prevention trials.

Our study, however, also had limitations that should be addressed. Although IG% has the potential to be a simple and practical biomarker for the prediction of ARDS development in AP patients, it remains unclear whether IG% could serve as an early marker for ARDS in other pathogenic conditions such as pneumonia, severe sepsis, trauma, or aspiration. Therefore, the association between IG% and ARDS in critically ill patients should be further confirmed in a multi-center, prospective cohort study.

Compared with previously studied protein biomarkers, IG% is a totally new type of biomarker of ARDS in patients with AP. Nevertheless, IG% is a biomarker that could be tested within minutes without additional cost, which would help identify patients at high risk for ARDS in the early stages of disease. More importantly, IG% could also help to efficiently screen patient populations at high risk for ARDS for future investigations of ARDS mechanisms and prevention trials.

Ethics approval and consent to participate

Written informed consent was obtained from each patient before the study, which was approved by the Ethics Committee of the Hunan Provincial Hospital and the third Xiangya Hospital of Central South University, Hunan, China.

Consent for publication

Consent for publication was obtained from the patients.

Availability of data and materials

The data are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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