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Retrospective Cohort Study

Development and external validation of models to predict severe acute pancreatitis related acute respiratory distress syndrome

Li YL *et al*. SAP and ARDS

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Abstract

BACKGROUND

Acute respiratory distress syndrome (ARDS) is a major cause of death in patients with severe acute pancreatitis (SAP). Although a series of prediction models have been developed for early identification of such patients, the majority are complicated or lack validation. A simpler and more credible model is required for clinical practice.

AIM

To develop and validate a prediction model for SAP related ARDS.

METHODS

Patients diagnosed as acute pancreatitis (AP) from four hospitals located at different regions of China were retrospectively grouped into derivation and validation cohort. Statistically significant variables were identified using the least absolute shrinkage and selection operator regression method. Prediction models with nomograms were further built using multi-logistic regression analysis with these picked predictors. The

discrimination power of new models was compared with some common models. The performance of calibration ability and clinical utility of the prediction models were also evaluated.

RESULTS

Out of 597 patients with AP 139 were diagnosed with SAP (80 in derivation cohort and 59 in validation cohort) and 99 patients were diagnosed with ARDS (62 in derivation cohort and 37 in validation cohort). Four identical variables were identified as independent risk factors for both SAP and ARDS: Heart rate [odds ratio (OR) = 1.05; 95%CI: 1.04-1.07; $P < 0.001$; OR = 1.05, 95%CI: 1.03-1.07, $P < 0.001$], respiratory rate (OR = 1.08, 95%CI: 1.00-1.17, $P = 0.047$; OR = 1.10, 95%CI: 1.02-1.19, $P = 0.014$), serum calcium concentration (OR = 0.26, 95%CI: 0.09-0.73, $P = 0.011$; OR = 0.17, 95%CI: 0.06-0.48, $P = 0.001$) and blood urea nitrogen (OR = 1.15, 95%CI: 1.09-1.23, $P < 0.001$; OR = 1.12, 95%CI: 1.05-1.19, $P < 0.001$). The area under receiver operating characteristic curve was 0.879 (95%CI: 0.830-0.928) and 0.898 (95%CI: 0.848-0.949) for SAP prediction in derivation and validation cohorts, respectively. This value was estimated to 0.892 (95%CI: 0.843-0.941) and 0.833 (95%CI: 0.754-0.912) for ARDS prediction, respectively. The discrimination power of our models was improved compared with that of other widely used models and the calibration ability and clinical utility of the prediction models performed adequately.

CONCLUSION

The present study constructed and validated a simple and accurate prediction model for SAP related ARDS in patients with AP.

Key Words: Acute pancreatitis; Acute respiratory distress syndrome; Nomogram; Calibration; Early identification; Prediction model

Li Y, Zhang D, Xiong Y, Wang R, Gao X, Gong H, Zheng S, Wu D. Development and external validation of models to predict severe acute pancreatitis related acute respiratory distress syndrome. *World J Gastroenterol* 2022; In press

Core Tip: Severe acute pancreatitis (SAP) related acute respiratory distress syndrome (ARDS) affect the mortality of patients with acute pancreatitis. Early identification of patients at high risk for SAP and ARDS can aid clinicians to adopt interventions to stop disease progression. However, current prediction models are either too complicated due to various parameters or unreliable due to lack of validation. This study developed new models to predict SAP and ARDS using only four routine clinical items within 24 h of admission. New models were externally validated and performed as well as or with a higher efficiency than other widely used models.

INTRODUCTION

Acute pancreatitis (AP) is a common event during gastrointestinal surgery and the majority of the patients who present with mild organ injury and self-limited course are diagnosed as mild acute pancreatitis (MAP) or moderately severe acute pancreatitis (MSAP) cases[1,2]. However, it is estimated that approximately 20% patients are critically ill and develop severe acute pancreatitis (SAP), leading to consistent organ failure and a significant incidence in mortality[2,3]. Our previous studies indicated that lung is the most commonly affected organ in SAP[4,5], whereas acute respiratory distress syndrome (ARDS) is recognized as an important cause of respiratory failure with a high mortality rate[6-8]. It's reported that 4%-15% of AP patients were complicated with ARDS[9], while this proportion might be as high as one third in SAP[10]. However, to date, the therapeutic options for SAP and ARDS are very limited. Therefore, it is necessary to identify patients at risk and adopt interventions to prevent MAP or MSAP from progressing to SAP and ARDS. The protective effect of early intervention for patients with predicted SAP or patients at risk of ARDS has been confirmed by numerous clinical trials and meta-analysis studies, although the inclusion criteria for patients are variable according to different studies[11-15].

A plethora of models have been published to predict the risk of SAP in AP patients, including acute physiology and chronic health evaluation II (APACHE-II) score, Ranson criteria, computed tomography severity index (CTSI), and bedside index for severity in acute pancreatitis (BISAP)[16,17]. Lung injury prediction score (LIPS) and other models were also used to evaluate the risk of ARDS in patients with non-AP[18-20]. However, to date the models used to predict ARDS in AP are scarce. Furthermore, the majority of the SAP prediction models are hard to use in practice due to various parameters, complicated computation and dependence on radiological assessment. The majority of the models also lack internal or external validation, which reduces their reliability in other cohorts[16]. Therefore, a new concise model may be more practical in the emergency department in order to identify SAP and ARDS at the early course of AP.

This model should involve limited available clinical data and should not rely on radiological examinations.

The objective of the present study was to develop and validate models to predict SAP and ARDS in patients with AP based on multicenter retrospective cohorts. The comparison of novel models with quick sequential organ failure assessment (qSOFA), systemic inflammatory response syndrome (SIRS) and BISAP is essential in order to display the power of different models with a low number of variables. These models usually contain three, four and five items respectively[21,22].

MATERIALS AND METHODS

Study design and participants

The present study was a multicenter retrospective study. Sample size was calculated with PASS 11.0. Specifically, according to what mentioned above, the proportion of SAP was set to 20%, and the incidence of ARDS in SAP and non-SAP patients was set to 1/3 and 4%, respectively. Considering that the dropout rate was very low in hospitals, we set it to 5%. In the end, with $\alpha = 0.01$ and $\beta = 0.10$, a total of 211 participants were needed. Patients diagnosed with AP between 1 January 2017 and 31 December 2019 were recruited from different regions of China (Peking Union Medical College Hospital and The Sixth Hospital of Beijing at Northern China, The Fourth Affiliated Hospital of Harbin Medical University at Northeastern China, West China Longquan Hospital Sichuan University at Southwestern China). The patients were categorized into the derivation cohort in order to develop a clinical prediction model. The independent external validation cohort consisted of patients diagnosed with AP between 1 January 2020 and 31 May 2021 at the Peking Union Medical College Hospital. AP was diagnosed if at least two of the three following criteria were met: Abdominal pain consistent with AP, serum lipase or amylase levels that were more than three times the upper limit of the normal range and characteristic radiological findings of AP on computed tomography (CT) and magnetic resonance imaging or ultrasonography[23]. SAP was identified by the presence of persistent organ failure for > 48 h[23]. ARDS was diagnosed

based on Berlin definition[24]. Patients aged < 18 years old who lacked the necessary information provided by the Atlanta Classification or relevant etiology information were excluded.

Clinical variables

The following demographic and laboratory data were collected from the electronic medical record system within 24 h of admission: Age, sex, temperature, heart rate (HR), respiratory rate (RR), systolic blood pressure, Glasgow coma score (GCS), white blood counts, hematocrit, platelet, serum electrolyte concentration (K, Na, Ca), creatine, blood urea nitrogen (BUN) and glucose. Other clinical information, such as, admission date, local complication, length of hospital stays, length of intensive care unit stays, mortality and ventilator use, was also collected. Weekend admission corresponded to admission on Saturday or Sunday and local complication included acute peripancreatitc fluid collection, acute necrosis collection, pseudocyst and walled-off necrosis. The ventilator included invasive or noninvasive mechanical ventilation. qSOFA, SIRS and BISAP scores were calculated based on the aforementioned data. All data was collected and checked by two or more authors independently. Missing items were added following review of the clinical records. The data that could not be completed were removed and the complete-case dataset was finally analyzed.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared using χ^2 or Fisher's exact tests. Normally distributed continuous variables were described as the mean ± SD and compared using a two-sided Student's t test. Non-normally distributed continuous variables were expressed as the median with the interquartile range and compared using the Mann-Whitney U test.

Continuous variables were analyzed in their original forms to preserve information[25]. The least absolute shrinkage and selection operator (LASSO) regression method was used to select predictors in the derivation cohort. The prediction models

were further built using multi-logistic regression analysis. The nomogram was formulated based on multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve and the area under ROC curve (AUC) were employed to evaluate the discriminative power of the prediction model, which referred to the ability of a prediction model to differentiate between the subjects that did or did not experience the outcome event[25]. The calibration curves were plotted to measure the predictive accuracy of the model, which reflected the agreement between predictions from the model and observed outcomes. A well-calibrated model indicated that the prediction was lying on or around the 45° line of the calibration plot[25]. Hosmer-Lemeshow (H-L) fit goodness test was used to quantify the calibration curve. The P value was determined by the H-L test. $P > 0.05$ suggested an optimal consistency between model prediction and the criteria required for standard diagnosis. Decision curve analysis (DCA) was used to assess the clinical utility of the model, which indicated he relationship between a model-predicted probability threshold and the relative value of net benefit[25].

Statistical analysis was performed using R 4.0.3[26] and MedCalc 15.8 statistical software. A two-side $P < 0.05$ was considered to indicate a statistically significant difference. The nomogram and calibration curve were plotted using rms package and DCA was plotted using rmda package. ROC was plotted with MedCalc 15.8.

RESULTS

Baseline characteristics

Between January 1 2017 and May 31 2021, 628 patients with AP were recruited from four hospitals and reviewed. The exclusion criteria included the following: Age < 18 (n = 2 patients), lack of Atlanta Classification or etiology (n = 26 patients) and incomplete data (n = 3 patients). Following screening, a total of 407 and 190 patients were involved in the derivation and validation cohorts, respectively. The number of participants in each cohort met the requirement of sample size. The detailed demographic and clinical information were described in Tables 1 and 2.

Predictors and model construction

Four variables (HR, RR, Ca, BUN) were extracted as the predictors of SAP through LASSO regression. Supplementary files shown this process in more detail (see Supplementary Figure 1 and Supplementary Table 1). Multivariable logistic regression revealed that all four variables were independent predictors (Table 3). The probability (PA) of SAP could be calculated according to the following formula: PA = 1/{1 + exp [-(-6.42 + 0.05 × HR + 0.08 × RR - 1.30 × Ca + 0.14 × BUN)]}. Analysis of ARDS obtained similar results (Table 3). The following formula was used for ARDS: PA = 1/{1 + exp [-(-5.46 + 0.05 × HR + 0.10 × RR - 1.78 × Ca + 0.11 × BUN)]}. Two nomogram plots were displayed using prediction models (Figure 1).

Model performance

The new model indicated a great power of discrimination for SAP. Following 1,000 interactions of bootstrapping to minimize the risk of overfitting to the original models, the AUC in the derivation cohort was estimated to 0.879 (95%CI: 0.830-0.928), which was significantly superior to that of SIRS (AUC = 0.808, 95%CI: 0.757-0.859, $P = 0.002$) and qSOFA (AUC = 0.730, 95%CI: 0.672-0.789, $P < 0.001$) and not inferior to that of the BISAP score (AUC = 0.888, 95%CI: 0.847-0.929, $P = 0.6629$) (Figure 2A, Table 4). In addition, the model indicated an optimal behavior in the validation cohort (AUC = 0.898, 95%CI: 0.848-0.949) (Figure 2B). The AUC of the new model in derivation was 0.892 (95%CI: 0.843-0.941) for ARDS prediction, which was superior to SIRS (AUC = 0.815, 95%CI: 0.766-0.864, $P = 0.001$) and qSOFA (AUC = 0.742, 95%CI: 0.678-0.807, $P < 0.001$) and not inferior to BISAP (AUC = 0.871, 95%CI: 0.827-0.916, $P = 0.344$) (Figure 2C, Table 4). Despite the assessment of the model in the validation cohort, its performance was moderate (AUC = 0.833. 95%CI: 0.754-0.912) (Figure 2D). When the cut-off value was set as PA > 25% for SAP prediction, the novel model suggested an optimal performance in the combined dataset (sensitivity 0.78, specificity 0.88) (Table 4). The

best cut-off value was PA > 18% for ARDS prediction, with a sensitivity of 0.78 and a specificity of 0.85 (Table 4).

Graphical assessment indicated a strong agreement between prediction and observation in both new models (Figure 3). The H-L test indicated that the difference between prediction and observation was not significant both in the derivation (χ^2 = 12.675, P = 0.124) and validation cohorts (χ^2 = 5.852, P = 0.664) with regard to SAP prediction. The model for ARDS prediction revealed improved performance with regard to the calibration in the derivation (χ^2 = 3.753, P = 0.879) and validation cohorts (χ^2 = 2.933, P = 0.939).

DCA indicated that if the threshold PA was < 80%, using the new model to recognize and manage SAP had a positive net benefit compared with either the treat-all or treat-none (Figure 4 A). In case the threshold probability was set to < 70%, the prediction and intervention for ARDS also produced net-benefit (Figure 4 B).

DISCUSSION

In the current study, novel prediction models were established for SAP and ARDS in patients with AP. The models were also externally validated and exhibited remarkable discriminative power and high degree of consistency with the observation both in the derivation and external validation cohorts. These models suggested that patients with AP who manifested a higher heart rate, respiratory rate, blood urea nitrogen concentrations and lower serum calcium concentrations at admission exhibited a higher risk of developing SAP and ARDS.

AP is a major cause of acute abdomen. Patients with AP usually present with multiple organ dysfunction syndrome (MODS). Although organ dysfunction is mild and transient (less than 48 h), approximately 20% of patients will proceed to consistent organ failure (more than 48 h), leading to SAP and a high risk of mortality[27]. AP primarily affects the respiratory system and to a lesser extent the renal and cardiovascular systems[23]. ARDS is the critical event, which is noted during lung injury in AP[28]. Cyclooxygenase-2 inhibitors and enteral nutrition have been shown to prevent

SAP, shorten the length of hospital stay and reduce infectious complications and mortality in patients with predicted SAP[11,12,29]. Administration of antiplatelet therapy, withdrawal of prehospital amiodarone treatment and administration of nebulized heparin may decrease the incidence of ARDS, inhibit the progression of lung injury and accelerate the recovery of patients at risk of developing ARDS[13-15,30]. Therefore, early identification of patients at risk of developing SAP and ARDS is clinically significant for improving the prognosis of AP.

Various models have been developed to predict SAP and organ dysfunction for AP management[16]. Although the majority of the models were deficient due to some limitations, such as relatively small sample size, single center study and lack of internal or external validation, several SAP models have been widely used and validated in different cohorts. These validations were performed using APACHE-II score, Ranson criteria, CTSI and BISAP[31-34]. BISAP contains only 5 variables and is much simpler than APACHE-II score (18 items) and the Ranson criteria (11 items). However, their prediction power is equal[35]. In addition, ultrasound is preferred to CT as an efficient and non-radioactive examination used in the emergency department to initially evaluate potential development of AP. Therefore, pleural effusion and CT presentation could not be evaluated in this case in order to gain the BISAP and CTSI scores. Although LIPS is a popular model to predict ARDS for patients at risk, its calculation is considerably complicated[18]. In addition, its original developing cohort involved only a small part of patients with AP. LIPS had not been previously validated in patients with AP.

Therefore, a simple model with a low number of parameters and without radiology findings would be more practical. The novel prediction model reported in the current study involved only four parameters for both SAP and ARDS prediction and all these variables were routinely tested. The discrimination power of the novel model was not inferior to that of BISAP. To the best of our knowledge, the prediction of SAP or ARDS for patients with AP has not been previously assessed by models that were as simple and accurate as this reported in the current study.

Using lasso regression, calcium was identified as a predictor for both SAP and ARDS. Multi-logistic regression analysis indicated that serum calcium concentration was also the independent predictor. The models of the present study were easier to use than the APACHE-II, Ranson, CTSI and BISAP models and demonstrated improved efficacy than the other two simple models, suggesting their potential clinical significance. ARDS was a non-negligible manifestation of MODS in patients with AP. The majority of the models have mainly focused on the severity classification or mortality prediction of ARDS, whereas the identification of ARDS at an early stage is still challenging. Although LIPS was widely used to predict ARDS, the calculation of the LIPS score was complicated for patients admitted to the emergency department, since certain parameters may have been unavailable[18]. The pathogenesis of ARDS involves the activation of signaling pathways, which include various cytokines and inflammatory mediators. Certain molecules, such as IL-6, IL-8, protein C, angiopoietin-2 and microRNAs and specific imaging examinations (X-ray and lung ultrasound) were also identified as predictors of ARDS in single or combined forms[8,36-38]. The data indicated that these new predictors seemed promising. However, the molecules and the examinations identified were not part of the routine clinical practice, which limited their clinical utility. Fei *et al*[10] used an artificial neural network algorithm to predict ARDS following SAP. The model by Fei *et al*[10] indicated high accuracy. However, the variable pancreatic necrosis rate was hard to assess when CT was not used and was not evident in the early course of AP.

The pathogenesis of SAP and ARDS involves a series of acute inflammatory reactions[2,39]. SIRS is widely adopted to assess the severity of diseases associated with acute inflammation. Both HR and RR are used in the SIRS model. Therefore, it is reasonable that both HR and RR were identified as predictors of SAP and ARDS. BUN has been shown to reflect volume depletion, renal function, the quality of resuscitates and even the ischemic injury of the pancreas during AP[40]. It has been reported that BUN can independently predict both SAP and the mortality of SAP[40-44]. Therefore, BUN was also involved in other predictive models of SAP, such as GCS, Ranson criteria

and BISAP in addition to our new model. The levels of BUN have not been used as a direct predictor of ARDS. However, this marker can be used as a predictor of pathogenesis in association with other risk factors, such as pancreatitis[39]. Calcium concentration has been closely associated with AP[45]. Hypocalcemia was quite common in the cohort of the present study and in other AP cohorts, notably in critically ill patients[46]. Elevated cytosolic calcium of pancreatic acinar cells causes premature trypsinogen activation, vacuolization and acinar cell death, which play critical roles in the pathogenesis of AP[47]. However, during the development of certain models for the prediction of SAP, serum calcium was excluded for a variety of factors[48]. Calcium is also involved in the pathogenesis of ARDS as a signaling molecule, leading to paracellular hypermeability through endothelial-junction-cytoskeleton dissociation[49]. The current model suggested that calcium was an independent predictor of SAP and ARDS in AP, indicating the potential of developing novel drugs for the treatment of AP[50]. To the best of our knowledge, the model of the present study was the simplest model used to predict SAP and ARDS within 24 h of AP admission. It is also the first model that involved serum calcium concentration to predict ARDS in AP.

The present study contains several limitations. Initially, organ dysfunction occurred mainly in the first week of AP, whereas accurate onset time was not available in the present study. Therefore, certain patients with SAP or ARDS may be missed. Moreover, the exact onset time of ARDS was not involved, so new model only predicts the risk of ARDS during the whole admission (range from 7 to 15 d) using the scores gained within 24 h of admission. It might not be very appropriate, and new model couldn't tell the clinicians when they should prepare for the possible onset of ARDS neither. Further studies are needed to verify the value of new models on a dynamic time-scale. Secondly, the derivation cohort comprised tertiary and secondary hospitals from different regions of China. However, model validation was performed in a tertiary teaching hospital. Although the result of validation was also encouraging, it is hard to ignore that the incidence of SAP and ARDS in the validation cohort was considerably higher than that of the derivation cohort, which could reduce the generalizability in

primary or secondary class hospitals, where MAP and MSAP exhibited high proportions. Moreover, certain laboratory examination technologies were different among four hospitals, which increased the systemic error of the data. It must be mentioned that mechanical ventilation will attenuate systemic inflammation of ARDS and the effect varies with patterns[51]. It's unavoidable that new score to predict ARDS will also be affected. Unfortunately, detailed information of mechanical ventilation was not collected in this study, and further researches are needed to investigate the influence of different ventilatory patterns on new models. Thirdly, selection bias was inevitable in a retrospective study. Furthermore, any missing value was deleted to obtain a complete-case dataset to be analyzed rather than completed missing data with statistical methods (*e.g.*, multi-imputation), which were not recommended. However, in the present study, only three individuals were removed due to missing data, accounting for a tiny part of the cohort. It was considered that complete data analysis would not affect the overall conclusion. Finally, other common prediction models, such as APACHE-II score, Ranson criteria, CTSI and LIPS were not evaluated due to lack of essential parameters. Therefore, direct comparison among different models was unavailable.

CONCLUSION

Novel models were developed containing only four items to predict SAP and ARDS in patients with AP, which were as accurate as BISAP but much simpler. Serum calcium was identified as an important predictor, indicating a potential new strategy for management of AP. Further prospective studies are required to reveal whether early intervention based on novel prediction models could reduce the incidence of SAP and ARDS and finally improve the outcome of patients with AP.

ARTICLE HIGHLIGHTS

Research background

Acute respiratory distress syndrome (ARDS) is a major cause of death in patients with severe acute pancreatitis (SAP), but simple and credible prediction models are absent.

Research motivation

Use models to predict and early identify patients with SAP and SAP related ARDS, so that clinicians could early manage these patients to decrease mortality during admission.

Research objectives

To develop and verify new models to predict SAP and SAP related ARDS.

Research methods

Clinical data from four centers were retrospectively collected. Items selected with least absolute shrinkage and selection operator regression method were involved in multi-logistic regression to develop the final model in development cohort. New models were than verified in validation cohort and assessed with c-index, calibration curve and decision-curve analysis.
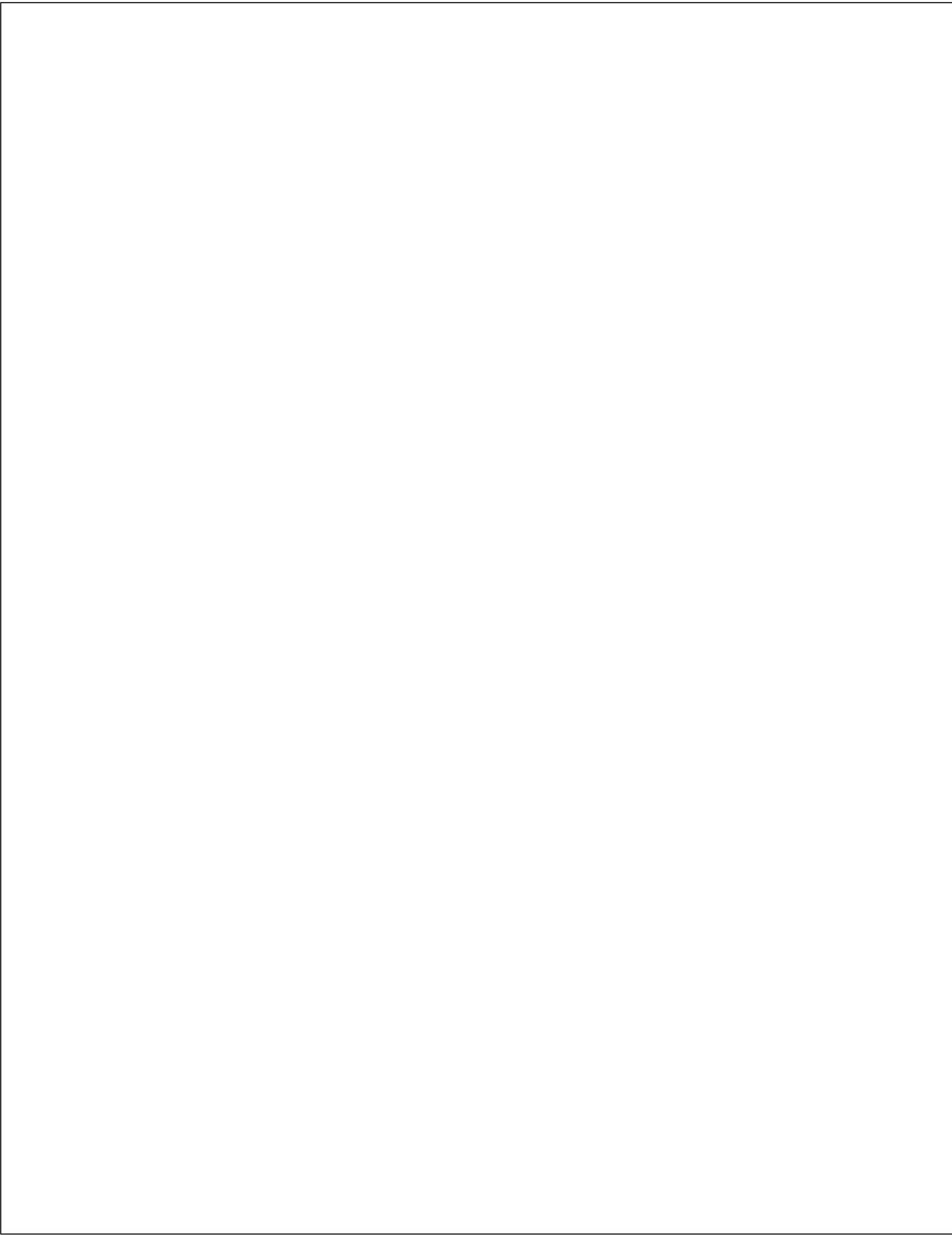
Research results

New models could predict SAP and SAP related ARDS with four easy-available items, and performed well.

Research conclusions

We developed and verified simple and reliable models to predict SAP and SAP related ARDS.

Research perspectives

To verify new models in a larger size of sample, and to investigate the questions raised by reviewer.

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