

Integrated Use of Bedside Lung Ultrasound and Echocardiography in Acute Respiratory Failure

A Prospective Observational Study in ICU

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BACKGROUND: It has been suggested that the complementary use of echocardiography could improve the diagnostic accuracy of lung ultrasonography (LUS) in patients with acute respiratory failure (ARF). Nevertheless, the additional diagnostic value of echocardiographic data when coupled with LUS is still debated in this setting. The aim of the current study was to compare the diagnostic accuracy of LUS and an integrative cardiopulmonary ultrasound approach (thoracic ultrasonography [TUS]) in patients with ARF.

METHODS: We prospectively recruited patients consecutively admitted for ARF to the ICU of a university teaching hospital over a 12-month period. Inclusion criteria were age ≥ 18 years and the presence of criteria for severe ARF justifying ICU admission. We compared both LUS and TUS approaches and the final diagnosis determined by a panel of experts using machine learning methods to improve the accuracy of the final diagnostic classifiers.

RESULTS: One hundred thirty-six patients were included (age, 68 ± 15 years; sex ratio, 1). A three-dimensional partial least squares and multinomial logistic regression model was developed and subsequently tested in an independent sample of patients. Overall, the diagnostic accuracy of TUS was significantly greater than LUS ($P < .05$, learning and test sample). Comparisons between receiver operating characteristic curves showed that TUS significantly improves the diagnosis of cardiogenic edema ($P < .001$, learning and test samples), pneumonia ($P < .001$, learning and test samples), and pulmonary embolism ($P < .001$, learning sample).

CONCLUSIONS: This study demonstrated for the first time to our knowledge a significantly better performance of TUS than LUS in the diagnosis of ARF. The value of the TUS approach was particularly important to disambiguate cases of hemodynamic pulmonary edema and pneumonia. We suggest that the bedside use of artificial intelligence methods in this setting could pave the way for the development of new clinically relevant integrative diagnostic models.

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ABBREVIATIONS: ARF = acute respiratory failure; AUC = area under the curve; LUS = lung ultrasonography; PLS = partial least squares regression; ROC = receiver operating characteristic; TUS = thoracic ultrasonography

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Lung ultrasonography (LUS) has been proposed as a versatile tool for accurate, fast, bedside examination of most acute respiratory disorders.¹ Formerly believed to be poorly accessible to ultrasound, the lung has instead revealed rich and easily reproducible sonographic semiotics.²⁻⁵ It is worth noting that individually, the sensitivity of each LUS feature seems low and highly variable but with a high specificity.⁶ In combination using a tree-based classification model, however, the sensitivity improves and provides a more accurate assessment.⁷

The complementary use of echocardiography has been suggested to contribute importantly to improving the diagnostic accuracy of LUS in patients with acute respiratory failure (ARF).⁸ Actually, it has been hypothesized that only such an integrative approach could give access to an accurate online assessment of lung and heart status and dynamic interactions specifically disrupted in pathological states. A recent study investigated this hypothesis

and explored the clinical relevance of such a combined thoracic ultrasonography (TUS) approach in patients with ARF and demonstrated a significant improvement in initial diagnostic accuracy compared with a standard approach encompassing clinical, radiologic, and biologic data.⁹ Nevertheless, the additional diagnostic value of echocardiographic data when coupled with LUS is still debated in this setting.¹⁰ The extent to which (1) echocardiography can be integrated into a clinically relevant predictive mathematical model encompassing cardiac and pulmonary ultrasound data and (2) the obtained cardiopulmonary ultrasonographic approach (TUS) performs better than the isolated pulmonary approach (LUS) in the acute care management of patients with ARF remains to be seen. The aim of the current study was to compare, for the first time to our knowledge, the diagnostic accuracy of LUS and TUS in patients with ARF, using machine learning methods¹¹ to improve the accuracy of the final diagnostic classifiers.

Materials and Methods

Patients

We prospectively recruited patients consecutively admitted for ARF to two ICUs of a university teaching hospital between October 2012 and April 2013. Inclusion criteria were age ≥ 18 years and the presence of the following criteria of ARF: respiratory rate of at least 25/min, $\text{PaO}_2 < 60$ mm Hg, oxygen saturation as measured by pulse oxymetry $< 90\%$ while breathing room air, and $\text{PaCO}_2 > 45$ mm Hg with arterial $\text{pH} < 7.35$. The ethics committee of the University Hospital of Toulouse, France (Comite Consultatif pour la Protection des Personnes, CHU Toulouse, Ref 2012-A01225-48), approved the therapeutic and investigational procedures and waived the requirement for written informed consent.

Experimental Design

Routine Clinical Assessment: For every patient, standard medical care¹² provided by the senior ICU physician in charge included the following: medical history; physical examination findings; arterial blood gas analysis while breathing room air; 12-lead ECG; chest radiography; and routine blood tests, including plasma levels of cardiac troponin I and B-type natriuretic peptide. ICU physicians were blinded to the ultrasound results.

Pulmonary and Cardiac Ultrasound: As previously described,⁹ all patients underwent a combined cardiothoracic ultrasound test by investigators who did not participate in patient management (B. B., B. R., P. E. M., and S. S.). The investigators used standardized criteria and followed a pattern analysis. Transthoracic echocardiography and lung ultrasound assessment were performed with HP Sonos 5500 (Hewlett-Packard Development Company, LP) and 2- to 4-MHz probes. All patients were studied in the semirecumbent position.

The echocardiographic examination included left ventricular systolic function (visual estimation of the left ventricular ejection fraction at $< 30\%$, 30% to 50% , and $> 50\%$),¹³ left ventricular end-diastolic pressure estimation (pulsed Doppler echocardiography-recorded mitral inflow and Doppler tissue imaging with the sample cursor placed in the lateral mitral annulus to record the following: E-wave velocity, A-wave velocity, e' velocity, and E/A and E/ e' ratios),¹⁴ right ventricular function (assessment of the interventricular septal configuration and dynamic M-mode measurement of the inferior vena cava diameter, including

paradoxical septal motion, right ventricular dilatation, and central venous pressure estimation),^{15,16} and pericardial evaluation (detection of pericardial effusion as either absent or present).¹⁷ For the lung ultrasound examination, the anterior chest wall was delineated from the clavicles to the diaphragm and from the sternum to the anterior axillary line.⁵ The lateral chest walls were divided into three lung regions. The pleural line was defined as a horizontal hyperechoic line visible 0.5 cm below the rib line. A normal pattern was defined as the presence in every lung region of lung sliding with A lines (A profile).¹⁸ Pleural effusion was defined as a dependent collection limited by the diaphragm and the pleura with an inspiratory movement of the visceral pleura from depth to superficial.¹⁹ With the use of TM mode, pneumothorax was defined by the loss of pleural sliding (A' profile) in association with the presence of lung point.²⁰ Alveolar consolidation was defined as the presence of poorly defined, wedge-shaped hypoechoic tissue structures (C profile).²¹ Within the consolidation, hyperechoic punctiform images can be seen that correspond to air-filled bronchi (ie, bronchograms).³ Pleural effusion can also be associated with the patterns of alveolar consolidation (ie, posterolateral alveolar consolidation and pleural effusion syndrome).¹⁹ Alveolar-interstitial syndrome was defined as the presence of more than two B lines in a given lung region (B profile).^{4,22,23} Peripheral vascular Doppler sonography or ultrasonographic assessment of diaphragm activity were not performed because we wanted to integrate this protocol with routine care practice.

Final Diagnosis: The final diagnosis of ARF was determined by two independent senior experts from an examination of the complete medical chart, including all initial clinical findings, as follows: emergency laboratory tests, including plasma levels of cardiac troponin I and B-type natriuretic peptide; chest radiographic data; the results of high-resolution CT imaging (performed in 55% of the patients)^{24,25}; and independent transthoracic Doppler echocardiography performed by a senior cardiologist (performed in 26% of the patients). In case of disagreement between the two experts, a consensus was reached with the help of a third expert. The main diagnoses finally proposed were cardiogenic pulmonary edema, including left-sided heart failure; community-acquired pneumonia; acute exacerbation of chronic respiratory disease; pulmonary embolism; and pneumothorax. To simplify this study, patients given several final diagnoses were subsequently excluded. Validated criteria were used, and response to treatment was specifically analyzed as recommended and described in detail in a previous study.⁹

Statistical Analysis

Continuous data are expressed as mean \pm SD or median (interquartile range) according to their distribution (Kolmogorov-Smirnov test). Categorical variables are expressed as numbers and percentages. Two means were compared with Student *t* test or Mann-Whitney *U* test and two proportions with χ^2 or McNemar test. Spearman rank correlation was used to test linear correlation. Sensitivity, specificity, and diagnostic accuracy were calculated using standard equations²⁶ to evaluate the diagnostic performance of LUS and TUS.

Ultrasound data were split into two time series to enable further analysis. A learning sample (first 67 patients) was used to establish the best classification model, and a validation sample (last 69 patients), which was not used during the previous phase, was used to test the generalization of the model (Fig 1). Next, echocardiographic and lung ultrasound data (used as independent variables) were used to estimate partial least squares regression (PLS)¹¹ to predict four final diagnoses (cardiogenic edema, pneumonia, pulmonary embolism, and pneumothorax) using a unique linear multivariate model (e-Appendix 1, e-Fig 1). Finally, receiver operating characteristic (ROC)²⁷ curves were calculated for each final diagnosis during each testing phase, and the highest sum of sensitivity and specificity was considered the optimal threshold. Positive and negative likelihood ratios were also estimated from this optimal threshold.

The level of agreement among observers for the ultrasound findings was evaluated in a previous study.⁹ All statistical tests were two sided, and

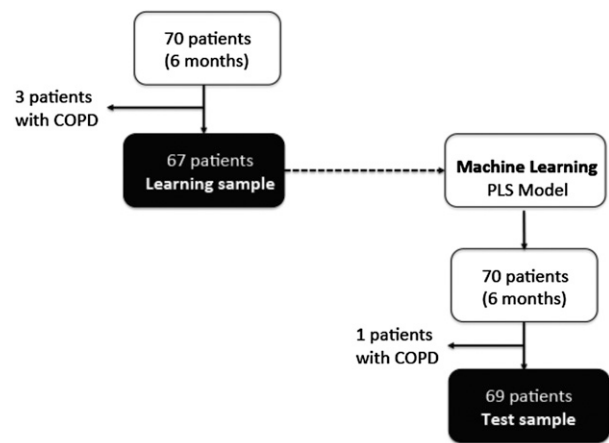


Figure 1 – Flowchart of the patient inclusion process. PLS = partial least squares regression.

$P < .05$ was required to reject the null hypothesis. Statistical analysis was performed with STATISTICA 8.0 software (StatSoft Inc), Stata 10.0 (StataCorp LP), and TANAGRA 1.4.50 (Ricco Rakotomalala, Lyon University, Lyon, France).

Results

Patients

One hundred thirty-six patients with severe ARF (mean age, 68 ± 15 years) were prospectively included in the study. At inclusion, patients had a mean P_{aO_2}/F_{iO_2} ratio of 156 ± 82 (Table 1). The ultrasound assessment was performed without interrupting management at the time of ICU admission (ie, within 16 ± 3 min) and lasted 9 ± 2 min. The final diagnoses established by the experts were acute hemodynamic pulmonary edema ($n = 34$), pneumonia ($n = 77$), pulmonary embolism ($n = 13$), and pneumothorax ($n = 12$). Patients given a final diagnosis of acute exacerbation of chronic pulmonary disease were poorly represented in the cohort ($n = 4$) and subsequently excluded to allow for the elaboration of predictive classifiers. A cardiac and pulmonary ultrasonography assessment was performed in all cases.

Artificial Intelligence Modeling

A three-dimensional PLS model was developed using the ultrasound learning sample data (67 patients). The validity and generalization ability of the obtained mathematical model was tested using an independent group of patients from the same cohort ($n = 69$). Overall, two models were developed to enable a performance comparison between an exclusively lung ultrasound approach (LUS) and an integrative cardiac and pulmonary assessment (TUS). The correlation of each ultrasonographic parameter with the three PLS components

included in the model are shown in e-Appendix 1, e-Figure 1, and e-Table 1.

Comparative Diagnostic Accuracy

Overall, the diagnostic accuracy of TUS was significantly greater than LUS in both the learning and the testing samples (Fig 2). During the learning phase, ROC

TABLE 1] Demographic Data

Demographic	Value
No. patients	136
Age, y	68 ± 15
Sex	
Female	57 (42)
Male	79 (58)
Weight, kg	76 ± 18
Height, cm	167 ± 9
P_{aO_2}/F_{iO_2}	156 ± 82
Tracheal intubation	19 (14)
Use of catecholamine	13 (10)
SAPS II	34 ± 10
Diagnosis	
Cardiogenic edema	34 (25)
Pneumonia	77 (57)
Pulmonary embolism	13 (10)
Pneumothorax	12 (9)

Data are presented as mean \pm SD or No. (%) unless otherwise indicated. SAPS II = Simplified Acute Physiology Score II.

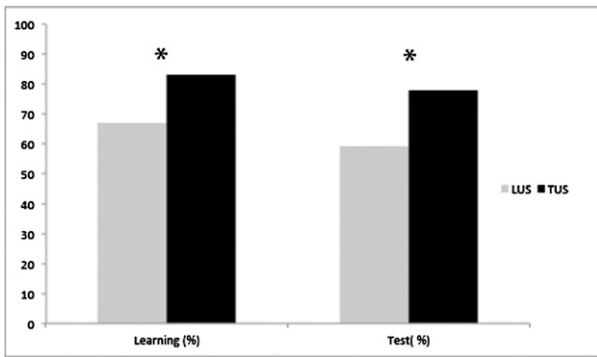


Figure 2 – Comparative diagnostic accuracy. LUS and integrative cardiopulmonary ultrasound (TUS) classifiers were compared against the final diagnosis determined by a panel of experts. Data are shown for both learning and testing periods. * $P < .05$. LUS = lung ultrasonography; TUS = thoracic ultrasonography.

analysis (Fig 3, Tables 2, 3) showed that the TUS area under the curve (AUC) was better than the LUS AUC for the diagnosis of cardiogenic edema ($P < .001$), pneumonia ($P < .001$), and pulmonary embolism ($P = .001$). During the testing phase, the ROC analysis showed that the LUS AUC was also better for the diag-

nosis of cardiogenic edema ($P < .001$) and pneumonia ($P < .001$) but not for the diagnosis of pulmonary embolism ($P = .71$) (Fig 3). Of note, the exclusive use of LUS patterns to detect cardiac edema (B profile) was highly unreliable because B lines were also detected in 33% pneumonia cases (ie, false-positive diagnosis) and absent in 37% of cardiogenic edema cases (ie, false-negative diagnosis). A detailed description of this point is provided in e-Table 2.

Computational Aspects

Opposite to tree-based diagnostic algorithms, the PLS model adequately managed three important issues frequently encountered in a large-scale dataset. First, the PLS model significantly reduced the observed colinearity between variables (e-Table 3). Second, missing data were taken into account during the analysis phase and elude further exclusion of patients. If we focus on the testing population, 7% of pulmonary and 10% of cardiac ultrasonographic data were missing at the recording time (e-Table 2). Finally, a mixed diagnosis could be accurately assessed using

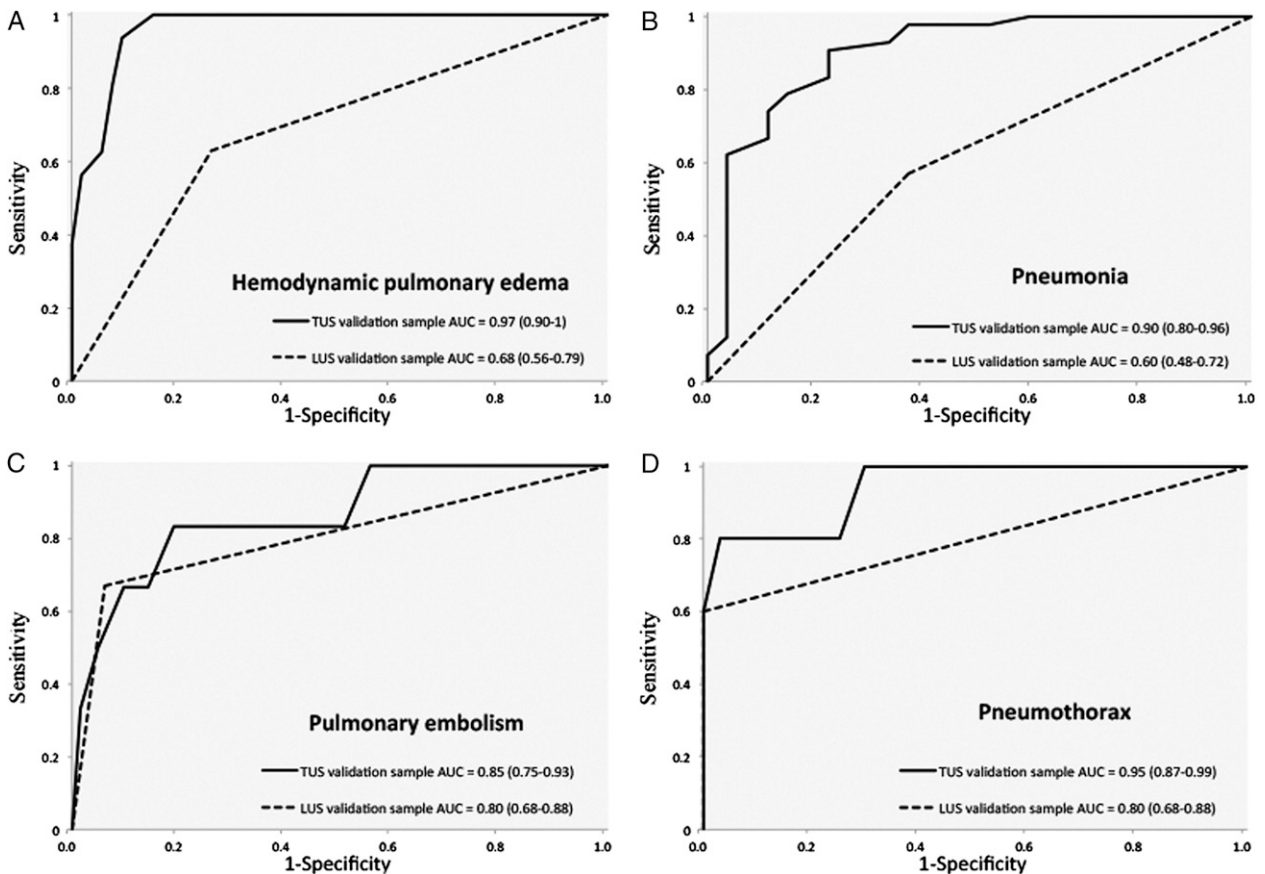


Figure 3 – Diagnostic performances. Receiver operating characteristic curves depicting the relationship between the proportion of true-positive findings and the proportion of false-positive findings. The isolated LUS and combined cardiopulmonary ultrasound (TUS) approaches are represented for each diagnosis. AUC = area under the curve. See Figure 2 legend for expansion of other abbreviations.

TABLE 2] Correct Diagnosis Performed Using Each Strategy

Final Diagnosis	Correct Diagnosis		P Value
	LUS	TUS	
Cardiogenic edema (n = 34)	22 (65)	32 (94)	.003 ^a
Pneumonia (n = 77)	51 (66)	64 (83)	.016 ^a
Pulmonary embolism (n = 13)	5 (38)	5 (38)	1
Pneumothorax (n = 12)	7 (58)	9 (75)	.67

Data are presented as No. (%). LUS = lung ultrasonography; TUS = thoracic ultrasonography.
^aSignificance at $P < .05$.

PLS models because contrary to an all-or-none prediction provided by tree-based algorithms, PLS models estimate a diagnostic probability for each ARF etiology (e-Fig 1, e-Table 1).

Discussion

Lung ultrasound is a diagnostic tool increasingly used in the critical care setting to provide standardized data.¹ Nevertheless, it has been suggested that in complex clinical conditions, such as ARF, only a combined cardiac and pulmonary evaluation can accurately assess the multifaceted interactions disrupted in these contexts.⁹ In agreement with this hypothesis, the current study demonstrates the additional diagnostic value of simultaneous echocardiographic and pulmonary ultrasound recordings (TUS) compared with an exclusive pulmonary ultrasonographic assessment (LUS) in the management of these highly distressed patients. To our knowledge, this study is the first to use a homogenous methodology to prospectively compare an isolated lung ultrasound assessment (LUS) with an integrative cardiopulmonary approach (TUS) in this clinically relevant setting.

Can we usefully integrate the large-scale ultrasonography recordings to improve standard diagnostic methods and guide the initial treatment of patients with ARF? A pioneering study provided a first response to this question⁷ and showed that although individually the sensitivity of each LUS feature seems low and highly variable, a simplified interpretation of these data using a tree-based classification model significantly improves the sensitivity and provides an accurate assessment. Nevertheless, it could be argued that the use of such a binary classification for the analysis of high-dimensional data constitutes an oversimplification and could have a potentially deleterious impact on the initial management of patients with ARF. Alternatively, we proposed and

validated a new, supervised, learning machine classifier¹¹ by combining random ensembles of predictors. Notably, the performance of the proposed model was very satisfactory for both the learning and the testing sessions. This robust method handled high-dimensional²⁸ data and improved the prediction accuracy by reducing the correlation among the variables (ie, multicollinearity), took into account the missing data, and provided a probability for each diagnosis to enable the detection of mixed diagnoses.

Furthermore, the current findings demonstrate that cardiac Doppler echocardiography examination has a significant added value and contributes to accurately disambiguating ARF caused by left-sided heart dysfunction from that resulting from noncardiac causes. In agreement with previous studies showing that the specificity threshold of B lines to detect cardiogenic pulmonary edema is low²⁹ and opposite to studies suggesting that an exclusive ultrasonography assessment could be used to estimate a patient's hemodynamic status,³⁰⁻³² the current findings highlight the potential flaws of isolated pulmonary semiotics and provide a reliable and comprehensive bedside diagnostic alternative by combining echocardiographic and pulmonary ultrasound recordings.

This study has several limitations. First, the intensivists could not be blinded to obvious clues of diagnosis that might be readily apparent to an experienced observer while performing an ultrasound examination. Second, patients with acute exacerbation of a chronic pulmonary disease had low representation in the cohort and, thus, were not included in the proposed mathematical models. Future studies will need to explore this approach in larger samples of patients.

Conclusions

This study demonstrated a significantly better performance of TUS compared with LUS in the diagnosis of ARF. Interestingly, the additional value of the TUS approach was particularly important in cases of acute hemodynamic pulmonary edema and pneumonia, highlighting the unavoidable place of echocardiography in the diagnosis and management of ARF, especially when extravascular lung water ultrasonography is identified (B lines). The performance of learning machine ultrasonographic classifiers was highly accurate in all conditions. We suggest that this mathematical approach derived from artificial intelligence methods has several concrete clinical implications in ARF diagnosis and early management, including (1) improved TUS diagnostic

TABLE 3] Predictive Classifiers Accuracy

Diagnosis	Sample	AUC (95% CI)	P Value	Cutoff	Se, %	Sp, %	PPV, %	NPV, %	Correctly Classified	LR+	LR-
Cardiogenic edema	Learning										
	TUS	0.97 (0.90-1)	<.001 ^a	0.34	94	94	85	98	94	15.43	0.06
	LUS	0.76 (0.64-0.85)	...	1	67	85	63	87	80	4.57	0.39
	Test										
	TUS	0.97 (0.90-1)	<.001 ^a	0.49	100	91	76	100	93	10.60	0
	LUS	0.68 (0.56-0.79)	...	1	63	74	42	87	71	2.37	0.51
Pneumonia	Learning										
	TUS	0.95 (0.87-0.99)	<.001 ^a	0.42	97	87	89	97	92	7.77	0.03
	LUS	0.69 (0.57-0.80)	...	1	76	63	68	71	70	2.04	0.38
	Test										
	TUS	0.90 (0.80-0.96)	<.001 ^a	0.34	81	81	87	73	81	4.37	0.23
	LUS	0.60 (0.48-0.72)	...	1	57	63	71	49	59	1.54	0.68
Pulmonary embolism	Learning										
	TUS	0.88 (0.78-0.95)	.001 ^a	0.32	57	93	50	95	90	8.57	0.46
	LUS	0.54 (0.40-0.65)	...	1	14	93	20	90	85	2.11	0.92
	Test										
	TUS	0.85 (0.75-0.93)	.71	0.34	83	84	33	98	84	5.25	0.20
	LUS	0.80 (0.68-0.88)	...	1	67	94	50	97	91	10.50	0.36
Pneumothorax	Learning										
	TUS	0.99 (0.92-1)	.12	0.36	86	97	75	98	96	25.71	0.15
	LUS	0.86 (0.76-0.94)	...	1	71	100	100	97	97	NA	0.29
	Test										
	TUS	0.95 (0.87-0.99)	.13	0.39	80	98	80	98	97	51.20	0.20
	LUS	0.80 (0.68-0.88)	...	1	60	100	100	97	97	NA	0.40

AUC = area under the curve; LR- = negative likelihood ratio; LR+ = positive likelihood ratio; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Sp = specificity. See Table 2 legend for expansion of other abbreviations.

^aSignificance at $P < .05$.

accuracy through the automatized optimization of the sensitivity/specificity trade-off of recorded parameters (ie, use of contextual instead of absolute thresholds); (2) faster and more accurate bedside interpretation of complex lung ultrasound and echocardiography data (e-Appendix 2); (3) expansion of the use of ultrasonography diagnostic tools to mixed cases of ARF; and

(4) development of new diagnostic models to integrate clinical, ultrasonographic (diaphragm,³³ venous Doppler sonography³⁴), and biologic data (biomarkers) at the patient's bedside.³⁵ Doing so, we could expect to improve the prognosis of patients with ARF by implementing earlier ICU therapeutic decisions based on bedside-recorded online physiologic data.

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Author contributions: B. B. and S. S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S. S. had final responsibility for the decision to submit the manuscript for publication. B. B. contributed to the study concept and data acquisition and analysis; B. R., F. F., P. E. M., A. M., E. B., J. R., M. M., O. F., and M. G. contributed to the data acquisition; B. R. and M. M. contributed to the study design; S. S. contributed to the study design, data acquisition, data analysis and interpretation, and writing of the manuscript; and B. B., B. R., F. F., P. E. M., A. M., E. B., J. R., M. M., O. F., M. G., and S. S. contributed to the critical revision of the manuscript for important intellectual content and final approval of the manuscript.

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Additional information: The e-Appendixes, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

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