

The PLEURA I Study: Development of a New Multisite Ultrasound-Based Model for Estimation of Pleural Fluid Volume and Paul's Formula

Akhil Paul ^{1*}, Jasla TH ¹

¹ Department of Pulmonary and Sleep Medicine, MOSC Medical Mission Hospital, Thrissur, Kerala, India.

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ABSTRACT

Introduction: From 2010 onwards, guidelines, including those of the British Thoracic Society (BTS), recommend the use of ultrasound in all pleural fluid evaluation procedures. There are various established formulas to estimate the pleural fluid volume using ultrasonography. The two formulas by Goecke and Schwark, Einberger's formula, Balik's formula, and Usta's formula are some of the most commonly used ones. But considering only a single or a couple of measurements to estimate the total volume of pleural effusion, especially moderate to large effusions, will definitely have its own disadvantages. The objective of the PLEURA 1 study was to develop a new multi-site ultrasound-based model for a more accurate estimation of the pleural fluid volume and to compare it with the existing formulae.

Materials and Methods: PLEURA 1, a prospective observational study, was conducted in a tertiary care center in South India. A novel multisite parameter (Mean9) was defined using nine different ultrasonographic dimensions. Pearson correlation coefficients (r) were calculated to assess the strength of association between predicted and actual pleural fluid volume. Model performance was assessed using the coefficient of determination (R^2), mean absolute error (MAE), and root mean square error (RMSE) and compared with that of the existing erect position formulas.

Results: The study cohort consisted of twenty-four patients with pleural effusion. Mean9 demonstrated a strong linear relationship with actual pleural fluid volume (Pearson $r = 0.853$, 95% CI 0.68–0.94; $p < 0.0001$). 'Paul's formula', ' $V = 41.4 + 270.8 \times \text{Mean9}$ ' was derived using linear regression. Paul's formula maintained the highest predictive performance among all evaluated models (LOOCV $r = 0.820$, LOOCV $R^2 = 0.672$, MAE = 422 mL, RMSE = 504 mL), and demonstrated better correlation to actual pleural fluid volume than the established erect-position formulas.

Conclusion: PLEURA 1 study and Paul's formula suggest that incorporating multiple dimensions of the pleural effusion into a predictive model may improve the estimation of pleural fluid volume. PLEURA 2 validation study will be the second phase of the study, where Paul's formula will be applied along with other established formulae in an entirely new and larger cohort.

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* Corresponding authors: **Akhil Paul**; Head of the Dept of Pulmonary and Sleep Medicine, MOSC Medical Mission Hospital, Thrissur, Kerala; India- 680503; Tel: +91 9626590131; E-mail: akhil_paul@yahoo.com

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Introduction

Since 2010, guidelines, including those of the British Thoracic Society (BTS), have recommended the use of ultrasound in the evaluation of pleural fluid and during pleural procedures (1). Various established formulas have been developed to estimate pleural fluid volume using ultrasonography. The formulas proposed by Goecke and Schwerk, Einberger, Balik, and Usta are among the most commonly used (2). However, estimating the total volume of a pleural effusion using only a single or a limited number of measurements, particularly in moderate-to-large effusions, has inherent limitations. The dimensions of the thoracic cavity, including its diameter and height, may have a significant influence on the total volume of pleural fluid.

The objective of the PLEURA I study was to assess the correlation between volumes calculated using established formulas and the actual pleural fluid volume in a cohort of patients with significant pleural effusion and to develop a new multisite ultrasound-based model for more accurate estimation of pleural fluid volume.

Methods

PLEURA I was a prospective observational study conducted in the Department of Pulmonary and Sleep Medicine of a tertiary care academic center in South India. All patients presenting with pleural effusion to the department during a six-month study period were considered for inclusion. Permission was obtained from the Institutional Review Board and Ethics Committee, and informed consent was obtained from all patients before enrolment. A total of 52 pleural effusions were considered during the study period. Six pleural effusions were too small to warrant diagnostic evaluation and resolved following treatment of the underlying cause. Ten pleural effusions were transudative on diagnostic evaluation and resolved following treatment of the underlying systemic cause. As these effusions did not warrant an evacuation procedure, the actual pleural fluid volume could not be determined. An additional 12 pleural effusions were excluded because they were loculated and did not represent freely mobile fluid collections. Loculated effusions were excluded because a

general formula based on minimum-dimensional assessment might not provide an accurate estimate of fluid volume in such effusions, as they might not gravitate down in the sitting position. Following these exclusions, the final study cohort consisted of 24 pleural effusions.

Ultrasonographic assessment of all pleural effusions was performed by the same operator, a trained senior pulmonologist. Chest ultrasonography was performed with the patient in the sitting position. Ultrasound-derived measurements included nine interpleural distances obtained at apical, mid, and basal levels of the pleural effusion and at the anterior, lateral, and posterior aspects of the hemithorax (AA, MA, BA, AL, ML, BL, AP, MP, and BP, respectively). Additional measurements included pleural fluid height (H), the maximal distance between the mid-height of the diaphragm and the visceral pleura/collapsed lung (D), and hemithoracic circumferences at the apical and basal levels of the pleural effusion (AC and BC, respectively). All measurements were recorded in centimeters.

All patients subsequently underwent medical thoracoscopy. The pleural fluid was completely drained during thoracoscopy, and the drained fluid volume was quantified (V). This measured volume was considered the reference standard.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range), as appropriate. As all ultrasound measurements were obtained with the patient in the erect position, comparisons were restricted to previously published ultrasound methods validated for use in the erect position.

The following published formulas were evaluated:

Usta Formula : $V = 160 \times D$

Goecke Formula 1: $V = 90 \times H$

Goecke Formula 2: $V = 70 \times (H + D)$

A novel multisite parameter (Mean9) was defined as:

$Mean9 = (AA + MA + BA + AL + ML + BL + AP + MP + BP) / 9$

Two novel predictive models were evaluated:

$$V = f(\text{Mean9})$$

and

$$V = f(\text{Mean9} \times H)$$

Pearson correlation coefficients (r) were calculated to assess the strength of association between predicted and actual pleural fluid volumes. Linear regression analysis was performed to derive predictive equations for the novel models. Model performance was assessed using the coefficient of determination (R^2), mean absolute error (MAE), and root mean square error (RMSE).

Internal validation was performed using leave-one-out cross-validation (LOOCV). Cross-validated correlation coefficients, cross-validated R^2 values, MAE, and RMSE were calculated for each model. Agreement between predicted and actual pleural fluid volumes was additionally assessed using Bland-Altman analysis. A two-sided p -value < 0.05 was considered statistically significant.

Results

Twenty-four patients with pleural effusion were included in the final study. The cohort consisted of 13 males and 11 females, with a mean age of 59 years. Malignant pleural effusion was present in 58.3% of the cohort, while the remaining 41.7% had tuberculous pleural effusion. Eleven patients had systemic

hypertension, nine had diabetes mellitus, three had coronary artery disease, and two had chronic kidney disease as comorbidities. Ultrasound measurements were obtained in the erect position before therapeutic drainage. The actual drained pleural fluid volume was used as the reference standard. The mean pleural fluid volume in the cohort was 1700 mL (range, 300–4000 mL).

Correlation of Individual Ultrasound Measurements

Among the individual ultrasound measurements, basal posterior interpleural distance (BP) demonstrated the strongest correlation with actual pleural fluid volume ($r = 0.767$). Other measurements demonstrated moderate correlations, including AA ($r = 0.723$), AL ($r = 0.720$), AP ($r = 0.707$), BL ($r = 0.679$), D ($r = 0.667$), ML ($r = 0.669$), MP ($r = 0.678$), and H ($r = 0.648$). Hemithoracic circumference measurements demonstrated minimal correlation with pleural fluid volume (AC: $r = 0.061$; BC: $r = 0.071$).

Performance of Published Erect-Position Methods

Among the established ultrasound formulas applicable to the erect position, Goecke Formula 2 demonstrated the best performance.

Table 1. Performance of published erect-position methods.

Formula	r	R^2	MAE (mL)	RMSE (mL)
Usta	0.679	0.461	520	646
Goecke 1	0.648	0.420	489	670
Goecke 2	0.733	0.537	497	598

Goecke Formula 2, which incorporates both pleural fluid height and basal lateral separation, demonstrated a stronger correlation and lower RMSE than Usta and Goecke Formula 1, suggesting that combining orthogonal dimensions of the pleural collection may improve volume estimation.

Development of Novel Multisite Ultrasound Models

A novel parameter, Mean9, was developed to represent the average interpleural separation across nine predefined thoracic locations. The Mean9 model demonstrated a

strong linear relationship with the actual drained pleural fluid volume (Pearson $r = 0.853$, 95% CI, 0.68–0.94; $p < 0.0001$).

Linear regression yielded the equation:

$$V = 41.4 + 270.8 \times \text{Mean9}$$

The regression coefficient for Mean9 was 270.8 mL per unit increase in Mean9 (95% CI, 191–351; $p < 0.001$). The model explained 72.8% of the variance in pleural fluid volume ($R^2 = 0.728$).

The derived formula, $V = 270.8 \times \text{Mean9} + 41.4$, was named Paul's formula for

ultrasound-guided pleural fluid volume estimation.

The Mean9 model demonstrated a strong positive linear relationship with actual pleural fluid volume ($r = 0.853$, $R^2 = 0.728$).

Although incorporation of pleural fluid height produced good predictive

Table 2. Performance of Mean9-based models.

Model	r	R ²	MAE (mL)	RMSE (mL)
Mean9	0.853	0.728	387	459
Mean9 × H	0.814	0.663	412	511

performance, it did not improve accuracy beyond that achieved by Mean9 alone.

The scatter plot (Figure 1) demonstrates the relationship between actual drained pleural fluid volume and volume predicted using Paul's formula.

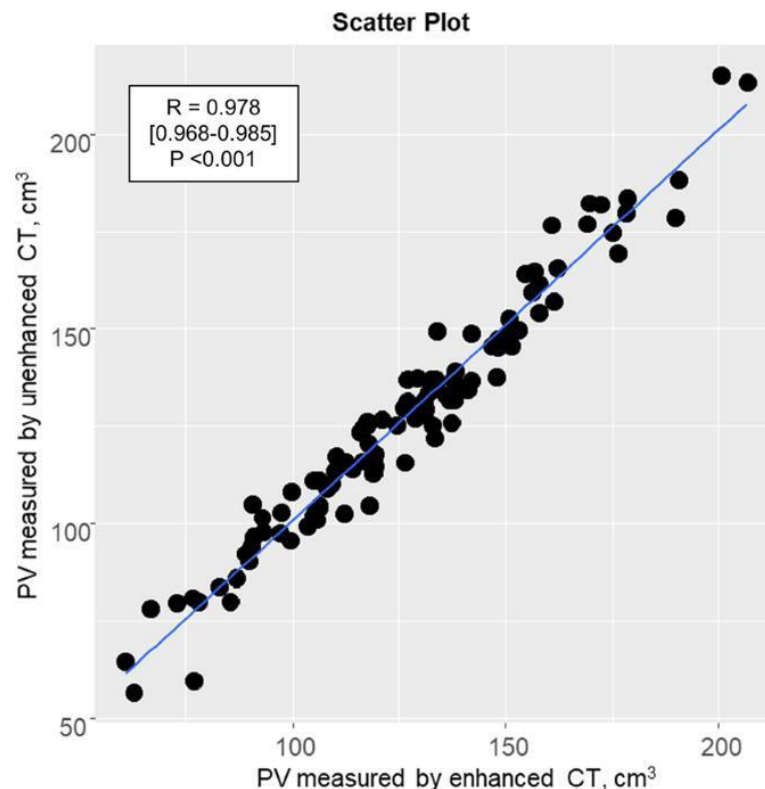


Figure 1: Predicted versus actual pleural fluid volume using Paul's formula.

Bland-Altman analysis demonstrated minimal systematic bias, with a mean difference of -7 mL between predicted and actual pleural fluid volumes. The 95% limits of agreement were -994 to $+980$ mL (Figure 2).

Internal Validation

During leave-one-out cross-validation, the Mean9 model (Paul's formula) maintained the highest predictive performance among all evaluated models (LOOCV $r = 0.820$, LOOCV $R^2 = 0.672$, MAE = 422 mL, RMSE = 504 mL), compared with the established erect-position methods described by Usta and Goecke.

The Mean9 model demonstrated the highest correlation, greatest explanatory power,

lowest prediction error, and strongest cross-validated performance among all evaluated models. The addition of pleural fluid height did not significantly improve model performance. Multisite assessment of pleural separation appeared to provide a more comprehensive representation of pleural fluid distribution than the previously described erect-position ultrasound methods.

Apical and basal hemithoracic circumferences demonstrated negligible correlations with actual pleural fluid volume ($r = 0.061$ and $r = 0.071$, respectively) and were therefore not incorporated into the final predictive model.

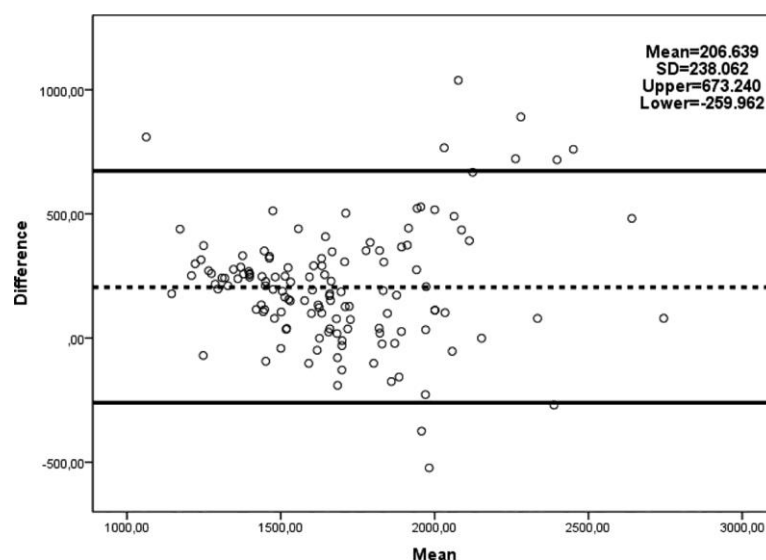


Figure 2: Bland–Altman plot comparing actual pleural fluid volume with the volume predicted by Paul's formula.

Table 3. Internal validation of the evaluated models.

Model	LOOCV r	LOOCV R ²	MAE (mL)	RMSE (mL)
Usta	0.597	0.350	571	709
Goecke 1	0.545	0.292	539	740
Goecke 2	0.673	0.451	540	652
Mean9	0.820	0.672	422	504
Mean9 × H	0.781	0.610	447	550

Discussion

Pleural effusion is defined as the pathological accumulation of pleural fluid within the pleural cavity. The mean rates of pleural fluid production and absorption are approximately 0.2 mL/kg/h (3), suggesting a rapid turnover of pleural fluid. Although both the visceral and parietal pleura play important roles in pleural fluid homeostasis, the parietal pleura has the more significant role in this process. The balance between oncotic and hydrostatic pressures in the systemic and pulmonary circulation and within the pleural cavity determines pleural fluid homeostasis. The most common causes of pleural effusion include congestive heart failure, renal failure, liver cirrhosis, pneumonia, malignancy, and tuberculosis (4). Bedside chest ultrasonography in patients with pleural effusion is a useful tool for quantifying pleural fluid (5,6). It also has an important role in decision-making regarding the need for invasive diagnostic or therapeutic intervention (7,8). Recent guidelines recommend the use of ultrasound

in the evaluation of pleural fluid and during pleural procedures (1).

Various established formulas have been developed to estimate pleural fluid volume using ultrasonography. The Goecke 1 and 2, Schwerk, Einberger, Balik, and Usta formulas are among the most commonly used (2). However, estimating the total volume of a pleural effusion using only a single or limited number of measurements, particularly in moderate to large effusions, has inherent limitations. Various parameters, including the dimensions of the thoracic cavity, such as its diameter and height, may significantly influence the total volume of the effusion.

Goecke 1 and 2 and Usta's formulas are applied with the patient in the erect position (9), whereas Einberger's and Balik's formulas are applied in the supine position (10,11). In the erect position, non-loculated free pleural fluid gravitates downward. In the supine position, however, free fluid tends to occupy the posterior aspect of the hemithorax. Although fluid volume estimation in the supine position is more difficult, it can be useful in bedridden patients in critical care

units and in patients receiving invasive mechanical ventilation.

In several validation studies, Goecke Formula 2 demonstrated the highest correlation with actual pleural fluid volume (12). Adding the parameter 'the distance between the lung base and the diaphragm' to Goecke Formula 1, which depends solely on the height of the effusion, has been shown to improve its correlation with pleural fluid volume (13). These observations suggest that incorporating additional dimensions may improve the accuracy of pleural fluid volume estimation.

The PLEURA I study was designed to identify easily assessable dimensions that could be incorporated into volume estimation to provide a more accurate predictive formula. In this study, among the various parameters assessed, basal posterior interpleural distance (BP) demonstrated the strongest correlation with actual pleural fluid volume ($r = 0.767$), while the other interpleural measurements demonstrated moderate correlations.

Hemithoracic circumference measurements, which were hypothesized to significantly influence pleural fluid volume, demonstrated minimal correlation with actual pleural fluid volume (AC: $r = 0.061$; BC: $r = 0.071$). As observed in several previous studies, Goecke Formula 2 also demonstrated the strongest correlation among the established formulas evaluated in the PLEURA I study. This formula incorporates both pleural fluid height and basal lateral separation, suggesting that combining orthogonal dimensions of the pleural collection may improve volume estimation (14,15).

A novel parameter, Mean9, was developed to represent the average interpleural separation across nine predefined thoracic locations. These included interpleural distances measured at the anterior, lateral, and posterior aspects of the hemithorax at the basal, mid, and superior-most levels of the pleural effusion. Mean9 demonstrated a strong linear relationship with actual drained pleural fluid volume (Pearson $r = 0.853$, 95% CI, 0.68–0.94; $p < 0.0001$).

A new equation incorporating Mean9, termed Paul's formula, was derived using linear regression:

$$V = 41.4 + 270.8 \times \text{Mean9}$$

The model explained 72.8% of the variance in pleural fluid volume ($R^2 = 0.728$). Although the Mean9 $\times$ H model demonstrated good predictive performance, incorporation of pleural fluid height did not improve accuracy beyond that achieved by Mean9 alone. This may be because the multiple parameters incorporated into Mean9 capture the relevant dimensions of the pleural fluid collection sufficiently well, thereby reducing the additional contribution of pleural fluid height to volume estimation.

Conclusion

Ultrasound-based estimation of pleural fluid volume is a useful tool in the management of patients with pleural effusion. An accurate formula incorporating easily measurable parameters may assist in clinical decision-making.

The small sample size of the PLEURA I study limits the reliability and generalizability of the proposed formula. However, the findings of this study and the proposed Paul's formula suggest that incorporating multiple dimensions of the pleural effusion into a predictive model may improve the estimation of pleural fluid volume.

Validation of the proposed formula will be undertaken in the PLEURA II study, the second phase of the study, in which Paul's formula will be applied alongside other pleural fluid volume estimation formulas in an entirely new and larger cohort.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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