# **Assessment of Volume Status in Chronic Hemodialysis: Comparison of Lung Ultrasound to Clinical Practice and Bioimpedance**

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#### **ABSTRACT**

**Objective:** Lung ultrasonography (LUS) has recently been used to evaluate extravascular lung water, and shown to be able to predict all-cause mortality in hemodialysis (HD) patients. This study aim to compare LUS with other volume assessment methods, and to verify the prognostic value of LUS in Thai chronic HD patients.

**Materials and Methods:** We conducted a prospective cohort study in 36 chronic HD patients. Volume status before the HD session was evaluated by physical examinations, bioimpedance analysis (BIA), and ultrasound lung comets (ULCs). Mortality and morbidities were recorded during a 1-year follow-up period.

**Results:** The degree of lung fluid accumulation was assessed by summation of the number of ULCs, and was classified into 3 groups: mild-to-moderate (ULC<15–29), severe (ULC=30–59), and very severe (ULC≥60) in 11.1%, 77.8%, and 11.1% of the patients, respectively. Either clinical edema or lung crackle had low sensitivity (20-32%) to detect extravascular lung water excess in patient with mild-to-moderate ULC and severe ULC. Overhydration assessed by BIA was found in 75% and 64.3% of patients with mild-to-moderate and severe ULC, respecively. In patients with very severe ULC, the admission rate due to volume overload was significantly higher, there was also a trend of increased mortality, as well as intradialytic complications.

**Conclusion:** Clinical assessment and BIA have limited value in determining extravascular fluid excess in the lung. Lung ultrasound is a useful tool to detect subclinical pulmonary congestion. The long-term outcome by using LUSguided fluid management needs larger population studies.

**Keywords:** Lung ultrasonography; extravascular lung water; hemodialysis; all-cause mortality; morbidities; intradialytic complications (Siriraj Med J 2023; 75: 224-233)

#### **INTRODUCTION**

The prevalence of end-stage kidney disease (ESKD) patients requiring renal replacement therapy (RRT) is rising annually. From the annual report of renal replacement therapy (RRT) in Thailand in 2019, the prevalence of RRT is almost 2,300 persons per million population, with hemodialysis (HD) as the most chosen mode of RRT.<sup>1</sup> Fluid retention and high inter-dialytic weight gain in HD patients were reported in previous studies as

among the important predictive factors for mortality and cardiovascular morbidity.2,3 The accumulation of fluid in the lung is considered a major consequence of fluid overload and cardiovascular complications. Routine examinations for the assessment of fluid overload, including by history taking, blood pressure measurement, peripheral edema, and lung auscultation, have been shown to have poor diagnostic accuracy in the detection of interstitial lung edema or total body fluid accumulation.<sup>4</sup>

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Several new objective methods, including bioimpedance analysis (BIA) and lung ultrasound (LUS), have been introduced and validated in chronic HD patients for the assistance of the volume status evaluation along with the routine physical examinations. Bioimpedance analysis is a noninvasive tool that has been applied in the setting of dialysis patients to evaluate the patient's body composition for nutritional assessment and quantitative determination of the total body water and extracellular fluid volume.<sup>5,6</sup> Water in the lungs can be inversely correlated with the systolic and diastolic functions from echocardiography but shows only a weak correlation with the fluid status from BIA.<sup>10</sup> Lung ultrasonography was initially used for extravascular lung water evaluation, mostly in critical care situations.<sup>7,8</sup> The degree of accumulation of fluid in the lung interstitial was quantified by assessing the ultrasound B-lines or ultrasound lung comets (ULCs), characterized by a comet-tail-like hyperechoic line continuing from the ultrasound transducer to the visceral pleural line. This was later adapted in a chronic HD setting, and was found to be associated with fluid loss during HD.<sup>9</sup> In the LUST study, Torino *et al*. found that the detection of extravascular lung water accumulation in chronic HD patients by using the ultrasound lung comet score had a higher sensitivity than by routine physical examination, which included lung auscultation and peripheral edema.<sup>4</sup> Fluid assessment by using lung ultrasound was also shown to be able to predict mortality in HD patients.<sup>11,12</sup> However, lung ultrasonography has not yet been studied in Thai chronic HD patients despite its many advantages seen in other studies worldwide. The aim of this study was to evaluate abilities of clinical assessment and bioimpedance for determining extracellular fluid excess comparing with lung ultrasonography, and to evaluate the prognostic value significance of the presence of ultrasound lung

# **MATERIALS AND METHODS**

comets in Thai chronic HD populations.

# **Study population**

This single-center prospective cohort study was conducted in the HD units of Siriraj Hospital, Bangkok from July 2017 to March 2018. The inclusion criteria were patients who had been on three-times weekly chronic HD for more than 3 months with a stable dry weight, defined as target dry weight changes within  $\pm 0.5$  kg in the past 3 months. The exclusion criteria were age under 18 years old, patients with current systemic infections, terminal cancers, lung diseases that may interfere with lung ultrasonography interpretation (e.g., lung fibrosis, interstitial lung disease, pleural effusion, patchy infiltration and consolidation), recent hospitalization within the past 3 months, patients with a cardiac pacemaker or defibrillator implantation, and a history of limb amputation. Of the total of 70 patients screened for enrollment, 36 patients were included in this study, while 29 patients denied informed consent, and 5 patients were excluded because of pleural effusion ( $n = 1$ ), current systemic infection  $(n = 1)$ , and current hospitalization  $(n = 3)$ .

# **Study design**

The patients' baseline characteristics, including age, sex, body mass index (BMI), comorbidities, dialysis vintage, blood pressure, ultrafiltration rate (UFR), and laboratory data, were collected. In each participant, all 3 methods of volume status assessment, namely clinical evaluation, lung ultrasonography, and BIA, were evaluated pre-HD in the same day at the beginning of the week of the HD session (after the longest interdialytic interval). The participants were followed up for 1 year for hospitalizations, all-cause mortality, and intradialytic complications.

# *Clinical evaluation of the volume status*

Clinical evaluation of the volume status included physical examination of clinical edema and lung auscultation. Clinical edema was examined at the mid-portion of both legs and classified according to the following scale: 1, no clinical edema; 2, more than 0 to 2 mm depth pitting; 3, more than 2 to 4 mm depth pitting; 4, more than 4 to 6 mm depth pitting; 5, more than 6 mm depth pitting.<sup>4</sup>

Lung auscultation was examined at the anterior and posterior sites of each hemithorax in a sitting position. Participants were asked to perform slow and deep inhalations during the evaluation for crackles. Lung crackle findings was classified according to the following scale: 1, no crackles; 2, uncertain about crackles; 3, fine crackles at the basal lungs; 4, half of the hemithorax crackles; 5, bilateral diffuse crackles.<sup>4,13</sup>

# *Lung ultrasonography*

Lung ultrasonography (using an ultrasound machine [GE Logiq E9] with a cardiac probe 3–9 MHz sector scan probe; "S4–10" was performed by 2 radiologists who were blinded from the results of the other volume status measurement methods. The ultrasound scanning was performed with the patient in a supine position in 8 areas of the chest wall (including the mid-axillary, anterior axillary, mid-clavicular, and parasternal areas) in the  $2<sup>nd</sup>$ ,  $3<sup>rd</sup>$ ,  $4<sup>th</sup>$ , and  $5<sup>th</sup>$  intercostal spaces at both the right and left hemithorax, as shown in Fig 1A. The degree of lung fluid accumulation was measured as the number of ultrasound lung comets (ULCs) (Fig 1B). The ULC score for each patient was quantified by summation of the ULCs found in all 8 zones.<sup>14</sup> The ULC score was divided into 4 categories: mild (< 15 ULCs), moderate **A**

Mid-Anterior Mid-Mid-Para-Para-Anterior Mid-ICS axillary axillary clavicular sternal sternal clavicular axillary axillary  $\overline{2}$ 3 4 5

**Right side** 

Left side



**B**

**Fig 1A.** Division of the chest wall into 8 areas for lung ultrasonography evaluation.

**Fig 1B** Ultrasound B-lines or ultrasound lung comets (ULCs), characterized by a comet-tail-like hyperechoic line continuing from the ultrasound transducer to the visceral pleural line *(Figure provided by Asso.Prof.Suwimon Wonglaksanapimon, Radiology Department, Siriraj Hospital).*

(15–29 ULCs), severe (30–59 ULCs), and very severe (> 60 ULCs).4,11,12,14

#### *Bioimpedance analysis*

Whole-body bioimpedance analysis (BIA) was used to measure the volume status by multi-frequency bioimpedance spectroscopy. Electrodes were attached to the participant's wrist on the non-vascular access side of the body and ipsilateral ankle in the supine position. Extracellular fluid volume was calculated as the percentage of overhydration compared with the relative hydration status in normal populations (ΔHS). The patients' hydration status were classified into 2 groups: 1) normohydration,  $\Delta$ HS < 15%, and 2) hyperhydration,  $\Delta$ HS > 15%.<sup>12</sup>

#### *Echocardiography*

Echocardiography, as performed according to the recommendations of the American Society of Echocardiography<sup>15</sup>, was evaluated in all available patients within 3 months of the lung ultrasound and BIA. The staff performing the echocardiography were unaware of the lung ultrasound and BIA results.

#### **Outcomes**

The primary outcome was to compare ultrasound

lung comets with physical examinations (clinical edema and lung crackle) and BIA in the evaluation of fluid overload. The secondary outcomes were: 1) to determine the sensitivity and specificity of physical examinations of clinical edema with BIA, 2) to study the associations of extravascular lung water evaluated by lung ultrasonography and 1-year all-cause mortality and cardiovascular events, as well as intradialytic complications, 3) to compare lung ultrasonography findings with echocardiography findings.

Intradialytic hypotension and intradialytic hypertension episodes were collected as the percentage of the complicated sessions to all hemodialysis sessions. Definitions from KDIGO were used: intradialytic hypotension was defined as any symptomatic decrease in systolic blood pressure (SBP) or a nadir intradialytic SBP < 90 mmHg, while intradialytic hypertension was defined as any rise of >10 mmHg from pre- to post-dialysis in the hypertensive range ( $>140$  mmHg).<sup>16</sup>

#### **Statistical analysis**

We estimate the minimum sample size required, based on the prevalence of fluid overload in chronic hemodialysis patients and the sensitivity of physical examinations (clinical edema and lung crackles) with

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the lung ultrasonography as the gold standard (p-value, is set to be less than 0.05). The sensitivity of the physical examinations from the LUST study was 26%<sup>4</sup>, we set the maximum marginal error of estimate to be 15% for constructing confidence interval of true value of sensitivity with the prevalence of fluid overload in our population of 50%, the total sample size of the sensitivity determines 972 patients. Continuous data were presented as the mean ± SD for normally distributed data and as the median with interquartile range (IQR) for non-normally distributed data. Categorical data were presented as the percent frequency. Comparisons among groups were made by p-value using one-way ANOVA analysis. The sensitivity and specificity of lung auscultation and clinical edema were also calculated. Statistical analysis was performed using SPSS software version 20.

This study was approved by the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 412/2017), and was conducted according to the principles of the Declaration of Helsinki. All participants received a detailed explanation of the study and gave their written informed consent.

# **RESULTS**

We report this preliminary result because the prolonged COVID-19 pandemic halted further enrollment in our study. The patients' baseline characteristics and biochemical data are shown in Table 1. The mean age of the patients was 63 years and 55.6% were male. The comorbidities included diabetes mellitus (41.7%), myocardial infarction (22.2%), and a history of coronary artery bypass graft (CABG) or stent (25%). Since there were only 4 patients in the mild and moderate group, we divided the patients into 3 groups according to the severity of ULC score as per the following; mild-to-moderate  $11.1\%$  (n = 4), severe 77.8% (n = 28), and very severe 11.1% (n = 4). A history of myocardial infarction and history of CABG or stent was found more frequently in the very severe and severe ULC groups, but the difference did not reach statistical significance. Patients in the very severe ULC group had a higher New York Heart Association (NYHA) functional class than in the other less severe ULC groups. No differences in the baseline characteristics data were found, apart from for gender, in which the proportion of males was found to be higher in the moderate and severe ULC groups.

# **Comparison of fluid overload assessement by lung ultrasonography with clinical evaluation and BIA**

Fluid overload was defined by using the following

criteria: BIA overhydration defined as ΔHS > 15%, clinical edema positive score  $\geq 2$ , and lung auscultation positive score  $\geq$  3. The severity of lung congestion assessed by ULC score was compared with physical examinations and BIA (Table 2). Clinical edema was found in 75% of the patients in the very severe ULC group, whereas it was found in only 25% and 21.4% of the patients in the mild-to-moderate and severe ULC groups, respectively. Lung crackle was positive in 100% of the patients with very severe ULC, whereas it was positive in only 25% and 32.1% of the patients with mild-to-moderate and severe ULC ( $p = 0.03$ ), respectively. When compared with lung ultrasound, lung crackles, either alone or in combination with clinical edema, poorly reflected lung congestion in patients with mild-to-moderate ULC and severe ULC. When comparing lung ultrasonography with BIA, hyperhydration (ΔHS >15%) was found in all patients with very severe ULC, whereas it was found in 75% and 64.3% of patients with mild-to-moderate and severe ULC, respecively. Overall, the vast majority of clinical assessments of fluid overload were not sensitive for detecting lung congesiton, especially in patients with mild-to-moderate and severe ULC. When lung ultrasonography was used as the gold standard for the assessment of extravascular fluid excess in the lung, it was found that clinical assessment and BIA had a limited value for determing pulmonary congestion.

# **Comparison of fluid overload assessment by clinical evaluation with BIA**

The comparison of the assessment of fluid overload by clinical evaluation with BIA is reported in Table 3. Overall, 25 patients (69.4%) were classified by BIA as overhydration. When using BIA as gold standard for diagnosed fluid overload, the sensitivity of detection of fluid overload by clinical edema and by lung crackle was 25% and 45.8%, respectively. The detection of fluid overload by either clinical edema or lung crackle increased the sensitivity to only 50%. Whereas, the presence of both clinical edema and lung crackle had a specificity of 83.3% to detect fluid overload, but the sensitivity was decreased to only 20.8%. Compared with BIA assessment, lung crackles and clinical edema, either alone or in combination, poorly reflected fluid overload, with an accuracy of 39%–55.6%.

# **Comparison between the ultrasound lung comet score and echocardiographic findings**

Echocardiogarphic findings in 25 patients were classified into 3 groups according to the severity of the ULC score, and the results were compared between the



**TABLE 1.** Patients' baseline characteristics and biochemical data according to the number of ultrasound lung comets.

**Abbreviations:** body mass index (BMI), coronary artery bypass graft (CABG), New York Heart Association (NYHA), pulse pressure (PP), heart rate (HR), low density lipoprotein–cholesterol (LDL–C).

\* Statistically significant: P-Value compared between group.

**TABLE 2.** Comparison of lung ultrasonography with clinical assessment and BIA for fluid overload.



† BIA hyperhydration, ΔHS > 15%, ††Clinical edema positive score > 2, †††Lung auscultation positive, score > 3. \*Statistically significant: P-Value compared between group.

**TABLE 3.** Comparison of the assessment of fluid overload by clinical evaluation with BIA.



† BIA hyperhydration, ΔHS > 15%, ††Clinical edema positive score > 2, †††Lung auscultation positive, score > 3. \*Presented as percentage and 95% confidence interval

3 groups, as shown in Table 4. The number of ultrasound lung comets showed a moderate negative correlation with the left ventricular ejection fraction (LVEF) ( $r = -0.48$ ,  $P =$ 0.02) (Table 5). The mean LVEF in patients with very severe ULC was 37.6±23.4%, which was significantly lower than those in the patients with mild-to-moderate and severe ULC ( $p = 0.03$ ). Other echocardiographic parameters such as the mean left ventricular mass index (LVMI), mean left atrial volume index, and mean pulmonary arterial pressure (mPAP) were not correlated with the number of ultrasound lung comets.

# **All-cause mortality, hospitalization, and intradialytic complications**

After a 1 year follow-up period, 3 deaths occurred (one patient in each ULC group), and the causes of all the deaths were infections (Table 6). Patients with very severe ULC had a significantly higher admision rate due to fluid overload. There was no significant difference in all-cause admission, admission due to infection, and admission due to cardiovascular disease (CVD) between the 3 groups. Intradialytic blood pressure, interdialytic weight gain, and ultrafiltration rate were not statistically



**TABLE 4.** Comparison of the cardiac echocardiography findings in each ULC group.

**Abbreviations:** left ventricle (LV), LV ejection fraction (LVEF), LV mass index (LVMI), left atrium (LA), mean pulmonary arterial pressure (mPAP), right atrial pressure (RAP), right ventricular systolic pressure (RVSP). \*Statistically significant: P-Value compared between group.

**TABLE 5.** Correlation between ultrasound lung comets and echocardiographic parameters.



**Abbreviations:** left ventricle (LV), LV ejection fraction (LVEF), LV mass index (LVMI), left atrium (LA), mean pulmonary arterial pressure (mPAP), right atrial pressure (RAP), right ventricular systolic pressure (RVSP). \*Statistically significant: P-Value compared between group.

different between the 3 groups. Patients in the very severe and severe ULC groups tended to have more frequent episodes of intradialytic hypotension and intradialytic hypertension; however, this did not reach statistical significance. (supplement Table 1)

# **DISCUSSION**

The present study showed that when BIA was used as the gold standard, routine physical examinations, either clinical edema or lung auscultation, had low sensitivity (25% and 45.8%, respectively) to detect extracellular





**Abbreviations:** ultrasound lung comet (ULC), cardiovascular disease (CVD).

\*Statistically significant: P-Value compared between group.

volume excess, and had specificities of 66.7% and 75%, respectively. Although the presence of both clinical edema and lung auscultation had high specificity (83%) in detecting fluid overload, the sensitivity was only 20.8%. When lung ultrasonography was used as the gold standard, the sensitivity of lung auscultation to detect extravascular lung fluid excess was 32% and 25% in the patients with severe ULC and mild-to-moderate ULC, respectively. Lung crackle was found to be associated with high accuracy for evaluating pulmonary congestion only in patients with very severe ULC. Similary, clinical edema was found in only 25% and 21.4% of the patients in the mild-to-moderate and severe ULC groups, respectively. Our findings were consistent with Torino *et al*.'s study, which reported a sensitivity of 10%–30% for peripheral edema and/or pulmonary crackles in the detection of extravascular water in ESKD patients as compared with lung ultrasonography.4 Likewise, another meta-analysis compared these two clinical parameters in the diagnosis of volume overload in patients presenting with dyspnea, compared with radio-isotropic study, which revealed a sensitivity of 50%-60%.<sup>17</sup> Although lung auscultation is a simple method, when compared with lung ultrasound it is evidently insensitive to detect extravascular lung water in many conditions, such as acute or chronic heart failure, critical care, and ESKD settings.4,8,18,19 Lung ultrasound, however, may help in detecting subclinical extravascular lung water excess and may provide a useful monitoring tool for fluid management in HD patients.

Many studies have shown a correlation between extracellular fluid volume status assessed by BIA and extravascular lung water evaluated with lung ultrasound. Siriopol *et al*. found a significant correlation between the lung ultrasound congestion score and BIA-derived parameters<sup>12</sup>, while Ngoh *et al*. found that more than 60% of chronic HD patients with a normohydration status had moderate or severe lung congestion on lung ultrasound.20 Consistent with these previous studies, our results showed that all the patients with very severe ULC had a hyperhydration status as assessed by BIA; whereas, 25% and 35.7% of HD patients with a normohydration status had mild-to-moderate ULC (15–29) and severe ULC (30–59) as assessed by lung ultrasound, respectively. This difference may be due to the principles of the fluid compartmental volume assessment of each technique; whereby, whole-body BIA evaluates the extracellular fluid component, while lung ultrasound evaluates only extravascular lung water, which is largely attributable to the severity of the underlying cardiac dysfunction. This could explain why clinical and BIA assessment have limited value in determining extravascular fluid excess in the lung. The presence of excess extravascular lung water is an important contributor to a patient's symptoms, and is a major predictor of hospitalization and mortality in  $HD$  patients<sup>21</sup>; whereas, BIA-guided fluid management may not be associated with long-term survival.<sup>12</sup>

The prevalence of pulmonary congestion determined as severe or very severe ULCs in the present study was 88%, which was higher than the prevalent reported in previous studies  $(27\%-32\%)^{4,12}$  The dissimilarity in these results might be associated with the longer dialysis vintage in the present study (mean 105.5±74.2 months) compared to the other studies (30–85 months). In patients with very severe ULC, LVEF was significantly lower than in the other less severe ULC groups, while the LVMI, left atrial volume index, mPAP, RAP, and RVSP tended to be higher. These echocardiographic findings are similar to previous studies<sup>12,22</sup> and it may be due to the direct effect of volume overload on the heart chambers, which may be associated with an increased risk of cardiovascular event-related mortality.

A previous study<sup>24</sup> demonstrated an independent predictive value of the severe lung ultrasound comet score for mortality and cardiac events. Our result showed that in patients with very severe ULC, the admission rate due to volume overload was significantly higher, and there was a trend of an increased mortality and all-cause admission rate at the 3-month and 1-year follow-up periods, as well as intradialytic complications. Our results did not demonstrate a strong correlation between the lung ultrasound comet score with mortality and morbidity as in previous studies<sup>4,12</sup>, which could be explained by the small sample size of our study and hence the limited preliminary data.

There are some limitations in this study to note. First, we did not assess the inter- and intraobserver agreement in lung ultrasound findings. However, the lung ultrasound scan in this present study was performed by 2 radiologists with 15 years' experience of ultrasound procedure, who were blinded from the results of the other volume status measurement methods. Second, the measurement of ultrasound lung comets has some patientdependent limitations (such as obesity, interstitial lung diseases), which may cause inaccuracy or false–positive ULC findings. We tried to combat this by excluding all possible known conditions that may interfere with image interpretation. Third, this preliminary result is limited by the small sample size, it needs a larger population study for provide more conclusive evidence of the benefit of fluid assessment by lung ultrasound and prognostic value significance of the presence of ULC in Thai chronic HD patients. However, this preliminary result shows the promising approach by using lung ultrasound to detect subclinical pulmonary congestion, and it may be a useful tool to guide management of extravascular lung water excess, which is a major factor for mortality and morbidities in HD patients.

#### **CONCLUSION**

Fluid overload assessed by physical examinations and BIA have limited value for early detecting extravascular lung water in HD patients. Lung ultrasound can be used as a noninvasive point-of-care tool for detecting subclinical pulmonary congestion and may provide semiquantitative guided fluid management in HD patients. The benefits for the long-term outcomes regarding morbidity and mortality by using lung ultrasound-guided fluid management to adjust patients' dry weight need to be studied in a larger population.

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