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ORIGINAL RESEARCH

Lung Ultrasound Estimates the Overhydration and Benefits Blood Pressure Control in Normal or Mild Symptomatic Hemodialysis Patients

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Introduction: Lung ultrasound (LUS) is used for dry weight guidance by assessment of pulmonary congestion in hemodialysis (HD) patients. The aim of this study was to estimate amounts of accumulated fluid by total LUS scores (TLUSS), which were scarcely reported in HD patients who were normal or had a mild functional abnormality. In addition, the correlations between the LUS score of each area and TLUSS were determined to suggest fewer specific areas valuable to shorten the examination time of LUS.

Methods: This cohort study was conducted in adult HD patients who have New York Heart Association Classes I–II. LUS and multifrequency bioimpedance (BIA) were performed at baseline and the individual prescribed dry weight was set. Then each LUS was conducted at 28 areas of bilateral intercostal spaces and calculated as TLUSS weekly for eight weeks in which dry weight was adjusted. The second BIA was also measured at week eight. The difference of pre-HD weight and target weight (weight gain; WG) represented the amount of fluid accumulation.

Results: Twenty patients with a mean age of 62.2±14.0 years were enrolled. One hundred and sixty-six LUS were performed in which forty episodes of them were simultaneously measured with BIA. Optimum dry weight adjusted by TLUSS which benefited in mean reductions of blood pressure, and cardiothoracic ratios. WG amounts were significantly correlated with TLUSS (r=0.38), and with extracellular fluid (r=0.35) and overhydration fluid (r=0.39) assessed by BIA. Estimations of mean fluid overload were 2.18 (TLUSS ≤15), 2.72 (TLUSS 16–24), 3.17 (TLUSS 25–33), 3.65 (TLUSS 34–38) and 5.03 (TLUSS ≥39) in liters. The cut-off points of sum scores of 12 specific lung areas represented the none-mild were <8, moderate at 8–16, and severe pulmonary congestions were >16.

Conclusion: TLUSS estimated accumulated fluid useful for volume and blood pressure controls. Performance of LUS in 12 specific lung areas may reduce spending time and support routine uses of LUS in clinical practice.

Keywords: lung ultrasonography, bioelectrical impedance analysis, volume status, hemodialysis

Introduction

The hydration status of end stage renal disease (ESRD) patients undergoing hemodialysis (HD) is characterized by fluctuation and clinical features can range from euvolemia, hypervolemia presented by leg edema and pulmonary congestion, to dehydration, cramps, and hypotension.[1,2] Of importance, the fluid retention is associated with hypertension, increased arterial stiffness, left ventricular hypertrophy, heart failure, and eventually increased morbidity and mortality,[3–9] therefore, an achievement of dry weight is necessary. Although physical examinations of blood pressure (BP), lung crackles and/or peripheral edema are easily and routinely practiced, they are rather insensitive for estimation of overhydration.[10–12] Therefore, an assessment of pre-dialysis fluid status for optimum volume control and a target weight setting is suggested to combine clinical and technically derived parameters.[1,13] Bioimpedance analysis (BIA) and lung ultrasonography (LUS) are the two novel bedside methods to estimate fluid status, determine dry weight, and predict mortality in HD patients.[9,14–18] BIA

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is an indirect measurement of body composition where volume status is estimated as total body water (TBW), extracellular water (ECW), and intracellular water (ICW).

In contrast, LUS is used to assess the volume overload by measuring extravascular lung water (EVLW) accumulated in the lung interstitium producing the B-line, a reverberation artifact when the ultrasound waves reach the air–fluid interface.[1,19–21] Such that the presence of multiple B-lines indicates pulmonary congestion or edema from overhydration or heart failure, interstitial lung disease and lung fibrosis.[19,22] The B-lines number was proportionally related to the mitral gradient, left atrial volume and maximal inferior vena cava diameter, and was inversely related to the left ventricular ejection fraction (LVEF).[23,24] In addition, moderate to severe pulmonary congestion graded by LUS was demonstrated in a substantial proportion of normal and mild symptomatic HD patients (New York Heart Association classes (NYHA I–II).[24] Therefore, in a setting of HD patients without the definite lung or severe heart diseases, the presence of multiple B-lines eventually indicates pulmonary congestion caused by fluid overload or an early stage of cardiac dysfunction.

Although there are many studies using BIA and LUS to assess the severity of non-euvolemic status in HD patients in which BIA can measure the amount of over or under hydration, there were only a few previous studies that demonstrated the amount of accumulated volume estimated by total LUS scores (TLUSS).[20,25] Because those studies did not exclude some ESRD subjects who had symptomatic pulmonary congestion or poor NYHA (class III–IV) and severe cardiac dysfunction, therefore, the high TLUSS might be partially related to distinct left ventricular dysfunction rather than being directly associated with overhydration. Furthermore, knowledge of the fluid overload amount predicted by TLUSS in HD patients who have normal, or a mildly abnormal functional class will be valuable for early intervention. Therefore, this study was aimed to (a) estimate amount of fluid overload by using LUS, (b) determine a benefit of LUS in BP and volume controls, (c) find out the specific lung areas related to TLUSS for reduction of the time spent for LUS, and (d) analyze the association between LUS and BIA measurement in asymptomatic HD patients.

Materials and Methods

Study Subjects

The current prospective cohort study was conducted in the Srinagarind Hospital, Khon Kaen University, Thailand between December 2018 and March 2019. The inclusion criteria of the study were patients aged 18–80 years with ESRD, on regular HD for more than three months, and willing to provide consent for participation. Conversely, patients with ischemic heart disease or unstable angina within six months, severe valvular heart diseases (severe aortic stenosis, aortic regurgitation, mitral regurgitation, mitral stenosis or tricuspid regurgitation), severe heart failure of NYHA class III–IV, a cardiac arrhythmia, cardiomyopathy with a LVEF <40%, moderate to massive pericardial effusion, constrictive pericarditis, infiltrative heart disease, hemodynamic instability from autonomic dysfunctions, cerebrovascular disease within six months, peripheral vascular disease within six months, uncorrected vascular access dysfunction, body mass index (BMI) >40 or <18.5 kg/m^2, chronic obstructive pulmonary disease or pulmonary fibrosis, post lobectomy or pneumonectomy, metallic prosthesis insertion, decompensated liver cirrhosis, pregnancy, active infection, amputation and psychiatric problems were exempted from the study. Likewise, the withdrawal criteria were complications during the study including cardiac arrest, malignant arrhythmia (atrial fibrillation, atrial flutter, or ventricular tachycardia), shock defined as hypotension (BP <90/60 mmHg) with altered mental status, acute myocardial infarction, acute stroke and death or withdrawal from the study by the decision of participants. The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research, under the project number HE 611468 in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines. All subjects had signed informed consents to participate in the study.

Study Design and Protocol

Baseline characteristics, demographic and laboratory data were collected from interviews, physical examinations, and medical records. Echocardiography and chest X-rays (CXR) were performed before enrollment to exclude the participants who had severe valvular diseases, cardiomyopathy, and pulmonary diseases. Multifrequency BIA and LUS were performed before starting HD at baseline and overhydration volumes obtained from BIA and LUS findings were used for individual prescribed dry weight settings together with clinical considerations. Then LUS was performed weekly at pre-HD sessions for eight weeks

along with clinical assessment of volume overload including leg edema, puffy eyelids, and lung crepitation by another nephrologist who was blinded to the results of TLUSS and BIA. Each LUS was conducted on 28 areas of bilateral intercostal spaces and calculated as TLUSS in which target weight was gradually adjusted if indicated by clinical hypervolemia or moderate pulmonary congestion assessed by TLUSS (≥16 scores). The magnitude of dry weight reduction depended on TLUSS if scores ≥30, prescribed dry weight was reduced 0.1 kg/10 kg BW every two weeks or if TLUSS ≥16, prescribed dry weight was decreased 0.05 kg/10 kg BW every two weeks. If the patients developed clinical symptoms of intolerance with weight reduction such as cramps, dizziness or intradialytic hypotension, the target weight reduction was decreased to 50% of the goal. The second BIA was also measured at week eight of the study in the same period with LUS.

Routine data recorded in the HD chart were collected every time at dialysis including vital signs, prescribed dry weight, amount of weight grain (WG as a difference between pre-HD weight and prescribed dry weight), ultrafiltration volume, interdialytic weight gain (IDWG, a difference of current pre-HD weight and previous post-HD weight), and intradialytic complications. At the week eight of the study, parameters related to adequate volume control, ie, dry weight, pre-HD BP, number of antihypertensive drugs, serum N-terminal proB-type natriuretic peptide (NT-proBNP) levels, and cardiothoracic ratios assessed with CXR were assessed and compared with the baseline data.

Procedures and Definitions

A Prosound α10 premier ultrasound system (Hitachi Aloka Medical, Co. Ltd) with a standard imaging transducer was used for an echocardiography analysis according to the guidelines of the American Society of Echocardiography recommendations and indexed to the body surface area. Cardiomegaly was defined by evidence of a cardiothoracic ratio >0.5 in CXR and left ventricular hypertrophy was evidenced by an echocardiogram criterion of left ventricular mass indices (LVMI) of >115 g/m^2 in male and >95 g/m^2 in female patients.[26]

The LUS was conducted in a supine position using a Logiq Book XP (GE Parallel Design Inc.,Phoenix, USA) ultrasound machine equipped with 3.5 MHz cardiac probes to identify B-lines. A B-line was defined as an echogenic artifact with a narrow origin on the pleural line, deepening to the inferior border of the screen without fading and coherent with respiratory movements (Figure 1).[27–29] The LUS investigation involved 28 areas involving left/right second to fourth intercostal spaces and the right fifth intercostal space in midaxillary (MA), anterior axillary (AA), midclavicular (MC), and parasternal (PS) lines as detailed in Figure 2. Numbers of B-lines were counted from zero to ten in each area and a TLUSS was the summation of all B-lines. Several scales of pre-HD pulmonary congestion severity assessed by TLUSS in HD cases were described as following; the exclusion of congestion if TLUSS <5, mild ≥5 and <15, moderate ≥15 and <30, and severe ≥30;[19] absent or mild if TLUSS <16, moderate 16–30, and serious >30;[16] mild if TLUSS <14, moderate 14–30, and serious >30;[23,24] mild if TLUSS 5−15, moderate to severe 15–60, and very severe >60.[15]

The LUS examiners were two nephrologists (SW., EL.) who were trained by the specialized radiologist (AA) in which their reliability and agreements were compatible with only small intra- and interobserver variabilities. The ultrasound images were saved in electronic medical records. The number of B-lines were then confirmed and reported by the radiologist.

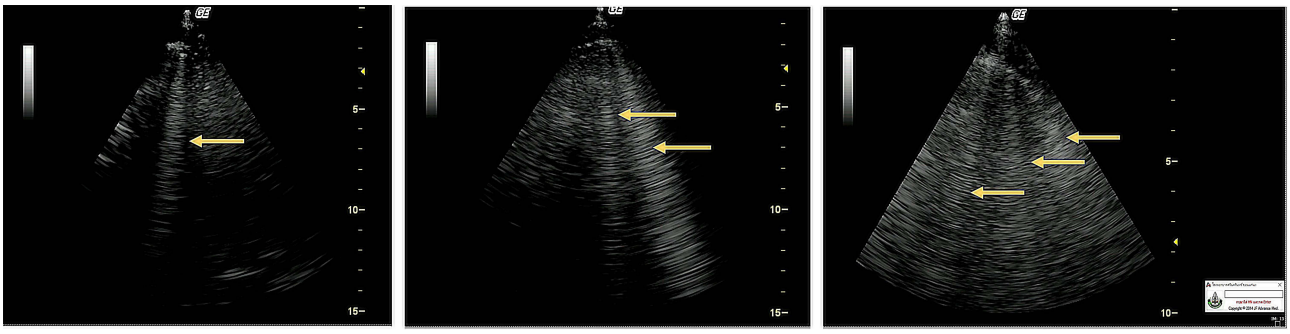

Figure 1 The lung ultrasonography demonstrates the B-lines (arrows).

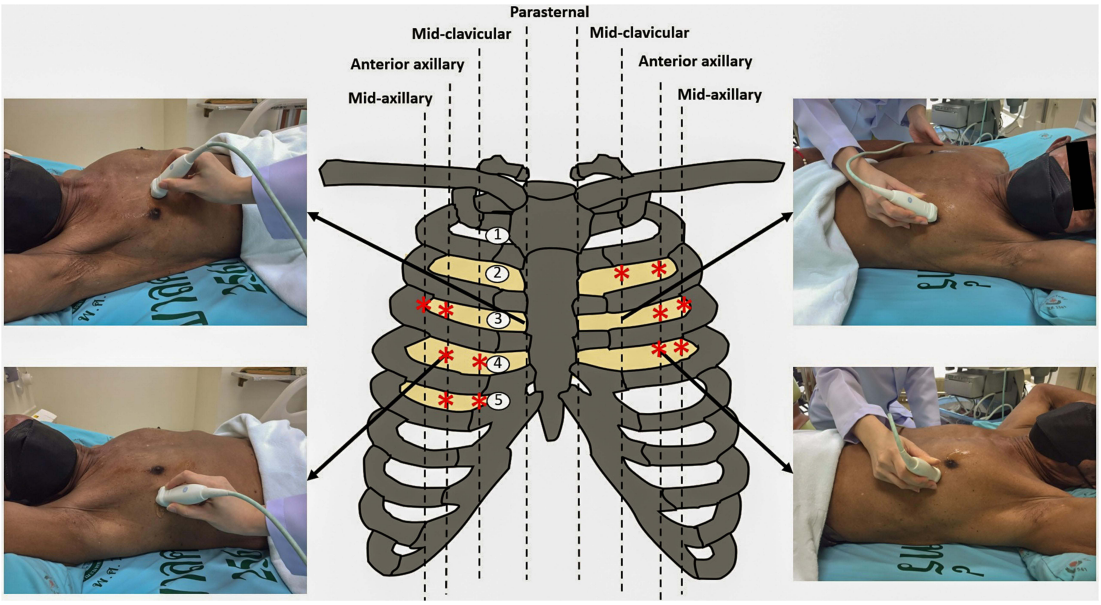

Figure 2 Twenty-eight areas of total lung ultrasonography prescribed by Jambrik et al.[29]
Notes: The asterisks (*) are demonstrating 12 specific areas which their sum scores of B-lines well related with total lung ultrasound score taken from 28 areas.

Body composition was monitored to assess fluid status by using the multifrequency bioimpedance spectroscopy (BCM, Fresenius Medical Care) with 50 frequencies between 5 kHz to 1 MHz. Two electrodes were placed with: one on the dorsal aspect of hand and second on the foot in the supine position as shown in the Supplementary Figure 1 (Supplementary Materials). TBW, ECW, ICW, absolute fluid overload (AFO; a difference between measured ECW and expected patient ECW under normal physiological conditions), and relative fluid overload (RFO; a percentage of the ratio between absolute fluid overload and extracellular water (100 × AFO/ECW) were measured at baseline and in week eight of the study. Overhydration is defined if the RFO >15%.[9,16]

The LUS and BIA were performed pre-HD at the first session of the week with longest interdialytic period in both twice and thrice-weekly HD patients.

Weight gain was calculated in all dialysis sessions including the sessions in which LUS and BIA were performed to represent the amount of fluid overload in liter. The definition of intradialytic hypotension in was decrease in SBP ≥20 mmHg or mean BP ≥10 mmHg with associated symptoms or need for intervention based on the KDOQI 2005 guideline.[30]

Outcome Measurements

The primary outcome was the amounts of the accumulated volume (WG) estimated by TLUSS. Secondary outcomes were the differences of parameters assessing adequacy of volume control between the baseline data and week eight data at the end of study, the correlations of LUS scores measured at specific lung areas and TLUSS and the correlations among the WG amount, TLUSS and BIA variables.

Statistical Analysis

Baseline characteristics of the participants were analyzed using descriptive statistics such as mean ±standard deviation (SD) or median ±interquartile range (IQR) for continuous variables and percentage for categorical variables. Histogram and Shapiro–Wilk analyses were used to assess the distribution of data. The primary outcomes, ie, fluid overload estimations by TLUSS were analyzed by using linear regression and linearity trend methods. The correlations among LUS scores at specific lung areas, TLUSS, WG and BIA as secondary outcomes were assessed by Pearson or Spearman's analysis accounting for repeated measurements. Comparisons of dependent outcomes such as before vs after treatment outcomes or repeated measurements were analyzed with a paired *t*-test for two groups and a generalized estimating equation (GEE) among multiple groups. Statistical analyses were performed by STATA version 17.0, where the p-value <0.05 was statistical significance.

Results

Baseline Characteristics

A total of 20 eligible patients were enrolled in the study. The mean age of patients was 62.15±14.0 years, of which 70% were male. All together 166 LUS measurements were performed in which 40 episodes of LUS, and BIA were measured simultaneously and then, analyzed for the correlations. The baseline characteristics are shown in Table 1.

Beneficial Controls of Dry Weight, BP, Overhydration, and Pulmonary Congestion by LUS

A gradual decrease of prescribed dry weight guided by LUS was achieved with a 0.94±0.81 kg mean difference between the baseline and week eight levels along with significant reductions of pre-HD weights, TLUSS, CT ratios, and NT-pro BNP levels (Table 2). According to evidence of volume control, the SBP, MAP and daily antihypertensive drugs usage were also significantly lessened at the end of study as shown in Table 2. The GEE analysis showed an average weekly

Table 1 The Baseline Characteristics of Patients in the Study (n=20)

Variables	Values
Age (years), mean ±SD	62.2±14.0
Male sex, n(%)	14 (70)
BMI (kg/m^2), mean ±SD	24.0±3.65
HD twice/thrice weekly, (%)	50/50
Pre-dialysis weight (kg), mean ±SD	62.5±10.8
SBP (mmHg), mean ±SD	146.2±16.9
DBP (mmHg), mean ±SD	73.9±10.7
Pulse rate (bpm), mean ±SD	77.8±11.3
Number of oral antihypertensive drugs (n), mean ±SD	2.75±1.41
CT ratio of initial chest radiography, mean ±SD	0.57±0.06
Dialytic duration (months), median (IQR)	14 (12–48.5)
Residual urine (mL), mean ±SD	283.8±220.8
History of smoking, n (%)	9 (45)
Comorbidities	
Diabetes mellitus, n (%)	9 (45)
Dyslipidemia, n (%)	14 (70)
Myocardial infarction, n (%)	2 (10)
Cerebrovascular disease, n (%)	2 (10)
Gout, n (%)	6 (30)
Left ventricular ejection fraction (%), mean ±SD	64.0±7.53
Hemoglobin (g/dL), mean ±SD	10.8±0.78
Hematocrit (%), mean ±SD	34.1±2.72
HbA1c (%), mean ±SD	5.78±1.74
BUN (mg/dL), mean ±SD	69.5±20.3
Creatinine (mg/dL), mean ±SD	11.3±2.83
Na (mEq/L), mean ±SD	138.6±3.65
K (mEq/L), mean ±SD	4.91±0.56
Cl (mEq/L), mean ±SD	95.5±3.2
HCO_3 (mEq/L), mean ±SD	22.2±1.99
Phosphate (mg/dL), mean ±SD	3.37±1.04
Calcium (mg/dL), mean ±SD	8.96±0.42
Uric acid (g/dL), mean ±SD	7.68±1.11
Albumin (g/dL), mean ±SD	4.13±0.27
PTH (pg/mL), mean ±SD	310.5±360.1
CRP (mg/L), median (IQR)	1.23 (0.51–1.86)

Abbreviations: SD, standard deviation; IQR, interquartile range (25th–75th percentile); BMI, body mass index; HD, hemodialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; CT ratio, cardiothoracic ratio; BUN, blood urea nitrogen; PTH, parathyroid hormone; CRP, c-reactive protein.

Table 2 Comparisons of Clinical Parameters, Total Lung Ultrasound Scores and Bioimpedance Values at Baseline and Week Eight

Parameters	Baseline	Week 8	*p*-value
Pre-HD BW (kg), mean ±SD	62.5±10.8	61.6±10.4	0.009
Prescribed dry weight (kg), mean ±SD	59.6±10.8	58.7±10.3	<0.001
Volume overload (WG) (L), mean ±SD	2.94±1.13	2.87±1.27	0.80
Ultrafiltration (L), mean ±SD	3.02±1.18	2.91±1.25	0.73
TLUSS (scores), mean ±SD	26.9±5.47	22.2±7.04	0.002
SBP (mmHg), mean ±SD	146.2±16.9	136.5±17.6	0.002
DBP (mmHg), mean ±SD	73.9±10.7	72.6±10.4	0.096
MAP (mmHg), mean ±SD	98.2±10.2	93.6±10.6	0.003
CT ratio by CXR, median (IQR)	0.57 (0.52–0.61)	0.54 (0.51–0.61)	0.026
NT-proBNP (pg/mL), median (IQR)	3758 (1574–10,846)	3714 (846.5–6457)	0.025
Number of anti-HT drugs (per day), median (IQR)	3.0 (2.0–3.5)	2.0 (0–3.0)	0.005

Abbreviations: SD, standard deviation; IQR, interquartile range (25th–75th percentile); kg, kilograms; L, liter; WG, weight gain; TLUSS, total lung ultrasound score; Pre-HD BW, pre-hemodialysis body weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CT ratio, cardiothoracic ratio; NT-proBNP, N-terminal proB-type natriuretic peptide; Anti-HT drugs, antihypertensive drugs.

decrease of pre-HD SBP and MAP were 0.82 and 0.42 mmHg. Intradialytic hypotension and cramps occurred in 7.78% and 5.19% of all HD sessions during the eight-week study period.

Estimation of Accumulated Weight Gains Classified by the TLUSS

Amounts of WG and TLUSS of the participants were simultaneously evaluated 166 times during eight weeks of the study. Means calculated for WG, IDWG and TLUSS were 3.01±1.32 L, 2.99±1.33, and 25.5±7.11 points. The correlation coefficients (r) between TLUSS and (1) WG was 0.377 (95%CI: 0.176–0.579, p=0.001, Figure 3), (2) IDWG was 0.365 (95%CI: 0.169–0.562, p=0.001, and (3) ultrafiltration volume was 0.323 (95%CI: 0.065–0.582, p=0.017).

Proportions of pulmonary congestion severity suggested by Siriopol et al[16] were 9.64% of absent or mild (TLUSS ≤15), 63.86% of moderate (TLUSS 16–30), and 26.51% of severe (TLUSS >30) with the means of accumulated weight gains were 2.18, 2.92, and 3.60 L (Table 3). Using the linearity trend for subgroup classification of TLUSS to estimate amounts of overhydration revealed the estimated mean fluid overloads in liters were for TLUSS ≤15 (2.18), 16–24 (2.74), 25–33 (3.13), 34–38 (3.81), and ≥39 (5.03), overall p<0.001, or 1.2911 plus 0.0681 L (95%CI: 0.042–0.095, p<0.001) for every increase of TLUSS by 1 point from baseline (Table 3 and Figure 4).

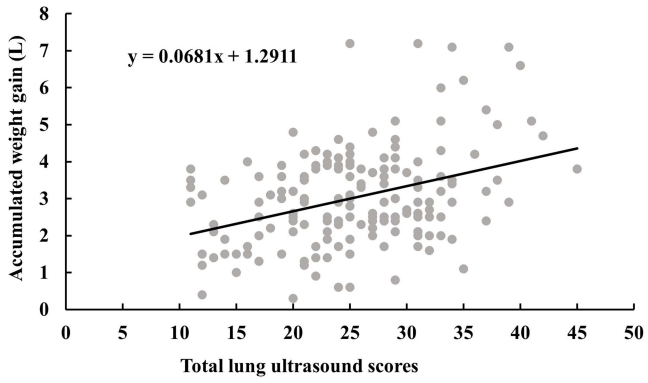

Figure 3 The correlation between the total lung ultrasound scores and accumulated weight gains (r=0.377).

Table 3 Comparison of Accumulated Weight Gains Categorized as Severities of Pulmonary Congestion and Total Lung Ultrasound Score Groups

Severities of Pulmonary Congestion	Weight Gain (L)			TLUSS	Weight Gain (L)		
	Mean ±SD	Mean Difference (95%CI)	*p*-value		Mean ±SD	Mean Difference (95%CI)	*p*-value
Absent or mild (TLUSS ≤15) (n=16)	2.18±1.04	0		≤15, (n=16)	2.18±1.04	0	
				16–24, (n=57)	2.74±1.08	0.56 (−0.10–1.22)	0.097
Moderate (TLUSS 16–30) (n=106)	2.92±1.12	0.74 (0.08–1.40)	0.027	25–33, (n=73)	3.13±1.22	0.95 (0.30–1.59)	0.004
Severe (TLUSS >30) (n=44)	3.60±1.60	1.42 (0.71–2.13)	<0.001	34–38, (n=14)	3.81±1.65	1.63 (0.77–2.48)	<0.001
				≥39, (n=6)	5.03±1.61	2.85 (1.73–3.97)	<0.001

Abbreviations: L, liter; TLUSS, total lung ultrasound score; SD, standard deviation; CI, confidence interval.

Correlations Among the LUS Scores in Different Regions with the TLUSS and WG

Means of TLUSS performed in the right and left intercostal areas were 15.5±4.84 points and 10.0±3.01 points. The LUS scores measured in the right intercostal spaces had better correlation with TLUSS and amounts of WG than left intercostal spaces (Table 4). Furthermore, LUS scores when placed at AA, MA, and MC lines have stronger correlations with the TLUSS than other areas as shown in Table 4. In order to shorten the time spent for LUS, the scores composed of specific 12 areas that related with the TLUSS and WG, ie, the AA lines of the right third, fourth, fifth and left second, third, fourth intercostal spaces (six areas), MA lines of right third, and left third, fourth intercostal spaces (three areas), and MC lines of right fourth, fifth and left second intercostal spaces (three areas) as illustrated by the asterisks in Figure 2, were analyzed which demonstrated the good correlation with TLUSS taken from 28 areas (r=0.918, $p<0.001$, Figure 5). Cut-off points for the LUS scores of 12 areas compared with the TLUSS to represent none or mild (TLUSS ≤15), moderate (TLUSS 16–30), and severe (TLUSS >30) pulmonary congestion were ≤7, 8–16 and >16 scores.

Correlations Between the TLUSS and BIA Parameters

The total 40 episodes of LUS were simultaneously measured with BIA (data presented in Supplementary Table 1 of Supplementary Materials). The correlations between LUS and BIA parameters are shown in Table 5. TLUSS positively

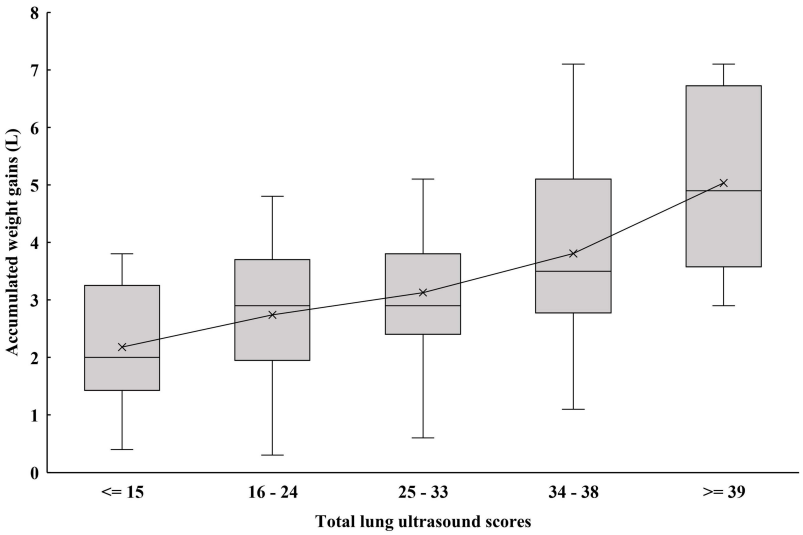

Figure 4 The box-and-whisker diagram shows median and interquartile ranges and the X-line represent the mean values of weight gain amounts categorized as the groups of total lung ultrasound scores.

Table 4 Correlations Between Lung Ultrasound Score in Each Position with Total Lung Ultrasound Score and Accumulated Weight Gain

Position (n=166)	r[a] (Total LUS Score)	r[a] (Amount of WG)
RTMA2	0.062	−0.097
RTAA2	0.379*	0.129
RTMC2	0.349*	0.178*
RTPS2	0.326*	0.036
RTMA3	0.579*	0.314*
RTAA3	0.658*	0.213*
RTMC3	0.513*	0.067
RTPS3	0.527*	0.226*
RTMA4	0.538*	0.176*
RTAA4	0.646*	0.259*
RTMC4	0.609*	0.221*
RTPS4	0.431*	0.318*
RTMA5	0.492*	0.171*
RTAA5	0.601*	0.245*
RTMC5	0.534*	0.196*
RTPS5	0.323*	0.177*
LTPS2	0.239*	0.085
LTMC2	0.471*	0.156*
LTAA2	0.423*	0.259*
LTMA2	−0.002	−0.094
LTPS3	0.145	−0.090
LTMC3	0.476*	0.121
LTAA3	0.598*	0.130
LTMA3	0.540*	0.220*
LTPS4	0.022	0.027
LTMC4	0.305*	−0.011
LTAA4	0.475*	0.285*
LTMA4	0.420*	0.202*

Notes: [a]Correlation accounted for repeated measurements was analyzed by Pearson correlation in case of normal data distribution and Spearman's correlation for non-parametric statistic. *Statistical significance ($p<0.05$).

Abbreviations: LUS, lung ultrasound; WG, weight gain; RT, right; LT, left; MA, mid-axillary area; AA, anterior axillary area; MC, mid-clavicular area; PS, parasternal area; 2–5, intercostal space second to fifth.

correlated but at weak to moderate levels with TBW, ICW, LTM, relLTM, relATM and negatively at moderate levels to ATM, fat mass and relFat. Moreover, the amount of WG was positively associated with ECW and AFO at weak to moderate levels.

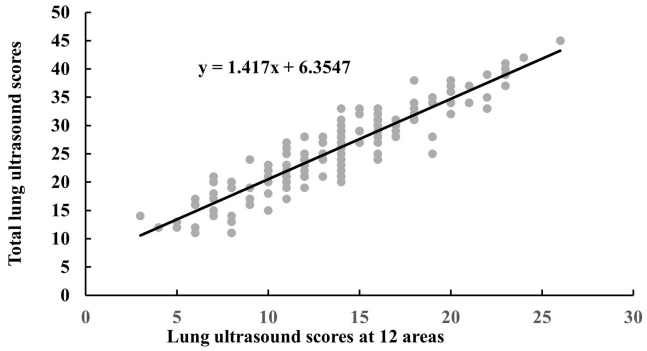

Figure 5 The correlation between sum scores of 12 specific lung area and total lung ultrasound scores placing on 28 lung areas (r=0.918).

Table 5 The Correlation Between BIA Parameters with Total LUS Score and WG

Parameters of BIA	Total LUS Score (n =40)		WG (n=40)	
	r[a]	*p*-value	r[a]	*p*-value
Pre-HD BW	−0.038	0.81	0.090	0.58
NHW	−0.064	0.72	−0.028	0.87
TBW	0.346*	0.04	0.307	0.07
ECW	0.327	0.06	0.345*	0.04
ICW	0.352*	0.04	0.209	0.23
AFO	0.269	0.09	0.386*	0.01
RFO	0.265	0.12	0.299	0.08
LTM	0.362*	0.03	0.229	0.19
relLTM	0.398*	0.02	0.194	0.26
ATM	−0.411*	0.02	−0.190	0.28
relATM	0.359*	0.03	0.229	0.19
Fat mass	−0.411*	0.02	−0.190	0.28
relFAT	−0.428*	0.01	−0.245	0.16

Notes: [a]Correlation accounted for repeated measurements was analyzed by Pearson correlation in case of normal data distribution and Spearman correlation for non-parametric statistic. *Statistical significance.
Abbreviations: BIA, bioimpedance analysis; LUS, lung ultrasound; WG, weight gain; Pre-HD BW, pre-hemodialysis body weight; NHW, normal hydration weight =(Pre-HD BW- AFO); TBW, total body water; ECW, extracellular water; ICW, intracellular water; AFO, absolute fluid overload; RFO, relative fluid overload =(100 × AFO/ECW); LTM, lean tissue mass; relLTM, relative lean tissue mass =(100 × LTM/Pre-HD BW); ATM, adipose tissue mass =(Pre-HD BW – LTM – AFO); relATM, relative adipose tissue mass =(100 × ATM/Pre-HD BW); relFAT, relative fat mass =(100 × fat mass/Pre-HD BW).

In the overhydrated group defined as RFO >15%, 92.6% of them had pulmonary congestion as detected by LUS, ie, 66.7% at the moderate degree (TLUSS 16–30) and 25.9% at the severe degree. Interestingly, in the non-overhydrated subjects classified by BIA, only 30.8% of them had none or mild pulmonary congestion (TLUSS ≤15) but another 69.2% presented moderate pulmonary congestion. In contrast, proportions of overhydration as a BIA criterion were 33.3%, 66.7%, and 100% in the none-mild, moderate and severity pulmonary congestion groups classified by LUS. Findings of echocardiograms revealed that diastolic dysfunction was noted in 42.9% of non-overhydrated subjects who had pulmonary congestion and no diastolic dysfunction reported in non-overhydrated cases without pulmonary congestion. Furthermore, presence of pulmonary hypertension (0, 21.7, and 34.1%, p=0.016 in mild-, moderate- and severe pulmonary congestion) and right ventricular systolic pressure (RVSP) were higher in more severe degrees of pulmonary congestion (27.3±7.85, 37.1±11.4 and 42.0±12.0 mmHg, p=0.006 in mild-, moderate- and severe pulmonary congestion).

Relevance of Clinical Signs of Overhydration with WG and TLUSS

Analyses of WG and TLUSS with severity of leg edema, presences of puffy eyelids and lung crepitation to explore the clinically relevance and how sensitive of these signs for pulmonary congestion were performed and the results are shown in Supplementary Table 2 (Supplementary Materials). The data demonstrates significant increasing of WG and TLUSS along with the severity of edema and presences of puffy eyelids and lung crepitation. Although these clinical signs have high specificity and positive predictive values for prediction of pulmonary congestion, however, they were insensitive because leg edema, puffy eyelids, and lung crepitation could be detected in only 40.6%, 17.5%, and 17.0% of the moderate pulmonary congestion group, and 70.5%, 30%, and 17.5% in the severe pulmonary congestion group. Supplementary Table 3 shows results of sensitivity, specificity, positive predictive value, negative predictive value, of these clinical signs for prediction of lung congestion (Supplementary Materials).

Discussion

In HD patients, a LUS is useful for assessment of EVLW which may relate with volume overload and/or left ventricular dysfunction evidenced as a negative correlation between TLUSS and the left ventricular ejection fraction.[5,21,23–25] In addition, severe pulmonary congestion as defined by TLUSS was the predictor of cardiac events, hospitalization, and death.[15,31] The

present study excluded the participants who had a cardiomyopathy and NYHA class III–IV to focus on a correlation of TLUSS directly with the accumulated volume per se not from definitive heart failure which the results demonstrated as the proportional increase of overhydration severity along with higher TLUSS in HD patients who had asymptomatic or mild functional abnormalities. These estimated amounts of accumulated overhydration will help for volume control in these subjects especially following the trend of TLUSS in an individual dialysis patient. The prevalence of pulmonary congestion detected by TLUSS in the non-overhydrated subjects classified by BIA was 69.2% similar to the recent study of Giannese et al conducted in an euvolemic HD patient which reported the prevalence of baseline pulmonary congestion was 67% and persistent or recurrent pulmonary congestion defined as TLUSS >15 at least 50% of measurements during the six-month study period was 46% which developed higher cardiovascular events and hospitalization than the non-persistent group.[32] Diastolic dysfunction might be a cause of pulmonary congestion in the non-overhydrated participants as discovery of a higher proportion of diastolic dysfunction in their baseline echocardiogram findings. Furthermore, the severity of pulmonary hypertension accelerated with degrees of pulmonary congestion and the significant correlation between RVSP and WG was demonstrated ($r=0.342$, $p<0.001$) consistent with the report of Yılmaz et al, which found an association of volume overload and pulmonary hypertension.[33]

Previous studies have compared several methods for dry weight guidance in HD patients which demonstrated the promise of the LUS-guided technique as an increase of TLUSS correlated with interdialytic weight gains, and a reduction of B-lines possibly related with lost volumes during HD including inferior vena cava diameters and atrial dimensions.[15,21,25,31,34–36] Torino et el, evaluated the fluid accumulation by using physical examination, ie, standardized lung auscultation and quantification of peripheral edema compared with LUS which found that lung crackles, either alone or in combination with peripheral edema, poorly reflected the interstitial lung edema in HD patients and these findings support using add-on LUS to evaluate fluid accumulation and lung congestion.[12] This study supported an insensitivity of the clinical signs and a value of LUS-guided treatment by achievement of target weight by reduction of prescribed dry weight if moderate pulmonary congestion was presented (TLUSS ≥16) resulting in controllable pre-HD, SBP, MAP and reduction of heart size and NT-proBNP levels. Currently, the LUST (lung water by ultrasound guided treatment to prevent death and cardiovascular complications in high risk end-stage renal disease patients with cardiomyopathy) sub-study revealed a beneficial effect of dry weight reduction guided by LUS during the eight-week period on ambulatory BP and arterial stiffness improvements with more stringent methods on dry weight adjustment compared with this present study, ie, a decrease of prescribed dry weight if TLUSS ≥5 in participants without a history of cardiovascular disease and NYHA class III–IV.[37,38] Although the decreased magnitudes of B-line numbers, dry weight, and BP including the percentage of intradialytic complications were quite similar between the LUST sub-study and the present study, the higher pre-HD levels of TLUSS, accumulated weight gain, and the proportion of twice-weekly HD suggested that a LUS-guidance might further benefit from a more strict dry weight reduction. Moreover, the current study enrolled HD patients who were asymptomatic or had mild functional abnormality, however, most of them were classified as 66.27% of moderate (TLUSS 16–30) and 24.10% of severe (TLUSS >30) pulmonary congestion which agrees with previous studies that the EVLW is substantial and has an effect on quality of life although with fewer symptoms and these patients should be monitored and managed to achieve appropriate dry weights.[15,21,24]

The main LUST trial is currently published which showed no significant differences of primary outcome, ie, all-cause death, nonfatal myocardial infarction, and decompensated heart failure, between the LUS-guidance group and the usual care group in HD patients with a high cardiovascular risk and/or cardiac dysfunction (structural or functional or both).[39] Reductions of lung congestion, recurrent decompensated heart failure, and cardiovascular events, however, were demonstrated in the LUST trial and some issues which might explain this nonsignificant composite end point was inadequate numbers of participants, a need for a longer follow-up time to reveal significant outcomes, and the unblinded intervention bias.[39] Different points between the present study and the main LUST trial were normal or mild dysfunctional participants enrolled in this study and although a short-term study of the LUST sub-project demonstrated a similar reduction of TLUSS, BP, and dry weight as this study;[37,38] but in the main, LUST revealed no significant change of post dialysis weight and BP between the LUS group and the usual care group which might imply inadequate ultrafiltration or non-adhered protocol by the investigators for the long period.[39] Another concern of LUS-guidance is labor and time consumption which impeded regular volume monitoring. A LUS performed at eight areas of bilateral thoraxes in midclavicular and midaxillary lines of upper and lower anterior chests was suggested instead of a routine 28 areas with a cut-off of ≥4 B-lines to define lung congestion.[40] This study

also revealed the compatibility of total B-lines scores placed on 12 areas with the TLUSS and classification of the severity of pulmonary congestion as none or mild (<8 scores), moderate (8–16 scores), and severe (>16 scores) degrees.

The current study found LUS scores of right hemithorax had better correlation with the accumulated weight gain and the TLUSS rather than the left thorax similar to a previous study.[41] Jambrik et al compared EVLW measured from LUS and a radiologic score from chest radiography. They found that there was a significant correlation between the LUS score and the radiologic score (r=0.78, $p<0.01$) and a stronger correlation between the radiologic score and LUS measured from the right third intercostal space in the anterior axillary line (r=0.64, $p<0.01$).[29] A possible explanation is poorer lymphatic drainage on the right side of lung by a small-caliber right bronchomediastinal trunk in comparison to a larger thoracic duct in the left.[42] Evidence supports this explanation that a right thorax revealing fluid overload or pulmonary congestion more than a left thorax is especially found in the minimal fluid overload.

Previous studies reported that both overhydration detected by BIA and high EVLW discovered by LUS predicted mortalities in ESRD patients ongoing dialysis.[9,14–16] LUS correlated with thoracic BIA which similarly represented lung congestion but was controversially related with total body BIA, an indication of systemic congestion.[16,24,41,43] In the present study, the TLUSS, ECF, and AFO correlated with the accumulated weight gain, and the TLUSS positively correlated with TBW, ICW, LTM, and relLTM, and a trend of correlation with the ECW. It was also found that 69.2% of pre-HD non-overhydration cases defined by total BIA really had moderate pulmonary congestion and 33.3% of none-mild pulmonary congestion still had systemic overhydration, therefore, BIA and LUS, which reflect different over-fluid compartments, are complementary and valuable techniques for dry weight guidance.

The strength of this study is to estimate the steps of fluid overload from TLUSS, and that these results can then be used to accurately estimate fluid overload by using either LUS or BIA which have better estimations than clinical evaluation alone. Performing of LUS in 12 specific lung areas which are related with the classical 28 areas of TLUSS may reduce time spent and support routine use in clinical practices. Nevertheless, the limitations of the study were the small numbers of BIA tests (40 tests) which might be insufficient to demonstrate a strong correlation with TLUSS, small numbers of total participants that validated fewer characteristics of relevant cases and absent of the control group to compare the clinical benefit of LUS-guided ultrafiltration strategy. Moreover, although the previous study found that survival and hospitalization of twice-weekly HD cases were comparable with thrice-weekly HD patients with a minimal effect of spKt/V on mortality,[44] 50% of the study population were on twice-weekly HD which made a limitation of generalized application of results to all thrice-weekly HD setting.

Conclusion

LUS score can estimate the amount of volume overload in HD patients complimentary with clinical assessment and total body BIA measurement for volume and blood pressure controls in HD patients who have none or mild functional abnormalities.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its Supplementary Materials File.

Ethics and Consent

The study was approved by the Ethics Committee for Human Research, Faculty of Medicine, Khon Kaen University, Thailand as per the guideline of Helsinki Declaration (HE611468). Written informed consents were applicable in all subjects which their confidentiality was ensured by data protection and privacy legislation. Out of 20 patients, two subjects have given consent for using their pictures for the publication and the consents for publication of another 18 cases are not applicable. The photos presented in this publication comply with relevant standards identity protection and participant authorization.

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Disclosure

The authors report no conflicts of interest in this work.

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