Lung Ultrasound as a Tool to Evaluate Fluid Accumulation in Dialysis Patients

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Keywords

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Abstract

Background: Volume overload is the main mechanism of BP elevation in end-stage kidney disease (ESKD) patients undergoing hemodialysis or peritoneal dialysis and has been linked to adverse outcomes and increased mortality in this population. **Summary:** This review discusses current knowledge on lung ultrasound as a tool for detection of extracellular volume overload through evaluation of extravascular lung water content. We describe the principles of lung US, the main protocols to apply it in clinical practice, and accumulated data evidence regarding its associations with cardiovascular events and mortality. We also summarize available evidence on the effect of lung ultrasound-guided volume management strategies on BP control, echocardiographic parameters, and major outcomes in patients undergoing dialysis. **Key Messages:** Among interventions attempting to reduce the burden of cardiovascular disease in ESKD, effective management of volume overload represents an unmet clinical need. Assessment of hydration status by lung ultrasound is a cheap, easy to employ, and real-time technique that can offer accurate dry weight assessment leading to several clinical benefits.

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Introduction

Fluid excess is common in ESKD and is one of the main mechanisms associated with high blood pressure (BP) levels, as well as increased cardiac preload and ventricular filling pressures, ultimately leading to left ventricular hypertrophy, heart failure (HF), and death in dialysis patients [1–3]. The cyclic variation in the prevalence of cardiovascular events, demonstrating a day-of-week pattern, is well known in patients undergoing hemodialysis (HD). This is a typical consequence of the intermittent nature of the modality, with interdialytic weight gain (IDWG) alternating with the consequent fast intradialytic volume removal causing intermittent cardiovascular stress [4]. This adverse phenomenon is more pronounced in patients with excessive IDWG [5], or during the long, 3-day interdialytic interval compared to the typical 2-day interdialytic interval [4, 6, 7]. Patients undergoing peritoneal dialysis (PD) are free from this intermittent volume gain and removal; however, the majority of these individuals are also considered to be steadily volume overloaded [8], a fact that also has adverse consequences for the heart structure [9].

The accurate determination of volume status and adopting reliable strategies for the management of fluid accumulation and dry weight adjustment in ESKD patients represent the “holy grail” of the practicing nephrologist for decades [3]. Evaluation of hydration status in the clinical setting has been traditionally guided by clinical

examination, including assessment of BP, evaluation for presence of lung crackles, pedal edema, or jugular vein distension, and simple diagnostic tools. However, clinical evaluation has been repeatedly shown to have limited diagnostic performance for detecting volume overload and interstitial edema in ESKD and other disease states [10, 11]. In both dialysis modalities, presence of pedal edema did not reliably reflect fluid status compared to parameters obtained from other volume assessment methods and markers [12, 13].

Isotope dilution analysis is the gold standard method for body volume assessment; total body water and extracellular volume are preferably determined by deuterium/tritium dilution and bromide chloride/sucrose dilution, respectively [14]. Combination of dual-energy X-ray absorptiometry with a trace dilution method, in order to overcome limitations from incorrect estimation of lean soft tissue, is superior for determining fat, lean soft, and bone tissue mass composition in dialysis patients [14–16]. However, application of these methods in daily clinical routine is unfeasible due to high cost, invasive nature, and poor applicability at bedside. To this end, several diagnostic methods have been developed, including inferior vena cava diameter measurement, echocardiography (i.e., left ventricular [LV] filling pressures and E/e' ratio), biochemical parameters (i.e., BNP/NT-proBNP), use of chest X-ray, and bioimpedance techniques, that are widely used and provide reliable estimates of total tissue fluid content [3, 8, 17].

In recent years, growing attention has been given to lung ultrasound (US) as a tool to evaluate fluid accumulation in ESKD. This was due to its simple, noninvasive, radiation-free nature and accumulating data on its prognostic utility for cardiovascular events and mortality, as well as its usefulness in accurate dry-weight determination to help BP control and improvement in heart structure [18]. This review discusses the principles of lung US and the current protocols for evaluation of fluid accumulation in dialysis patients, as well as existing evidence regarding its associations with other cardiovascular risk factors and adverse events and its utility in achieving dry weight and improving clinical outcomes.

Principles of Ultrasonography of Pulmonary Parenchyma

For many decades, lung ultrasonography had been a neglected area, given standard textbook knowledge about the utility of this modality in air-rich organs; that is, the

lack of interface of structures with different acoustic impedance in normal lung parenchyma that would permit reflection of the US beam, rendering the lung ultrasound of limited use [19, 20]. In a normally aerated parenchyma, the beam is scattered, and no structure can be visualized. The only exception to this is the pleural line that produces the characteristic reverberation artifact of a hyperechoic horizontal line (i.e., A-lines) (shown in Fig. 1); this is formed due to multiple reflections of the US beam from the interface of soft tissues of the chest wall and the air-filled alveoli beneath the pleura [21]. The rhythmic respiration-induced movement of this pleural line is known as “lung-sliding,” the absence of which constitutes one of the main sonographic criteria of the pneumothorax [22].

During the last decade, this original technical “limitation” of lung US has been transformed to an “advantage”: under pathological conditions that decrease the air content and increase the lung density (i.e., presence of extravascular water or blood and consolidation due to an infection or a tumor), partial reflection of the ultrasound beam at deeper zones and creation of other reverberation artifacts or even direct visualization of a solid parenchyma can be enabled [20]. In this context, B-lines, the vertical hyperechoic reverberation artifacts that belong to the family of comet-tail artifacts, represent the reflection of the US beam by thickened subpleural interlobular septa and are considered the sonographic sign of lung interstitial syndrome (Fig. 1) [22]. The image that is formed in this state consists of discrete high-echogenic laser- or comet-tail-like vertical structures that arise from the pleural line and dissipate to the bottom of the screen without fading, moving synchronously with lung sliding [22]. Thus, lung US takes advantage of basic principles of ultrasonography in order to scan for presence and quantify extravascular water excess in the lungs.

Extravascular lung water (EVLW), i.e., the water content of the lung interstitium, constitutes a body fluid compartment of major importance. It is strongly related to pulmonary capillary wedge pressure which reflects the driving force that determines fluid extravasation in the lung, and therefore LV filling pressures, and is the hemodynamic parameter used as the golden standard for optimizing fluid management in the critical care setting [23, 24]. The lung US technique has been previously validated for detection of EVLW against pulmonary artery thermodilution CO measurements after cardiac catheterization. In particular, in a pilot study undertaken in 20 patients evaluated with lung US and the indicator dilution method (PiCCO System) before, immediately after, and 24 h following cardiac surgery [23], a significant positive correla-

Fig. 1. Principles of lung ultrasound technique and sonographic signs of A- and B-lines in euvoemia state (normal lung water content) on the left and fluid accumulation state (increased lung water content) on the right.

tion was detected between the B-lines score and EVLW determined by PiCCO. In another study with 50 mechanically ventilated patients in the intensive care unit, an even stronger association was observed ($r = 0.91$, $p = 0.0001$) between B-lines score and EVLW by PiCCO. Furthermore, a B-lines score >1.5 had a sensitivity and specificity of 92.1% and 91.7%, respectively, for detection of presence of EVLW above the normal value of 7 mL/kg (area under the curve [AUC] = 0.9419) [25].

Lung Scanning Protocols

The technical requirements to perform a lung US can be easily met. Any conventional 2D scanner may be appropriate, regardless of the presence of Doppler imaging mode capability [20]. Recently, pocket-sized sonographic devices have been developed offering the convenience of

portability at a lower expense [26]. Several types of probes have been used, including low-frequency (2.5–3.5 MHz) phased-array, low- to medium-frequency (3.5–5.0 MHz) convex and microconvex, and high-frequency (8.0–12.5 MHz) linear probes [27]. The convex and microconvex are the most commonly used types of probe, owing to their intermediate frequency values that allow a reasonable scanning of the pleural line and the subpleural space [20]. The phased-array probe may be also successfully used to detect B-lines that are best visualized with low-frequency bands and also provide deeper views of the chest, with limited ability in detecting pneumothorax [20]. Whether different types of transducers affect the visualization and therefore quantification of B-lines is still a matter of debate, with one study showing significantly higher scores when using the convex compared to the linear probe [28] and others reporting similar results [23, 24, 29]. The penetration depth of the beam should be ideally

Fig. 2. Graphic depiction of scanned intercostal spaces in two lung ultrasound protocols: the 28-site approach (a), the 8-site approach (b), the 6-site approach (c), and the 4-site approach (d).

set between 4 and 8 cm from the pleural line, and focus of the image should be set at the level of the pleural line (to achieve maximal concentration of the energy for reflection and reverberation) [27].

Lung US is performed with the probe placed in the intercostal spaces, avoiding the ribs, in an oblique, along the intercostal space, position or in a longitudinal position, perpendicularly to the ribs [20]. In the oblique scanning position, the pleural line is visualized horizontally, covering the major part of the image; in the longitudinal, the pleural line is located in the center and is adjacent to the upper and lower rib that extend to the upper and outer part of the image, forming the so-called bat-sign [30].

During the lung US, the patient may be evaluated in any lying position (supine, prone, or lateral decubitus) or even standing or sitting, since localization of pleural abnormalities, with the exception of pleural effusion, is not immediately altered, and redistribution of EVLW excess tends to remain the same without inducing clinically significant differences [20]. Assessment of lung congestion is traditionally performed with the patient placed firstly in the supine position, with the anterior part of the chest available for scanning, and subsequently in the semi-supine position with the upper body tilted at approximately

45° to the left decubitus to scan the right axillary lines and subsequently to the right to scan left axillary lines [20]. On the contrary, scanning of the posterior chest is preferred for detection of pulmonary fibrosis. In each intercostal space, the number of visible B-lines is determined either in a quantitative method, by enumerating separate B-lines, or in a semiquantitative method, by estimating the percentage of the image that is occupied by B-lines (i.e., 40% corresponding to 4 B-lines). In each site, zero defines the complete absence of comet-tail images and thus EVLW content, while ten corresponds to a completely white image, full of comet-tail structures [31]. The total sum of B-lines found in all investigated areas is calculated.

With regard to protocols applied for detection of pulmonary congestion as the source of lung interstitial syndrome, several approaches have been used, with all relevant scanning sites located at the anterior and lateral part of the chest (as shown in Fig. 2). The one most commonly employed is the 28-site zone [31], used in the two aforementioned validation studies of Agricola et al. [23] and Enghard et al. [25], as well as in most observational studies and randomized clinical trials in patients with renal diseases [10, 24, 32–37], including pediatric populations

Table 1. Observational studies on dialysis patients using lung ultrasound to assess overhydration and its association with echocardiographic indexes, mortality, and other volume-related outcomes

Author	N	Study design	Lung US protocol	Other measured parameters	Main outcome and results
Mallamaci et al. [24]	71 HD patients	Cross-sectional	28-scanning site lung US with a 3.0-MHz probe (Toshiba NemioXG) before and after dialysis	Echocardiography Overhydration volume assessed by BIA	Prevalence of lung congestion Moderate (14–30 B-lines) and severe (>30 B-lines): 63% Multiple regression analysis for pre-dialysis B-lines score LVEF: $\beta = -0.61, p < 0.001$ Spearman's correlation (pre-dialysis) r (B-lines ~ LVEF) = $-0.55, p < 0.001$ r (B-lines ~ LA volume) = $-0.39, p = 0.001$ r (B-lines ~ E/e') = $-0.48, p < 0.001$
Panuccio et al. [36]	88 PD patients (61 patients underwent echocardiography)	Cross-sectional	28-scanning site lung US with a 3.0-MHz probe (Toshiba NemioXG)	Echocardiography overhydration volume assessed by BIA BP NYHA class Edema Urine output	Prevalence of lung congestion Moderate (15–30 B-lines): 23% Severe (>30 B-lines): 24% Multiple regression analysis for B-lines score For the total population NYHA class: $\beta = 0.31, p = 0.006$ Residual diuresis: $\beta = 0.3, p = 0.006$ SBP: $\beta = -0.16, p = 0.12$ Edema: NYHA class: $\beta = -0.11, p = 0.31$ For patients that underwent echocardiography EF: $\beta = -0.36, p = 0.007$ LA volume: $\beta = 0.29, p = 0.05$ NYHA class: $\beta = 0.07, p = 0.64$ Residual diuresis: $\beta = 0.23, p = 0.09$ SBP: $\beta = -0.16, p = 0.22$ Edema: $\beta = -0.23, p = 0.06$ NYHA class: $\beta = -0.11, p = 0.31$
Zoccali et al. [32]	392 HD patients	Prospective cohort (duration 2.1 years)	28-scanning site lung US with a 3.0-MHz probe before dialysis	All-cause mortality Cardiac events	All-cause mortality HR = 4.20, 95% CI: 2.45–7.23 Cardiac events HR = 3.20, 95% CI: 1.75–5.88
Siriopol et al. [33]	96 HD patients	Prospective cohort (duration 1.19 years)	28-scanning site lung US before and after dialysis	Overhydration volume assessed by BIS Echocardiography All-cause mortality	Prevalence of lung congestion Mild (<16 B-lines): 67.7% Moderate (≥ 16 to ≤ 30 B-lines): 19.8% Severe (>30 B-lines): 12.5% All-cause mortality (for pre-dialysis B-lines score) HR 5.03 (1.5–16.5) for severe congestion versus other two groups Cox regression analysis B-lines score: $\beta = 0.975, p = 0.026$ LVMi: $\beta = 0.020, p = 0.015$
Paudel et al. [44]	27 PD patients	Cross-sectional	28-scanning site lung US with a 3.0-MHz probe	Overhydration volume assessed by BIS BP NT-proBNP	Prevalence of patients with B-lines score >5: 14.8% Spearman's correlation r (B-lines ~ NT-proBNP) = 0.65, $p < 0.0005$ r (OH volume ~ NT-proBNP) = 0.47, $p < 0.02$ r (OH volume ~ B-lines) = 0.31, $p = 0.12$

Table 1 (continued)

Author	N	Study design	Lung US protocol	Other measured parameters	Main outcome and results
Torino et al. [10]	79 HD patients	Baseline evaluation of the LUST study	28-scanning site lung US with a 3.0-MHz probe (Toshiba NemioXG) before and after dialysis	Clinical examination (crackles, pedal edema)	<p>Prevalence of lung congestion</p> <p>Moderate (≥ 15 to ≤ 30 B-lines): 13%</p> <p>Severe (> 30 B-lines): 11%</p> <p>Reproducibility study</p> <p>Mild congestion: AUC = 0.61, 95% CI: 0.57–0.64</p> <p>Moderate congestion: AUC = 0.65, 95% CI: 0.61–0.70</p> <p>Severe congestion: AUC = 0.68, 95% CI: 0.62–0.74</p>
Saad et al. [46]	81 HD patients	Prospective cohort (duration 1.19 years)	28-scanning site lung US with the a portable ultrasound machine (Sonosite, Edge) performed after the dialysis session	<p>Echocardiography (revision of recent echocardiograms for evaluation of LVEF and the E/e' ratio)</p> <p>All-cause mortality</p>	<p>Associations according to multiple regression analysis</p> <p>B-lines with E/e': OR = 0.893, 95% CI: 0.817–0.977</p> <p>B-lines with LVEF: OR 1.009, 95% CI: 0.954–1.066</p> <p>Associations according to multinomial logistic regression analysis</p> <p>B-lines with NYHA class: OR = 8.95, 95% CI: 1.78–39.5, $p = 0.007$, for NYHA classes 1 and 2 versus class 3</p> <p>Multivariate Cox regression analysis</p> <p>All-cause mortality</p> <p>HR 2.98, $p = 0.025$, for moderate and severe OH</p> <p>HR 7.98, $p = 0.013$, for very severe OH</p>
Sevinc et al. [47]	21 PD patients	Cross-sectional	28-scanning site lung US with a 1.6-MHz convex probe	<p>Urine output</p> <p>NT-proBNP</p> <p>VEGF-C levels</p> <p>Echocardiography</p> <p>Overhydration volume assessed by BIS</p>	<p>Spearman's correlation</p> <p>r (B-lines ~ Urine output) = 0.582, $p = 0.007$</p> <p>r (B-lines ~ VEGF-C levels) = 0.447, $p = 0.042$</p> <p>r (B-lines ~ LVMi) = -0.456, $p = 0.038$</p> <p>r (B-lines ~ OH volume [BIA]) = -0.094, $p = 0.685$</p> <p>r (B-lines ~ LV filling velocity) = 0.03, $p = 0.896$</p> <p>r (B-lines ~ E/e' ratio) = -0.136, $p = 0.556$</p> <p>Grouping according to B-lines score</p> <p>Daily urine volume: 225 (62.5–487.5) for B-lines ≤ 1 versus 875 (350–1,775) mL for B-lines > 1, $p = 0.025$</p> <p>VEGF-C levels: 0.25 (0.21–0.32) for B-lines ≤ 1 versus 0.33 (0.27–0.35) ng/mL for B-lines > 1, $p = 0.039$</p>
Alexandrou et al. [9]	38 HD patients 38 PD patients	Case-control	28-scanning site lung US performed during an interdialytic day for HD patients	Echocardiography	<p>B-lines score</p> <p>HD: 4.00 [6.00] versus PD 3.00 [4.25], $p = 0.623$</p> <p>Spearman's correlation</p> <p>r (B-lines ~ LA volume index) = 0.465, $p < 0.001$</p> <p>r (B-lines ~ RVSP) = 0.431, $p < 0.001$</p> <p>r (B-lines ~ E/e' ratio) = 0.304, $p = 0.009$</p> <p>Associations according to multiple regression analysis</p> <p>B-lines with LVMi: $\beta = 0.892$, $p = 0.034$</p>

AUC, area under the curve; BIA, bioimpedance analysis; BIS, bioimpedance spectroscopy; e', early tissue Doppler diastolic velocity; E', peak early diastolic velocity; LA, left atrial; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NYHA, New York Heart Association; OH, overhydration; SBP, systolic blood pressure; RR, rate ratio; RVSP, right ventricular systolic pressure.

[38]. The study protocol includes scanning from the second to fifth intercostal space on the right and from the second to fourth intercostal space on the left along the parasternal, midclavicular, anterior, and midaxillary lines (16-sites on the right and 12-sites on the left) [31]. According to this approach, a score of <15 comets can be characterized as mild pulmonary congestion, a score of 15–30 comets as moderate, and a score >30 comets as severe lung congestion [24].

Other commonly applied protocols, used mainly in the emergency and intensive care settings due to reasons of simplicity, are the 8-point, the 6-point, and the 4-point approaches, shown in Figure 2 [39–42]. The 8-site method includes assessment of two anterior sites (between the sternum and the anterior axillary line) and two lateral sites (between the anterior and posterior axillary line) on each hemithorax. According to this approach that was firstly performed in a study with 300 patients from an emergency unit [39], a score of >3 B-lines in a given scanning site is considered positive for detection of lung congestion [42]. In the 6-site approach, that was first implemented in a cohort with 1,005 patients from 7 Italian centers for diagnosis of acute decompensated HF [40], the second space at the midclavicular line, the fourth space at the anterior axillary line, and the fifth space at midaxillary line are scanned at each side, with a positive examination defined as detection of >3 B-lines in a given or two scanning sites [42]. The 4-site approach, also known as the BLUE protocol, conducted in 260 dyspneic patients in the intensive care unit, is an even more simplified evaluation including scanning of the second intercostal space at the midclavicular line and of the fourth intercostal space at the anterior axillary line, with detection of >3 B-lines defining similarly a positive exam [41]. In a study assessing the diagnostic performance of the 4 different scanning site approaches, the 4-site protocol had the lowest C-index (63.7, 95% CI: 58.5–8.8), an index very similar to AUC, compared to other methods [42]. In ESKD population, the prognostic performance of the 28-site and the 8-site B-lines score for mortality and cardiovascular events was recently studied in a cohort of 303 HD patients, showing a very high interrelation between the two techniques (Spearman's $\rho = 0.93$, $p < 0.001$) and a fairly good concordance index ($k = 0.79$, 95% CI: 0.74–0.84) [43]. To date, no consensus has been reached regarding the standardization of the procedure or the classification of the overhydration status according to different levels of B-lines total score. However, a properly designed and detailed protocol, executed step-by-step in a repeatable method, is expected to be sufficiently accurate for detecting fluid accumulation.

Observational Studies with Lung Ultrasound in Dialysis Patients

Prevalence of Volume Overload

In 2010, Mallamaci et al. [24] undertook the first feasibility study of lung US for detection of fluid accumulation in a population of 71 HD patients, as shown in Table 1. They found moderate (14–30 comets) and severe (>30 comets) lung congestion in 63% of patients prior to dialysis session, with the majority of them being fully asymptomatic and persistence of overhydration in 31% of patients after dialysis. Furthermore, no correlation was shown between B-lines score and bioimpedance-assessed hydration status parameters. In a preliminary analysis of data from baseline evaluation of 79 high cardiovascular risk HD patients in the Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy Trial (LUST), 13% of patients were found to be moderately (≥ 15 to ≤ 30 comets) and 11% severely (>30 comets) congested [10]. In this study, clinical examination, including crackles and peripheral edema, had a very poor discriminatory capacity to detect any degree of lung water excess evidenced by lung US (AUC for crackles: mild congestion: AUC = 0.61, 95% CI: 0.57–0.64; moderate congestion: AUC = 0.65, 95% CI: 0.61–0.70; severe congestion: AUC = 0.68, 95% CI: 0.62–0.74).

With regard to patients undergoing PD, in a cross-sectional study from Italy with 88 patients, lung US revealed moderate (15–30 B-lines) and severe (>30 B-lines) congestion in 23% and 24% of patients, respectively [36]. Both New York Heart Association (NYHA) class and total residual diuresis volume were found to be associated with the B-lines score ($\beta_0 = 0.31$, $p = 0.006$, and $\beta_0 = 0.3$, $p = 0.006$, respectively); in contrast, important discordance was noted with results obtained by bioimpedance analysis. In particular, in the subset of 61 patients who underwent echocardiography, only 15% of those with moderate and 11% of those with severe lung congestion (classified by lung US) were identified as overhydrated by the bioimpedance technique. In another study with 27 PD patients [44], the prevalence of lung congestion, defined as a B-lines score >5, was substantially lower (14.8%). Moreover, a statistically significant correlation between B-lines score and measured NT-proBNP values was detected ($r = 0.65$, $p < 0.0005$), along with a trend for presence of an association between lung score and volume of overhydration estimated by bioimpedance ($r = 0.31$, $p = 0.12$) [44]. Such results may identify differences in treatment practices regarding volume regulation in different parts of the world.

Discrepancies in the prevalence of volume overload between lung US and bioimpedance could be attributed to different information on body compartments offered by the two methods. Bioimpedance techniques evaluate fat, lean, and cell mass and provide estimates of total body water (TBW) and extracellular and intracellular water (ECW and ICW, respectively), but cannot discriminate between the two components of the ECW compartment, i.e., the interstitial and intravascular volume. In ESKD patients, loss of lean muscle mass and gain in adipose tissue, as well as hypoalbuminemia, result in increased ECW/TBW ratio provided by bioimpedance, again without estimates of intravascular fluid compartment [17]. Underestimation of dry weight by bioimpedance was recently reported in malnourished patients with a low fat mass undergoing HD [45].

Associations of Volume Overload Revealed by Lung Ultrasound with Echocardiographic Indexes

As shown in Table 1, several observational studies have associated lung water content assessed with lung US with echocardiographic parameters in dialysis patients. The aforementioned study of Mallamaci et al. [24] was also the first to examine this association, showing a significant correlation of B-lines score with LV ejection fraction (LVEF) before dialysis ($r = -0.55$, $p < 0.001$), left atrial (LA) volume ($r = 0.39$, $p = 0.001$), and E/e' ($r = 0.48$, $p < 0.001$), as well as after dialysis. In another study, with 81 HD patients, multiple regression analysis revealed a significant association of B-lines score with E/e' , an index of diastolic function (odds ratio [OR] = 0.893, 95% CI: 0.817–0.977), but not with LVEF (OR 1.009, 95% CI: 0.954–1.066) [46].

With regard to PD populations, in the subset of 61 patients who underwent echocardiography in the study of Panuccio et al. [36], the B-lines score was strongly associated with LVEF ($r = -0.40$, $p = 0.002$) and LA volume ($r = 0.30$, $p = 0.020$); LVEF and LA volume were the only parameters that independently predicted B-lines score in multiple regression analysis ($\beta_0 = -0.36$, $p = 0.007$, and $\beta_0 = 0.29$, $p = 0.05$, respectively) [36]. In a recent small cross-sectional study with 21 PD patients, an inverse relationship of B-lines with LV mass index was noted ($r = -0.456$, $p = 0.038$) [47]. Furthermore, a moderate correlation was observed between B-lines and daily urine output ($r = 0.582$, $p = 0.007$), suggesting, according to authors, an increase in urine output as a response to overhydration to prevent obvious and symptomatic congestion [47]. In a recently published study of our group, comparing hydration status between 38 HD and 38 PD patients, by means

of lung US, no significant differences were noted in the B-lines score between the two dialysis modalities (4.00 [6.00] vs. 3.00 [4.25], $p = 0.623$). The B-lines score was found to be moderately correlated with LA volume index ($r = 0.465$, $p < 0.001$), right ventricular systolic pressure ($r = 0.431$, $p < 0.001$), and E/e' ratio ($r = 0.304$, $p = 0.009$), but not with LVEF ($r = -0.166$, $p = 0.153$) [9]. According to the results of multiple regression analysis, B-lines score ($\beta_0 = 0.892$, $p = 0.034$) and male gender were the only independent predictors of LVMi. All the above results suggest that LV dysfunction and pulmonary congestion may be interlinked conditions, although a causative relationship could not have been established based solely on observational studies.

Associations of Volume Overload Revealed by Lung Ultrasound with Cardiovascular Events and Mortality

The association of lung congestion, evaluated by lung US, with mortality and other hard clinical outcomes, which are considered to be related to the harmful effect of chronic volume overload, has been examined so far in 3 observational studies that have been all undertaken in HD populations (Table 1) [32, 33, 46]. In the study of Zoccali et al. [32], including 392 HD patients, the presence of severe lung congestion was associated with a 4.2-fold higher risk for death (hazard ratio [HR] = 4.20, 95% CI: 2.45–7.23) and a 3.2-fold higher risk for cardiac events (HR = 3.20, 95% CI: 1.75–5.88). Siriopol et al. [33] evaluated 96 HD patients and, by comparing parameters obtained by lung US, bioimpedance spectroscopy, and echocardiography, showed that only the pre-dialysis B-lines score and LV mass index independently predicted all-cause mortality. Similarly in the study of Saad et al. [46], which studied 81 HD patients after the dialysis session, classification of lung congestion as severe or very severe (>60 lines) was an independent predictor of all-cause mortality and cardiac events (HR 2.98 for severe and HR 7.98 for very severe congestion).

Interventional Studies Using Lung Ultrasound for Assessment of Volume Status in Dialysis Patients

As of this writing, few interventional studies have been undertaken in HD patients aiming to adjust dry weight and optimize volume control and volume-related outcomes using lung US (Table 2). In the Extravascular Lung Water Monitoring by Combined Bioimpedance and Ultrasonography as a Guide for Treatment in Hemodialysis Patients (BUST) study [48], 250 HD patients were ran-

Table 2. Randomized studies on dialysis patients using lung ultrasound to assess BP, echocardiographic indexes, mortality, and other volume-related outcomes

Author	N	Study design	Duration	Type of intervention	Comparator	Lung US protocol	Measured parameter	Main outcome and results
Siripol et al. [48] (BUST study)	250 HD patients	Open-label RCT	21.3±5.6 months	Adjustment of dry weight according to lung US or BIS	Assessment of dry weight according to standard practice	Lung US performed pre-dialysis repeated once a week if score ≥15 B-lines, until goal achieved (<5 B-lines) and then once a month	Primary endpoint: composite (all-cause mortality, first CVE) Predialytic dyspnea Intradialytic cramps PWV NT-proBNP hs-TNT	Log rank test Primary endpoint: HR = 1.09, 95% CI: 0.64–1.86 All-cause mortality: HR = 1.02, 95% CI: 0.53–1.96 CVE: HR = 0.89, 95% CI: 0.49–1.59 Predialytic dyspnea: RR 0.81, 95% CI: 0.68–0.96 Intradialytic cramps: RR 1.26, 95% CI: 1.16–1.37
Loutradis et al. [34, 35] (LUST sub-study)	71 euvolemic HD patients	Single-blinded RCT	8 weeks	Lung US-guided dry-weight reduction strategy	Assessment of dry weight according to standard practice based on symptoms, physical examination, weight, and hemodynamic instability	28-scanning site lung US with the VScan device (GE Healthcare, Horten, Norway) performed during an interdialytic day (24 h after previous dialysis)	Dry weight 48-h ABPM with Mobil-O-Graph NG (IEM, Stolberg, Germany) at baseline and at 8 weeks	Delta during follow-up B-lines: AG –5.31±12.53 versus CG 2.17±7.62, p < 0.001 Dry weight: AG –0.71±1.39 versus CG 0.51±0.98 kg, p < 0.001 48-h brachial SBP: AG –6.61±9.57 versus CG –0.67±13.07 mm Hg, p = 0.033 48-h brachial DBP: AG –3.85±6.34 versus CG –0.55±8.28 mm Hg, p = 0.031 % of patients that had their dry weight reduced: AG: 54.3% versus CG 13.9%, p < 0.001 % of patients who experienced ≥1 episode of intradialytic hypotension: AG 34.3% versus CG 55.6%, p = 0.072 Delta during follow-up IVC: AG –0.43±4.00 versus CG 0.71±4.82 cm, p = 0.03 LA surface: AG –1.09±4.61 versus CG 0.93±3.06 cm ² , p = 0.03 LAVi: AG –2.43±13.14 versus CG 2.95±9.42 mL/m ² , p = 0.05 LVEDD: AG –4.97±21.55 versus CG 1.59±16.94 mm, p = 0.05 LVEDVi: AG –2.55±11.65 versus CG 0.93±9.63 mL/m ² , p = 0.08 RA surface: AG –1.56±6.17 versus CG 0.47±2.31 cm ² , p = 0.02 LVEF: AG 1.97±8.61 versus CG –0.61±7.47%, p = 0.100 E wave LV: AG –5.45±23.56 versus CG 1.90±21.41 m/s, p = 0.200 A wave LV: AG –1.36±15.66 versus CG 7.92±22.80 m/s, p = 0.02 TAPSE: AG –1.71±5.06 versus CG –0.48±4.21 mm, p = 0.300 Deceleration time: AG 35.43±85.25 versus CG –18.44±50.69 ms, p = 0.002 E/e' LV: AG –0.38±3.14 versus CG 1.36±3.54, p = 0.030
Zoccali et al. [37] (LUST study)	367 HD patients with high cardiovascular risk	Single-blinded RCT	1.49 years	Lung US-guided dry-weight reduction strategy	Assessment of dry weight according to standard practice based on symptoms, physical examination, weight, and hemodynamic instability	28-scanning site lung US with a 3.0-MHz probe (Toshiba NemioXG) before and after dialysis	Primary endpoint Composite (all-cause mortality, nonfatal myocardial infarction, or decompensated heart failure Cardiovascular hospitalization B-lines reduction <i>Post hoc analysis</i> All episodes of decompensated heart failure, and repeated cardiovascular events analyzed by the zero inflated binomial regression	% of patients who had B-lines reduced <15: AG 78% versus CG 56%, p < 0.001 Primary endpoint: HR 0.88, 95% CI: 0.63–1.24 Death: HR 0.89, 0.61–1.29 Cardiovascular hospitalizations: HR: 1.02, 95% CI: 0.71–1.46 Decompensated heart failure: HR 0.37, 95% CI: 0.15–0.93 Cardiovascular events: HR 0.63, 95% CI: 0.41–0.97

AG, active group; CG, control group; CVE, cardiovascular event; DBP, diastolic blood pressure; e', early tissue Doppler diastolic velocity; E', peak early diastolic velocity; HR, hazard ratio; IVC, inferior vena cava; LV, left ventricle; LA, left atrium; LAVi, left atrial volume index; LVEDD, left ventricle end-diastolic diameter; LVEDVi, end-diastolic volume index; RA, right atrium; RCT, randomized controlled trial; SBP, systolic blood pressure; TAPSE, tricuspid annulus plane systolic excursion.

Fig. 3. Cumulative (repeated) episodes of decompensated HF (a) and cardiovascular events (b) in the Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy Trial (LUST). Reproduced with permission from Zoccali et al. [37].

domized in an active lung US and bioimpedance-guided treatment arm, or in a control group, where dry weight was assessed on clinical criteria. After a median follow-up of 21.3 months, the lung US and bioimpedance-guided strategy was not found to be associated with a reduction in all-cause mortality (HR = 1.02, 95% CI: 0.53–1.96) and cardiovascular events (HR = 0.89, 95% CI: 0.49–1.59) compared to standard clinical practice.

The LUST study was an international, multicenter randomized controlled trial where the effect of a lung US-guided treatment strategy on major outcomes (all-cause death, nonfatal myocardial infarction, and decompensated HF) was compared to standard-of-care in high-risk HD patients (history of myocardial infarction or unstable angina, acute coronary syndrome, or stable angina pectoris with documented coronary artery disease or HF with NYHA class III–IV) [37]. After a median follow-up of 1.49 years and randomization of 367 patients, no difference between the active and control arm was seen for the primary composite endpoint (all-cause death, nonfatal myocardial infarction, or decompensated HF) (HR 0.88, 95% CI: 0.63–1.24) or the secondary outcome of cardiovascular hospitalization (HR: 1.02, 95% CI: 0.71–1.46). However, the risk for recurrent decompensated HF episodes (HR 0.37, 95% CI: 0.15–0.93) and cardiovascular events (HR 0.63, 95% CI: 0.41–0.97) was significantly reduced in the active arm (Fig. 3).

A substudy of the LUST trial including 71 hemodialysis patients with hypertension (home BP $\geq 135/85$ mm Hg covering 6 nondialysis days over a 2-week period) showed that a lung US-guided treatment strategy for dry-weight

probing compared to usual care resulted in a significant reduction of 48-h ambulatory systolic BP after 8 weeks of treatment (-6.61 ± 9.57 vs. -0.67 ± 13.07 mm Hg, $p = 0.033$) [35]; this BP difference remained after 12 months of follow-up (-7.78 ± 13.29 vs. -0.10 ± 14.75 mm Hg, $p = 0.021$) [49]. With regard to echocardiographic indexes, a significant reduction in LV filling pressures ($E/e' -0.38 \pm 3.14$ vs. 1.36 ± 3.54 , $p = 0.03$) and borderline differences in LA volume (-2.43 ± 13.14 vs. 2.95 ± 9.42 mL/m², $p = 0.05$) were observed in the active group at 8 weeks (Fig. 4) [34]. These were accompanied by a significant reduction in 48-h PWV (-0.23 ± 0.59 vs. 0.05 ± 0.45 m/s, $p = 0.030$), indicating a positive effect of guided dry-probing on central arterial parameters [50]. In contrast, no differences were shown between the two study groups in BP variability indexes [51], a fact indirectly supporting that BP lowering should be rather attributed to reduction of volume overload. Of note, intradialytic hypotensive episodes were marginally lower for patients in the active arm of this LUST substudy compared to those that had their dry weight adapted based on standard clinical criteria at 8 weeks (34.3% vs. 55.6%, $p = 0.072$) [35] and 12 months (71.4% vs. 88.9%, $p = 0.065$), despite the fact that more patients in that group had undergone dry-weight reduction (71.4% vs. 22.2%, $p < 0.001$) [49].

The above findings may suggest that detection and quantification of lung congestion via ultrasonography may offer a detailed assessment of fluid overload in a critical interface, enabling strategies based on lung US to objectively assess dry weight and help toward BP reduction and improvement of cardiac chamber dimensions and

Fig. 4. Between-group comparisons for changes during the study in LA surface (a), LVEDD (b), RA surface (c), E wave deceleration time (d), tissue Doppler peak late a' wave (e), and E/e' LV ratio (f). Reproduced with permission from Loutradis et al. [34]. LA, left atrial; LVEDD, left ventricular end-diastolic diameter; RA, right atrial.

LV diastolic function, without the deleterious effects of intravascular volume depletion. In patients undergoing PD, the effects of US-guided strategy on BP levels, echocardiographic parameters, and cardiovascular outcomes warrant examination by future controlled trials.

Advantages and Limitations of Lung Ultrasound Use in Everyday Clinical Practice for Dialysis Patients

Lung US is a sonographic technique that possesses all the advantages of a classical US exam: it is an easy to apply, quick (time needed varies between 3 and 10 min), noninvasive, nonionized radiation method that may be performed in real time by the patient's bedside [3, 8]. In

the aforementioned feasibility study in HD patients, good interobserver (concordance index = 0.83, 95% CI: 0.60–0.93) and intraprobe reproducibility was shown, even when assessed with different ultrasound devices [24]. With regard to training demands, the lung US technique is characterized by a steep-learning curve. Results from a web-based training program with 44 participants (30 nephrologists and 14 cardiologists) showed a high intraclass correlation coefficient between trainees and the expert trainer (0.81 ± 0.21) when the first were asked to evaluate 47 videos at the end of the training period. For trainees that had underperformed, the coefficient was adequately increased following additional training [52].

However, this method has some limitations, the most important of which being related to lack of specificity of

B-lines; these are a sonographic sign of lung interstitial syndrome that cannot discriminate between thickening of interlobular septa due to presence of lung water excess (wet B-lines) and fibrotic thickening (dry B-lines) in pulmonary fibrosis; the latter sign can be found in patients with systemic sclerosis, representing a histological pattern of progressive inflammation and scarring in interstitial lung disease [27, 53]. Limited capacity to distinguish the etiology of EVLW accumulation (acute respiratory distress syndrome or decompensated HF) has been also reported; however, in the former condition, a more inhomogeneous and irregular pattern may be evident, accompanied by subpleural consolidation, a highly fragmented pleural line, and multiple B-lines alternating with spared areas [22, 30]. Differentiation of lung water excess from other causes that increase the lung density (i.e., blood and consolidations due to an infection or a tumor) can be easy in most cases based on the patient history and clinical characteristics. However, attention should be given in the interpretation of the exam in patients with evidence or suspicion of such diseases. The cost of the equipment may pose another constraint for lung US application in some low-income environments; however, this seems to be now overridden due to development of newer pocket-size devices that are cheaper. The actual time needed for evaluation of hydration status according to the traditionally used 28-site zone protocol (approximately 8–10 min) is not substantially longer than that needed for evaluation by the bioimpedance technique (approximately 5 min). If the 8-site zone protocol for lung US is used, then the actual time is substantially shortened [43].

As discussed above, lung US and bioimpedance provide different types of information. Lung US provides estimates of EVLW, i.e., the water content of lung interstitium, a body compartment where volume excess can have direct consequences. Bioimpedance provides information on TBW, ECW, and ICW excess. As such, the two methods should be considered complementary and not competitive. In settings where the cost of lung US is an issue, evaluation with this procedure should be preferred over bioimpedance for patients in whom it is critical to know what is the situation in the lung interface, such as patients with borderline cardiac function and repeated episodes of congestive heart failure, or patients with increased ECW according to bioimpedance due to hypoalbuminemia or poor nutrition status, as bioimpedance cannot discriminate between increase in interstitial fluid and intravascular volume.

With regard to the use of lung US over natriuretic peptides, such as BNP, NT-proBNP, and most recently MR-

proANP, while the latter are considered valid markers of fluid accumulation in patients with heart failure, they cannot substitute lung US in patients with ESKD. Both BNP and NT-proBNP are passively filtered by the glomerulus, and while BNP is degraded by neprilysin at the proximal convoluted tubule, NT-proBNP (having no neprilysin binding domain) is not degraded by neprilysin and has therefore a slower clearance. Therefore, their levels are increased in the context of reduced GFR, and presence of CKD is considered one of the main caveats in interpretation of their measurements [54, 55]. In ESKD, this interpretation is even more complex, as the majority of dialysis patients have no considerable residual renal function, while removal through hemodialysis session may also interfere with their serum levels [56]. Further, in ESKD, their levels are strongly affected by cardiac systolic dysfunction [54]. As such, lung US is considered a more valid method for volume overload estimation in dialysis than natriuretic peptides.

Conclusion

Lung ultrasound is a cheap, noninvasive, nonionized radiation, portable, real-time method to evaluate volume overload in ESKD patients that has gained growing attention in the last decade. It provides reliable estimates of EVLW content as shown in validation studies against thermodilution measurements of wedge pressures after cardiac catheterization. It is a method with sufficiently good interobserver and intraprobe reproducibility when performed by trained physicians. In patients undergoing HD, a strong correlation between ultrafiltration volume and decrease in B-lines sum, and therefore interstitial lung congestion, has been observed during dialysis session. Furthermore, a strong correlation of B-lines score and LV mass and indices of LV systolic and diastolic performance has been shown, as well as a predictive value for cardiovascular morbidity and mortality. Results from randomized controlled trials show a beneficial effect of US-guided dry weight probing on ambulatory BP levels, central pressures, arterial stiffness, and echocardiographic indexes, as well as a risk reduction of recurrent episodes of decompensated HF compared to standard practice based on clinical assessment. These were accompanied by reduced episodes of intradialytic hypotension which could lead to decreased end-organ perfusion. For all the above reasons, lung US can be a quite useful tool for the practicing nephrologist in the complex quest for volume management and should rather be integrated in training programs and future recommendations.

Conflict of Interest Statement

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Author Contributions

Review concept and design: P.S. Literature search in databases: M.-E.A. and M.T. Drafting of the manuscript: M.-E.A. Critical revision of the manuscript for important intellectual content: P.S. All authors contributed important intellectual content during manuscript drafting and have read and approved the final version of the manuscript.

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