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Marc M Saad

Jeanne Kamal

E. Moussaly
Northwell Health

B. Karam
Northwell Health

W. Mansour
Northwell Health

See next page for additional authors

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Authors
Marc M Saad, Jeanne Kamal, E. Moussaly, B. Karam, W. Mansour, Emad Gobran, Saqib Hussen Abbasi, Ahmed Mahgoub, Puja Singh, Ross Hardy, D. Das, C. Brown, M. Kapoor, S. Demissie, M. J. Kleiner, E. El Charabaty, and S. E. El Sayegh

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Original Paper

Relevance of B-Lines on Lung Ultrasound in Volume Overload and Pulmonary Congestion: Clinical Correlations and Outcomes in Patients on Hemodialysis

Marc M. Saad[a, c] Jeanne Kamal[b, c] Elias Moussaly[c] Boutros Karam[c] Wissam Mansour[c] Emad Gobran[d] Saqib Hussen Abbasi[c] Ahmed Mahgoub[c] Puja Singh[c] Ross Hardy[e] Devjani Das[e] Cara Brown[e] Monica Kapoor[e] Seleshi Demissie[f] Morton J. Kleiner[d] Elie El Charabaty[c, d] Suzanne E. El Sayegh[c, d]

[a]Department of Nephrology, Emory University Hospital, Atlanta, GA, [b]Department of Nephrology, New York University Langone Medical Center, New York, NY, and Departments of [c]Internal Medicine, [d]Nephrology, [e]Emergency Medicine and [f]Research, Staten Island University Hospital, Staten Island, NY, USA

Keywords
Volume overload · Hemodialysis · Lung ultrasound · Cardiovascular outcomes

Abstract
Background: Volume overload in patients on hemodialysis (HD) is an independent risk factor for cardiovascular mortality. B-lines detected on lung ultrasound (BLUS) assess extravascular lung water. This raises interest in its utility for assessing volume status and cardiovascular outcomes. ***Methods:*** End-stage renal disease patients on HD at the Island Rehab Center being older than 18 years were screened. Patients achieving their dry weight (DW) had a lung ultrasound in a supine position. Scores were classified as mild (0–14), moderate (15–30), and severe (>30) for pulmonary congestion. Patients with more than 60 were further classified as very severe. Patients were followed for cardiac events and death. ***Results:*** 81 patients were recruited. 58 were males, with a mean age of 59.7 years. 44 had New York Heart Association (NYHA) class 1, 24 had class 2, and 13 had class 3. In univariate analysis, NYHA class was associated with B-line classes (<0.001) and diastolic dysfunction (0.002). In multivariate analysis, NYHA grade strongly correlated with B-line classification (0.01) but not with heart function (0.95). 71 subjects were followed for a mean duration of 1.19 years. 9 patients died and 20 had an incident cardiac event. A Kaplan-Meier survival analysis demonstrated an interval decrease in survival times in all-cause mortality and cardiac events with increased BLUS scores (p =

Marc M. Saad
1091 Overlook Parkway, Apt 326
Macon, GA 31210 (USA)
E-Mail marcsaadmd@gmail.com

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0.0049). Multivariate Cox regression analysis showed the independent predictive value of BLUS class for mortality and cardiac events with a heart rate of 2.98 and 7.98 in severe and very severe classes, respectively, compared to patients in the mild class (p = 0.025 and 0.013). ***Conclusion:*** At DW, BLUS is an independent risk factor for death and cardiovascular events in patients on HD.

Background

End-stage renal disease (ESRD) patients form a population with a unique risk profile. Volume overload in hemodialysis (HD) patients is an independent risk factor for death from cardiovascular events [1, 2]. Many methods have been utilized to assess HD patients' volume status. Dry weight (DW) is assessed clinically and despite often being inaccurate, it remains the only widely used and acceptable method. Getting the optimal DW is a clinical challenge that needs an objective estimation and a tool for quantification.

Lung ultrasound used to detect B-lines has proven to be an excellent reliable tool to assess extravascular lung water (EVLW) and to quantify lung congestion [3–6]. These lines are perceived on the ultrasound as dynamic sliding lung comets. They are identified as hyperechoic lines with 5 mandatory characteristics: arise from the pleural lines, appear as a laser beam, spread to the edge of the screen without fading, erase A-lines, and move with lung sliding. B-lines are the manifestation of an interstitial syndrome secondary to pulmonary edema, interstitial pneumonia or pneumonitis, or diffuse parenchymal lung disease such as pulmonary fibrosis [7]. Specific sonographic patterns of interstitial syndrome may be seen in atelectasis, pulmonary contusion, pulmonary infarction, pleural disease, or neoplasia [7]. Although no anatomical or histological structures correspond to this artifact, its occurrence is believed to result from internal reverberation of the water-parenchyma interface [8, 9]. These ultrasound lung comets represent a change in interstitial space volumetric expansions or a decrease in subpleural structure aeration [8]. Ultrasound lung comet correlation with extravascular water has been largely confirmed with gold standard tests in pigs and rats using lung gravimetric studies [10, 11]. Studies showed a real-time decrease in these B-lines after the dialysis session with a good intraobserver and interobserver agreement [12].

The syndromic set of ESRD is mainly caused by the chronic expansion of the extravascular volume, of which the EVLW is a small but fundamental part. The development of congestion starts with hemodynamic congestion of the pulmonary circulation associated with increased left ventricle filling pressure, followed by capillary interstitium membrane failure and increase in hydrostatic pressure resulting in interstitial edema (detected as B-lines), which defines the hallmark of pulmonary congestion. When higher hydrostatic pressure jeopardizes the alveolar-capillary membrane, pulmonary edema develops, leading to clinical congestion. A positive linear correlation exists between B-lines and wedge pressure, allowing for indirect measurement and early detection (preclinical state) of pulmonary congestion appearing below the threshold of alveolar edema [5].

Pulmonary congestion, assessed by B-lines on lung ultrasound (BLUS) is common among asymptomatic HD and peritoneal dialysis patients [2]. BLUS was found to be inversely associated with physical performance independent of New York Heart Association (NYHA) classification. This correlation was maintained even in dyspnea-free patients of the NYHA class 1 subgroup. The 2 grading systems (BLUS and NYHA) can be considered complementary in predicting the physical functioning of patients on HD [13, 14].

Studies conducted on patients with acute decompensated heart failure concluded that their clinical improvement did not correlate with change in their weight (excluding patients with chronic kidney disease) [11]. This validates the idea that symptoms resulting from volume expansion are secondary to redistribution rather than the accumulation of fluids [4, 11]. DW is unable to assess fluid redistribution, thus it is a less reliable tool to predict pulmonary congestion.

The aim of this study is to determine the degree of pulmonary congestion in HD patients by using lung sonography and counting B-lines at the end of HD treatment when patients are at their clinical DW. We will study the association between the number of B-lines and the physical performance assessed by the NYHA classification, and the prognostic ability of BLUS predicting death, cardiovascular events, and hospitalizations in ESRD patients on HD, supporting that BLUS may be considered as a parameter for assessing the adequacy of dialysis, which helps refine the prognosis of patients on HD.

Methods

Population

After IRB approval (Northwell Health IRB), all patients on maintenance HD in the Staten Island University Hospital affiliated Island Rehab Center being older than 18 years were screened. Patients diagnosed with interstitial lung disease or recent pneumonia, pregnant females, patients who had previous lung surgery, and those whose activity level could not be assessed were excluded.

All subjects gave informed consent. They underwent lung ultrasound in supine or near-supine position after they had completed their regularly scheduled HD session and had achieved their target weight. Patient data were collected from chart review with the most up-to-date values available. This included demographics (age, sex, race), treatment parameters (dialysis vintage, urea reduction ratio), cause of chronic renal disease, urine output/24 h, laboratory parameters (serum creatinine, calcium, phosphate, sodium, potassium, albumin, hemoglobin), body size as body mass index (BMI) and weight, as well as DW, predialysis blood pressure and heart rate, and comorbidities including diabetes, chronic obstructive pulmonary disease, and previous cardiovascular events (electrocardiography-documented angina and myocardial infarction, stroke, transient ischemic attacks, heart failure, arrhythmias, or peripheral vascular disease), and treatment with antihypertensive and erythropoiesis-stimulating agents. Recent transthoracic echocardiograms were reviewed for evaluation of systolic dysfunction using left ventricular ejection fraction and diastolic dysfunction with the E/E′ ratio [15, 16].

The 2 emergency medicine physicians who had performed the initial training weekly reviewed all ultrasound images obtained on patients. Results were compared for study interoperator reliability.

After the initial assessment, patients were then followed for a period of at least 1 year. Hospitalizations and cardiovascular events and death were collected from the patients' medical records. Cardiac events are defined as: myocardial infarction on the basis of serial changes of electrocardiogram (ECG), creatine kinase, and troponin; ECG-documented angina episodes; heart failure; ECG-documented arrhythmia; cerebrovascular accident or transient ischemic attack; and unexpected sudden death highly suspected to be of cardiac origin.

Investigator Training

All participating investigators underwent a 3-h introductory course that explained the principles of ultrasound techniques, focusing on its use in lung imaging. It included a didactic lecture and hands-on training by 2 registered diagnostic medical sonographer-certified emergency medicine attending physicians. Both emergency medicine physicians have completed an additional postgraduate year of ultrasound training, have independently completed over 1,000 ultrasound scans, and use ultrasound in daily clinical practice. After their training, the investigators were certified to perform lung ultrasound at the bedside using a portable ultrasound machine (Sonosite, Edge®).

Lung Ultrasound and B-Line Score

The investigators visualized a total of 28 anatomical points on the subjects' chest as validated by Zoccali et al. [17] and approved internationally as a general consensus [7, 17]. Twenty-eight different lung windows were scanned in the midaxillary, anterior axillary, midclavicular, and parasternal spaces: 16 windows on the right hemithorax in the 2nd through 5th intercostal spaces and 12 on the left hemithorax in the 2nd through

Table 1. Main demographic, clinical and post hemodynamic data of the study population

	NYHA class			ANOVA	
	1	2	3	F value	Pr > F
Number	44	24	13		
Age, years	58±14.6	60.25±17.6	64.5±17.4		
BMI	28.4±4.8	29.5±6.6	28.7±6.4	0.48	0.62
LVEF	56±10	54±11	48±12	2.71	0.074
E/E′ ratio	15.6±6.5	14.7±7	26.6±14.2	6.6	0.002
Mean arterial pressure, mm Hg	101.4±15.8	99±15.1	99±18.8	0.22	0.80
Heart rate, beats/min	76±11	76±11	73±10		
IDWG	2.9±1.1	2.7±1.3	3.3±1.3		
Hemoglobin	10.7±1.5	10.6±1.3	10.4±1.3	0.35	0.70
Albumin	4±0.3	3.9±0.5	3.7±0.3	3.78	0.027
Sodium	139±3	141±3.5	140±3		
Potassium	4.7±0.9	4.7± 0.8	4.9±1		
CO_2	22.6±2.4	23±2.3	23.2±2.4	0.35	0.71
Phosphate	5.4±1.5	5.5±1.6	4.7±2		
Crea	10.6±10.8	8.4±3.6	8±3	0.83	0.44
BUN	63.6±21.3	59.7±20	54.7±18.8	1.01	0.36
Urea reduction ratio	71.4±5.7	71±4	70±5	0.4	0.67

Data are expressed as mean ± SD or as percent frequency, as appropriate. BMI, body mass index; LVEF, left ventricular ejection fraction; IDWG, interdialytic weight gain; NYHA, New York Heart Association.

4th intercostal spaces. Within each window, the number of B-lines was counted the sum of which was used to compile a comet tail score. This score was then used to semiquantitate the degree of pulmonary edema or EVLW.

Statistical Analysis

Sample Size

An endpoint sample of 81 patients was calculated to obtain a power of 0.80 to detect an association between B-lines and physical performance assessed by NYHA class. This has been calculated using a hypothesized low effect size of 0.15 and an alpha of 0.05.

Analysis

Baseline characteristics are examined with means and SD. The examination of NYHA class and its correlation with B-lines and other possible predictors of performance status will first be analyzed with univariate analysis utilizing one-way ANOVA. A stepwise multiple regression analysis will then be utilized to develop a predictive model using DW and quality of life as dependent variables, and the number of B-lines and NYHA classification, left ventricular ejection fraction (LVEF) and others as independent variables. Furthermore, a multinomial logistic regression analysis will be used to determine if the number of B-lines is associated with physical performance using NYHA classification at a clinical DW at the end of a dialysis session. Lastly, a Cox regression and Kaplan-Meier method will be used to analyze several risk factors of survival. Statistical significance will be set at 0.05.

Results

Eighty-one patients on HD were recruited on high-flux membranes. Fifty-eight were males, the mean age of the study population was 59.7 years (SD 15.9) with a mean dialysis vintage of 49.04 months (SD 56.3), and the hemoglobin level was 10.6 g/dL. Comorbidities

Table 2. Multivariate analysis (OR estimates)

Effect	Point estimate	95% Wald confidence limits	
Age	1.017	0.973	1.064
LVEF	1.009	0.954	1.066
E/E′ ratio	0.893	0.817	0.977
IDWG	0.914	0.506	1.654
Alb	5.091	0.906	28.595
Hgb	1.323	0.756	2.316
BUN	0.995	0.958	1.033
URR	1.024	0.903	1.162
Gender	0.447	0.089	2.252
High blood pressure	0.297	0.019	4.738
DM	0.514	0.114	2.319
B-line class 0, 1 vs. B-line class 2, 3	8.364	1.771	39.498

LVEF, left ventricular ejection fraction; IDWG, interdialytic weight gain; URR, urea reduction ratio; DM, diabetes mellitus.

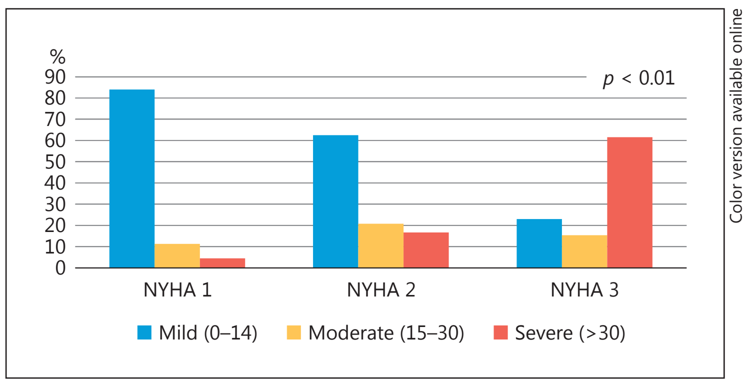

Fig. 1. Prevalence of B-line severity by NYHA class.

were prevalent in our cohort: 51.8% had diabetes mellitus (DM) and 93.8% had hypertension. 44 had NYHA class 1, 24 had class 2, and 13 had class 3. The corresponding LVEF was 56 ± 10, 54 ± 11 and 48 ± 12%, respectively, for the 3 NYHA classes and they were not different ($p = 0.074$).

Table 1 shows the main baseline characteristics of the patients divided into 3 groups on the basis of physical performance assessed by NYHA class.

In univariate analysis, the number of B-lines on lung ultrasound was higher in patients with a higher NYHA class, and more severe NYHA classes ($p < 0.001$) were highly associated with greater B-line grades (mild moderate and severe) and diastolic dysfunction (E/E′; $p = 0.002$) (Fig. 1). Decreased physical performance was also associated with low albumin ($p = 0.03$). No significant association was found with hemoglobin ($p = 0.71$), BMI ($p = 0.62$), BUN ($p = 0.36$), CRE ($p = 0.44$), CO_2 ($p = 0.71$), urea reduction ratio ($p = 0.67$), LVEF ($p = 0.07$), mean arterial pressure ($p = 0.80$), left atrial diameter ($p = 0.59$), and interdialytic weight gain ($p = 0.47$).

To better define the factors that can explain the severity of NYHA class and the variability in the number of B-lines among its classes, we included all variables that showed an association with NYHA class severity in univariate analysis as well as variables that had shown an

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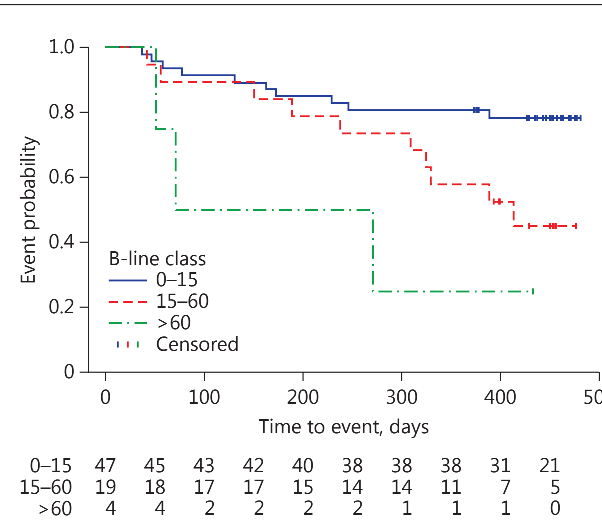

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Fig. 2. Survival probability for patient groups according to the number of B-lines (0–14, 15–60, and ≥60). Number of events based on B-line class as well as number of subjects at risk are shown.

effect on the number of B-lines in previous studies. In this model, B-line classes had a strong association with NYHA classes. Statistical association was found with diastolic dysfunction assessed by E/E′ (OR = 0.893, 95% confidence interval 0.82–0.98; p = 0.013) but not with heart systolic function (p = 0.95). However, this statistically significant association has no clinical correlations. Forcing BMI, age, sex, and interdialytic weight gain into the model did not show independent relation with NYHA classes and did not affect the strength of the relationship between NYHA and B-line classes.

Multinomial logistic regression analysis showed that for each increase in B-line severity classes, there is an 8-fold increase in the logistic regression for NYHA poor physical performance (NYHA classes 1 and 2 vs. class 3) (OR = 8.95, 95% confidence interval 1.78 – 39.5, p = 0.007), and this was again independent of heart function (Table 2).

This cohort of patients was then followed for at least 1 year and hospitalizations, cardiovascular events, and death were recorded. Ten were lost to follow-up: 6 patients were transferred to another dialysis center and 4 patients received kidney transplant. The remaining 71 subjects were followed for a mean duration of 1.19 years. Fifty of those were males and had a mean age of 60. Nine patients died and 20 had an incident cardiac event.

A Kaplan-Meier survival analysis demonstrated an interval decrease in survival times in all-cause mortality and cardiac events with increased BLUS scores (p = 0.0049) (Fig. 2).

Multivariate Cox regression analysis showed the independent predictive value of BLUS for mortality and cardiac events: patients in moderate and severe classes (grouped) and very severe classes had hazard ratios of 2.98 and 7.98, respectively, compared to patients in a mild class (p = 0.025 and 0.013).

The number of hospitalizations for each patient was collected in the follow-up period, including all diagnoses and not exclusively those related to cardiovascular events. The average hospitalization rate (1.88) was not significantly different between the categories (p = 0.1).

We compared the counting of B-lines between the residents and emergency physicians. The mean difference between physicians' and residents' scoring was 3.77 ± 16.9 (p = 0.048). We studied the possible effect of patients' demographics such as age, sex, and BMI on this difference observed, but no significant contribution was observed. However, this difference was not significant after classification (mild, moderate, and severe) and scores were in agreement (kappa = 0.56; 95% confidence interval 0.42–0.71) (Table 3).

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Table 3. Results comparison between residents and emergency physicians (EP)

B-line class (EP)	B-line class (residents)			Total
	mild	moderate	severe	
Mild	51 (62.97%)	3 (3.70%)	1 (1.23%)	55 (67.9%)
Moderate	9 (11.11%)	3 (3.70%)	0 (0.00%)	12 (14.81%)
Severe	4 (4.94%)	1 (1.23%)	9 (11.11%)	14 (17.28%)
Total	64 (79.01%)	7 (8.64%)	10 (12.35%)	81 (100%)

Discussion

Volume overload in HD patients is an established independent risk factor for death from cardiovascular events, rendering optimization of volume control in ESRD patients on HD crucial for survival. Achieving this requires an accurate and reliable objective tool to help in early diagnosis of overhydration before its clinical manifestation [1, 2]. The challenge of reaching and maintaining euvolemia is more difficult, especially in patients with cardiomyopathy and hemodynamic frailty. The detection of mild to moderate degrees of volume overload is one of the main quests that challenges clinicians, considering symptoms that may be attributed to other prevalent comorbidities in ESRD patients [17–19].

We conducted a cross-sectional observational study to determine the number of B-lines in our population and its associations with hemodynamics and clinical characteristics of our dialysis patients. At the end of dialysis sessions, many patients had a moderate to severe B-line score. When these patients are grouped according to their NYHA class, the severity of B-lines seemed to be correlated well with a worse class and decreased physical performance.

Our population had a moderate to severe class of B-lines. Multivariate analysis showed that the B-line class has an odds ratio of 8 when the NYHA class increases in severity. However, no significant correlation was found with left ventricular systolic and diastolic dysfunction. EVLW represents a hemodynamic state dependent on circulating volume and heart function and appears as a comprehensive parameter to guide volume optimizing therapy.

Similarly to prior studies, our patients with ESRD on HD demonstrated EVLW at a clinically assessed DW. Severe pulmonary congestion was also described in few asymptomatic patients. This subtle lung congestion state was found in different studies to correlate with physical performance in ESRD patients on HD, independent of their NYHA score [20].

Patients with higher B-line scores had more cardiac events and had a higher death rate compared to those with lower B-line score. BLUS is an independent risk factor for death and cardiovascular events in HD patients. Chest ultrasound helps detecting lung congestion among ESRD patients on HD, even at its early stage when clinically asymptomatic. The prognostic value of total extracellular body water has been clearly demonstrated to be the most relevant finding, in predicting clinical outcomes, the risk of death and cardiovascular events independent of the NYHA score, and classical risk factors in patients with heart disease [17]. It surpasses the overall hydration status, inflammation (assessed by C-reactive protein), and cardiac parameters in predicting the risk of death and cardiac events. The BLUS score, which correlated with the body water content, has become a strong, independent predictor of death and cardiac events in this population [2, 3, 14, 21, 22].

BLUS in patients with heart disease guides clinical outcome. It furthermore predicts death and cardiovascular events independently of the classical risk factors (diabetes) and NYHA score. It is stronger than the standard echocardiographic parameters and it adds a prognostic value to established clinical scores like the Global Registry in Acute Coronary Events score [23, 24].

Many studies described the B-line inverse relationship with cardiac systolic (EF) and diastolic function (E/E′) and its direct correlation with parameters assessing hemodynamic congestion such as pulmonary artery systolic or wedge pressure, before and after dialysis [12, 22]. However, the association was very limited [25]. In our study, we did not find a significant correlation with LVEF; furthermore, the statistically significant association with E/E′ was not clinically correlated (OR <1). This fact highlights the predominant effect of volume overload in our study population. Pulmonary congestion is not always related to high left ventricular filling pressure, and can be partly explained by increased total body water or volume redistribution, indicating that B-lines describe a water compartmental redistribution [17].

Lung ultrasound has emerged as a new technique, readily available at bedside, providing immediate results. Our study shows that a short training course can render novice users of ultrasound capable of performing this quick evaluation. This can aid in objectively assessing volume overload in a timely manner in HD patients who present a unique clinical challenge. Many studies have reported an excellent learning skill, and interobserver reproducibility with only 10% difference between the experts and trainee readings [14].

These results highlight the prevalence of overlooked volume overload in HD patients. The imminent role of BLUS in predicting physical performance, morbidity, and mortality raises interest in BLUS to be considered a parameter for assessing adequacy of dialysis and help detect pulmonary congestion, at a subclinical state occurring few days to weeks before pulmonary edema that characterizes clinical congestion [26]. In addition to volume overload, ESRD patients were observed to have altered lung permeability secondary to intrinsic lung alterations triggered by dialysis membranes or uremic symptoms putting this population at high risk for cardiopulmonary complications. [17].

In conclusion, BLUS showed a great association with the NYHA classification and highlighted EVLW in ESRD patient to be associated with decreased physical performance. And even more so, it is an independent risk factor for cardiovascular morbidity and death. Patients at their DW can still have a volume overload, which is proven to be an independent risk factor for cardiovascular morbidity and mortality.

The risk carries an important influence for determining adequacy of a HD session and limiting EVLW. BLUS is rising as a feasible and more reliable method to evaluate volume overload and redistribution and it is considered a prognostic indicator for cardiovascular events and mortality. The application of chest ultrasound in the ESRD population on HD may improve patients' clinical outcome and help refine their prognosis.

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Statement of Ethics

All subjects or their legal representatives have given their informed written consent. The study protocol was approved by the Northwell Health-Staten Island University Hospital Institutional Review Board.

Disclosure Statement

All authors have no conflicts of interest to report.

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