

In Focus

Lung congestion as a hidden threat in end-stage kidney disease: a call to action

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Volume overload is perhaps the most common and concerning risk factor in end-stage kidney disease (ESKD) [1], and research on clinical strategies to optimize volume control in dialysis patients is listed as a priority by authoritative investigators in the field [2]. Volume expansion predicts mortality, also independent of hypertension in this population [3, 4], and experimental studies testing the effect of nocturnal [5] or frequent dialysis [6], i.e. strategies associated with better volume control stand among the very few positive trials among the several trials aimed at improving clinical outcomes in this population.

Three main issues hinder the quest for optimization of volume control in ESKD. First, mild and moderate degrees of volume expansion are difficult to diagnose by clinical criteria and easily escape medical attention. Second, because of cardiomyopathy [7] and haemodynamic frailty, [8] euvolaemia is difficult to achieve and maintain in these patients [1]. Third, a simple method that may help the early diagnosis and quantification of the most concerning sequel of volume overload in ESKD, i.e. lung congestion, is lacking. Herein, I will briefly review these problems and comment on an interesting study on the prognostic potential of lung congestion by chest ultrasound (US). The important novelty in this study is that lung water, as quantified by this technique, is a stronger predictor of death than state-of-the-art measures of hydration status by bioimpedance analysis (BIA) [9].

However reliable [10], estimates of hydration status may be insufficient for guiding dialysis prescription in patients with left ventricle (LV) disorders and heart failure, a highly prevalent subpopulation in today's dialysis scenario. Even a modest volume subtraction at standard UF may precipitate haemodynamic instability and collapse in susceptible patients [8]. Ideally, ultrafiltration prescription in these patients should be

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based on the most critical haemodynamic parameter which is currently used for guiding fluid therapy in intensive care patients and in patients with heart failure, i.e. on the basis of pulmonary capillary wedge pressure (PCWP). Measurement of PCWP demands right heart catheterization and the wedging of a balloon into a peripheral branch of the pulmonary artery. When the balloon is inflated, the vascular bed downstream is insulated from the pulmonary artery, and the right ventricle and pressure at the tip of the catheter, the PCWP, equilibrates with downstream pressures equalizing the pressure in the left atrium and in the left ventricle at the end of diastole. The PCWP estimates the degree of filling of an area extending from the lung capillaries to the left ventricle, the most critical area of the whole cardiovascular system. A high PCWP underlies *haemodynamic congestion*, a condition which leads to *pulmonary congestion*, i.e. to extravasation of fluid into the lung interstitium. A high PCWP in dialysis patients almost always results from a combination of volume overload and LV dysfunction. Therefore, this parameter would offer the critical, integrated information the nephrologist needs for ultrafiltration–dialysis prescription. However, this is an invasive and potentially risky measurement which in some cases may not adequately reflect left ventricular filling pressure [11], and therefore, it is inherently unsuitable for clinical application in chronic dialysis patients. The main scope of volume control in these patients is to prevent the deleterious effect of haemodynamic and pulmonary congestion and the resulting dyspnoea, the most concerning symptom of LV failure. Several factors, including hypoalbuminaemia and inflammation [12], exposure to dialysis membranes [13] and perhaps the lack of renal function *per se* [14], concur in making dialysis patients particularly predisposed to lung congestion in the presence of volume overload and haemodynamic congestion.

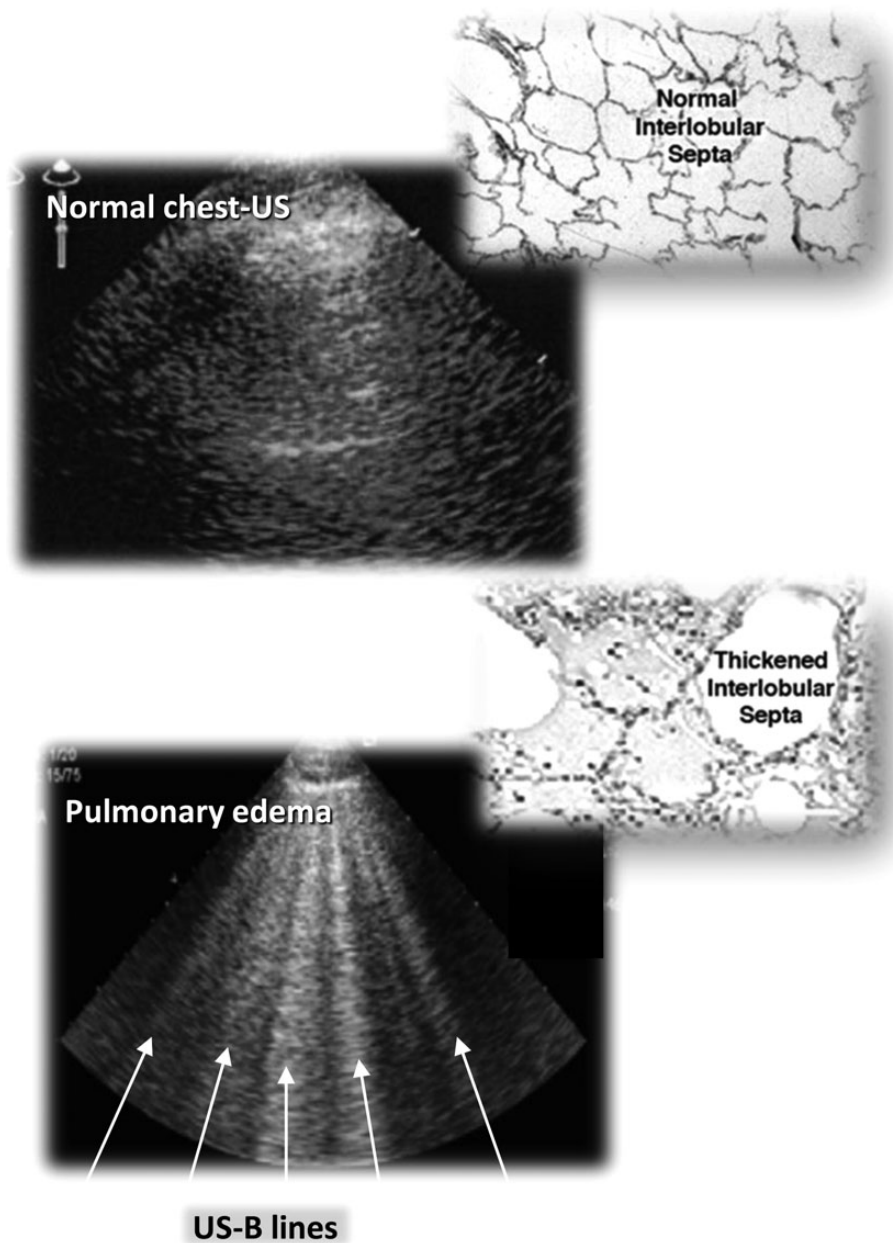


FIGURE 1: Chest US under normal conditions (left panel) and in pulmonary oedema (right panel). The reflection of the US beam by oedematous, thickened alveolar septa generates reverberations that are the US equivalent of Kerley B-lines in the standard chest radiogram.

The observation that lung congestion is common in ESKD is not new. In haemodialysis patients without apparent pulmonary disease, carbon oxide transfer is reduced suggesting subclinical pulmonary oedema [15]. In a study performed in the nineties [16], lung water, measured by a double-indicator dilution technique, was higher in dialysis patients without overt heart disease than in healthy controls, and such an alteration largely regressed after dialysis. These findings were fully confirmed in a study applying a modified optical density dilution and US velocity technique [17]. However, progress in this research area has been hindered by the lack of a bedside, easy-to-perform technique for systematic measurement of lung water in everyday clinical practice.

Chest US is now emerging as a reliable, easy-to-apply and safe method for measuring lung water, both in clinical

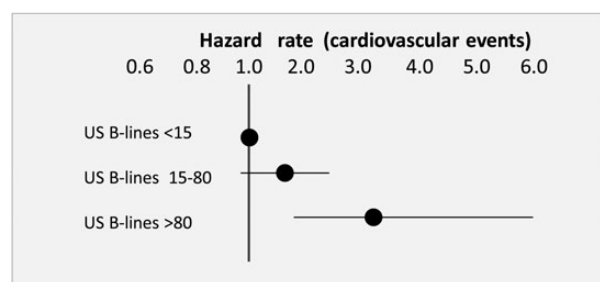
physiology studies [18] and in disease states [28]. The US beam normally transverse the lung tissue unhindered. However, in the presence of excessive lung water, it is reflected by oedematous, thickened interlobular septa. These US reverberations are the equivalent of Kerley B lines in chest roentgenograms and are therefore defined as ‘US-B lines’. These hyperechoic signals (Figure 1) can be recorded by applying virtually all US probes and instruments, including US machines for imaging of the kidney and abdominal viscera and echocardiography machines. A chest US is sufficiently sensitive for detecting lung water accumulation in high-altitude climbers [18]. In cardiology, the technique is recommended for monitoring lung congestion in patients with heart failure [19] and its diagnostic potential is being explored in various diseases [20]. The reliability of chest sonography in

haemodialysis patients was tested in a study by Mallamaci *et al.*, published in 2010 [21]. The interobserver concordance coefficient between an expert sonographer and a nephrology trainee after a 2-h training session on chest US was as high as 0.96 and the inter-probes (standard 3.0-mHz echocardiography probe and standard 3.5-mHz abdominal probe) coefficient of concordance as high as 0.98, denoting the considerable simplicity and reliability of the technique. Lung congestion, as measured by this technique, is not unique to haemodialysis patients [21] being also quite common in peritoneal dialysis (PD) patients [22], and in both haemodialysis [23] and PD patients [24] this alteration associates with poor physical performance. Importantly, in the study by Mallamaci, lung water was largely independent of total body water by BIA, suggesting that LV dysfunction rather than overhydration *per se* is an important driver of pulmonary congestion in HD patients. Along with this hypothesis, the number of US-B lines was associated in an inverse fashion with ejection fraction and the early filling to early diastolic mitral annular velocity (E/E' ratio), two parameters, respectively, measuring systolic and diastolic function [21]. The high prevalence of lung congestion in ESKD was recently established in a large ($n = 392$), multicentre study [25] where moderate-to-severe lung congestion was evident in about a half of the patients and very severe congestion in 14%.

In patients with pre-existing heart disease admitted to a department of cardio-pulmonary medicine for acute dyspnoea or chest pain [26] and in patients with coronary heart disease [27] chest US predicted death and incident cardiovascular events independently of ejection fraction and established clinical scores like the New York Heart Association (NYHA) score and the Global Registry in Acute Coronary Events score. The strong relationship of lung water by chest US with all-cause mortality and CV events was specifically confirmed in ESKD in the multicentre study discussed above [25]. Importantly, the presence of moderate-to-severe and very severe lung congestion added relevant predictive value not only for death but also for incident cardiovascular events (Figure 2) to a model based on the Framingham factors, NYHA score and risk factors peculiar to ESKD like hypoalbuminaemia, hyperphosphataemia and inflammation. These findings support the hypothesis that chest US provides information which may be useful for the clinical management of dialysis patients. However, notwithstanding the

multicentre design, the generalizability of this study is limited because external validation is a pre-requisite for establishing the consistency and validity of the findings in cohort studies. The first external validation is now provided in a single-centre study in Romania by Siriopol *et al.* [9], which is published in this issue of the journal. Importantly, this study is the first comparing the predictive power of chest US with measures of hydration status made by a tetrapolar BIA machine which provides very accurate estimates of hydration status [10]. Of relevance, chest US and the LV mass index—an established, strong risk factor for adverse clinical outcomes in ESKD—were the sole significant death predictors in the Romanian cohort. Notwithstanding, the multivariate survival analysis in this cohort was internally confirmed by a bootstrapping technique and the number of events in this study was quite small ($n = 13$); therefore, further observations in larger cohorts and longer follow-up in this Romanian cohort are necessary to definitively confirm the independent relationship of lung water with mortality in ESKD. Another important observation by Siriopol is that total body water, extracellular volume (ECV) and a hydration state normalized to the ECV index were only weakly related to lung water, the shared variance (r^2) of these parameters ranging from 4.4 to 8.8%, again suggesting that LV disorders play an important role in lung congestion in ESKD. Yet, at variance with the study by Mallamaci [21], lung water was completely independent of ejection fraction. This finding most likely depends on the fact that patients in the Siriopol study had better systolic function (on average $61.5\% \pm SD7.7\%$) than those in the Mallamaci study, where ejection fraction had a wide range of values spanning from very low (15%) to high (70%). Overall, studies performed so far in ESKD [9, 21–25] show that chest US is a valid instrument for measuring the degree of lung congestion in dialysis patients, and that the detection of lung congestion has relevant prognostic potential in this population.

Performing sound clinical studies on biomarkers of volume overload in ESKD is a priority [1]. Research in this area is indeed still limited and, for the most part, methodologically questionable. Until now, only one study has applied an experimental approach to test the clinical usefulness of the most used biomarker of volume expansion, total body water by BIA [28], and there is still no clinical trial on biomarkers based on the clinical end points, which is the definitive test for establishing the clinical utility of biomarkers. The issue is fundamental because the usefulness and the safety of instruments used to probe dry weight cannot be taken for granted. In a trial testing volume tracking across dialysis by continuous haematocrit monitoring [29], the application of this technique was associated with worse rather than with better clinical outcomes. A Pan-European clinical trial testing whether the application of chest US may improve clinical outcomes has been designed by the EURECA-m investigators. This trial, the lung water by US-guided treatment to prevent death and cardiovascular complications in high-risk dialysis patients with cardiomyopathy (LUST), funded by the ERA-EDTA, has just started patient enrolment [30]. LUST will provide the much-needed definitive test for establishing whether this novel, promising technique that is worth applying in clinical practice.



Fully adjusted risk of lung congestion of increasing severity. The figure was made on the basis of data reported in ref. 25

FIGURE 2: Hazard rate for death associated with lung congestion of various severity.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Siriopol *et al.* Predicting mortality in haemodialysis patients: a comparison between lung ultrasonography, bioimpedance data and echocardiography parameters. *Nephrol Dial Transplant* 2013; 28: 2851–2859.)

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