Detecting and Treating Lung Congestion with Kidney Failure

Carmine Zoccali 1, Francesca Mallamaci, 2,3 and Eugenio Picano 4

Abstract
Fluid overload is a common complication in patients with CKD, particularly patients with kidney failure, a population with a very high risk for pulmonary edema. Lung ultrasound is now a well-validated technique that allows for reliable estimates of lung water in clinical practice. Several studies in patients with kidney failure documented a high prevalence of asymptomatic lung congestion of moderate to severe degree in this population, and this alteration was only weakly related with fluid excess as measured by bioimpedance spectroscopy. Furthermore, in these studies, lung congestion correlated in a dose-dependent fashion with death risk. In the Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk Kidney Failure Patients with Cardiomyopathy (LUST) trial, a treatment strategy guided by lung ultrasound safely relieved lung congestion but failed to significantly reduce the risk for a combined end point including death, nonfatal myocardial infarction, and decompensated heart failure. However, in line with three trials in patients with heart failure, a post hoc analysis of the LUST trial showed that the use of lung ultrasound reduces the risk for repeated episodes of acute heart failure and repeated cardiovascular events. Given the high cardiovascular risk of pulmonary edema in patients with predialysis CKD, defining the epidemiology of lung congestion in this population is a public health priority. Specific trials in this population and additional trials in patients with kidney failure will establish whether targeting lung congestion at an asymptomatic phase may improve the severe cardiovascular prognosis of both patients predialysis and patients on dialysis.

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Introduction
Volume overload and the related complications—hypertension, left ventricular (LV) hypertrophy, and heart failure—are very common in patients with CKD. The prevalence of these complications starts to rise in patients with stage G3 CKD to become very frequent in patients with kidney failure maintained on regular dialysis (1). Volume overload has a 45% prevalence among patients on hemodialysis (2) and contributes to asymptomatic and symptomatic lung congestion as detected by lung ultrasound (US) (3), a condition predisposing to a high risk of pulmonary edema (4) and other cardiovascular complications (5) in this population. Current CKD guidelines stipulate that volume control is an absolute priority for the treatment of CKD at all stages (6).

The sodium and volume overload across CKD stages goes along with a gradual increase of interstitial fluid volume and pressure, and the process extends to the lung, which is the organ system more sensitive to the adverse effects of fluid overload (7). Lung congestion as detected by standard x-ray studies is at least three times more common among patients with kidney failure than among patients with predialysis CKD (8). Heart failure is notoriously prevalent in the CKD population, and de novo heart failure among patients with CKD has an incidence rate ranging from 17% to 21% (9). Predictably, lung congestion is particularly severe in patients with kidney failure with concomitant heart failure (10). In a large study on the basis of Centers for Medicare and Medicaid Renal Management information (4), at least 14% of patients on hemodialysis experienced one or more pulmonary edema episodes over 2 years. A moderate to severe degree of lung congestion is also evident in some asymptomatic patients on dialysis (3,5), and therefore, this alteration should not be equated to pulmonary edema. On the other hand, water accumulation in the lung by US in asymptomatic and symptomatic patients on dialysis has a dose-response relationship with cardiovascular mortality, implying a continuum in the risk for adverse outcomes by this alteration (5). Studies focusing on the most appropriate approach to relieve lung congestion are considered a priority issue in a consensus document issued by Kidney Disease Improving Global Outcomes (KDIGO) investigators (11).

The microcirculation dynamics in lung capillaries, basic pathophysiology of alterations in lung capillaries forces, and related modifiers of permeability are illustrated in Figure 1. Over the last decade, lung US has emerged as a reliable technique for quantifying lung water and monitoring lung congestion in patients with heart failure (12). In 2019, the European Society of Cardiology endorsed lung US to monitor these patients
The basic mechanism underlying the generation of lung US B lines, which are an equivalent of B lines on chest x-rays, is illustrated in Figure 2. These lines associate with LV filling pressures (14) and reduce across hemodialysis (3,15). The key technical aspects of this method are illustrated in Figure 3. A special, simplified algorithm (“the Blue protocol”) has been proposed by Lichtenstein and Mezić (16) for US assessment of the lung in acute respiratory failure.

In this review, we focus on lung congestion as assessed by lung US in patients with kidney failure. We will expand on descriptive studies, cohort studies, and clinical trials aimed at testing treatment of decongestion guided by lung US in kidney failure. We will conclude by indicating several open questions related to the problem in the kidney failure population.

Lung Congestion in Patients with CKD

Pulmonary congestion is a key feature in decompensated heart failure (7) and advanced kidney insufficiency (17). In heart failure, the high pressure in the LV chambers is transmitted back to pulmonary veins and capillaries, resulting in high pulmonary capillary wedge pressure (le., “hemodynamic congestion”). This alteration sets the stage for extravasation of fluid into the lung interstitium and into the alveoli (le., “lung congestion”) (18). If not timely treated, hemodynamic congestion is bound to evolve into lung congestion, a condition characterized by dyspnea of varying severity depending on the peculiar hemodynamic setting and the volume status. Studies in patients with kidney failure on dialysis, a population marred by chronic volume expansion (1) and background cardiovascular disease...
Figure 3. Twenty-eight sites and 4 sites lung US scores. The first well-standardized US method for quantifying lung water was on the basis of recordings made at 28 precise points in the intercostal spaces (upper panel) (58). Shorter methods taking 1 minute or less focus on eight (59) or just four points (60). The four sites score measures the number of US B lines in the third intercostal space in two areas per side of the thorax (lower panel). These methods apply different scores but provide substantially similar information (61,62). Automated software on the basis of artificial intelligence has already been implemented in some commercially available machines and may allow operator-independent quantification of lung water.

As previously remarked, volume expansion is a factor predisposing to lung congestion in patients with kidney failure (1). Various studies compared lung US with other methods for fluid status assessment in patients on dialysis (3,5,22–31) and found a variable, generally weak degree of agreement between the number of US B lines and fluid overload as measured by bioimpedance spectroscopy or other techniques. A weakness of these descriptive studies is that the comparator measurements of fluid volume still remain inadequately validated. In addition, a series of studies tested the relationship between US B lines, left atrial volume—a metric of fluid volume status (32,33) and LV dysfunction (34) in patients on dialysis—and other echocardiographic parameters. Some of these studies (30,31,35) had a modest sample size and reported inconsistent relationships. The first of these descriptive studies by Mallamaci et al. (3) in 76 patients registered robust and coherent relationships between predialysis US B lines, LV mass index, left atrial volume, left ventricular ejection fraction (LVEF), pulmonary pressure, and the E/e’ ratio. The US B lines versus LVEF was the strongest among these relationships (rho=0.59). Importantly, these links were all confirmed postdialysis (i.e., after fluid overload correction). This phenomenon implicates LV dysfunction, a common alteration in this population (36), as a relevant causal factor in lung congestion in the same population. The association of US B lines with LVEF (37), left atrial dimension (24), and pulmonary pressure (38) was confirmed in studies by Pardala et al. (37), Siriopol et al. (24), and Wang et al. (38), respectively. As alluded to before, lung congestion is at least three times more common among patients with kidney failure on dialysis than among patients with predialysis CKD (8). In most of the descriptive lung US studies (3,24,38), the number of US B lines reflected the severity of functional
impairment of the heart as assessed by the New York Heart Association (NYHA) class, as it did in a study focusing on patients on peritoneal dialysis (39). Of interest, in a sub-study (40) of the Lung Water by Ultra-Sound Guided Treatment to Prevent Death and Cardiovascular Complications in High Risk Kidney Failure Patients with Cardiomyopathy (LUST) trial (41), which we will discuss in another section of this review, a reduction in left atrial and ventricular volumes as well as of the E/e’, a surrogate of the LV filling pressure, were registered along with lung congestion improvement.

Cohort Studies on the Risk of Lung Congestion in Patients with CKD

The association with death and cardiovascular events of lung congestion by lung US was tested in four studies published in the English literature (5,24,42,43) (Table 1). In the first of these studies, the numbers of patients and clinical outcomes (death and cardiovascular events) were much larger than the corresponding total numbers in the other three studies. The presence of severe lung congestion in patients in the first study entailed a quadrupling in the risk of death and a tripling in the risk for cardiovascular events in models adjusting for risk factors correlated to death (age, smoking, cardiovascular comorbidities, NYHA class, pulse pressure, albumin, serum phosphate, and C-reactive protein) or to cardiovascular events (age, sex, smoking, diabetes, cardiovascular comorbidities, dialysis vintage, pulse pressure, and NYHA class). These analyses clearly support the notion that lung congestion may be causally implicated in the high risk of death and cardiac events in patients with kidney failure. On the other hand, in the same study, lung US added significant prognostic information for death (6%) and cardiac events (5%) to classic risk factors, the NYHA class, and risk factors peculiar to kidney failure, like hypoalbuminemia, hyperphosphatemia, and inflammation. Furthermore, the severity of lung congestion as assessed by US improved by 10% the risk reclassification of patients who remained free of cardiac events and by 8% the risk reclassification in survivors. The other three studies (Table 1) coherently confirmed that severe lung congestion entails a high death risk. Siriopol et al. (29), in another study extending the dimension and the follow-up of their original cohort (24), tested whether lung US and fluid overload (as assessed by bioimpedance analysis) add significant discriminant power to a simple model on the basis of NYHA class, diabetes, C-reactive protein, and LV mass index. In this new analysis, fluid overload but not lung congestion added significant discriminant power to the model. However, the gain in power was very modest (+0.058%), and this analysis was on the basis of 31 deaths only. Overall, additional studies are needed to ascertain whether the application of lung US may serve to refine the prognosis in patients with kidney failure.

Clinical Trials in Patients with CKD and Patients with Heart Failure Testing Lung Ultrasound-Guided Treatment Strategies Aimed at Relieving Lung Congestion

Relieving lung congestion in patients with heart failure is considered a priority in an international consensus document issued by cardiologists (44) and a relevant treatment target in patients with CKD in a consensus document (11) issued by KDIGO investigators. Because of its simplicity, reproducibility, and sensitivity at capturing changes in lung fluid, lung US appears well suited for the detection and the monitoring of lung congestion (12,18,45). The key question of whether a lung US-guided treatment strategy can reduce hospitalizations for recurrent acute heart failure and death in patients with chronic heart failure until now has been examined in only three small trials. In the first, a 6-month study by Riva-Lasarte et al. (46) in 123 patients (61 allocated to the intervention arm and 62 allocated to the control arm), the lung US-guided treatment strategy produced a substantial risk reduction (~48%) for the main end points, including mortality, time to an urgent visit, and hospitalization for worsening heart failure. The number of combined events was 25 in the control arm and 14 in the active arm (hazard ratio [HR], 0.52; 95% confidence interval [95% CI], 0.27 to 0.99). Such a reduction was mainly attributable to a reduced number of urgent visits for worsening heart failure rather than to hospital admissions. Mortality did not differ (two deaths in the control group and three deaths in the active group). In the second, a 6-month study (47), 63 patients were allocated to the lung US arm, and an equal number was allocated to the control arm. The primary end point (identical to that adopted by Riva-Lasarte et al. [46]; see above) occurred in 20 patients (32%) in the lung US arm and in 30 patients (48%) in the control group, and the corresponding risk reduction was 45% (HR, 0.55; 95% CI, 0.31 to 0.98). Again, like in the trial by Riva-Lasarte et al. (46), such a risk reduction was entirely explained by a reduction in urgent heart failure visits, with no significant differences in rehospitalizations for heart failure or death. In the third study (48) that randomized 127 patients to the lung US arm and 117 patients to the control arm, a similarly impressive risk reduction for hospitalization (~56%; 12 hospitalizations in the lung US arm and 25 hospitalizations in the control arm; HR, 0.44; 95% CI, 0.23 to 0.84) was registered. Also in this trial lasting just 3 months, mortality (five deaths in the lung US arm group and four deaths in the control arm) was similar in the two groups. As expected, CKD (eGFR <60 ml/min per 1.73 m²) was much more common among patients in these trials (37% in the first [46], 25% in the second [47], and over 50% in the third [48] trial), but no analyses in the CKD subpopulations were produced in these studies. Whether the presence of CKD modifies the relationship between the lung US-guided treatment strategy and the risk of hospitalization is a relevant issue that can be explored in a meta-analysis of the three trials discussed above.

These trials are unquestionably groundbreaking contributions to research aimed at optimizing treatment of congestion in patients with heart failure. However, because of the small sample sizes and the fact that the effect of the intervention on the main end point was almost entirely attributable to the reduction of urgent visits, these studies should be considered as a proof of concept. Larger multicenter, adequately powered trials on the basis of hard clinical end points are needed to prove the usefulness of lung US for the treatment of lung congestion in patients with heart failure. No descriptive studies or clinical trials have been performed in patients with predialysis CKD, a population at very high risk for heart failure. Investigating the epidemiology of lung congestion at a predialysis stage and testing whether this alteration is causally implicated in the
<table>
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<th>Reference</th>
<th>Dimension of the Cohort, n</th>
<th>Follow-Up, yr</th>
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<th>Type of Dialysis</th>
<th>Clinical Outcomes</th>
<th>Quality of Statistical Adjustment</th>
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<tbody>
<tr>
<td>Zoccali et al. (5)</td>
<td>392</td>
<td>2.1 (median); interquartile range, 1.8–2.4</td>
<td>65±SD 15; 58%</td>
<td>HD</td>
<td>n=97; 4.2 (severe lung congestion versus mild or no congestion)</td>
<td>Not specified; low power for allowing statistical adjustment</td>
</tr>
<tr>
<td>Siriopol et al. (24)</td>
<td>96</td>
<td>1.1 (median); interquartile range, 0.6–1.4</td>
<td>59.1 (mean) ±SD 14.2; 51%</td>
<td>HD</td>
<td>n=13; 3.6 (severe lung congestion versus mild or no congestion)</td>
<td>Adjusted only for hydration status and NYHA; low power for allowing statistical adjustment</td>
</tr>
<tr>
<td>Saad et al. (42)</td>
<td>81</td>
<td>Mean 1.19</td>
<td>59.7±SD 15.9; 72%</td>
<td>HD</td>
<td>n=9; n=20; combined analysis death and cardiac events: HR (very severe versus no congestion), 7.98; HR (moderate to severe versus no congestion), 2.98</td>
<td>Not specified; low power for allowing statistical adjustment</td>
</tr>
<tr>
<td>Kawaci et al. (43)</td>
<td>61</td>
<td>Mean 1.4±1.0</td>
<td>75.2±SD 10.7; 47%</td>
<td>HD</td>
<td>n=24; ≤5 US B lines versus &lt;5 US B lines; HR, 1.2; pre-HD/post-HD US B lines; HR, 0.13</td>
<td>Unadjusted data; low power for allowing statistical adjustment</td>
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HD, hemodialysis; NYHA, New York Heart Association; HR, hazard ratio; US, ultrasound.
very high risk of this population are clinical and research priorities.

Only two trials have been performed in both patients with CKD and patients with kidney failure on regular hemodialysis treatment. Both trials originated from the LUST trial collaboration. IASI investigators who participated in this trial adapted the LUST protocol for an independent, single-center trial looking at low-risk patients on hemodialysis without heart failure or coronary heart disease (49). The baseline median US B-line number in the active arm of this trial was just seven, indicating that the vast majority of patients in this trial had modest or no lung congestion, and predictably, no benefit of the lung US-guided strategy was registered. Interestingly, another study corollary to LUST in hypertensive patients on hemodialysis showed that the systematic use of lung US improves BP control as measured by ambulatory BP monitoring (50). Indeed, 48-hour systolic BP reduced more in the active arm of the trial (systolic: $-6.61\pm 9.57$ mm Hg; diastolic: $-3.85\pm 6.34$ mm Hg) than in the control arm (systolic: $-0.67\pm 13.07$ mm Hg; diastolic: $-0.55\pm 8.28$ mm Hg). The intervention was safe because intradialytic hypotensive episodes were less frequent in the active group (34%) than in the control group (56%). Of note, the reduction in 48-hour ambulatory BP monitoring in the active group was accompanied by a reduction in pulse wave velocity (51), left atrial volume, and LV end diastolic volume (40), further pointing to a favorable effect of the lung US-guided intervention on the heart and the vascular system.

The LUST study was an international, multicenter, randomized controlled trial that investigated whether a lung US-guided treatment strategy improved a composite end point (all-cause death, nonfatal myocardial infarction, and decompensated heart failure) versus usual care in patients with kidney failure at high cardiovascular risk receiving long-term hemodialysis; 367 patients took part in the trial (active arm $n=183$, control arm $n=180$). During a mean follow-up of 1.49 years, lung congestion gradually improved in the active arm but worsened in the control arm (Figure 4), and the intervention was safe. However, the primary composite end point did not significantly differ (HR, 0.88; 95% CI, 0.63 to 1.24). Only in a post hoc analysis did a reduction in recurrent episodes of decompensated heart failure (HR, 0.63; 95% CI, 0.41 to 0.97) and cardiovascular events (HR, 0.37; 95% CI, 0.15 to 0.93) emerge in the active arm. Importantly, in LUST, decongestion was smoothly and safely achieved as witnessed by a reduction in the number of hypotensive episodes during dialysis. This is important because volume overload correction by other interventions, like intradialytic blood volume monitoring, was associated with a higher risk of mortality in a randomized trial by Reddan et al. (52). The lack of effect on the primary end point justifies further trials for establishing the usefulness of lung US for tailoring lung decongestion in patients with kidney failure. The divergence in lung water

![Figure 4. Trend of US B lines in the active and control groups.](image-url)

(A) Data are means and 95% confidence intervals (95% CIs). (B) Data (means and 95% CIs) are data fitted by the linear mixed model (LMM). Reprinted from ref. 41, with permission.
among the two study groups developed gradually over time (Figure 4), and it is possible that lung decongestion may have a favorable effect on cardiovascular outcomes in the long term. Like in trials in patients with heart failure (44–46), post hoc analyses in LUST showed that the use of lung US reduced the risk for repeated episodes of acute decompensated heart failure. Furthermore, in LUST, repeated cardiovascular events were lower in the active arm of the trial. Trials larger than LUST focusing on decompensated heart failure and with a longer follow-up are needed to definitively test the usefulness of lung US in kidney failure.

In conclusion, studies in patients with kidney failure have coherently documented that lung congestion is common and often asymptomatic in this population. Furthermore, the severity of lung congestion associates in a dose-response manner with the risk of incident heart failure and cardiovascular disease in the same population. Patients on hemodialysis represent just a small segment of the CKD population. At the population level, the prevalence of predialysis patients with stages G3b–G5 CKD is at least 80 times higher than that of patients maintained on long-term dialysis. These patients more often present risk factors for lung congestion, including volume expansion, LV dysfunction, heart failure, inflammation, and hypoalbuminemia. Given the high cardiovascular risk of pulmonary edema in patients with advanced CKD not yet on dialysis (8), defining the epidemiology of this alteration in the predialysis population is a public health priority. Specific trials are needed to establish whether targeting lung congestion at an asymptomatic phase may improve the severe cardiovascular prognosis of both predialysis patients and patients on dialysis.

Disclosures
F. Mallamaci reports honoraria from Fresenius; serving as the theme editor of Nephrology Dialysis and Transplantation; serving as a member of the editorial board of International Journal of Nephrology; serving as past Editor-in-Chief of Journal of Nephrology; and serving as a member of the editorial board of Turk Nefroloji, the official journal of the Turkish Society of Nephrology. C. Zoccali reports a consultancy agreement with Fresenius Medical Care, Europe; serving as a scientific advisor or member of MONDO Board; and serving as a member of the editorial boards of American Journal of Kidney Diseases, CJASN, and several internal medicine and nephrology journals. The remaining author has nothing to disclose.

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References


randomized controlled trial. *Int Urol Nephrol* 49: 143–153, 2017


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