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Review Article

Improving Prognosis Estimation in Patients with Heart Failure and the Cardiorenal Syndrome

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The coexistence of heart failure and renal dysfunction constitutes the "cardiorenal syndrome" which is increasingly recognized as a marker of poor prognosis. Patients with cardiorenal dysfunction constitute a large and heterogeneous group where individuals can have markedly different outcomes and disease courses. Thus, the determination of prognosis in this high risk group of patients may pose challenges for clinicians and for researchers alike. In this paper, we discuss the cardiorenal syndrome as it pertains to the patient with heart failure and considerations for further refining prognosis and outcomes in patients with heart failure and renal dysfunction. Conventional assessments of left ventricular function, renal clearance, and functional status can be complemented with identification of coexistent comorbidities, medication needs, microalbuminuria, anemia, biomarker levels, and pulmonary pressures to derive additional prognostic data that can aid management and provide future research directions for this challenging patient group.

1. Introduction: The Scope of the Cardiorenal Syndrome

Cardiac and renal dysfunctions often coexist. Approximately 70% of patients from community-based studies of heart failure (HF) have renal impairment, and 29% have moderate to severe renal dysfunction [1]. Furthermore, a published series from the Mayo Clinic reported that the serum creatinine levels of HF patients have increased steadily from 1987 to 2002 [2]. An analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials demonstrated that the prevalence of renal dysfunction was similar among patients with preserved ejection fraction and those with systolic dysfunction [3]. Moreover, a comparison of patients with ischemic HF and idiopathic dilated cardiomyopathy revealed that renal dysfunction was common in both patient groups [4]. This suggests that renal dysfunction in HF does not simply reflect the degree of left ventricular dysfunction or systemic atherosclerosis. While a universal, simple definition of the cardiorenal syndrome (CRS) remains elusive, a classification scheme based on the underlying precipitant of the CRS has been proposed [5] (see Table 1).

Renal function is one of the strongest prognostic factors among patients with HF. In a meta-analysis of approximately 78,000 patients with HF, Smith et al. [1] showed that renal impairment portended an increased risk of death, with an adjusted hazard ratio (HR) of 1.56 (95% CI: 1.53–1.60, $P < .001$). Hillege et al. [3] demonstrated that this risk was observed across the range of eGFRs below 60 mL/min/1.73 m^2. The negative prognosis associated with a 10 mL/min/1.73 m^2 decline in eGFR was comparable to that of a 5% decline in left ventricular ejection fraction (LVEF). Moreover, the prognostic value of eGFR was not significantly different among patients with reduced or preserved left ventricular ejection fraction. However, it has been

Table 1: Classification scheme of the different types of the cardiorenal syndrome.

Type	Name	Description
1	Acute CRS	Acute worsening of heart function leading to kidney injury and/or dysfunction
2	Chronic CRS	Chronic abnormalities in heart function leading to kidney injury and/or dysfunction
3	Acute renocardiac syndrome	Acute worsening of kidney function leading to heart injury and/or dysfunction
4	Chronic renocardiac syndrome	Chronic kidney disease leading to heart injury, disease, and/or dysfunction
5	Secondary CRS	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney

suggested that renal dysfunction might be associated with worse outcomes in patients with idiopathic cardiomyopathy, compared to those with an ischemic HF etiology [4].

Accordingly, patients with combined cardiac and renal dysfunction constitute a high risk group that is also large and heterogeneous, supporting the need for additional parameters to further delineate their risk of death and/or disease progression. The strongest prognostic information for these patients will continue to be derived from LVEF, estimates of renal function and New York Heart Association (NYHA) functional status. However, other clinical variables may play an increasingly important role in risk stratifying this large patient group with the ultimate aim of targeted interventions to improve outcomes.

2. Measurement of Renal Dysfunction in Heart Failure

Renal function can be estimated in several ways, yielding different estimates of eGFR. This becomes especially prominent among CHF patients whose body compositions might be markedly different than the chronic kidney disease (CKD) populations in whom these formulas were derived. Smilde et al. prospectively validated the accuracy and prognostic value of the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and simplified MDRD (sMDRD) equations among patients with HF by comparison with the gold standard of ^{125}I-iothalamate clearance [6]. All three formulas overestimated GFR in the lower ranges (<35 mL/min/1.73 m^2), underestimated it in the upper ranges (>65 mL/min/1.73 m^2), and functioned best in patients with NYHA classes III and IV. The MDRD was the most precise formula, while the CG was marginally more accurate. In comparison with directly measured GFR, the best prognostic value for cardiovascular outcomes came from creatinine clearance measurements using 24-hour urines and the MDRD equation, while the CG equation provided the least prognostic value. It has been reported that serum urea levels can also provide valuable prognostic information in CRS [7].

Accordingly, 24-hour urine collections should be periodically considered for determination of creatinine and urea clearance in HF patients with eGFR <35 mL/min/1.73 m^2, especially if heart transplantation or renal replacement therapy are being considered. Since creatinine is actively excreted into urine while urea is actively reabsorbed, measured creatinine clearance can significantly overestimate GFR in advanced CKD while urea clearances underestimate it. Thus, one method to estimate the GFR is to average both the creatinine and urea clearances, although this will require further study. There may be other potentially useful approaches to determine cardiorenal prognosis for HF patients including CG adjusted for body surface area [8], cystatin-C [9–14], and the Mayo eGFR formula [7].

3. Identifying Patients at Risk for Worsening Renal Function Based on Comorbid Conditions

A careful history of coexistent medical conditions can identify features that may increase the risk of subsequent renal compromise. Forman et al. examined risk factors for worsening renal function (WRF; defined as rise in serum creatinine of >0.3 mg/dL) among 1,004 consecutive patients admitted for a primary diagnosis of HF [15]. The highest risk of WRF was associated with elevated creatinine at admission. However, the presence of diabetes (adjusted hazard ratio [HR] 1.40) and a systolic blood pressure >160 mmHg (adjusted HR 1.37) were associated with a comparable risk of WRF to that of a history of prior HF (adjusted HR 1.31). A score derived from the regression model was useful in stratifying patient risk of WRF as shown in Table 2.

Other reported risk factors for WRF that can be identified at the time of admission for HF include

(i) rales/pulmonary edema [16, 17],

(ii) tachycardia [16],

(iii) female gender [16],

(iv) atrial fibrillation [17],

(v) peripheral arterial disease [17].

4. Cardiorenal Syndrome and Medications

The medications used by a patient can also provide insight into the stability of their cardiorenal axis. Furosemide is the one of most commonly prescribed medications among patients with HF, being used in over in 85% of outpatients at the time of hospital discharge [18]. Furosemide doses also frequently change among outpatients with HF [18]. In a study of 4,406 elderly patients discharged from an HF hospitalization, the prescription of higher furosemide doses (≥120 mg/day) was more common among patients with higher creatinine levels, preadmission furosemide use, ischemic or valvular HF etiology, diabetes, atrial fibrillation, and COPD. Patients who were prescribed higher furosemide

Table 2: Risk score developed by Forman et al. to predict worsening renal function [15].

Risk factor			Points	
History of HF			1	
Diabetes			1	
Systolic blood pressure >160 mmHg at admission			1	
Creatinine levels ≥1.5 and <2.5 mg/dL			2	
Creatinine levels ≥2.5 mg/dL			3	
Score	*n*	% of patients with score	% of Patients with worsening renal function	Relative risk
0	123	12.3	9.8	Referent
1	257	25.6	18.7	1.9
2	251	25	20.3	2.1
3	155	15.4	30.3	3.1
4+	218	21.7	52.8	5.4

doses were also more likely to exhibit hypotension, cardiomegaly, hyponatremia, and lower haemoglobin levels.

After extensive adjustment for covariates, exposure to higher furosemide dose was found to be predictive of death, hospitalization and renal dysfunction over five years of followup. Compared with the low-dose group (≤59 mg/day of furosemide), medium dose exposure (60–119 mg/day) was associated with increased mortality with an adjusted hazard ratio of 1.96 (95% CI: 1.79–2.15) while high dose exposure conferred an even greater mortality risk with a hazard ratio of 3.00 (95% CI: 2.72–3.31; both $P < .001$). There was a comparable increase in the risk of death both in and out of hospital, raising the possibility of an increased risk of both pump failure and sudden death. These potential mechanisms of death were supported by the observation of a higher risk of arrhythmias with increasing furosemide doses. Moreover, there was a dose-dependent increase in hospitalization risk that was strongest for HF events, suggesting that the adverse outcomes are most specifically related to HF progression. Similarly, the risk of renal dysfunction rose with increasing furosemide exposure, such that medium dose and high dose furosemide were associated with adjusted hazard ratios of 1.56 (95% CI: 1.38–1.76) and 2.16 (95% CI: 1.88–2.49) compared to the low dose group [18]. These findings were concordant with prior observations [19–22], suggesting that furosemide dose may represent a valuable "pharmamarker" of cardiorenal dysfunction, whose utility is enhanced by its ubiquitous use and dynamic nature that may indicate changes in HF control over time.

Treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) was associated with improved prognosis in this study of furosemide use. As a reflection of their heightened risk, the high-dose furosemide group was less likely to be treated with ACE inhibitors [18]. This mirrors the results of a retrospective analysis of the Minnesota Heart Survey where ACE inhibitor or ARB use was compared among 2,169 patients hospitalized with HF. There was progressively lower utilization of ACE inhibitors with declining eGFR. However, the in-hospital use of ACE inhibitors or ARBs was independently associated with significantly reduced 30-day mortality with an adjusted odds ratio of 0.45 (95% CI: 0.28–0.59). Moreover, the discharge prescription of an ACE inhibitor or ARB was associated with a significant reduction in adjusted 1-year mortality with odds ratio of 0.72 (95% CI: 0.58–0.91) [23]. However, there appears to be no mortality benefit associated with ACE inhibitor or ARB use among dialysis patients [23].

The most common concerns with ACE inhibitors and ARBs include worsening renal function and/or hyperkalemia [24]. However, patient subgroups with perceived contraindications to ACE inhibitors, including those with renal dysfunction, may tolerate high-dose ACE inhibitors well [25]. In a review of 12 randomized clinical trials of ACE inhibitors in patients with renal dysfunction (serum creatinine >1.4 mg/dL), acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACE inhibitor therapy were strongly predictive of long-term preservation of renal function. This prompted the authors to recommend that ACE inhibitors should only be withheld when the creatinine rise exceeds 30% above baseline within the first 2 months of initiation or if hyperkalemia develops [26]. Moreover, an analysis from the Digitalis Investigation Group trial showed that among patients with perceived contraindications to ACE inhibitors (most commonly renal insufficiency), use of ACE inhibitors was associated with significant survival benefit at four-year followup [24].

5. (Micro)albuminuria

Albuminuria is a convergence point for several physiological derangements common in HF and CKD such as volume overload, hypertension, diabetes, and inflammation [27–29]. The presence of proteinuria can serve as a marker of structural kidney damage [30–32] that can precede overt declines in renal function [33, 34]. Indeed, the presence of dipstick proteinuria with nearly normal renal function portends a higher risk of reaching end-stage renal disease than stage 4 CKD in the absence of a positive dipstick test [33, 34]. HF can also lead to albuminuria even in the absence of overt kidney dysfunction [35]. Nevertheless, albuminuria is more prevalent in HF patients with lower eGFR [35–37]. In the Valsartan in HF Trial, 5.6% of patients without CKD

(i.e., those with eGFR ≥60 mL/min/1.73 m^2) had dipstick-positive proteinuria compared to 10% of those with renal dysfunction [35]. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-HF) trial, impaired renal function (eGFR <60 mL/min/1.73 m^2) was present in 30.1% of patients with normal urinary albumin excretion, 45.0% of those with microalbuminuria, and 53.0% of those with albuminuria [37]. It has been well reported that albuminuria is associated with worse outcomes in apparently healthy subjects as well as patients with cardiovascular disease, diabetes, and CKD [33, 34, 38–44].

The urinary albumin to creatinine ratio may further refine risk in patients with HF. In an analysis of 2,310 patients from the CHARM program [36], those with an elevated urinary albumin to creatinine ratio were older, had worse renal function, and had higher diabetes prevalence. They were also more likely to have been admitted for HF, and a higher proportion had NYHA functional class III or IV symptoms at randomization. The presence of microalbuminuria independently predicted a higher rate of adverse events, with hazard ratios for death of 1.62 (95% CI: 1.32–1.99) for microalbuminuria and 1.76 (95% CI: 1.32–2.35) for macroalbuminuria compared to normoalbuminuria (both comparisons $P < .001$) [36]. Similar observations were reported in two subsequent studies [35, 37], one of which demonstrated a progressive increase in the risk of death throughout the range of UACR's [37]. The proposed mechanisms of the increased risk associated with proteinuria are beyond the scope of this paper but have been reported elsewhere [45].

6. Anemia

Anemia is a common condition in both HF and CKD. Its estimated prevalence in patients with HF varies between 12–50% based on the cutoffs used [46–51]. In a meta-analysis of 153,180 HF patients from 34 studies, 37.2% were anemic [49]. The prevalence of anemia appears to be similar in patients with preserved and reduced left ventricular systolic function [51–53]. It is also a well-established feature of CKD, with anemia prevalence of 27% when eGFR is ≥60 mL/min/1.73 m^2 to 75.5% in the presence of end-stage renal disease [54]. While the etiology in advanced kidney disease is believed to be mostly related to decreased erythropoietin production [55, 56], the anemia of HF is marked by elevated erythropoietin levels, although the elevation is often lower than expected for the degree of anemia [57, 58]. This may be a consequence of the heightened inflammatory state that marks the HF syndrome [48, 57–59]. These factors may explain the inconsistent responses to erythropoietin stimulating agents in HF. Positive responses were observed in early, small trials but were not consistently replicated in larger trials with hard endpoints [60–63], including the TREAT trial which showed a higher stroke risk with darbepoetin alfa among patients with CKD and type 2 diabetes, approximately 1/3 of which had HF [61].

HF and CKD also share other elements that could contribute to anemia such as iron deficiency, B12, folate and other nutritional deficiencies, and hemodilution [55–57, 60, 64–67]. In addition, both disease states commonly require the use of ACE inhibitors which decrease erythropoietin levels [68] and impair the breakdown of hematopoeisis inhibitors [58]. In a study of 59,772 adults with HF, the prevalence of anemia was 37% in patients with eGFR >60 mL/min/1.73 m^2 compared to 82% in those with stage 5 CKD [69]. Thus, HF and CKD may act synergistically to increase the prevalence of anemia. Additionally, anemic HF patients are more likely to be older with comorbid diabetes, lower blood pressure, higher diuretic use, higher NYHA functional class, reduced exercise capacity, worse quality of life, and increased neurohormonal activity [46–48, 50, 51, 57, 60, 62, 65]. The presence of anemia is also linked to a greater risk of death and hospitalization among patients with HF [48, 49, 53, 69]. In the meta-analysis by Groenveld et al., 46.8% of anemic patients died compared with 29.5% of non-anemic patients among 153,180 patients followed for a minimum of 6 months [49]. Anemia was also associated with a hazard ratio of 1.43 for HF hospitalizations among 3,029 patients with NYHA class II to IV functional status and left ventricular ejection fraction <35% [53].

The mortality risk associated with anemia appears to be similar among patients with preserved or reduced ejection fraction [52]. However, the mortality risk is nonlinear so that it is disproportionately weighted towards patients with more severe anemia [48, 53, 69]. Some reports have suggested that the relationship is better approximated by a J-shaped curve such that the risk of death may also be increased in patients with supranormal hemoglobin levels [53, 69]. Among patients with CKD, anemia is also predictive of development of end-stage renal disease [70], cardiovascular events [71], and death [70, 71]. The contribution of anemia to mortality risk is dependent on the degree of renal dysfunction, likely reflecting the dominant effect of renal dysfunction on mortality risk in the CRS. For example, in the study by Go et al., the presence of hemoglobin <9.0 g/dL was associated with a hazard ratio for death of 5.91 in patients with eGFR >60 mL/min/1.73 m^2, while the hazard ratio was 1.99 in patients with eGFR <30 mL/min/1.73 m^2 [69].

7. Biomarkers

The introduction of cardiac troponin assays revolutionized the management of acute coronary syndromes (ACS) by providing a powerful diagnostic and prognostic tool. With widespread use came the recognition that cardiac troponins can also serve as strong prognostic markers in HF and CKD outside the ACS setting. Serum troponin levels are elevated in 6–50% of patients with acute HF and have been linked to an increased risk of death and cardiovascular events among hospitalized and ambulatory patients with HF throughout the spectrum of the disease [72–76] in a dose-response relationship [74]. In the setting of CKD, troponin measurements are frequently elevated in the absence of overt cardiac pathology [77–84], partly due to decreased renal clearance [85]. This CKD-associated elevation is more prominent for troponin T relative to troponin I [77, 78, 83].

Troponin elevation in CKD reflects ongoing myocardial damage and necrosis and is strongly associated with diabetes,

left ventricular dilatation, and impaired left ventricular systolic and diastolic function, without necessarily indicating the presence of severe coronary artery disease [86]. Elevations in troponin T have been more consistently linked to a poor prognosis in patients with CKD [77–84, 87–89], while studies conducted using troponin I have provided conflicting results [77, 78, 83]. In a meta-analysis of 3,931 patients from 28 studies, elevated troponin T (>0.1 ng/mL) was associated with increased all-cause mortality with a relative risk of 2.64 (95% CI: 2.17 to 3.20) in the setting of end-stage renal disease [78]. An important caveat is that blood measurements of troponin should be obtained just before dialysis [90].

B-type (brain) natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) have also emerged as valuable markers of HF severity [91]. Since they have different clearance kinetics, their levels are not interchangeable, although they often correlate with each other. In particular, the clearance of NT-proBNP appears to be more affected by renal dysfunction than that of BNP [92]. However, both natriuretic peptides are elevated in patients with advanced CKD, suggesting that the elevation is multifactorial and not simply a result of decreased clearance [93–96]. Elevated levels of either natriuretic peptide are predictive of adverse outcomes among patients with HF. In a meta-analysis of 19 studies, each 100 pg/mL increase in BNP was associated with a 35% increase in the relative risk of death [97]. There is less data on the prognostic value of NT-proBNP in unselected patients with HF but it appears to confer similar information to BNP [98]. Natriuretic peptides are also predictive of outcomes in patients with preserved systolic function, where the severity of diastolic dysfunction has been found to correlate with increased levels of both BNP and NT-proBNP [99, 100]. The negative prognosis associated with natriuretic peptide elevation in CKD has been demonstrated in several studies [92].

The prognostic effects of these biomarkers are maintained in those with combined HF and renal disease. Their levels are still well correlated with left ventricular wall stress [101] and prognosis, although a higher NT-proBNP cutoff value is needed to separate patients with poor and intermediate prognosis. Bruch et al. compared the prognostic value of NT-proBNP in 183 ambulatory HF patients with CKD and 153 with eGFR >60 mL/min/1.73 m^2 and concluded that a cutoff value of 1,474 pg/mL best separated patients with poor and intermediate prognosis. Among patients with HF and CKD, cardiac event-free survival was 48% in patients above this cut-off compared with 93% in patients below it [102]. Anwarrudin et al. performed a similar analysis in patients presenting to the emergency department with HF, reaching the conclusion that NT-proBNP elevation was the strongest overall independent risk factor for 60-day mortality among those with eGFR <60 mL/min/1.73 m^2 with hazard ratio of 1.61 (95% CI: 1.14–2.26). NT-proBNP also independently predicted HF hospitalization with a hazard ratio of 1.26 [103].

The use of natriuretic peptides as prognostic variables requires attention to a few caveats. Firstly, natriuretic peptide levels are lower in obese patients, although they do maintain good diagnostic and prognostic value when used with appropriately lowered cut-offs [104]. Natriuretic peptides are also less useful in evaluating HF due to causes other than left ventricular dysfunction such as mitral stenosis or pericardial disease [91, 105, 106]. Ideally, natriuretic peptide levels should be used as a continuous variable that takes into account the patient's baseline levels if available [91].

The use of biomarkers in this setting will undoubtedly continue to grow. Neutrophil gelatinase-associated lipocalin (NGAL) is an early marker of acute kidney injury with improved kinetics in comparison to traditional markers of renal clearance [107, 108], which may independently predict prognosis in CRS [109–113]. Similarly, Cystatin C is a small serine protease inhibitor which is also being touted as a more accurate and earlier marker of renal dysfunction [10–14] and has already been shown to be a potent predictor of cardiovascular events and all-cause mortality in patients with and without overt cardiac or renal dysfunction [114–120]. The increasing utility of such biomarkers has sparked growing interest in "multimarker" approaches to assess disease severity and prognosis in the setting of the CRS [121–127]. However, it should be emphasized that biomarkers should be used as an adjunct to rather than a replacement for a full clinical assessment [128].

8. Pulmonary Hypertension

Pulmonary hypertension is a well-recognized consequence of HF, which constitutes Group 2 within the World Health Organization's classification of pulmonary hypertension [129]. Patients with CKD often have cardiac disease and pulmonary comorbidities such as sleep apnea that can lead to the development of pulmonary hypertension via increased left atrial pressure or chronic hypoxia in the absence of pulmonary arterial pathology [130–133]. The disproportionate prevalence of pulmonary hypertension in the absence of these causes within the CKD population is much less appreciated. In one study of patients with end-stage renal disease who did not have overt cardiac dysfunction or pulmonary disease, Doppler 2D echocardiography was used to estimate right ventricular systolic pressure 1-hour postdialysis, while at their dry weight. Of the study cohort, 39.7% had an estimated right ventricular systolic pressure >35 mmHg, while 13.8% had values >45 mmHg [130]. This high prevalence of pulmonary hypertension was replicated in two other studies from different continents [134, 135]. It is controversial whether pulmonary hypertension relates to the presence of end-stage renal disease itself or whether it is a consequence of dialysis, particularly via an arteriovenous fistula [130]. However, with reported prevalence of pulmonary hypertension as high as 39.1% in patients awaiting dialysis, and the improvement (and possible normalization) of right ventricular pressures among patients with end-stage renal disease after renal transplantation, evidence of an association is strengthened [130, 136].

The development of pulmonary hypertension in the presence of advanced CKD may be a harbinger of poor outcomes. In a study of 127 hemodialysis patients, 17 patients had pulmonary hypertension at dialysis outset, and 20 more developed elevated right-sided pressures after its

initiation. After multivariate adjustment, the presence of pulmonary hypertension prior to dialysis was associated with a hazard ratio of 3.6 for death (95% CI: 1.8–7.0) compared to patients without the condition at baseline. The development of new pulmonary hypertension after initiation of dialysis was associated with an adjusted hazard ratio for death of 2.1 (95% CI: 1.1–4.3) [133]. It remains unclear why the presence of pulmonary hypertension increases risk of death so prominently in the end-stage renal disease population that already has a high rate of events. The presence of pulmonary hypertension may be associated with higher risk of adverse outcomes because it may reflect (a) advanced cardiac or respiratory disease, (b) greater severity of kidney disease-associated endothelial dysfunction secondary to nitric oxide and endothelin-1 derangements [136–139], (c) greater derangement of calcium metabolism with greater subsequent vascular calcification [135], (d) a state of high cardiac output in patients with arteriovenous fistulas [130, 135, 136, 140, 141] which can induce high output HF, and (e) undiagnosed diastolic dysfunction, chronic volume overload, chronic hypoxia, or recurrent pulmonary embolic events [134, 135, 142].

9. Conclusion

The development of the CRS is linked to a marked increase in the rates of death and morbidity compared to patients with either HF or CKD in isolation. However, there are multiple widely available noninvasive factors that can help the clinician estimate prognosis more accurately within this large and heterogeneous patient group. An assessment of left ventricular ejection fraction, renal function, and functional status remain paramount. The identification of co-existent diagnoses may indicate a high risk of worsening renal failure during HF hospitalization. The use of high furosemide doses or nonuse of ACE inhibitors or ARBs may identify patients with a tenuous cardiorenal axis or possibly suboptimal medical management. The presence of concomitant microalbuminuria or anemia may also provide clues to greater severity of cardiorenal compromise. The use of biomarkers such as BNP, troponin, NGAL, and cystatin-C can provide additional information in monitoring this patient group. Finally, surveillance for pulmonary hypertension in patients with end-stage renal disease might allow for further refinement of prognosis in this patient group with its exceedingly high risk of death or morbidity.

Conflict of Interests

The authors have no conflicts of interest to declare.

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