

Diagnosis of Fluid Overload: From Conventional to Contemporary Concepts

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Abstract

Fluid overload has been associated with morbidity and mortality in various clinical scenarios including heart failure and critical illness. It exerts pathologic sequelae in almost all the organ systems. Proper management of patients with fluid overload requires knowledge of the underlying pathophysiology, objective evaluation of volume status, selection of appropriate therapeutic options, and maintenance and modulation of tissue perfusion. There are several methods to appraise volume status but none without limitations. In this review, we discuss the diagnostic utility, prognostic significance, and shortcomings of various bedside tools in the detection of fluid overload and evaluation of hemodynamic status. These include clinical examination, biomarkers, blood volume assessment, bioimpedance analysis, point-of-care ultrasound, and remote pulmonary pressure monitoring. In our opinion, clinicians must adopt a multiparametric approach offsetting the limitations of individual methods to formulate a management plan tailored to patients' needs.

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Introduction

Recognizing and treating fluid overload (FO) is a key component of managing patients with heart failure (HF). The pathophysiology of FO is complex and involves an interplay of absolute volume gain, fluid redistribution from venous capacitance beds to the central venous circulation, and inadequate elimination due to renal dysfunction, salt and water retention, and endothelial dysfunction. FO leads to hemodynamic congestion characterized by elevated cardiac filling pressures, which subsequently results in clinical congestion manifested by signs and symptoms such as orthopnea, elevated jugular venous pressure (JVP), peripheral edema, and rales [1]. It is well recognized that in patients hospitalized for decompensated HF, persistent congestion at discharge portends worse outcomes [2–5]. In the recent past, the deleterious effects of FO are being increasingly recognized in other clinical settings such as critical illness where empiric administration of intravenous fluid (IVF) is a common scenario. In a meta-analysis including 19,902 patients admitted to the intensive care unit (ICU), the cumulative fluid balance after 1 week of ICU stay in nonsurvivors was found to be 4.4 L more than in survivors. Moreover, a restrictive fluid management was associated with a lower mortality compared to liberal fluid administration (24.7

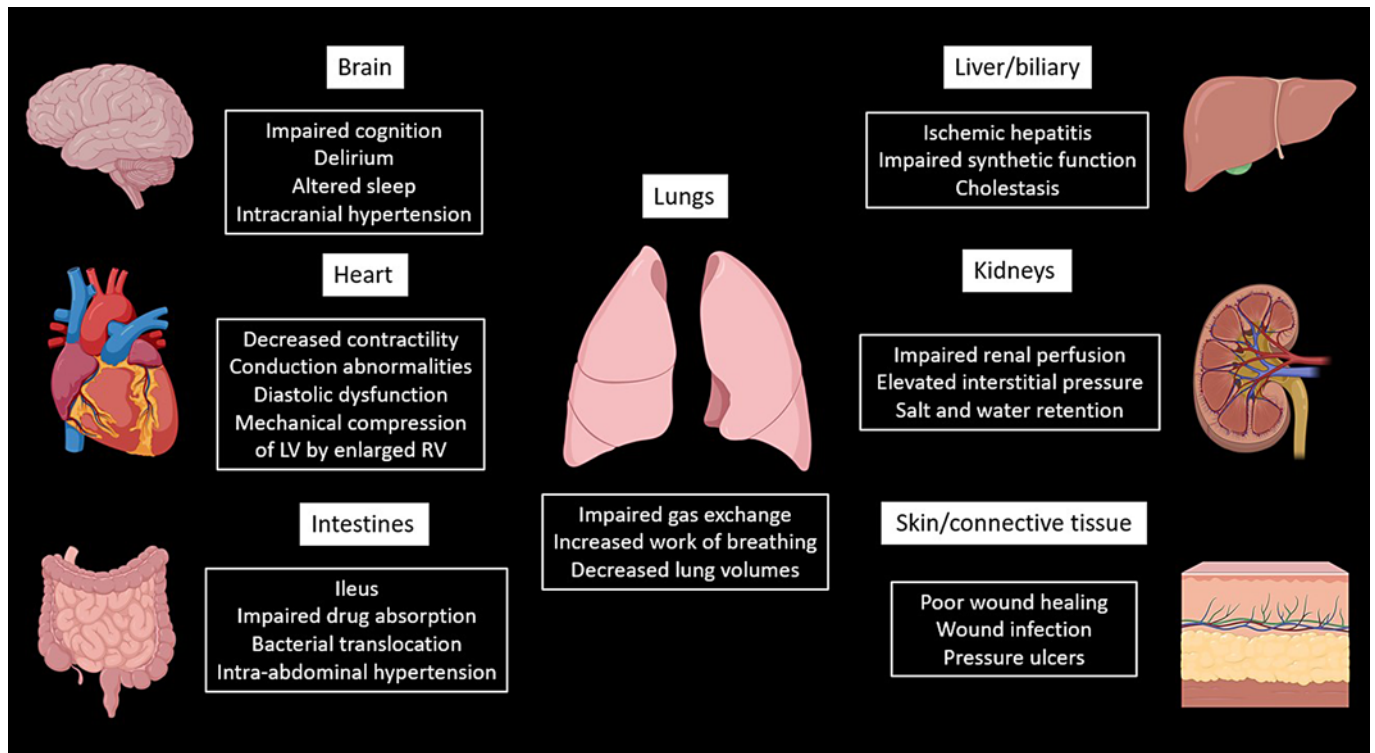


Fig. 1. Pathologic effects of fluid overload in various organs/organ systems. BioRender[®] was used to create the figure.

vs. 33.2%; $p < 0.0001$) [6]. Similarly, in a cohort of critically ill patients with cirrhosis, a higher median fluid balance 7 days post-ICU admission (+13.50 vs. +6.90 L; $p = 0.036$) was associated with an increased risk of in-hospital mortality [7]. Interestingly, a recent clinical trial demonstrated that restrictive fluid management strategy is safe in patients with septic shock compared to standard care (i.e., liberal strategy); although the outcome was not superior in the restrictive group, it is notable that the standard care group received substantially less fluid compared to prior studies (a median of 3.8 L) [8]. While a direct causative relationship cannot be established between FO and mortality based on the current evidence, it is a potentially preventable cause of iatrogenic morbidity; there are data that suggest FO adversely affects almost all the organ systems [9, 10] (Fig. 1). For example, FO leads to pulmonary edema, low lung compliance, increased work of breathing [11, 12]; delirium, raised intra-cranial pressure [13–15]; prolonged ileus, impaired hepatic synthetic function, cholestasis, impaired drug absorption [16, 17]; impaired cardiac contractility and conduction abnormalities [18, 19]; acute kidney injury (AKI) [20, 21]; impaired wound healing [22]; and so forth. Furthermore, the contribution of FO to venous congestion and conse-

quent impaired organ perfusion is gaining recognition challenging the traditional forward flow-centric paradigm and shifting the focus from “fluid responsiveness” to “fluid tolerance” [23, 24]. Objective assessment of fluid status is a critical step in timely detection of FO and titrating therapy to optimize hemodynamics. Though accurate, the utility of invasive modalities such as pulmonary artery catheterization is limited to a small subset of critically ill patients and does not necessarily improve outcomes [25]. In this review, we will provide an overview of various bedside tools/laboratory tests in the evaluation of FO and congestion focusing on but not limited to HF.

Clinical Examination

Careful history taking and physical examination of the cardiopulmonary system are the first steps in the management of patients with FO. These are intended to detect increased cardiac filling pressures and their consequences. However, as mentioned, hemodynamic congestion may exist in the absence of clinical congestion. Therefore, it is conceivable that the sensitivity of these findings is relatively low to detect ongoing congestion; sole reliance

on them to manage patients eventually leads to clinically apparent FO and recurrent hospitalizations. For instance, in a study including 50 HF patients with severely reduced ejection fraction (18%), the combined sensitivity of rales, edema, and elevated mean JVP was just 58% to detect an elevated pulmonary capillary wedge pressure of ≥ 22 mm Hg despite good specificity [26]. Similarly, in a meta-analysis of 22 studies including patients presenting with dyspnea [27], pooled sensitivities of orthopnea, peripheral edema, JVP, third heart sound, and rales were only 50%, 51%, 39%, 13%, and 60%, respectively, to diagnose congestive HF. Only parameter among these with a positive likelihood ratio above 10 was the third heart sound (S3 gallop), which ironically had the lowest sensitivity. In summary, most of the conventional physical examination findings are helpful when present, but their absence does not exclude congestion. Patients' weight is useful but limited by documentation errors, inaccurate calibration of the equipment, and inability to detect redistribution-related FO.

Biomarkers

Several biomarkers have been studied in patients with HF, which can be broadly classified into markers of inflammation (C-reactive protein, myeloperoxidase), fibrosis and extracellular remodeling (procollagen, galectin-3, ST2), mechanical strain/stretch (natriuretic peptides, CD146, carbohydrate antigen 125 [CA125]), markers of hemodynamic homeostasis (adrenomedullin, copeptin), tissue perfusion (lactate), and cardiomyocyte injury (troponins) [28, 29]. Herein, we discuss some of the commonly tested biomarkers in clinical practice. In the ICU setting, their utility is often limited because of variable specificity and presence of multiple confounding factors.

Natriuretic Peptides

Natriuretic peptides are frequently used as an adjunct to clinical assessment in patients presenting with symptoms suggestive of HF. In fact, B-type natriuretic peptide (BNP) levels have an excellent negative predictive value (96% at levels ≤ 50 pg/mL) for HF diagnosis in such patients [30]. In addition, they carry prognostic significance with observational studies showing better outcomes in patients whose levels decrease in response to decongestive therapy [28, 31]. Similar findings have been observed in critically ill patients with septic cardiomyopathy though the data are sparse; a decline in BNP over time (to

< 500 pg/mL) conferred a favorable outcome in one study [32]. Nevertheless, natriuretic peptide-guided therapy was not associated with superior cardiovascular outcome compared to standard care in patients with HF with reduced ejection fraction in two recent clinical trials [33, 34]. Moreover, approximately 20–35% of outpatients with HF with preserved ejection fraction may exhibit a state of intermittent or chronic natriuretic peptide deficiency despite coexisting hemodynamic congestion [35, 36]. Additionally, the concentrations of natriuretic peptides are elevated in patients with renal dysfunction owing to impaired clearance limiting their utility [28].

Lactate

HF is classically described as a condition in which the cardiac pump is not able to support adequate oxygen delivery to the tissues [37]. Surprisingly however, blood lactate, a marker of tissue hypoperfusion, is normal in $\sim 75\%$ of patients with advanced HF and a widened arterio-venous oxygen difference [38]. On the other hand, the risk of mortality is higher in patients with acute HF who have elevated lactate levels on hospital admission [39]. Although HF treatment may reduce lactate levels, it is unclear whether lactate-guided treatment translates into better clinical outcomes. This is even more vague in the context of septic shock where reduced lactate clearance (as opposed to increased production) may prompt the clinician to administer IVF in the absence of tissue hypoperfusion, contributing to iatrogenic FO [40]. For instance, in the ANDROMEDA-SHOCK trial, lactate-guided resuscitation group received an excess of 400 mL of IVF within the first 8 h compared to the capillary refill time-guided group while having more organ dysfunction at 72 h [41].

Hemoglobin and Hematocrit

Expansion of plasma volume (PV) leads to decreased red blood cell concentration (hemodilution) and vice versa. Therefore, hemoconcentration or increasing hematocrit with fluid removal has been purported as a surrogate for evaluating decongestion and plasma refill rate [42]. In a study including 102 patients hospitalized for acute HF, hemodilution during the first 3 days was associated with a severe degree of pulmonary edema compared to those who had hemoconcentration (85 vs. 63%, $p < 0.01$). Additionally, HF-related readmission rate was higher in the hemodilution group (34 vs. 9%, $p < 0.01$) [43]. Likewise, in the post hoc analysis of the PROTECT trial [44], a rapid increase in hemoglobin level during the first week was independently associated with a favorable outcome, de-

spite a slight decline in renal function in patients hospitalized with HF. Conversely, a subset of patients with HF may have true polycythemia as a response to chronic low cardiac output state, hypoxemic tissue perfusion, and tissue acidosis; this may predispose to increased risk of thrombosis and myocardial work burden from blood hyperviscosity. In such cases, clinicians must exercise caution not to mistake dilution-related pseudo-anemia for true anemia, especially if contemplating erythropoietin therapy [45, 46]. Quantitative analysis of PV may be helpful in some cases to titrate diuretic therapy based on adjusted red blood cell volume.

Carbohydrate Antigen 125

CA125 is a high molecular weight transmembrane glycoprotein used in the diagnosis and prognostication of ovarian cancer. In the recent past, there has been a renewed interest in its role as a biomarker for congestion in HF. It has been proposed that CA125 is shed from mesothelial cell surfaces in response to mechanical stress such as FO, and inflammatory stimuli. High CA125 levels are associated with the presence of serosal fluid and positively correlate with inflammatory markers including serum TNF- α , IL-6, and IL-10 levels in patients with HF [47]. In a systematic review and meta-analysis including 23 studies investigating its role in HF management, serum levels of CA125 were found to increase in parallel with decline in cardiac function from the New York Heart Association (NYHA) class I/II to III and further from class III to IV. Further, HF patients with higher CA125 level had poorer outcomes [48]. In a recent prospective observational study including 191 patients admitted with acute HF, CA125 has demonstrated a positive and independent association with the presence of peripheral edema, pleural effusion, and an increased diameter of the inferior vena cava (IVC). On the other hand, NT-proBNP was associated with pleural effusion and IVC diameter but not peripheral edema. Notably, CA125 exhibited a better correlation with IVC diameter [49]. These findings have led to the premise that CA125 is a better marker for right heart dysfunction and venous congestion whereas NT-proBNP is more indicative of left-sided filling pressures and pulmonary congestion.

Quantitative Blood Volume Analysis

Blood volume analysis (BVA) is based on the indicator-dilution technique, in which a known quantity of a substance (q) is dissolved in a fluid compartment of un-

known volume (V) and its concentration (C) is measured. Then, the unknown volume can be calculated by the formula, $V = q/C$ [46]. In the method that is commercially available currently (BVA-100 Blood Volume Analyzer; Daxor Corp., New York, NY, USA), a standard dose of radioactive iodine-labeled albumin (I-131) is injected intravenously. A pre-injection blood sample is collected followed by a series of samples at timed intervals once the tracer has fully circulated in the bloodstream. Plasma radioactivity of each sample is then measured using a semi-automated computerized counter which calculates patient's PV by comparing the concentration of undiluted tracer prior to injection to the tracer concentration diluted over time due to transudation of albumin into extracellular space (Fig. 2). Total BV is determined based on the measured PV and patient's hematocrit [50]. Normal total BV is generally defined as measured volumes within $\pm 8\%$ (approximately 3 standard deviations) of the expected normal for the patient, and red blood cell mass and PV as measured volumes within $\pm 10\%$ of expected normal. Mild to moderate total BV expansion is defined as $>8\%$ ($>10\%$ for red blood cell mass and PV) to $<25\%$, and severe expansion as $\geq 25\%$ of the normal volume [51]. In a cohort of 177 patients hospitalized for HF (mixed ejection fraction), decongestion strategy guided by admission BVA was associated with lower 30-day mortality and re-admission rates compared to propensity-matched controls (2.0 vs. 11.1% and 12.2 vs. 27.7%, respectively; $p < 0.001$) [52]. In another study including 26 HF patients, 24 of whom were hypervolemic at hospital admission (BV +39%), there was only marginal decrease (+30%) in BV at discharge despite large reductions in body weight (-6.9 kg) [53]. This observation is in line with previously reported data raising concerns about inadequate decongestion when using conventional monitoring tools.

The utility of BVA is generally limited in critically ill patients with hemodynamic instability or those undergoing acute volume transitions as the analysis presumes steady-state conditions. Nevertheless, carefully selected patients at increased risk for FO may benefit from this technique. In a clinical trial including 100 critically ill surgical patients, Yu et al. [54] have demonstrated that BVA-guided fluid management strategy is associated with improved outcome compared to control group managed according to pulmonary artery catheter parameters (mortality rate 8 vs. 24%, $p = 0.03$). As mentioned, BVA can provide information about albumin transudation rate based on the dilution of tracer over time. In an interesting case series including 4 critically ill patients with COVID-19, Bakker et al. [55] leveraged this characteristic

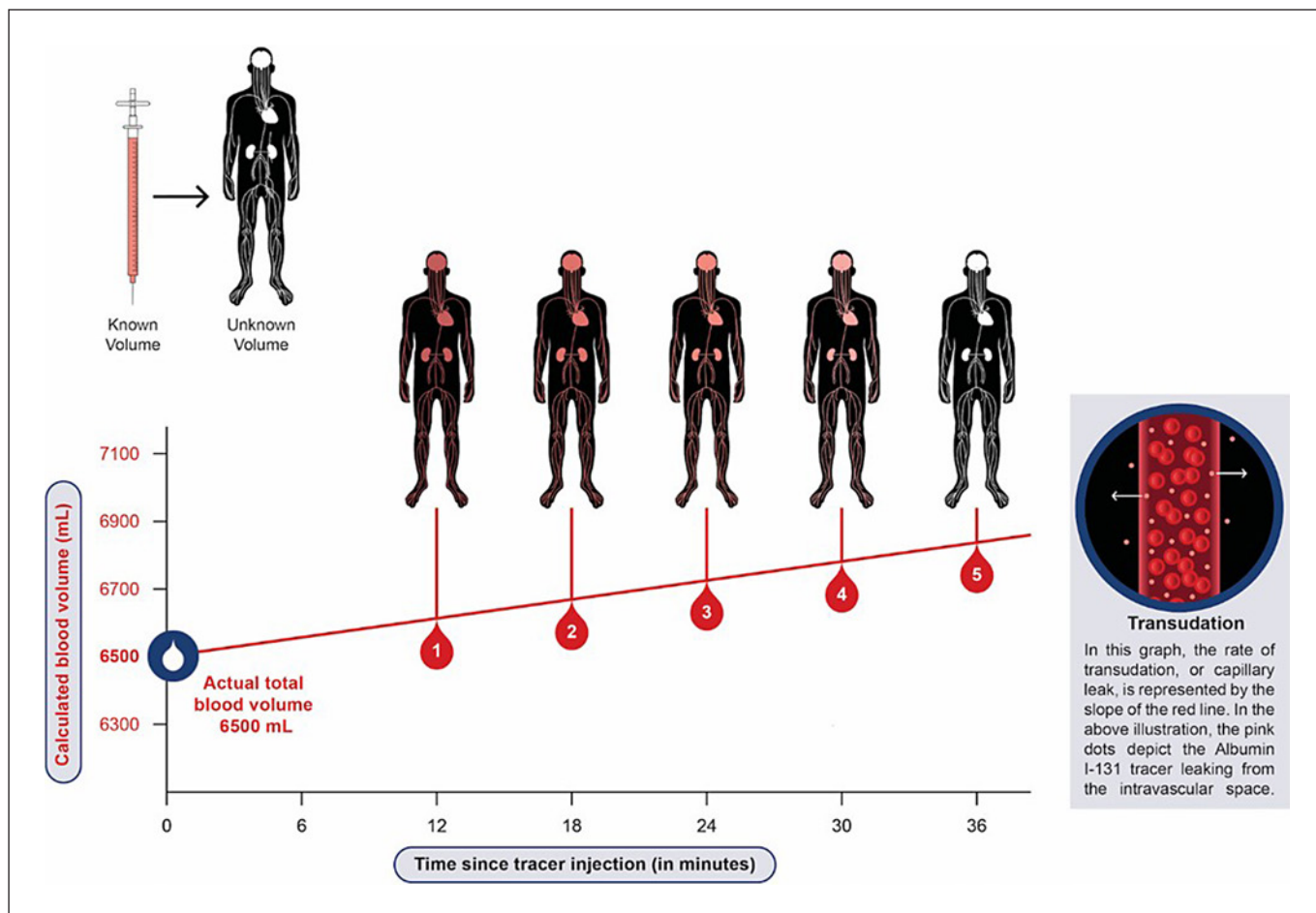


Fig. 2. Principle of blood volume assessment: a dose of albumin I-131 tracer is injected intravenously. Once the tracer has fully circulated in the bloodstream, a series of small blood samples are drawn. The blood volume analyzer automatically calculates patient's blood volume by comparing the concentration of undiluted tracer prior to injection to the tracer concentration diluted in the patient blood samples. The human figures represent sequential calculated blood volumes at the recommended intervals for drawing blood samples after tracer injection. As the tracer transudates

from the intravascular to the extravascular space (depicted as the pink dots moving outside the red vein), its quantity decreases intravascularly implying a higher dilution factor and therefore higher blood volume. Red line represents the regression calculation of the analyzed draws to time 0 or time of injection, which indicates the level of true total intravascular blood volume. The red line is also a measure of albumin transudation, a measure of capillary permeability. Figure adapted from <https://www.daxor.com/how-bva-100-works/> with kind permission of Daxor Corporation.

to assess capillary permeability. Larger studies are needed to understand how this information can be utilized to titrate therapy.

Chest Radiography

Chest radiography is the most common modality used in the diagnosis of acute HF and FO. Key findings include central vascular congestion, interstitial edema with Kerley B-lines, cardiomegaly, and pleural effusions. It may also

reveal alternative causes of dyspnea, coexisting thoracic diseases, and valvular or pericardial calcification. Notably, a normal chest radiograph should not be used to exclude the diagnosis of HF as up to 20% of the patients presenting with acute HF do not demonstrate any radiographic abnormalities. A supine chest radiograph further limits the diagnostic utility [56, 57]. Having said that, residual pulmonary congestion at hospital discharge assessed by radiographic scoring has shown to predict worse outcome outperforming physical assessment, echocardiographic parameters, and BNP [58]. In our practice, we prefer lung

ultrasonography over chest radiographs to diagnose and monitor congestion. In addition to being radiation-free, ultrasound has better diagnostic accuracy for the detection of cardiogenic pulmonary edema. For instance, in a recent meta-analysis, sensitivity and specificity for lung ultrasound compared to chest radiography were 91.8% versus 76.5% and 92.3% versus 87%, respectively [59].

Bioimpedance Analysis

Bioimpedance analysis (BIA) involves application of alternating current to the body and measuring changes in impedance/resistance as it relates to changes in volume. It can be used to quantify total body water, intracellular water, extracellular water, protein, and fat levels. BIA has been successfully employed in the assessment of peri-operative fluid depletion, measuring body composition in chronic HF, liver disease, and kidney disease [60–63]. In patients undergoing maintenance dialysis, there are conflicting data on whether routine BIA-guided dry weight adjustment portends favorable outcomes. For example, a single-center study showed BIA-guided ultrafiltration strategy confers mortality benefit compared to routine care (hazard ratio [HR] 0.1, $p = 0.03$) [64]; these findings were not replicated in other clinical trials in hemodialysis as well as peritoneal dialysis patients though there was a suggestion toward better FO control [65–67]. It might still benefit a selected subset of these patients with difficult to manage fluid status as FO negatively impacts quality of life [68]. In patients with acute HF, BIA reliably reflects changes in hydration status, correlates with echocardiographic parameters, natriuretic peptide levels, and predicts hospital length of stay. However, BIA-guided decongestive therapy has not shown to be superior compared to standard care with respect to outcome [69–72]. In critically ill patients, the accuracy of BIA as a measure of hydration status remains unclear at this time [73]. A key limitation of BIA is its inability to detect the location of extracellular volume expansion (e.g., pleural effusion vs. pulmonary edema vs. ascites vs. venous congestion). Further, misinterpretation of the results can occur if the patient's body position is not correct, or electrodes cannot be appropriately placed due to chest hair, diaphoresis, or skin lesions.

Point-Of-Care Ultrasonography

Point-of-care ultrasonography (POCUS) is a limited bedside ultrasound examination performed by the clinician to answer focused questions to confirm a diagnosis

or narrow the differential or guide a procedure. Over the past several years, multi-organ POCUS has evolved as an adjunct to physical examination in specialties such as emergency medicine, critical care, and nephrology [74, 75]. We previously proposed the *pump-pipes-leaks* approach to conduct a goal-directed POCUS-assisted hemodynamic evaluation in patients with HF and FO [76]. Pump represents focused cardiac ultrasound (FoCUS), pipes represent IVC ultrasound and Doppler assessment of venous congestion, and leaks signify extravascular lung and abdominal fluid. This allows assessment of both forward flow and effects of elevated cardiac filling pressures.

Focused Cardiac Ultrasound

In patients presenting with symptoms and signs of FO, a quick subjective assessment or “eyeballing” of the left ventricular (LV) size and motion provides a qualitative estimate of EF, which is reasonably accurate when performed by noncardiologists with short training [77]. In addition, presence or absence of pericardial effusion, gross valvular dysfunction, and chamber enlargement can be evaluated. Volume overload and acute pressure overload are associated with right ventricular (RV) enlargement and interventricular septal flattening in diastole (leading to a D-shaped LV assessed in the parasternal short axis cardiac view), whereas chronic pressure overload causes flattening in both systole and diastole [78, 79]. RV enlargement is often associated with functional tricuspid regurgitation, which further exacerbates RV overload at end-diastole as well as causes increased right atrial pressure (RAP) and central venous congestion [80]. IVC ultrasound can be used to estimate RAP. Figure 3 shows FoCUS images obtained from a patient who presented with HF exacerbation and FO. There was near-complete resolution of the septal flattening and tricuspid regurgitation after approximately 14 L fluid removal. Users trained in Doppler applications can assess stroke volume at the bedside by measuring LV outflow tract velocity time integral. This helps get an idea of the cardiac index and also evaluate fluid responsiveness in selected patients, potentially avoiding iatrogenic FO [76]. Furthermore, ability to perform Doppler-enhanced FoCUS allows assessment of LV filling pressures, which can be used to titrate diuretic therapy in the outpatient setting. For example, in a study including 1,135 patients with HF with reduced ejection fraction, the group in which management was guided by LV filling pressures and BNP level had a lower incidence of death (HR 0.45, $p < 0.0001$), and death or worsening renal function (HR 0.49, $p <$

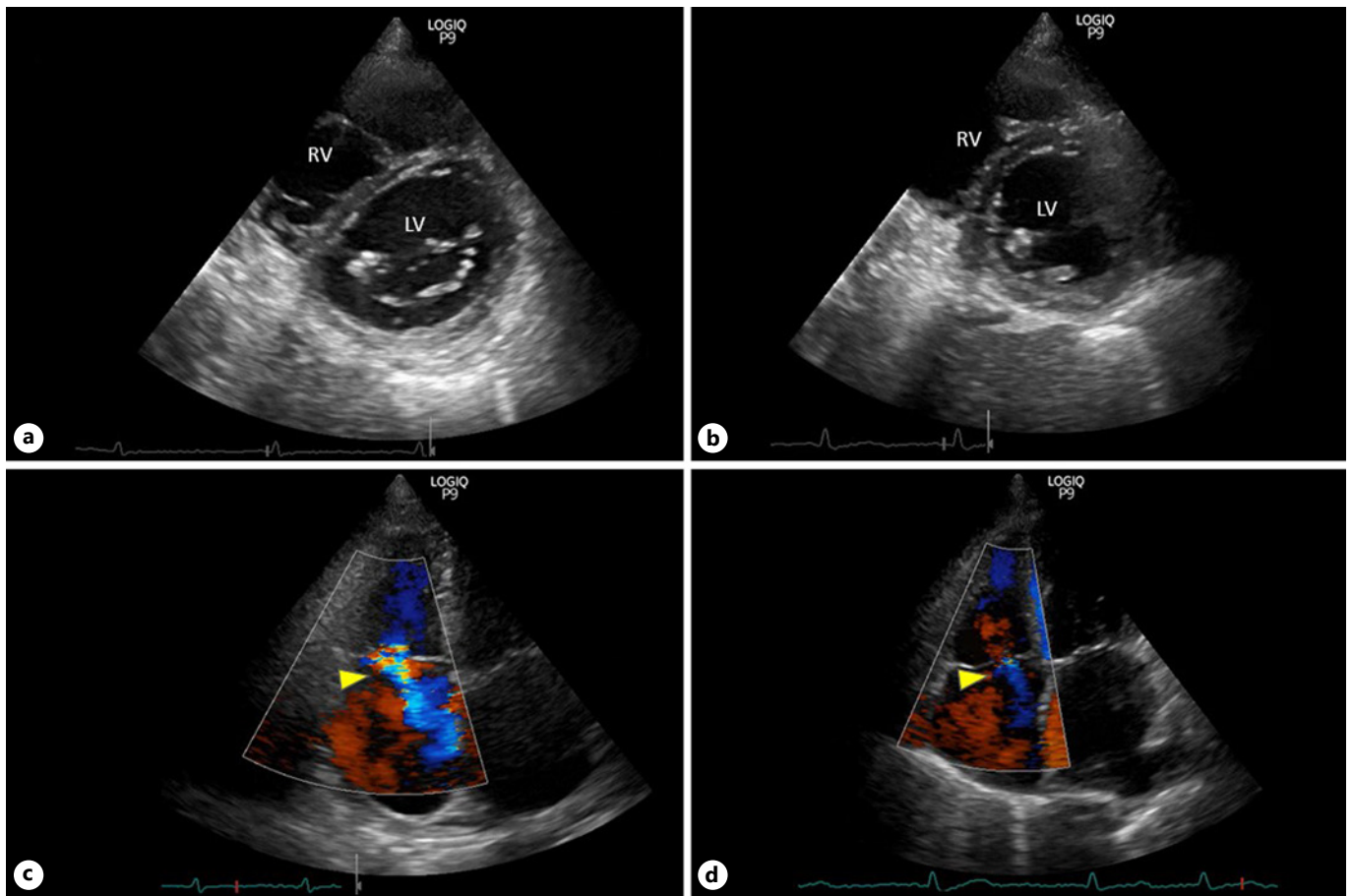


Fig. 3. Cardiac ultrasound images obtained from a patient with heart failure exacerbation: at presentation, diastolic interventricular septal flattening is seen on the parasternal long axis view (**a**), qualitatively moderate to severe tricuspid regurgitation [arrow-

head] on the apical 4-chamber view (**c**); images at hospital discharge (**b-d**) demonstrate near-complete resolution of these abnormalities. RV, right ventricle; LV, left ventricle.

0.0001) compared to standard care group over a median follow-up of 37.4 months [81]. In critically ill patients, the diagnostic utility of FoCUS is well established, particularly in the context of undifferentiated hypotension and acute respiratory failure [82–85]. With respect to prognostication, echocardiographic markers of both LV and RV dysfunction have shown to be associated with increased mortality in these patients [86, 87]. Currently, there are no randomized controlled trials that have examined the effect of FoCUS on improving outcomes in critical illness. It is unlikely that such a trial will ever be performed owing to difficulty of defining outcome variables beyond mortality, the difficulty of recruiting ICU teams with clinical equipoise, and developing standardized treatment protocols based on FoCUS findings in heterogeneous groups [82].

IVC Ultrasound

IVC size and collapsibility are used to estimate RAP and are standard components of comprehensive echocardiography. However, the correlation between IVC parameters and right heart catheterization-derived RAP is modest at best [88–90] and not valid in mechanically ventilated patients [91]. In addition, IVC POCUS is subject to numerous technical pitfalls limiting its practical utility, especially when interpreted in isolation [24]. Having said that, IVC is a good indicator of *fluid tolerance* as a plethoric IVC almost always indicates elevated RAP in patients with high pretest probability of FO; in other words, such patients have elevated right-sided filling pressures and are *intolerant* to IVF administration. In patients with HF, an elevated IVC diameter has shown to be associated with adverse outcomes. For example, in a

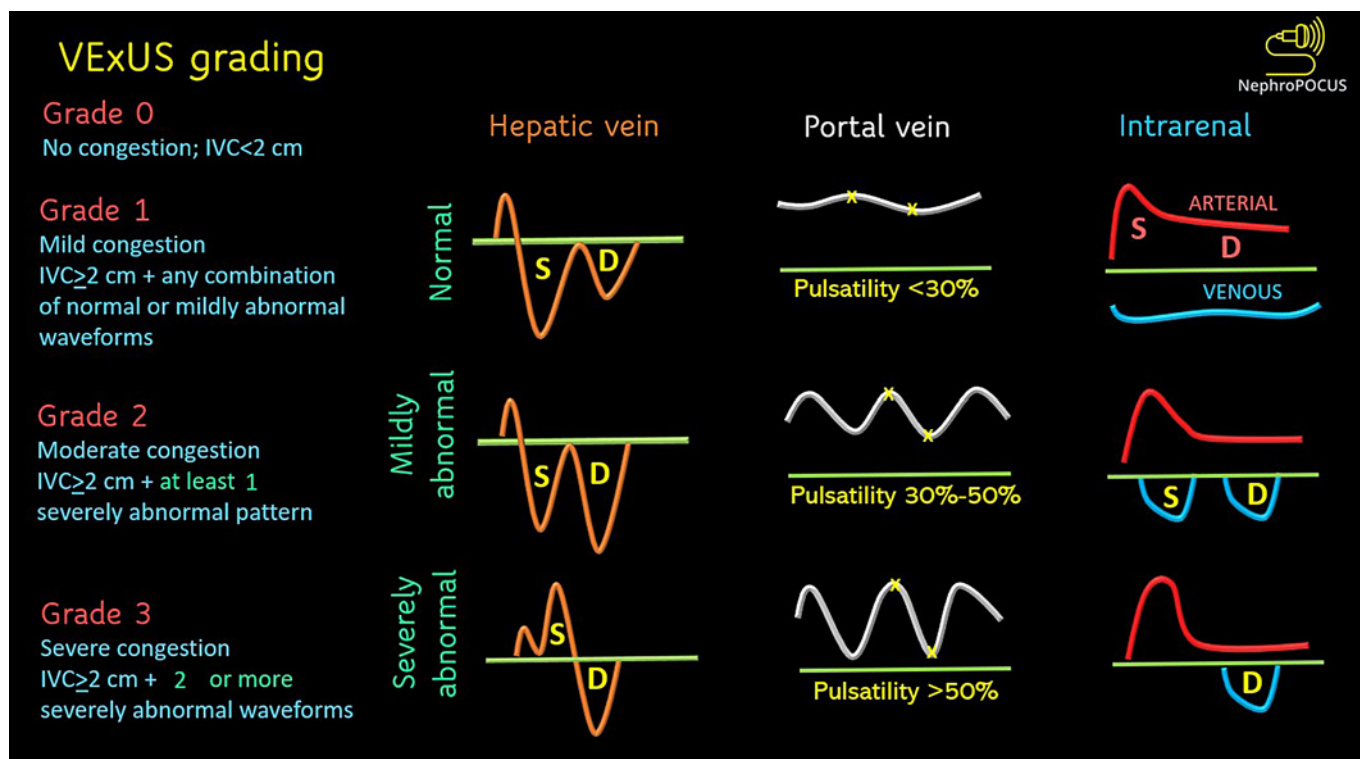


Fig. 4. Venous excess ultrasound (VExUS) grading: when the diameter of IVC is >2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (D) wave, but still below the baseline; it is considered severely abnormal when the S-wave is reversed. Portal vein Doppler

is considered mildly abnormal when the pulsatility is 30–50%, and severely abnormal when it is $\geq 50\%$. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S, D components, and severely abnormal when it is monophasic with D-only pattern. Figure adapted from NephroPOCUS.com with permission.

study involving 80 patients hospitalized for acute HF, an admission IVC diameter ≥ 1.9 cm was associated with a higher mortality at 90 days (25.4 vs. 3.4%; $p = 0.009$) and 180 days (29.3 vs. 3.4%; $p = 0.003$) [92]. Similarly, in a large cohort of HF patients ($N = 355$) managed in the ambulatory care clinic, every 0.5 cm increase in the IVC diameter was associated with a 38% increase in risk of HF admission (risk ratio [RR] 1.38, $p < 0.01$). The risk of HF admission increased proportionately in those with IVC diameter 2–2.49 cm (RR 1.79, $p < 0.01$) versus ≥ 2.5 cm (RR 2.39, $p < 0.01$) compared to patients with diameter < 2 cm [93].

Venous Congestion Assessment by Doppler Ultrasound

Doppler evaluation of the systemic veins allows us to gauge the downstream effects of elevated RAP. This is important as the organ perfusion depends on both in-flow and outflow pressures; increase in the outflow

pressure (RAP) impairs perfusion and leads to organ dysfunction (e.g., AKI). A protocol to quantify systemic venous congestion called venous excess ultrasound (VExUS) has been recently validated in cardiac surgery patients and is rapidly gaining acceptance in various clinical settings including HF and critical illness [94]. In a nutshell, VExUS involves assessing flow patterns in hepatic, portal, and renal parenchymal veins and assigning a score based on the severity of flow alteration. Figure 4 depicts the VExUS scoring system, and Figure 5 illustrates waveforms obtained from a patient with severe congestion. Notably, neither IVC nor components of VExUS can differentiate between pressure overload (e.g., pulmonary hypertension) and volume overload, and hence, the findings must be interpreted in the appropriate clinical context. Regardless of the cause, a high VExUS score still indicates end organ congestion. In the original study [94], presence of severe flow ab-

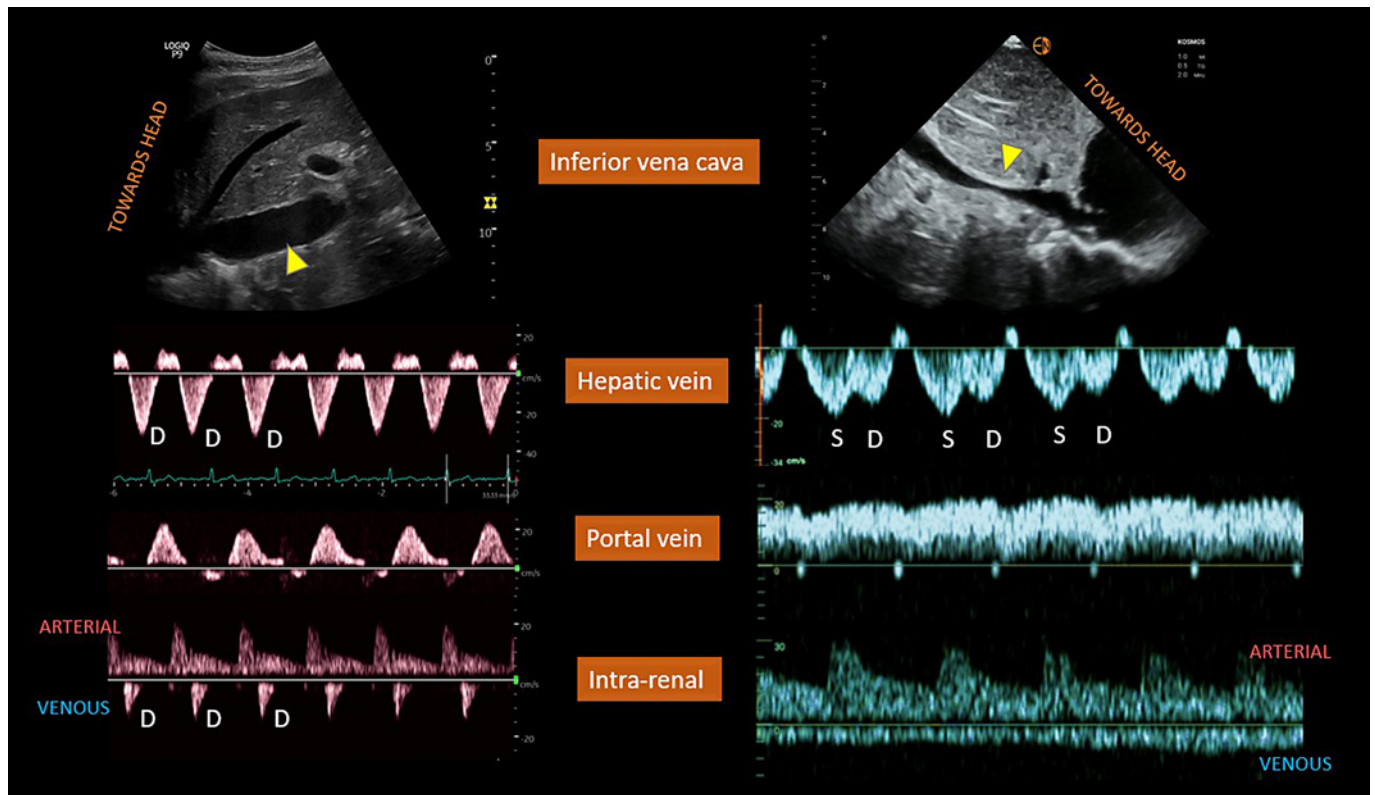


Fig. 5. Left panel: Plethoric IVC (arrowhead), diastolic (D)-only pattern on hepatic vein Doppler, pulsatile portal vein Doppler, and D-only or monophasic renal parenchymal vein Doppler obtained from a patient with fluid overload and severe venous congestion; right panel: normal-appearing IVC with <2 cm diameter (arrowhead) and normal venous waveforms.

normalities in two or more of the abovementioned veins together with a dilated IVC (≥ 2 cm) has shown to predict the risk of AKI (HR 3.69, $p = 0.001$), outperforming isolated central venous pressure measurement. Several other studies demonstrated prognostic significance of individual components of VExUS. For example, in another cardiac surgery cohort, portal vein pulsatility and altered intra-renal venous flow were associated with AKI (HR 2.09, $p = 0.02$, and HR 2.81, $p = 0.003$, respectively) [95]. A prospective observational study evaluated the prognostic utility of VExUS in 114 patients admitted to medical ICU [96]; abnormal hepatic vein Doppler flow has shown to predict 30-day risk of kidney events with an odds ratio of 4; however, portal and renal parenchymal venous abnormalities did not share this association. The heterogeneous nature of AKI in an unselected cohort of critically ill patients could have contributed to the discrepancy. In the context of HF, flow alterations in renal parenchymal veins have shown to confer worse prognosis in terms of car-

diovascular morbidity and death [97, 98]. A key advantage of these Doppler waveforms is that they are dynamic and allow monitoring the response to decongestive therapy in real time [99–105]. Clinical trials are in progress to study the effect of waveform-guided therapy on patient outcomes [24].

Lung POCUS

Lung POCUS can detect extravascular lung water before the onset of symptoms, even outperforming chest radiography in diagnosing cardiogenic pulmonary edema [59, 106]. In normal state, the *lung tissue* is not visualized on ultrasound as the underlying air scatters the ultrasound beam. Instead, a bright shimmering pleural line followed by equidistant hyperechoic horizontal artifacts called the A-lines is seen. B-lines, which are vertical hyperechoic artifacts, occur when the air content in the lung decreases due to interstitial thickening (typically from fluid). The number of B-lines correlates with the degree of pulmonary edema and dynamically re-

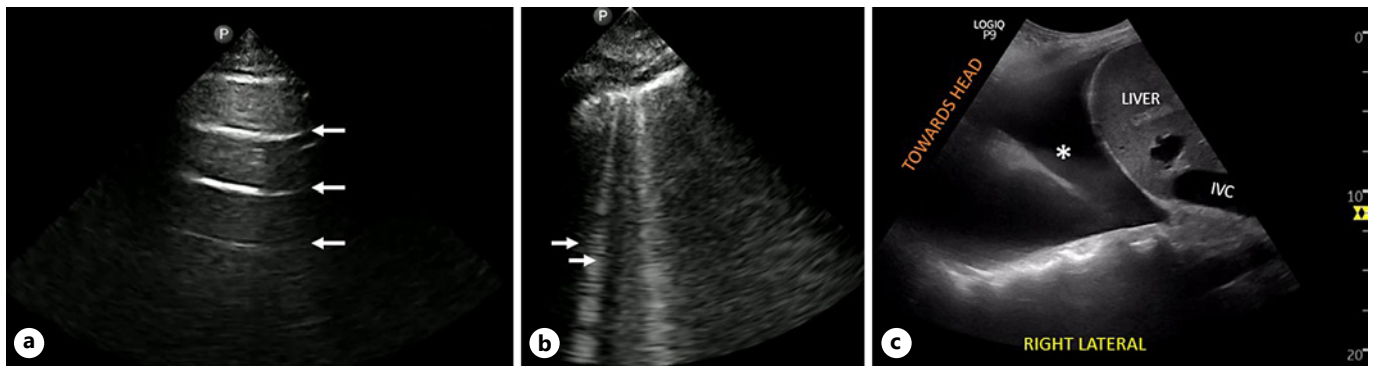


Fig. 6. Common lung ultrasound findings: A-lines (arrows; **a**); B-lines (arrows; **b**); right pleural effusion (asterisk; **c**). IVC, inferior vena cava.

duces with decongestive therapy [107]. Caution must be exercised as B-lines are not specific to cardiogenic pulmonary edema and can be seen in conditions such as acute respiratory distress syndrome, pneumonia, lung fibrosis, and contusion. A pleural effusion appears as an anechoic area above the diaphragm, around the atelectatic lung (Fig. 6). Prognostic significance of lung ultrasound-detected pulmonary congestion has been well established in multiple clinical settings including HF, hemodialysis, and critical illness [108]. For example, in a cohort of 185 HF patients who underwent lung POCUS in the outpatient clinic, those who had ≥ 3 B-lines on an 8-zone scanning protocol had 4-fold higher risk of the primary outcome, i.e., a composite of HF hospitalization or all-cause mortality (adjusted HR 4.08, $p < 0.001$) [109]. Notably, auscultation was normal in 81% of these patients, highlighting the poor sensitivity of conventional physical examination. Likewise, in a cohort of 349 patients admitted for acute HF, the risk of HF hospitalization or all-cause mortality was significantly higher in patients with a greater number of B-lines at discharge (HR 3.3 at 60 days, $p = 0.002$; 2.94 at 90 days, $p = 0.003$; 2.01 at 180 days, $p = 0.021$) [110]. In patients with end-stage kidney disease undergoing hemodialysis, those with severe congestion, defined as >60 B-lines on a 28-zone lung POCUS, had a 4.2-fold risk of death and 3.2-fold risk of cardiac events adjusted for NYHA class and other risk factors [111]. While lung POCUS-guided therapy has not shown to have mortality benefit, favorable outcomes have been demonstrated in terms of reduced hospital admissions in HF patients [112, 113]; improved ambulatory blood pressure and LV filling pressures in hemodialysis patients [114, 115]; and improved lung aeration scores in critically ill patients on mechanical ventilation [116].

Other POCUS Applications

In patients with FO, POCUS helps identify ascites, bowel wall edema, and ileus [76]. POCUS can also aid in the assessment of JVP in cases where the vein is difficult to visualize. JVP can be estimated by measuring the height of the collapse point (analogous to highest point of venous pulsation in the inspection method) or change in the vein diameter with respiration/head positioning or assessing change in the cross-sectional area with Valsalva maneuver in spontaneously breathing patients [117, 118]. Jugular vein POCUS has shown to correlate well with congestion parameters as well as mortality in patients with HF [119, 120]. However, it is prone to misinterpretation due to inadvertent excess transducer pressure, inappropriate patient positioning, restricted access to the neck because of the presence of catheters, tracheostomy collars, braces, etc. Requirement of additional instruments such as a ruler and a card to accurately measure the height of the collapse point is another limitation, especially in the acute care settings [121, 122].

Remote Pulmonary Pressure Monitoring

Wireless implantable hemodynamic monitoring systems (e.g., CardioMEMS HF System [Abbott Medical, Inc., Abbott Park, IL, USA]) allow remote monitoring of the pulmonary artery pressures and titrate decongestive therapy. In a prospective multi-center study, ambulatory patients managed using CardioMEMS had a 39% reduction in HF-related hospitalization compared with the control group (HR 0.64, $p < 0.0001$) during a mean follow-up of 15 months [123]. Due to its partially invasive nature (right heart catheterization is needed to implant the sensor) and the need for trained personnel to manage therapy based on the readings, patients who might benefit from this modality must be carefully selected. Fur-

thermore, pressure-based assessment of congestion in ambulatory HF patients does not accurately represent intravascular volume and diuretic titration may not always be the appropriate therapeutic choice [124].

Conclusions and Future Directions

It is well recognized that FO has detrimental effects on organ function and portends worse patient outcomes. While several bedside tools and techniques are available for objective assessment of fluid status, each suffers from inherent limitations. Physicians must be aware of these limitations and adopt a multiparametric approach to formulate individualized management plan for their patients. Such an approach eventually needs standardization, independent validation with a randomized controlled trial design to demonstrate precision, and reproducibility of the findings as well as impact on the measurable outcomes.

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Author Contributions

Abhilash Koratala drafted the initial version of the manuscript. Amir Kazory and Claudio Ronco reviewed and revised the manuscript for critical intellectual content. Abhilash Koratala, Claudio Ronco, and Amir Kazory have approved the final version for submission.

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