Review

Is modern medicine in need of an overhydration marker in kidney failure? The accuracy of available fluid overload markers and the potential of the new ones.

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Review

Is Modern Medicine in Need of An Overhydration Marker in Kidney Failure? The Accuracy of Available Fluid Overload Markers and The Potential of The New Ones

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Abstract: Overhydration (OH) is a prevalent medical problem occuring in patients with kidney failure, but a specific marker has still not been found. Currently, clinicians employ techniques such as bioimpedance spectroscopy (BIS), ultrasound (US) markers of fluid overload or markers of heart and kidney function such as NT-pro-BNP, GFR or creatinine levels. New serum markers, including but not limited to Ca-125, Galectin-3 (Gal-3), Adrenomedullin (AMD) and Urocortin-2 (UCN-2), are presently under research, displaying promising results. The necessity to ascertain a more precise marker of overhydration is urgent mainly because physical examination is exceptionally imprecise. Signs and symptoms of fluid overload, like edema or gradual increase of body mass, are not always present, notably in patients with chronic kidney disease. This review paper summarizes actual knowledge of a patient's hydration status estimation, focusing specifically on kidney diseases.

Keywords: Fluid status 1; overhydration 2; hydration status 3; renal failure 4 ; kidney failure 5; heart failure 6; Ca-125 7; NT-pro-BNP 8 ; VEXUS 9 ; BIS 10

1. Introduction

Fluid state assessment is one of the most crucial measurements which doctors perform in patients with kidney disease. Total body water (TBW) consists approximately 50% to 60% of an adult's total body weight and it is over 73% of a lean body mass [1]. The hydration status varies depending on muscle mass, fat body mass, electrolyte balance or physiological states like pregnancy. Naturally, the percentage of TBW tends to decrease with advancing age, due to decrease in muscle mass and metabolism. Fluid overload is recognized as a known risk factor of hypertension, heart failure (HF) and increased mortality in patients with kidney failure [1–3]. A study performed by Zoccali et al. demonstrated that overhydrated patients with end stage kidney disease (ESKD) have a 62% higher risk of mortality compared to non-overhydrated ones [2] . Similarly, a study by Hung et al. revealed that among a research group of 338 patients with chronic kidney disease (CKD) only 48% were euvolemic [4]. Zoccali, Hung et al. were not the only researchers who acknowledged and described the dependency between normohydration and long-term survival in patients with kidney diseases [2–20]. Taking this into consideration, it presents a significant challenge for modern physicians to precisely assess and treat the patients overhydration (OH), as it can lead to irreversible damage to the organism and consequently to death [7,11]. Clinical symptoms of OH may include distal and proximal swelling, dyspnoea, hypertension, jugular venous pressure assessment. During the physical examination, which includes auscultation, palpation, percussion, doctors can also hear crackles in the lungs, particularly in the lower parts. In addition, the hepato-jugular reflux might be observed when the pressure applied to the liver causes a sustained rise in jugular blood pressure, which can be observed as an under-skin pulsation. The symptoms may be present not only in OH caused by kidney failure, but also in heart or liver diseases, infections and cancerogenesis. A presence or absence of

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clinical symptoms does not exclude OH due to kidney diseases. One of the first symptoms of OH is presence of pitting pedal oedema, but this symptom can also be caused by stasis or excessive vascular permeability [18] . A cross-sectional study of hemodialysis patients established that it correlates with body mass index but does not reflect volume status [18]. Individuals who suffer from CKD may also develop HF, hepatic failure, and pneumonia, which additionally influences volume status. This makes the physical examination extremely difficult to interpret, as visible symptoms can be caused by factors other than the fluid status. Patients' diagnosis should be confirmed with use of additional available clinical tests, for example estimation of the dry body weight, which according to a definition proposed by Daugirdas et al. includes: shortest postdialysis recovery time, least intradialytic hypotension/symptoms, longest patient survival, fewest cardiovascular/cerebrovascular events, fewest hospitalizations, hypovolemia-related access thromboses and postdialysis falls [21]. Doctors should have a holistic approach to OH problem and combine various available methods to establish the patient's hydration status and manage between methods depending on the individual's needs, particularly in the case of cardiorenal syndrome and HF [11]. Present-day medicine encompasses assessing the dry body weight through blood pressure, signs and symptoms of OH, blood volume monitoring and bedside ultrasound [22]. The gold standard of testing body composition and body water distribution in healthy, non-overweight population is called bioimpedance spectroscopy (BIS). It allows measuring intracellular and extracellular water, aiding in the precise determination of cell mass [23]. This method is non-invasive as it only requires placement of electrodes on patients' bodies to measure tissue conductivity, hence the water balance [23]. The electrical resistance of external cell water increases during OH with increasing cell mass and size, and consequently the length of the pathway around the cells. Those advantages made BIS also a tool applied in dialysis patients. However Moissl et al. indicated that BIS calculations should be revised to be more precise in an overhydrated, dialysed population. [24]. Among patients who undergo dialysis, results vary according to the researcher and the device used [23]. It has also limited clinical application in certain conditions, not only connected to kidney diseases. This method cannot estimate the accurate water cell ratio in pregnant women with multiple volume changes over time. Its usefulness in patients after limb amputations or with implanted electronic devices like a pacemaker is also diminished. While effective on healthy individuals, this approach exhibits variability in results when applied to clinical populations [11,23]. BIS seems to be a gold standard in theory, but in practice not all clinics or dialysis stations possess the necessary equipment. This sophisticated and modern tool is relatively expensive, rendering it financially unfeasible for some public health institutions. Nephrologists also use laboratory markers to help determine the hydration state, such as NT-pro-BNP or BNP. The primary difference between two markers is that BNP is a biologically active marker, whereas NT-pro-BNP is not. The inactive pro peptide is more stable in the bloodstream, and it correlates strongly with heart failure, cardiovascular congestion and death [22]. Adrenomedullin and its pro-adrenomedullin derivative (MR-pro-AMD), which are markers of endothelial injury, are being actively studied mainly in populations with HF, sepsis, or kidney failure. Both tend to correlate with clinical state and available indirect markers of OH like NT-pro-BNP. Gal-3 appears to be more responsive to the kidney failure and mortality rate than OH itself but shows a precise correlation during the clinical and pre-clinical studies as an organ failure indicator. Ucn-2 is a protein sensitive to vasodilatation due to an increase in fluid volume, but it gives diverse results when considered as a strict OH marker. Another new and promising marker is Ca-125, which is now being extensively studied by cardiologists in patients with heart failure. This marker tends to increase with OH status but needs further study.

Volume status can also be assessed with imaging methods. POCUS (point-of care ultrasonography) allows to observe the signs of OH, such as the presence of fluid in pleura or peritoneum, higher diameter of the jugular vein, IVC (inferior vena cava), abnormal flow through the hepatic vein, portal vein or renal vein and estimation of pressure within these structures [25]. A specific protocol called the Venous Access Ultrasound Score (VEXUS) has also been developed and validated.

The holistic approach in hydration estimation of the hydration status in CKD patients is illustrated in the Figure 1.1

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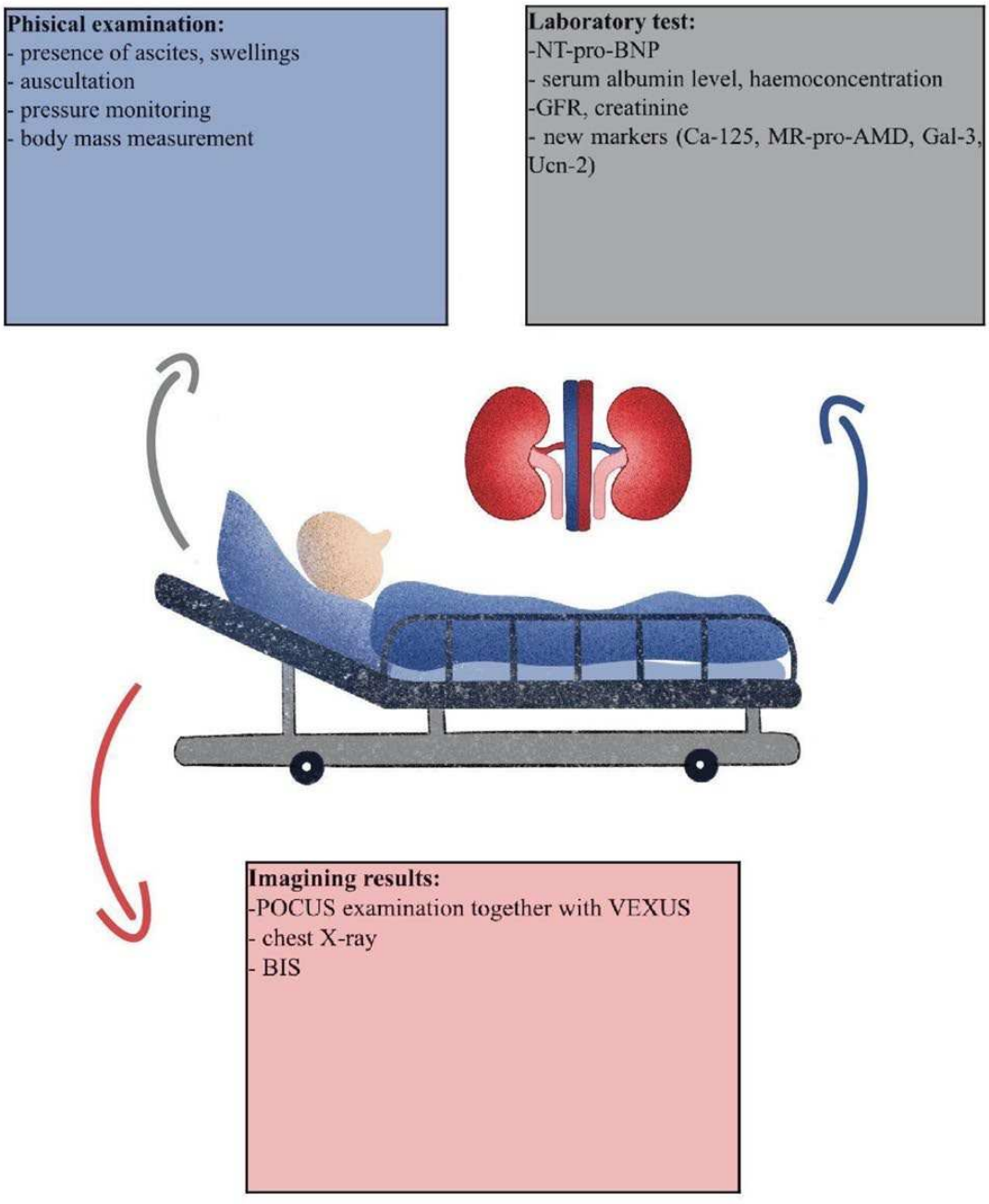

Figure 1.1- the combination of available and future methods of OH status diagnosis in CKD patients.

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During the brief research in both literature and clinical work, we assume that there is a lack of a precise hydration status marker, but it is highly required to improve the available methods of treatment.

2. Materials and Methods

The main aim of this metareview is to determine whether modern medicine is in need of a new overhydration marker. We used the SPIDER method identifying sample and phenomenon of interest as an overhydrated CKD population and due to scarcity of data including studies of all design and research type and not evaluating them.

We undertook a systematic search through the PubMed database from inception to November 10, 2022. We searched both with individual keywords with all subheadings included. Individual keywords used were "overhydration renal disease", "overhydration NT-pro BNP", "overhydration creatinine", "overhydration dialysis", "overhydration bioimpedance", "bioimpedance renal disease", "renal failure Ca-125", "VEXUS", "POCUS nephrology", "Adrenomedullin", "pro-ADM dialysis" "Galectin-3 renal", "Ucn-2 renal". The results were merged with duplicates discarded. Remaining articles were screened for relevance (based on their title, abstract, or full text). Articles were included only if they were clearly related to other subject matters or were only published in English.

3. Results

Of the 1480 identified in PubMed records, 991 were screened, 39 were retrieved and assessed for eligibility, and 33 were finally included in the review (25 original studies and 8 reviews/commentaries). The entire selection process is illustrated in Figure 1**.** The main features of the original articles on the topic under study are summarized in Tables 1 and 2. We identified 1 experimental study.

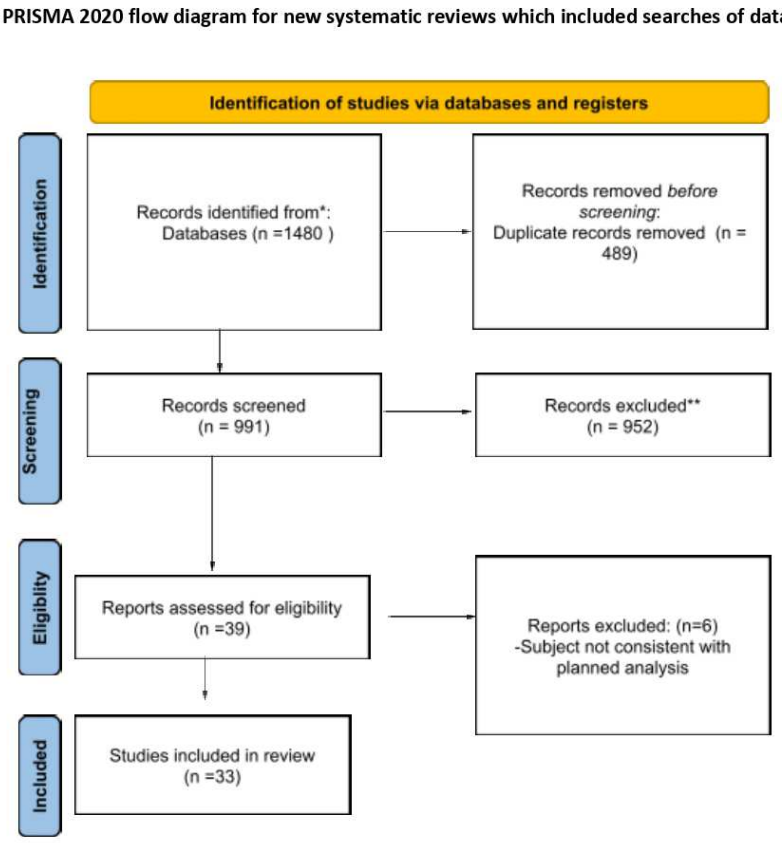

Figure 1. Research strategy.

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Table 1. Available methods of estimation of the volume status.

Name of the test	Includes kidney function?	Includes water balance?	Clinical application	Limitation
BIS	No	Yes	Content of ICW and ECW	Not all clinical conditions
US	No	Yes	IVC diameter, VEXUS protocol, IJV?.	Not all structures are always available during the test. Depends on doctors' experience
NT-pro-BNP	No	No	Correlation with OH consequences like heart failure and inflammation process.	Neither kidney nor OH direct marker
Ca-125	No	Yes	Cancer marker, research among the usage in HF and CKD	Novel approach, needs further research
ADM/ MR-pro-ADM	No	Yes	Marker of vasodilatation and vessel injury due to fluid overload	Does not correlate in all studies with other available markers, needs further investigation
Gal-3	Yes	No	Marker of renal injury, inflammation and fibrogenesis	Does not correlate directly with OH, but with kidney function, needs further investigation
Ucn-2	No	No	Increases heart dynamic properties, stimulates diuresis and sodium excretion	Needs further investigation as mixed results are obtained

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Currently, as shown in Table 1, the best method of volume status assessment is to combine many methods together with the patient's examination. It is crucial to develop, investigate and combine all available methods and their correlations. Table 2 lists research papers that combine some of the methods mentioned in this article and their correlation with OH.

Table 2. Markers researched with correlation to hydration status.

Author	BIS	NT-pro-BNP	Ca-125	USG
Schork et al.[26]	+	+	N/M	N/M
Hung et al. [4]	+	+	N/M	N/M
Yilmaz et al. [51]	N/M	+	+	+
Wijayaratne et al. [45]	+	+	+	N/M
Guedes et al. [33]	+	N/M	N/M	+
Núñez-Marín et al. [47]	N/M	-	+	+ (vexus)
Beaubien-Souligny [16]	N/M	+	N/M	+
Beaubien-Souligny et al. [25]	N/M	+	N/M	+

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Vega et al. [5]	+	+	N/M	N/M

+ correlation found. - correlation not found. N/M- marker not mentioned in the paper. * -creatinine/albumin ratio.

4. Discussion

1. *Available markers*

As mentioned in Table 1, modern medicine can estimate volume status using a variety of the following methods.

2. *Gold standard: Bioimpedance spectroscopy (BIS)*

Bioimpedance spectroscopy is a useful non-invasive tool to distinguish between ECW (external cell water) and ICW (internal cell water). It only requires the placement of electrodes on the distal part of the body (ankle-wrist) to measure water conduction inside the body [23]. The difference between the two values measured by the Body Composition Monitor (BCM) can be defined as normo- or overhydration [4]. ECW is measured at very low frequencies because there is almost no conduction, whereas TBW is estimated at high frequencies when there is complete conduction across cell membranes [23]. The conducted electricity is not harmful to the patient and has no influence on further diagnosis or daily life. This is a modern gold standard to estimate the water balance in healthy individuals' bodies, however it is not without limitations, as not all clinical conditions are well calculated by the device and therefore difficult to interpret [11,23]. For instance, BIS gives mixed results in pregnant women, patients post-CABG procedure, with gastrointestinal diseases, kidney disorders, after limb amputations or in obese individuals [23]. Clinical cases cited above are characterized by alterations in body water distribution. Another BIS limitation is the assumption that the body shape is cylindrical with uniform cross-sectional areas, and this homogenous composition is again different in overweight people [23]. This tool is also quite expensive and not all healthcare facilities can afford to purchase it.

- BIS usage in CKD

Vega's et al. original paper showed that there is an association between OH status calculated by BIS and higher mortality in patients with CKD stages 4-5 who are not yet undergoing kidney replacement therapy. Kaplan-Mayer analysis confirmed higher mortality in patients with an excessive fluid overload [5]. A study performed by Hung et al in 2013 focused on the dependency between calculated OH and known risk factors for cardiac incidents in patients with CKD. This research showed that results obtained by BCM contributed to other risk factors of cardiac incidents, such as male sex, diabetes mellitus, high systolic blood pressure, previous cardiac incident and proteinuria [4]. However, there is a major limitation of this paper, as there is no data presented on patients diet and fluid intake [4].

BIS hydration status calculations may correlate with other OH tests available in the hospital setting. A study of 138 patients from Spain with CKD level between G3a-G4 revealed a positive correlation between OH status obtained by BIS and albuminuria, creatinine increase or dyslipidemia [19]. It appeared that OH patients had approximately a 4-fold higher probability of death, and that increase in urine volume reduced it significantly [19]. In a research study involving 179 non-dialysis CKD patients in all stages, OH measured by BCM correlated with urinary protease activity and progression of renal dysfunction, as well as with increases of NT-pro-BNP and systolic blood pressure [26]. The correlation was also true for other markers of renal malfunction like increase in creatinine, albuminuria and drop of eGFR [26]. Both creatinine and creatinine/albumin ratio has been used by the authors [4,5,16, 25,26,33,75,] as markers of OH, because these parameters correspond directly with a renal function. They are not ideal markers, but help to estimate the advancement of renal

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disease. However, even if it is easily available and used in renal diagnosis and dialyse maintenance, it does not reflect and corresponds directly with a hydration state [27,28].Progression towards ESKD correlates with higher OH status. This interaction was observed by Hung et al. in a nearly three-year study of patients with CKD stages 3-5. OH appeared to be a more important mortality risk factor than hypertension [10]. A rat model proved that fluid retention stimulated hypertension, albuminuria, expression of inflammation markers and atherosclerosis [10]. Some symptoms were alleviated after treatment with indapamide, which suggest that OH has a significant role in pathophysiological processes mentioned above. CKD patients' fluid status may also be affected by changes in haematocrit, and other clinical parameters [23,28]. Additionally, the assumption that the fat-free mass (FFM) is estimated at 73.2% does not apply to overweight patients, as they exhibit increased ECW:TBW ratio even after weight loss [23].

- BIS usage in dialyzed patients

Another research paper, which included patients on hemodialysis (HD), showed that OH calculated by BIS is an independent predictor of death in the dialysis population [13]. Unfortunately, patients with metallic joint prostheses, cardiac pacemakers, decompensated cirrhosis and limb amputations were excluded from the study due to BIS technique limitation. Optimisation of fluid status based on BIS calculations allows to reduce the fluid overload and leads to better control of hypertension according to Macheck et al. clinical study [30]. BCM (body composition monitor) results obtained before and after a HD were correlated with clinical indicators of OH, such as blood pressure and presence of abscesses. Unfortunately, again patients with pacemakers and large metallic implants were excluded from the study. In Kim et al. study on a group of 147 HD patients, OH correlated negatively with creatinine, serum albumin, white blood cells count, platelets, uric acid, potassium, phosphorus or triglycerides [31]. The rate of OH change per 1 kg before and after the HD was higher for ECW than ICW. After dialysis, there was a noticeable decrease in parameters like estimated protein mass, mineral mass and soft lean mass, while body fat increased. Segmental BIA analysis calculated that water loss was greater in the legs than in the arms, which may be caused by verticalization and consequent movement of the fluids according to the force of gravity. An important limitation of this study was the use of different equipment for the HD and control groups, as well as BIS for the research group was measured in the supine position and the control group in the upright one.

In a study by Siriopol et al on HD patients [9], BIS did not improve life expectancy or help maintain dry weight. In a systematic review and meta-analysis by Covic et al. on 1312 CKD patients, BIS-based dialysis therapy did not reduce all-time mortality. Together with this observation, BIS had no effect on body change, but improved systolic blood pressure [32].

In a study performed on peritoneal dialysis (PD) patients, BIS water balance calculations correlated with the urine protein loss and higher creatinine, regardless of the duration of dialysis therapy [33]. Another study, which included 711 patients on peritoneal dialysis, found that volume of OH calculated by BCM and peritoneal protein clearance were independent predictors of all-cause mortality.

In a meta-analysis by Wang et al. among almost 105 000 patients who underwent both types of renal replacement therapy, one third had fluid overload detected by BIS [3]. The estimated risk factor for mortality and cardiovascular events was ECW/TBW >0.4 [3].

In a study by Park et al. of dialysis patients, BIS did not detect the difference between hydration status between CKD population and a control group of healthy individuals, although other indicators of OH increased [32].

Nevertheless, several clinical trials have been performed with use of BIS and gave an encouraging result for other patients -A study of COVID-19 patients showed that a higher OH estimation by BIS correlates with intensive care unit (ICU) hospitalizations mortality [35]. The correlation between both variables may be explained by the contribution of protein loss due to hypoalbuminemia and fluid accumulation [6].

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Serum markers

(a) NT-pro-BNP

N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a peptide hormone synthesized mainly by ventricular cardiomyocytes in response to stretch, e.g., during the increased cardiac filling pressure, and cleared by kidneys [36,37]. Elevated serum level of NT-pro-BNP is observed in HF and during cardiac ischemia, pulmonary embolism, cor pulmonale, hypertension, hyperthyroidism, Cushing syndrome, hyperaldosteronism, cirrhosis, subarachnoid hemorrhage, and kidney failure. This marker also varies by sex, age and has lower values in obese individuals. Its blood concentration can be affected by medications like corticosteroids, diuretics, ACE inhibitors or thyroid hormones. It has been shown that monitoring NT-pro-BNP changes over time is a powerful diagnostic indicator, as life expectancy seems to be prolonged when its concentration decreases [37]. NT-pro-BNP also increases and remains significantly higher in patients with accompanying CKD [37]. HF in patients with CKD is a dangerous clinical issue with insufficient treatment results. It results not only from volume overload, but also from the development of anemia. All aforementioned pathologies cause an increase in both left ventricular end-diastolic volume and mass, which eventually leads to HF [38]. The African American Study of Kidney Disease and Hypertension enrolled patients with CKD to find an association between the risk of cardiovascular incidence and NT-pro-BNP levels in the population. It appeared that individuals with an increased plasma level of NT-pro-BNP were more likely to have cardiovascular complications and this risk was particularly evident in patients with albuminuria [39]. Elevated NT-pro-BNP levels indicate an increased risk of cardiovascular events in HD population with no other signs of HF according to the study by Goto et al. This marker was an independent risk factor, as it showed no correlation with age, body mass index, blood pressure and heart rate [40]. Therefore, NT-pro-BNP, mainly used in cardiology, has attracted the attention of nephrologists. A large clinical study performed on older Chinese patients (above 60 years of age) with concomitant coronary artery disease and with or without CKD revealed that a decrease in GFR independently affected NT-pro-BNP. It predicted death with a cut-off value of 369.5 pg/mL in patients with preserved kidney function and a cut-off value of 2584.1 pg/mL in CKD ones [41]. Its clinical application has also been discovered by nephrologists, as it tends to correlate with other OH indicators. In a meta-analysis involving 4287 patients, Schaub et al. asked whether NT-pro-BNP has a different diagnostic and prognostic utility in patients with kidney dysfunction. The correlation between GFR and natriuretic peptide was found to be statistically significant and ranged from −0.21 to −0.58, which means that during the decline in renal function, NT-pro-BNP level increases [42]. Elevated serum level of the peptide in patients with kidney dysfunction compared to patients with normal NT-pro-BNP confers an increased risk of mortality when compared to healthy controls [42]. The increase in serum level in patients with kidney disease may be due to a decrease in the blood clearance ability, but it still correlates with higher mortality among patients. NT-pro-BNP seemed to predict mortality better in patients with CKD than in non-CKD patients. An independent relationship between eGFR and NT-pro-BNP was also observed in a study on 599 dyspnoeic patients with renal malfunction. Elevated NT-pro-BNP was the strongest risk factor for 60-days mortality and was acclaimed as a marker of chronic heart failure (CHF) independently of kidney function [43]. Similar results were obtained by DeFilippi et al. investigation and one-year mortality rates were 36.3% in patients with CKD and 19.0% without CKD, respectively [44]. NT-pro-BNP showed a similar result in dialysis and patients in a study by Park et al. Its level was significantly higher in patients with any type of dialysis treatment compared to the control group. NT-pro-BNP also correlated with AMD, even though BMC did not detect any differences in OH status between the control and treatment group [34]. NT-pro - BNP tends to increase in individuals with fluid excess during clinical studies on various methods of estimating hydration status [10,11,26,33,45,46]. It was elevated during the increase in protein clearance during peritoneal dialysis [33] associated with pleural effusion and IVC diameter [11,46], ECW/TBW ratio [10,26,45], but not with peripheral oedema [11,18]. It has been compared when assessing hydration status with Ca-125 and in some studies both markers were elevated with fluid excess [45] and in some cases only Ca-125 increased [30]. Núñez-Marín et al. noticed that Ca-125 but

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no NT-pro-BNP correlated with VEXUS indicators of OH in patients with HF [47]. NT-pro-BNP correlated in establishing OH by BIS in Vega et al. study, along with a decrease in serum albumin, an increase in CRP and proteinuria [5]. Fluid retention in patients with CKD calculated by BIS corresponded to an increase in NT-pro-BNP, as the difference in euvolemia vs hypervolemia serum levels was 4.7 times higher [10]. In a study by Schork et al, NT-pro-BNP levels also corresponded to OH calculated using BIS in patients with CKD [47].

(b) Ca-125

Carbohydrate antigen 125 (Ca-125) is a complex glycoprotein that is widely used in cancer diagnosis, especially ovarian cancer [49]. It is mainly synthesized by mesothelial cells in pericardium, peritoneum or pleura [49]. It is not known exactly why cells produce Ca-125, but it seems to be stimulated by inflammatory processes and mechanical injury [11]. Recently, it has emerged as a promising marker for congestive heart failure [49]. It increases with a decline in heart function according to New York Heart Association (NYHA) I/II to stage III or IV [11]. In a study conducted by Arik et al. among various cancer markers and their correlation with kidney failure, only Ca-125 and Ca 19.9 were found to be significant. No correlation was found with PSA, AFP, or CEA [50]. Ca-125 also correlates strongly with the diameter of IVC, as well as with the presence of fluid in pleural cavity and peripheral oedema [49]. This phenomenon was investigated by Yilmaz et al. in patients with end-stage kidney disease [51]. It correlated with the advancement of CKD, as well as with the level of NT-pro-BNP, C-reactive protein and with a larger left ventricular end-diastolic diameter. The group of patients with a normal level of Ca-125 had higher albumin and haemoglobin levels compared with the group with elevated Ca-125. Núñez-Marín et al. found no correlation between IVC and Ca-125, but in their study the carbohydrate antigen was independently associated with a congestive pattern of intrarenal venous flow [47]. This study also showed that not NT-pro-BNP, but Ca-125 correlates with Doppler signs of volume overload. Carbohydrate antigen 125 appeared to increase with NT-pro-BNP, 24h peritoneal dialysate creatinine to serum creatinine ratio, decrease in albumin level and ECW/TBW ratio in an analysis including 489 adult patients on peritoneal dialysis [45]. There was no correlation between the Ca-125 level and 24h urinary creatinine clearance or CRP [45]. The researchers postulate that the observed decrease in albumin level was due to a dilution effect rather than a massive loss or cachexia. Ca-125, despite being a cancer marker, has a good chance to become a fluid balance indicator. Results are very promising; however, correlations are not always cohesive, and more studies are needed.

(c) Adrenomedullin and proadrenomedullin

ADM is a peptide hormone synthesized by endothelial and vascular smooth muscle cells of organs like lungs, brain, kidneys, heart and adrenal medulla in a response to increase in fluid volume [48,52]. Its function is vasodilatation, preservation of endothelial integrity and inhibition of a renin-angiotensin-aldosterone system (protects heart and kidneys from damage induced by angiotensin II) [52]. It tends to decrease during the use of diuretics, blockers of the RAA system, leading to the assumption that fluid overload activates the sympathetic nervous system, which stimulates its production [52]. It has also been shown in experimental and epidemiological studies to have anti-inflammatory and antioxidant properties and the ability to reduce arterial intimal membrane hyperplasia when organs are exposed to damage [53]. ADM is significantly elevated in HF, sepsis and other clinical states that lead to heart malfunction. The negative correlation between elevation of ADM and a decrease in left ventricular ejection fraction was noticed by Nishikimi et al., along with a positive correlation with hike in NYHA classes and NT-pro-BNP plasma level [51]. This marker can also be used by nephrologists to investigate its correlation with hydration status, not only in patients with concomitant HF, as it shows a very promising result in cardiological research. However, ADM is difficult to measure from a blood sample because it is rapidly removed from the circulation and, even when present in the bloodstream, it is covered by binding protein, making it inaccessible for immunometric analysis [50,52]. Pro-ADM is a precursor of ADM, the mid-regional fragment of which called mid-regional ADM (MR-pro-AMD) is more stable and may directly reflect blood levels of adrenomedullin [53,54]. It seems to be a better predictor of 90-days mortality due to cardiac incident than NT-pro-

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BNP, and its elevated level reflects poorer 12-months survival in patients with HF [55]. MR-pro-ADM also correlates with indicators of vascular failure and other important cardiological factors included not only in the SCORE scale. A cross-sectional study of almost 4,000 patients by Koyama et al. found that MR-pro-ADM was significantly higher in those with vascular insufficiency, defined by arm-bone pulse wave velocity along with risk factors such as obesity, hypertension, T2DM or dyslipidaemia [53]. It is also being studied in Intensive Care Units among critically ill patients with septic shock and systematic inflammatory response syndrome. The healthy control population had a mean value of MR-pro-ADM blood level 0.4 nmol/l, while ill one 2.5 nmol/l and it tends to gradually increase with a severity of sepsis and intensity of fluid resuscitation [54]. MR-pro-AMD also correlated with the APACHE II score, SAPS II score, IL-6, creatinine, and age [54]. In the ENVOL study, proadrenomedullin indicator correlated strongly positively with sodium imbalance, OH and current SOFA score [56]. In this study, only MR-pro-AMD and angiotensin II levels correlated significantly with sodium status, while Pro-atrial Natriuretic Peptide (MR-pro-ANP), renin, aldosterone, cortisol, norepinephrine, epinephrine, copeptin, pro-endothelin and EPO did not [56]. MR-pro-AMD was also studied in HD and PD population for up to 7 years in Austria. Majority of patients (82%) included in the study had an elevated MR-pro-AMD level ≥1.895 nmol/L and this was significantly higher in people who passed away during the study [57]. The peptide also correlated with another investigated marker, MR-pro-ANP, which was elevated in 99% of patients, and both parameters correlated with each other (r^2= 0.62). The two indicators were strongly related to the probability of the death due to HF, but not within the entire group of fatal and non-fatal cardiovascular disease events. ADM seems to reflect the decompensated organ's reaction to the multifractional injuries in preserving the integrity of the cardiovascular system in ESRD. MR-pro-AMD increased not only in patients with diagnosed HF, but also with the advancement of renal disease. MR-pro-AMD tends to correlate with a relative OH status in patients with both haemo- and peritoneal dialysis (n=40) in Park et al. study. Its growth increased with the advancement of CKD, correlating significantly with NT-pro-BNP and cardiac markers (LV mass, LV mass index, ejection fraction, and left atrial diameter) [34]. These results give both ADM and MR-pro-ADM great perspective to become independent indicators of OH.

(d) Galectin-3

Gal-3 protein was discovered in the early 80s and since then its role has been studied in several organs, including kidneys [58]. In pre-clinical models, it is overexpressed in diabetic nephropathy, toxic injury, cardiorenal syndrome or ischemia/reperfusion injury. In renal carcinoma cells, Gal-3 shows that hypoxia is crucial for its expression and its level elevates gradually with a disease stage [59]. Gal-3 is also connected to immune-associated kidney damage like sepsis, cancer or autoimmune diseases [58,60]. It increases also in a model of congenital polycystic kidney (CPK) and tends to elevate deliberately together with the stage of renal disease. Gal-3 increases gradually with the advancement of CPK according to the Ozkurt et al study [51]. At the cellular level, Gal-3 is associated with renal fibrogenesis and chronic inflammation [62]. Pathomorphological analysis indicated that higher Gal-3 concentration is associated with interstitial fibrosis, tubular atrophy, and vascular intimal fibrosis. In a 4-year clinical trial on 280 patients with renal disease, urinary Gal-3 also correlated negatively with eGFR and positively with proteinuria [63]. When considered as an OH marker, there is no direct connection, but the protein increases together with a renal and heart malfunction due to fluid overload. In a HF population, Gal-3 was associated with an increased risk of death after adjustment on a renal injury biomarker [51]. In an observational study of 1200 patients with HF, Gal-3 showed a negative correlation with eGFR, and a connection with a mortality risk when diminished renal function is present [64]. Patients with a higher Gal-3 concentration than established mean value (23.2 ng/ml) had a higher mortality rate. However, it has no prognostic value of mortality risk when renal function was preserved. Not only as a renal injury marker, but also as a heart injury indicator in the ESRD population. In HD children population, Gal-3 increases along with a left ventricular diastolic dysfunction [64]. The clinical guidelines announced by the American Heart Association/American College of Cardiology marked the capability of Gal-3 as a predictor of mortality and hospitalization in cases with HF [64]. This property makes Gal-3 a good marker to use both in ESRD

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when HF is suspected and vice versa. Even if it is not a direct indicator of OH, it should be considered as a marker of renal disease due to its correlation with organ damage.

(e) Urocortin-2

Ucn-2 is a peptide which has a similar structure to the corticotropin-release factor and binds via its receptor CRHRH-2 [65]. This receptor is mainly found in the central nervous system, heart and in endothelial and smooth muscle cells of the systemic vasculature. Its actions on animal tissues include vasodilation, positive inotropic and chronotropic effects along with cardioprotective abilities [66]. Ucn-2 increase is seen in HF, left ventricular systolic dysfunction, non-ischemic dilated cardiomyopathy and pulmonary arterial hypertension (PAH) [66]. The significant adverse effect is that it can cause a significant decrease in blood pressure, leading to worsening of renal function in patients with ESRD [66]. When its action was compared with metoprolol, it increased heart haemodynamic parameters due to its ino- and chronotropic effects along with an increase in mean arterial pressure (MAP) [67]. The peptide activity on neurohormonal and renal function is still not well understood. Ucn-2 acts on diuresis stimulation, increases creatinine clearance and inhibits sodium retention, but this phenomenon, which is seen in animals, is not always present in humans [68]. Experimental study on rat model investigated Ucn-2 action on renal arteries. Urocortin dilated renal arteries, and the magnitude of this effect did not vary between animals gender, but it seem that the mechanism is different in females (more dependent on Ca^{2+} released from sarcoplasmic reticulum) than in males (probably not cAMP or sarcoplasmic Ca^{2+} release- mediated) [69]. Due to its potential to become a marker of HF, Ucn-2 is still undergoing tests on both models. Study on a group of 8 healthy men confirmed the haemodynamic effect, as well as the ability to decrease MAP, vascular resistance, and increase the left ventricular ejection fraction [71]. The strong limitation of this study is the extremely small research group. In a combined clinical and experimental study, Ucn-2 was able to decrease PAH, improved right ventricle function, and improved pulmonary circulation [70]. The peptide did not alter the sodium, potassium, NT-pro-BNP concentrations, but it increased the release of angiotensin II and renin. However, Ucn-2 plasma level did not differ between the patients who suffered from PAH and the healthy group, but increased m-RNA expression was observed in people with right ventricle failure. Rats treated with the protein had a decrease in extra fluid build-up in the lungs, which is probably the effect of improvement of LV function. In a study on the HF population, its elevated level correlated positively with higher sodium retention score, uric acid concentration, peripheral oedema, and hepatomegaly presence. It correlated negatively with IVC collapse ability [66]. There was no association between Ucn-2 and renal function or haemoglobin level in this study. When considered as an OH status marker or factor which can improve the renal function, the results differ between studies. In a study of 12 sheep injected with mouse Ucn-2 (via a pulmonary artery catheter), there was a reduction in the effect of HF factors, as well as an improvement in renal function. It was able to decrease the MAP, left atrial pressure together with a suppression of cardiac remodeling factors production (aldosterone, arginine vasopressin, and endothelin 1) [65]. Decrease in creatinine and sodium blood level combined with the increase in urine output, indicate the improvement of renal function. The same scientific group compared Ucn-2 effect on heart and kidney function in a different sheep model but compared with dobutamine [71]. Effect on heart haemodynamic was comparable between the substances, but Ucn-2 expressed better improvement on central venous and left atrial pressures. Dobutamine and Ucn-2 improved renal function, but the significant sodium excretion was altered by Ucn-2. More interestingly, Ucn-2 decreased the overall OH status, while dobutamine increased it. It also gave better results in both HF and OH compared to the other drug. Similarly to the article mentioned above, in an animal study Ucn-2 noticed a better effect on diuresis, creatinine level and sodium balance than furosemide. It was able to reduce renin, aldosterone and vasopressin levels [72]. Heart function also improved. Ucn-2 attenuated furosemide function, which is a promising property as some patients with ESRD develop a diuretic resistance. Experimental study on rats investigating the possible Ucn-2 influence on renal dysfunction and injury caused by ischaemia or reperfusion showed that it was unable to decrease the organ failure [73]. Ucn-2 did not increase the

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creatinine clearance nor stopped anuria; higher dose of protein caused even decrease in renal function. The opposite effect was observed in human study by Chan et al., where Ucn-2 revised renal function and slashed RAA activity when compared to placebo [74]. The treated group required a lower dose of furosemide and the indirect OH marker NT-pro-BNP decreased after the infusion. Ucn-2 needs further study in the future, as it has shown good results in animal models.

Imaging studies

Ultrasonography (US) is one of the common tests performed in clinical trials either in a specific room or beside the patient's bed – POCUS. In terms of hydration status, doctors can visualize and measure the width of IVC, jugular veins, hepatic portal vein and renal veins. The assessment of fluid inside the pleural cavity or in the peritoneum can also be helpful. POCUS is nowadays one of the components of physical examination inextricably connected with auscultation, palpation and inspection [75]. It is used to verify standard diagnostic exams, as auscultation can be normal (81%) in patients with a lung fluid overload noticed in a US test [11]. Other simple radiological examinations are inconclusive, as the presence of pleural fluid can only be observed by X-ray if at least 200 ml of fluid is present [16]. POCUS accelerates the diagnosis or exclusion of some pathologies in real time without the need for consultation [76]. The dependency between POCUS and hydration status can be divided according to the stages of renal disease, dialysis method or HF.

- CKD

Koratala et al. gave an example of a patient with CKD who had missed one dialysis session and suffered from shortness of breath, POCUS revealed fluid around his heart in pericardium [75]. Lung POCUS can reveal an extravascular fluid as a diffuse B-line pattern. Both symptomatic and asymptomatic lung congestion worsens outcomes in patients with CKD [20]. A limitation of lung POCUS in OH diagnosis is the fact that there is no one specific protocol available in the literature, and the fact that B-lines are not specific for pulmonary edema [75].

- HD

Lung USG is also used by nephrologists to guide dry body weight estimation during HD [75]. When patients are closer to their ideal body mass, fewer symptoms of OH are present in USG. The most promising results in prediction of OH were obtained by lung USG [78]. The B-line results were more accurate than BIS and may help to diagnose asymptomatic pulmonary congestion in patients with HD [17]. Dynamical changes of B-lines during hemofiltration, the residual congestion at the end of HD, can be used to titrate dry body mass [20]. In another study guided by Lutradis et al., scientists studied the effect of estimation of dry body weight based on lung USG for 8 weeks in ambulatory conditions [79]. It appeared that patients guided by this protocol maintained dry body weight better and noticed a decrease in blood pressure compared to a group guided by normal criteria [79]. A positive correlation between line B score changes and dry body weight was observed [79]. On the other hand, a study on 250 HD patients to adjust dry body mass using lung POCUS together with BIS did not improve life expectancy or cardiovascular events [9]. Patients with fluid overload or right ventricle failure develop clinically significant organ congestion due to fluid retention, and it can be seen as IVC dilatation or fluid presence in a third space [25]. In a study on HD individuals, authors demonstrated that a decrease in dry body weight of 0.7 kg resulted in reduction of IVC diameter and improved left heart contraction function [17]. Extracellular fluid estimated by USG correlates also with the BIS method in HD patients [12].

POCUS, which appears to be a fantastic and easily available tool, also exhibits limitations. As noticed and described above, the width of IVC is not always an indicator of fluid overload, as its dilatation has been found in both healthy athletes and those with diseases such as valvular and pulmonary hypertension [78]. IVC diameter is used to estimate the right atrial pressure, but it does not provide any data about the organs congestion [75]. The strong limitation of the lung USG is the fact that it reflects only left heart pressure but gives no information about the venous congestion [75]. The measurements of hepatic vein flow via Doppler without a simultaneous performance of electrocar-

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diography leads to a number of errors, as waveforms are influenced by heart arrhythmias [75]. Furthermore, a lack of elevation in portal venous flow in right atrial pressure can be found in healthy individuals with a low body mass index. The physician's experience also plays a key role in assessing the hydration status of the patient using USG, which may differ in patients with obesity or hyperventilation, which may mask the real problem. Misinterpretation can also be caused by improper patient positioning or presence of catheter [11]. Combining the VEXUS protocole together gives promising results, particularly in patients with heart failure, but there is no specific data for patients who suffer from CKD only.

Table 3 presents available data on CKD patients and divides it according to the stage of disease, kidney replacement therapy type and results.

Table 3. Correlation of BIS and other available OH markers in dialysis dependent patients and results obtained.

Author	number of patients	duration	CKD stage	HD	PD	BIS control	Improvement noticed by other variables
Siriopol et al [9]	250	24 months	N/M	250	0	recorded at baseline and at every 3 months	lungs US
Onofriescu et al. [13]	221	33 months	4/5	221	0	before each dialysis, 3 times per week	incidence rate for all-cause hospitalizations
Loutradis et al. [17]	71	8 weeks	5	71	0	No	lungs US, IVC diameter, body mass
Agarwal et al. [18]	150	17 months	5	150	0	No	BMI,pedal edema, age, left ventricular hypertrophy
MacHek et al. [30]	52	12 months	5	52	0	before dialysis,at least 1 monthly	BP

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Kim et al. [31]	147	1 month	5	147	0	at mid-week dialysis sessions	BP, haemoglobin, creatinine, uric acid
Guedes et al. [33]	67	59 months	5	0	67	with empty abdomen	peritoneal clearance, NT-pro-BNP
Park et al. [32]	80	N/M	5	20	20	prior to dialysis in HD patients, and with a dry abdomen in PD patients	NT-pro-BNP, pro-ADM, LV mass, LV mass index, ejection fraction, and left atrial diameter
Wang et al. [36]	230	36 months	5	0	230	no	NT-pro-BNP, GFR, left ventricular ejection fraction and left ventricular mass index.
Goto et al. [38]	53	96 months	5	53	0	no	ANP, BNP
Wijayaratne et al. [45]	489	6 months	5	0	489	peritoneal dialysate drained out and after	Ca-125, Nt-pro-BNP

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						voiding	
Arik et al. [50]	105	N/M	1-5	35	0	no	Ca 125, Ca 19.9
Yilmaz et al. [51]	110	2 months	5	110	0	no	Ca 125, NT-pro-BNP
Gouya et al. [57]	201	72 months	5	201	0	no	MR-proANP, MR-proADM
Elsadek et al. [64]	67	30 months	5	67	0	no	Gal-3, left ventricular diastolic dysfunction
Loutradis et al. [79]	71	8 weeks	5	71	0	no	lungs USG, BP

- N/M data not mentioned in the research

As it can be clearly visible from the table, the majority of the studies had been performed on HD population and not all scientists performed BIS as a control parameter. It is not precise why they did not use the equipment to compare the electrical estimated body water balance with different OH markers. All studies on PD population with BIS calculations were performed on empty abdomen which excludes calculations error.

5. Conclusions

Modern medicine stands in a huge need for OH markers and, as described in this review, there are no specific and accurate ones. The presence or absence of symptoms during a simple physical examination does not exclude fluid overload. The combination of BIS, POCUS with VEXUS protocol together seem to have promising and good results. The addition of serum markers like NT-pro-BNP or Ca-125 broadens the viewpoint on volume status when compared to studies based on only one OH test. The great potential of Ca-125 noticed by cardiologists should be investigated further by nephrologists not only in patients with HF. The markers mentioned in the study: ADM, pro-ADM, Ucn-2, Gal-3 need to be further investigated as OH markers.

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Abbreviations

ADM- adrenomedullin
AKI- acute kidney injury
BCM- Body Composition Monitor
BIS- Bioimpedance spectroscopy
Ca-125 - Carbohydrate antigen 125
CKD- chronic kidney disease
CPK- congenital polycystic kidney
CT- computer tomography
ECW-internal cell water
eGFR- estimated GFR
ESRD- end stage renal disease
FDA -Food and Drug Administration
FFM- fat free mass
GFR- glomerular filtration rate
HD- haemodialysis
HF- heart failure
ICU- intensive care unit
ICW- internal cell water
IVC- inferior vena cava
MAP- mean arterial pressure
MRI- magnetic resonance imagining
MR-pro-AMD- Mid-regional AMD
MR-pro-AMP- Pro-atrial Natriuretic Peptide
NYHA- New York Heart Association
OH- overhydration
PAH- pulmonary arterial hypertension
POCUS- point of care ultrasonography
Pro-ADM- proadrenomedullin
TBW- total body water
USG- ultrasonography
VEXUS- Venous Excess Ultrasound Score

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