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ORIGINAL ARTICLE

Bioelectrical impedance analysis to assess hydration in critically ill patients: A practical guide demonstrating its use on artificially ventilated COVID patients

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Abstract

Determining body contents such as body water volume and body cell mass have significant uses in health and disease. Accumulation of extracellular water is particularly difficult to monitor using classical methods. Bioelectrical impedance analysis (BIA) is a simple, rapid, and noninvasive method, based on the principle that the flow of altering electrical current through a particular tissue differs depending on the content of water and electrolytes. It is thus able to measure body composition, including total body and extracellular water. Although bioimpedance holds up quite well compared to the gold standard that is dual-energy X-ray, it has certain limitations in critically ill patients. Specifically, it cannot distinguish between intravascular and interstitial volume in the extracellular compartment, and as it employs equations based on population measurement, compositions can diverge significantly with severe overhydration or in the morbidly obese. Bioelectrical vector analysis (BIVA) does not use the calculations and is part of the measurements in newer multifrequency bioimpedance devices.

There is growing evidence of the adverse effect of overhydration in critically ill patients and bioimpedance can be used to monitor hydration, but there is no information on how to use this method for bedside monitoring in practice. In this review we present a practical approach to Phase angle and BIA/BIVA interpretations for monitoring hydration status and rapid loss of skeletal muscle mass and their clinical use, on a cohort of critical COVID patients under artificial lung ventilation.

Abbreviations:

BIA	- Bioelectrical impedance analysis
BIVA	- Bioelectrical impedance vector analysis
SIRS	-Systemic inflammatory response syndrome
TBW	- Total body water
ECW	- Extracellular water
ICW	- Intracellular water
FO	- Fluid overload
CFO	- Cumulative fluid overload
Z	- Impedance
R	- Resistance
X	- Reactance
FFM	- Fat-free mass
FM	- Fat mass
BCM	- Body cell mass
SMM	- Skeletal muscle mass
ICU-AW	- Intensive care unit- acquired weakness
P.A.	- Phase angle
ESPEN	- The European Society for Clinical Nutrition and Metabolism
vvECMO	- veno-venous extracorporeal membrane oxygenation
ATH	- Active body mass
R/H	- height-adjusted resistance
Xc/H	- height-adjusted reactance
MRI	- Magnetic resonance imaging
DXA	- Dual-energy X-ray

INTRODUCTION

The administration of intravenous fluids is the first step in resuscitating critically ill patients. It is necessary to maintain perfusion pressure, ensure flux through organs in shock, and to prevent the development of multiple organ dysfunction (Delinger *et al.* 2013). The ROSE principle (Resuscitation, Optimization, Stabilization and Evacuation) is fully accepted for the administration of fluids during different phases of shock (Malbrain *et al.* 2014a). However, it is difficult to accurately determine the volume of fluids required to improve tissue perfusion in the patient. Monitor transitions between resuscitation/de-resuscitation phases is also quite complicated. Fluid requirements vary significantly among individual patients, mainly depending on the severity of the condition, the intensity of the systemic inflammatory response syndrome (SIRS) that is responsible for capillary leak and consequent fluid loss to the interstitium. Fluid overload is not without consequences for the patient as a positive fluid balance has been seen to increase morbidity and mortality (Vincent *et al.* 2006; Murphy *et al.* 2009; Acheampong & Vincent, 2015; Samoni *et al.* 2016).

Bioelectrical impedance analysis has been gathering attention as there is currently no simple, non-invasive method to assess extracellular water (ECW) that can be used repeatedly.

NEGATIVE IMPACT OF FLUID OVERLOAD

Intravenous fluid administration is one of the most common therapeutic interventions. Infusion solutions are necessary to rapidly make up intravascular volume upon the onset of shock states (septic shock, hemorrhagic-traumatic shock, etc.), as well as to maintain perfusion pressures and flux through organs (Vincent *et al.* 2006; Murphy *et al.* 2009; Acheampong & Vincent, 2015; Samoni *et al.* 2016).

There are five fluid phases of shock: Resuscitation, Optimization, Stabilization, Evacuation, and risk of Hypoperfusion (see Fig. 1).

Fluid management of therapy is particularly difficult to monitor both in the resuscitation and subsequent deresuscitation phases (Malbrain *et al.* 2014a).

Fluid overload

Many factors contribute to fluid retention e.g., endocrine factors or acute kidney injury, and fluid overload (FO) has a negative impact on virtually all organs and tissues. It delays oxygen delivery to intracellular sites of action, resulting in several functional impairments: hindered gas exchange, hypoxia, hypercarbia, decreased cardiac output, decreased glomerular filtration and bowel motility, ileus, cholestasis, and cardio-abdominal-renal syndrome. FO clearly worsens mortality and morbidity in patients, and the question remains whether this iatrogenic factor inevitably follows fluid resuscitation of the critically ill, or can it be handled as a modifiable source of mortality (Samoni *et al.* 2016; Silverides *et al.* 2022; Silverides *et al.* 2020; Casey *et al.* 2018).

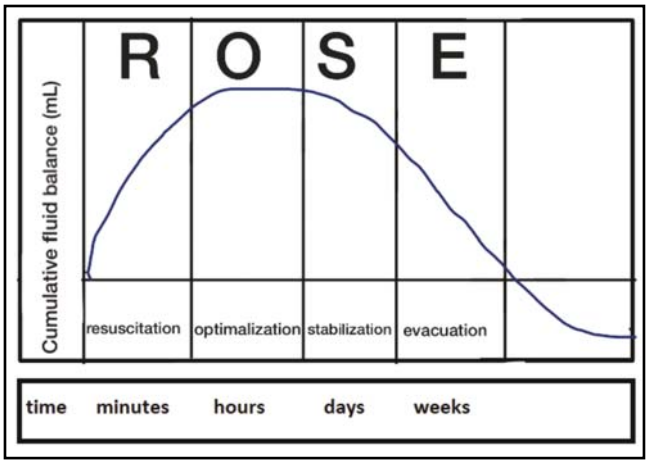

Fig. 1. ROSE *(in part from Malbrain et al. 2014a)* The five fluid phases of shock with evolution of patients' cumulative fluid volume status over time during each phase: (1) resuscitation, (2) optimization, (3) stabilization, and (4) evacuation (ROSE), followed by a possible risk of hypoperfusion (5) in cases where deresuscitation is too aggressive.

Definition of cumulative fluid overload

Overhydration in relation to body composition occurs when the cumulative fluid balance [calculated as total fluid input minus total fluid output] is positive and the cumulative fluid overload (CFO) exceeds 10% of the patient's initial weight. For example, when CFO is greater than +8l for an 80 kg patient (Malbrain

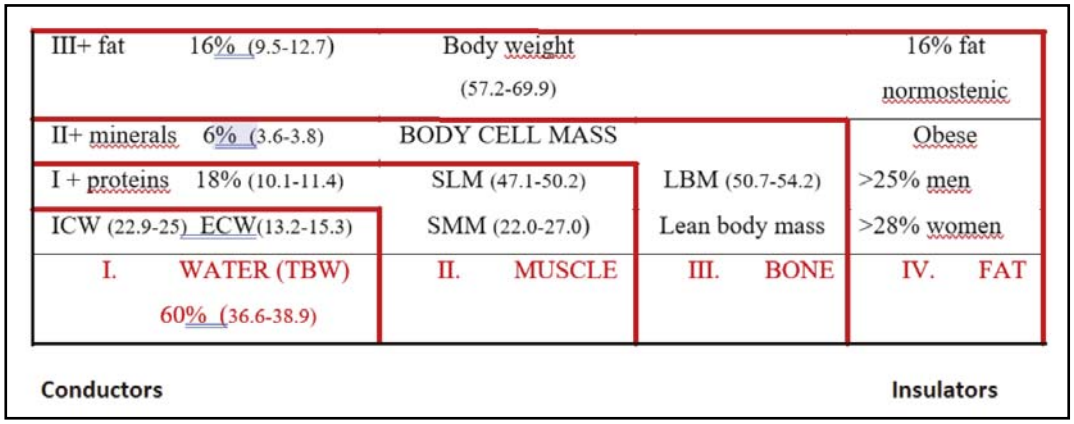

Fig. 2. The composition of four body compartments from Bioelectrical impedance analysis (BIA) based on impedance (partly due to Malbrain et al. 2014b). Conductors to Insulators from left to right: compartment I TBW (total body water, ICW + ECW, intracellular + extracellular water, which is about 60% of the weight); adding protein (18%) creates compartment II Muscle (SMM skeletal muscle mass and SLM soft lean mass). We then add minerals (~6%) to get compartment III LBM (lean body mass), containing muscles as well as bones, in total this makes up Body cell mass. Finally, when we add fat (~16% in normostenic people) we have the composition of the entire body – complete body weight

et al. 2014; Myatchin *et al.* 2020). Some authors make a distinction between mild CFO (5-9.99% body weight) and severe CFO over 10% (Samoni *et al.* 2016).

Total body water (TBW) is taken as the sum of 45% extracellular water (ECW), and 55% intracellular water (ICW), with the normal ECW/ICW ratio being less than 1. In the critically ill, especially in patients with septic shock, and significant capillary leak, water and electrolyte distribution is severely disturbed. They are prone to migration of fluid from the intravascular space to the interstitium. We therefore see increased ECW due to fluid shifting to secondary (interstitial) or tertiary space as fluidothorax, ascites (Dabrowski *et al.* 2014).

Classical methods cannot discriminate between water located in individual compartments, as they are based either on changes in patient weight or calculate cumulative water balance from the difference in fluid intake and output. These methods are rather imprecise, but bioimpedance is able to distinguish ECW from TBW because only higher frequency electric current can pass through cell membranes. Bioimpedance can therefore potentially be useful in setting up and monitoring a personalized fluid resuscitation (Van Haren, 2017; Samoni *et al.* 2016; Jones *et al.* 2015).

BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

BIA is a safe, simple, noninvasive method that enables the determination of body composition. Passing low frequency alternating electric current through a body, BIA measures impedance (Z), which is related to the length and the specific resistivity of the tissue and inversely related to its cross-sectional area (Prasad & Roy, 2020; Malbrain *et al.* 2014b). This electrical impedance has two components, resistance (R) and reactance (X). Resistance is inversely related to total body water - R decreases as edema increases (hyperhydration). Reactance, on the other hand, is related to cell membrane capacitance and reflects the body cell mass (BCM). X is higher in athletic and lower in cachectic patients. (Thanapholsart *et al.* 2022; Khalil *et al.* 2014; Di Somma *et al.* 2010; Kyle *et al.* 2004).

BIA is based on the different electrical characteristics of tissues: fat mass and fat-free mass (FFM). FFM contains large amounts of water and electrolytes, it is a better conductor with high conductivity (i.e., low impedance), compared fat and bone that have low amounts of fluid and electrolyte, and thus low conductivity (i.e., high impedance). The impedance is therefore inversely related to the volume of water in the body (Mattie,2008; Mulasi *et al.* 2008;).

In terms of conductivity, we can distinguish four compartments in the body (Fig. 2). The FFM set distinguishes body cell mass (BCM) with skeletal muscle mass (SMM) and bone, and total body water (TBW) with ECW and ICW (Malbrain *et al.* 2014b)

There are 2 types of BIA based on frequency: 50 kHz single frequency (SF-BIA) and the more accurate multiple-frequency (MF-BIA), using 1kHz-500kHz. Only high frequencies penetrate the cell membrane and can differentiate ICW (Marra *et al.* 2019; Thanapholsart *et al.* 2022). Therefore SF-BIA cannot determine differences in ICW, only the weighted sum of ECW and ICW resistivities (app 25%) (Kyle *et al.* 2004; Khalil *et al.* 2014).

We use bioimpedance spectroscopy methods (BIS) using a broad band of frequencies. Unlike MF-BIA, BIS is based on mathematical models of tissue electrochemical conductance (e.g., Cole-Cole plot) with more robust theoretical foundation and improved accuracy (Moissl *et al.* 2006; Kyle *et al.* 2004; Khalil *et al.* 2014; Cornish *et al.* 1996).

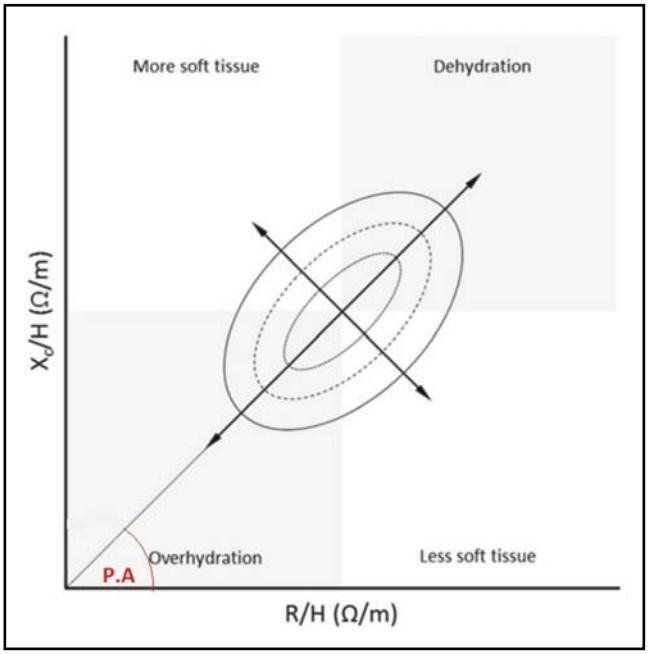

Fig. 3. Phase angle (P.A) plotted in a RX nomogram (for *illustration from Malbrain et al 2014b*). R resistance, X reactance. RX are normalized for height, and plotted on the RX graph with 50 percentile, 75 percentile and 95 percentile tolerance ellipses (increasingly further away from the center). Values outside the 95 percentile are abnormal. P.A is one of the best indicators of cell membrane function (Stapel *et al.* 2018). PA = arctan (reactance/resistance) × (180°/π). (Thanaphoisart *et al.* 2022)

ECW/TBW bioimpedance as a prognostic marker

Increases in TBW, ECW, and the ECW/TBW ratio together work as markers for poor prognosis. The ratio increases rapidly in critically ill patients, both with overhydration and fluid shift. This is also accompanied by a rapid loss of lean body mass and the development of ICU acquired weakness (ICU-AW; Preiser *et al.* 2014). Thus, increase in ECW masks the reduction in ICW/BCM along with loss of lean mass (Slobod *et al.* 2019; Joskova *et al.* 2019).

BIA parameters express the normal state of hydration as an ECW/TBW ratio of 0.36-0.39. A ratio above 0.39 (39%) indicates overhydration (Slobod *et al.* 2019). Using vector analysis (BIVA), any short vector, placed in the 1st left lower quadrant of the R/X nomogram, also indicates overhydration. For simplicity, "hydration scale of lean body mass" was introduced. Using this parameter, patients were classified as normohydrated (>72.7%-74.3%), mildly (>71%-72.7%), moderately (>69%-71%) and severely (≤69%) dehydrated, or mildly (>74.3%-81%), moderately (>81%-87%) and severely (>87%) hyperhydrated (Samoni *et al.* 2016).

How to measure

BIA is measured using a protocol where the patient is in a supine position with abduction of the upper (30°) and lower limbs (45°) on a bed; the bed is calibrated to measure patient weight (Khalil *et al.* 2014). Weight, height, age, and sex must be known and entered into the BIA calculations, for as already mentioned, BIA uses simple or multiple regression equations based on population measurements to make predictions for masses and for the volume of body compartments (Malbrain *et al.* 2014b; Khalil *et al.* 2014). Age and sex are of greatest importance for accuracy given the different proportions of fatty and muscle tissue (Malbrain *et al.* 2014b).

We use 4 electrodes for measurement itself, two current and two detecting electrodes placed on the wrists and ankles. The hands and feet are arranged at a 45-degree angle so that they do not touch the body (Moissl *et al.* 2006; Khalil *et al.* 2014).

Three assumptions have to be taken into account for determining body fluid volumes using bioimpedance. Firstly, electrical current at low frequencies cannot penetrate cell membranes, and thus flows through the ECW only but does not distinguish intravascular from interstitial fluid. High frequency current flows through both ECW and ICW. Secondly, resistivity of TBW depends on the ECW/ICW ratio because intracellular resistivity is 6-7 times higher than extracellular resistivity. Thirdly, resistivity of ECW may increase with the number of cells (Moissl *et al.* 2006; Kyle *et al.* 2004).

For critically ill patients, devices using multiple frequencies (in our case BIS Multiscan 5000 using 50 frequencies, from 5 to 1000kHz) are suitable and give more accurate body composition measurements. Multifrequency BIA will allow the resolution of ECW (a current with a frequency <100Hz will not pass through cell membranes) and TBW (a current with a frequency >100Hz will go through cells). Then ICW can be calculated as TBW – ECW (Moissl *et al.* 2006; Khalil *et al.* 2014).

Phase angle

The passage of current through the cell membrane leads to a time delay, i.e., a phase shift between the sinusoidal voltage and current waveforms. This can then be plotted on the resistance/reactance (R/X) curve for illustrative purposes as the phase angle [P.A. an arctangent of X to R (Fig 3); (Stapel *et al.* 2018)]. The normal value is between 4^0 and 15^0, and the greater the number of cell membranes the signal has to pass through, the longer the time delay, the greater the P.A. (Malbrain *et al.* 2018; Foster & Lukaski, 1996). Decrease in BCM (representing a protein-rich, metabolically active tissue) is seen as low P.A., and this worsens the prognosis. BCM is dependent on the patient's fluid status (TBW). This means that although low PA can be found on both malnutrition and fluid overload, it tends to be more specific to fluid overload than malnutrition (Colin-Ramirez *et al.* 2006; Gulatava *et al.* 2021; Scicchitano *et al.* 2020). BCM and P.A. are in a differential balance, and both are usually altered in the same direction, with a low BCM and low P.A. pointing to malnutrition (Malbrain *et al.* 2014b; Gupta *et al.* 2004; Di Vicenzo *et al.* 2021). Phase angle is proportional to muscle strength and is higher in

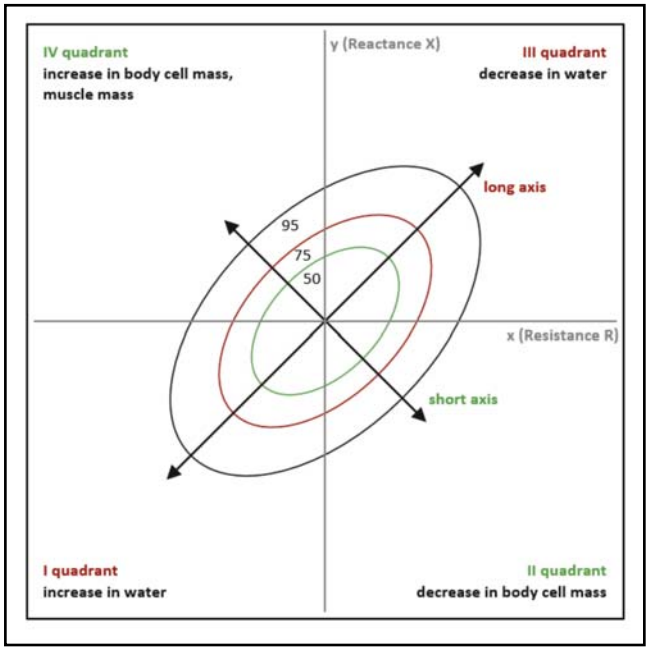

Fig. 4. Interpretation of the Bioelectrical impedance vector analysis (BIVA) nomogram (*partly according to Kroker et al. 2011*) 4 quadrants formed by plotting Resistance R on the X-axis and Reactance X on the Y-axis (grey). The origin [0,0] represents the healthy population. Quadrant I – overhydration; counterclockwise form there, quadrant II – decreased body cell mass BCM, malnutrition; quadrant III – dehydration; and quadrant IV – increased BCM, anabolic phase. The long axis of the ellipses divides quadrants I & III and the short axis divides quadrants II & IV

athletes. Conversely, it decreases with age, malnutrition, or the development of sarcopenia (Di Vicenzo *et al.* 2019; Tanaka *et al.* 2019). The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends the use of BIA, more specifically P.A., to assess sarcopenia and nutritional status (Kyle *et al.* 2004).

Bioelectrical impedance vector analysis (BIVA)

BIVA, a derivative of BIA measurements, shows raw impedance data corrected for height, plotted as a bivariate vector in a nomogram or R/X graph – with resistance on the X-axis and reactance on the Y-axis. . Resistance (R), the opposition to the passage of electric current through the body – plotted on the X axis – is inversely related to the water content. Reactance (X), the opposition of a circuit element to a change in electric current is plotted on the Y axis, and is related to BCM. The plot divides the field into four quadrants (Fig. 4; Malbrain *et al.* 2014b; Castizo-Olier *et al.* 2018).

There are 3 tolerance ellipses in the RX nomogram, corresponding to the 50th, 75th and the 95th percentile of the healthy reference population (Fig 4). The more the bivariate vector falls outside the 50th, 75th, 95th percentile, the worse the condition is (Thanapolsart *et al.* 2022). In acute heart failure patients with fluid overload, the bivariate vector falls outside of 75th percentile with 75% sensitivity, 86% specificity (Alves *et al.* 2015), while in chronic heart failure it falls outside the 50th percentile with 85% sensitivity and 87% specificity (Massari *et al.* 2016). The quadrant of the BIVA nomogram where the patient's data is located is informative (Malbrain *et al.* 2014). Critically ill patients show differences in body water composition compared to healthy individuals, with higher values for TBW, ECW and edema index (ECW/TBW ratio). The edema index is very sensitive in detecting fluid congestion (Park *et al.* 2018). The PA is lower in the critically ill (Huygh *et al.* 2013).

Although BIA has some limitations when used in patients with unstable conditions, this can be overcome by using BIVA. Unlike BIA, BIVA does not rely on a regression equation to calculate body composition (Castizo-Olier *et al.* 2018; Nwosu *et al.* 2019; Thanaphoisart *et al.* 2022).

The BIVA nomogram can be used to track patient shifts from the left lower quadrant (water increase, anasarca, edema) to the right lower quadrant (decreased BCM). According to Slotwinski *et al.* (2013) who studied critically ill patients with sepsis, about 49% of the cases placed above the 50th percentile in left lower quadrant. This was confirmed on cardiac patients with dyspnea (Piccoli *et al.* 2012), where they fell on the lower side of the 50th percentile tolerance ellipse as in other cases (Buffa *et al.* 2013). This will also allow disease progression to be monitored as BIVA values outside the 95th percentile of the tolerance ellipses move back inside the tolerance ellipses and move within the quadrants in measurements taken over the course of recovery (Basso *et al.* 2013; Myatchin *et al.* 2010; Jones *et al.* 2015; Samoni *et al.* 2016).

BIVA measures raw impedance data and is independent of hydration status and can be used for cross-checking and/or correction of BIA data interpretation (Walter-Kroker, 2011; Brantlov, 2019).

HOW TO APPROACH THE EVALUATION OF BIVA, USING OUR PATIENT COHORT FOR ILLUSTRATION

The evaluation of BIVA data takes place in 4 steps, depending on the location of the patient's data point in the BIVA nomogram:

1. Long axis score: if the data point lies above the long axis and above the 95th percentile – high BCM, muscle mass, anabolic state. If it is below the long axis – decrease in BCM, sarcopenia, malnutrition (Walter-Kroker *et al.* 2011).
2. Short axis score: if the data point lies above the short axis and the 95th percentile – dehydration. If it is below the axis – hyperhydration, edema, anasarca.
3. Scoring for quadrants: The quadrant in which the data point is located is informative. For simplification we use quadrants: Left lower Quadrant I – overhydration, Right lower Quadrant II – malnutrition, Right upper Quadrant III – dehydration and Left

Tab. 1. Patient NK: BIVA results for the 3 measurements.
R/H, height-adjusted resistance; Xc/H, height-adjusted reactance; PA, phase angle

measurement	R/H	Xc/H	vector length	PA
1	220.69	22.42	221.82	5.8
2	139.58	19.22	140.88	7.8
3	196.84	17.22	197.59	5

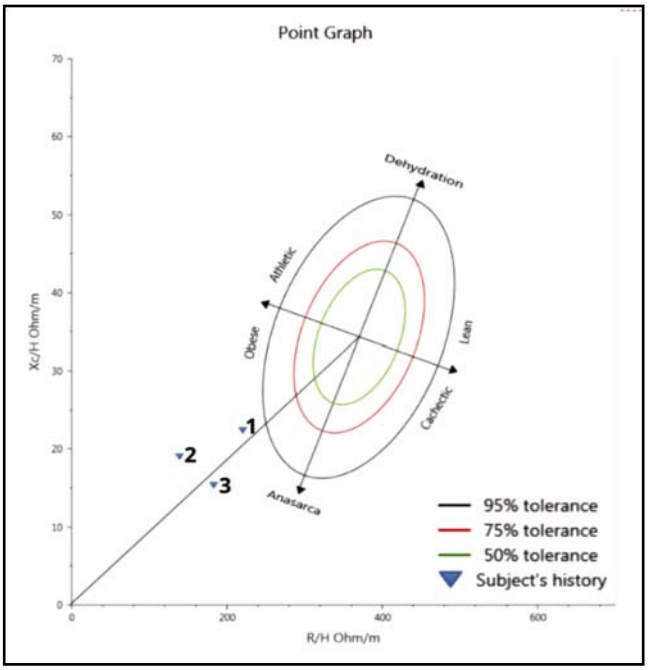

Fig. 5. Patient NK - BIVA results for 3 measurements, point graph
1st measurement
- Long axis above 95% percentile: (high BCM, e.g., muscle, internal organs).
- Short axis below 95% percentile: Water retention, obese patient (BMI 47.4)
- The first quadrant, vector length 221.8: overhydration
- PA phase angle 5.8° (normal range 4-15°)

2nd and 3rd measurement always after 1 week: the situation is even worse, shortening of vector length (221.8 to 140.8) - means severe overhydration, decrease in PA from start 5.8 to 5 - means loss of muscle, water retention is masking loss of muscle. Sarcopenic obese patient

upper Quadrant IV – BCM recovery, anabolic phase. The higher the content of body fluids, the shorter the resulting length of the BIVA vector.

4. Determination of the phase angle: norm = 4-15°. Lower values indicate decrease in BCM, fluid overload, worse prognosis (Gulatava *et al.* 2021).

What follows are some examples of the BIVA graph taken from our patients (COVID patients) and their interpretations. The first measurement was always performed after the patient's admission, and each of the following measurements were taken one week apart.

Patient NK, 31-yr-old female, 137 kg, BMI 47.4

Diagnosis: COVID pneumonia, on artificial ventilation and vvECMO (veno-venous extracorporeal membrane oxygenation).

When compared with BIA measurements, we observe some discrepancies in BIA versus BIVA hydration in this morbidly obese patient: TBW total body water is below the normal range (both ICW and ECW), which does not correspond to BIVA – quadrant I, overhydration, only in 2nd measurement the overhydration is +3.9%. SMM norm is 63-75.5% body weight for women (SMM 33.8 kg of 137 kg is only 24.7%) – the patient shows sarcopenic obesity according to BIA, while in BIVA patient´s point lies in quadrant I above the long axis, showing sufficient BCM, overhydration.

Conclusion: morbid obesity (BMI 47.4), overhydration, high FM, low SMM in BIA. Water retention in BIVA masks loss of muscle: sarcopenic obesity.

Patient DK, 61-yr-old female, 61 kg, BMI 24.2

Diagnosis. COVID pneumonia, on artificial ventilation. BIVA and BIA confirmed overhydration [overhydr. 6.1% (in 1st) to 2.7% (in 3rd measurement], a low SMM – in the 3rd measurement 16.8 kg of 61 kg body weight is only 27.5%; norm for ages 60-79: 70-84 percent for men, 60-72.5 percent for Caucasian women. Ethnicity can affect the normal body composition range (Khalil

Tab. 2. BIA results of patient NK
TBW, total body water, ICW, intracellular water, ECW, extracellular water, Overhyd., overhydration, FFM, fat free mass, FM, fat mass, SMM, skeletal muscle mass, BCM, body cell mass, ATH, active body mass; *BIA measurement 1-3; **Reference standard

Patient 1 (NK)	1*	2*	3 *	**
TBW (%)	35.00	39.20	55.50	50-60
ICW (%)	16.90	19.80	18.10	
ECW (%)	18.10	19.40	37.40	
OVERHYD. (%)	-0.10	3.90	-9.30	
FFM (%)	24.10	26.40	30.30	26-28
FM (%)	51.30	46.30	34.10	20-26
SMM (kg)	33.80	39.90	51.50	
BCM (kg)	37.00	39.30	71.10	
ATH (%)	48.70	53.70	65.90	74-80

Tab. 3. Patient DK: BIVA results for the 3 measurements.
R/H, height-adjusted resistance; Xc/H, height-adjusted reactance; PA, phase angle

measurement	R/H	Xc/H	vector length	PA
1	215.5	14.69	216	3.9
2	323.35	21.48	324.06	3.8
3	392.83	21.96	393.44	6.1

et al. 2014). This corresponds to a shift in BIVA in the next measurement to the 2nd quadrant, malnutrition.

Conclusion: normal weight patient. Initial overhydration masks progressive loss of muscle, development of polyneuromyopathy in critically ill patients (ICU-AW), confirmed by gradual decrease in SMM on BIA, shift to the II Quadrant in BIVA and a low phase angle indicating loss of cell membranes and unfavorable prognosis As the proportion of overhydration and muscle loss in the critically ill (ICU-AW) shifts from left to right lower quadrant, we have to take into account more factors, such as their clinical status and the trend in the measurement. Low PA signifies overhydration. Also, in case of low BCM and SMM, the BIVA plot would fall out of the 95% ellipse in the right lower quadrant. PA increases from 3.9 to 6.1. This might mean that PA turns back to normal because fluid was removed, and the patient recovered.

Patient JK, 36-yr-old female, 69 kg, BMI 28

Diagnosis: COVID pneumonia on artificial ventilation. Conclusion: gradually progressing poly-neuromyopathy. BIVA confirms this as the points move to the III quadrant. BIA confirms low and decreasing SMM, 20% body weight (13.8 kg of 69 kg body weight). Normal range for SMM: Ages 20-39:

63-75.5 percent for women. This patient shows muscle loss, development of polyneuromyopathy and a gradual decline in phase angle (from 4.4 to 4.1).

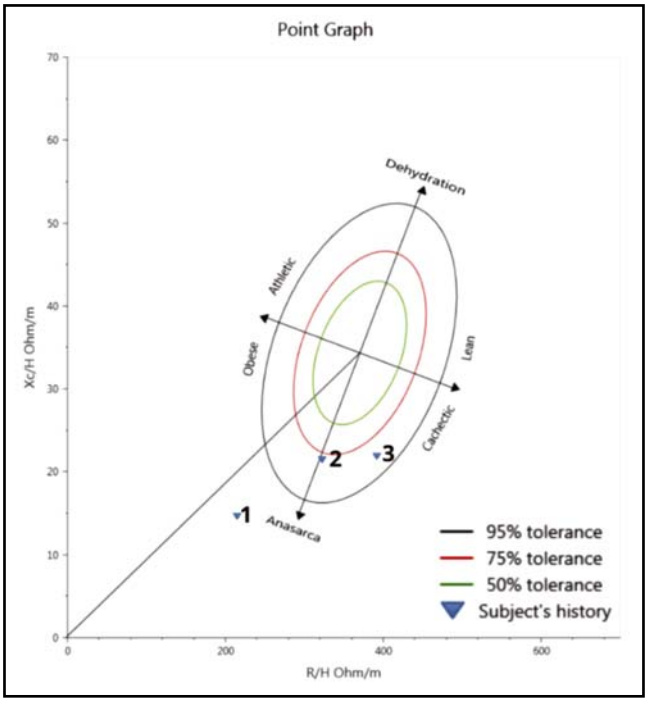

Fig. 6. Patient DK: BIVA results for 3 measurements, point graph
1st measurement
- Above 95th percentile of long axis, sufficient BCM body cell mass (BMI 24.2)
- Below short axis, overhydration, confirmed by BIA overhydr. 6.1%
- I Quadrant, vector length 216, overhydration
- Low P.A., 3.9° malnutrition (bad prognosis; (Kammar-García *et al.* 2021; Lyons et.al 2017; Alves *et al.* 2016; Colin-Ramirez *et al.* 2012)
- Again overhydration masks loss of muscle

2nd measurement after 1 week
Shift to between 75th and 95th percentile in long and short axis – vector length from 216 to 324, reduction of overhydration, shift to II. Quadrant describes muscle loss, confirmed by BIA: low SMM, decrease from 30.4 kg to 20.4 kg.
BIA parameters are helpful: 61year, female, BMI 24.2 - P.A 3.9° is low, a predictor of mortality.
It confirms malnutrition, even though BMI is in normal range, SMM, BCM is low
3rd measurement DK, after 1 more week, improvement, longer vector and increase in PA

Tab. 4. BIA results of patient DK
TBW, total body water, ICW, intracellular water, ECW, extracellular water, Overhyd., overhydration, FFM, fat free mass, FM, fat mass, SMM, skeletal muscle mass, BCM, body cell mass, ATH, active body mass; *BIA measurement 1-3; **Reference standard

Patient 2 (DK)	1*	2*	3 *	**
TBW (%)	54.40	43.20	40.00	50-60
ICW (%)	26.80	20.30	18.90	
ECW (%)	27.60	22.90	21.00	
OVERHYD. (%)	6.10	3.80	2.70	
FFM (%)	21.20	16.60	14.90	17-19
FM (%)	24.50	34.70	38.60	22-31
SMM (kg)	30.40	20.40	16.80	
BCM (kg)	27.50	18.80	16.80	
ATH (%)	75.50	65.30	61.40	69-78

Tab. 5. Patient JK: BIVA results for the 3 measurements.
R/H, height-adjusted resistance; Xc/H, height-adjusted reactance; PA, phase angle

measurement	R/H	Xc/H	vector length	PA
1	340.08	26.17	341.09	4.4
2	378.39	30.44	379.61	4.6
3	541.32	38.79	542.63	4.1

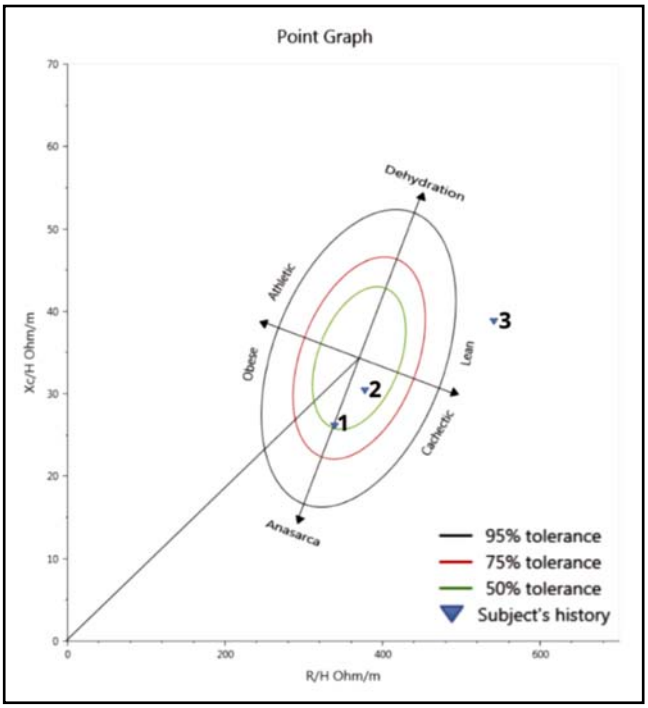

Fig. 7. Patient JK: BIVA results for 3 measurements, point graph
1st BIVA: Normal, area of 50th percentile of tolerance ellipses, normal P.A 4.4°
2nd BIVA after 1 week: Shift below long axis, decrease in muscle mass, but up to 50th percentile, still normal P.A. 4.6°
3rd BIVA after 1 more week: Moving outside the normal percentile range:
- Below Long axis – low BCM malnutrition confirmed by BIA: low SMM, BCM
- Above short axis – low TBW, dehydration confirmed by BIA

III quadrant: dehydration (above 95th percentile), gradual decrease in PA 4.1 – confirmed low muscle mass 13.8 kg

Patient IF 40-yr-old male, 100kg, BMI 23

Diagnosis: COVID pneumonia, on artificial ventilation, vv-ECMO.

The BIA confirms lower SMM, but the absolute values are too low. SMM (31% in our patient) is low from start; norm for ages 20-39: 75-89% for men; BIVA does not match. This is a patient on vvECMO, severely limiting the accuracy of BIA. BIVA is more accurate, as it measures raw impedance data. There is not enough information to use hydration monitoring by BIA in patients fitted with an extra-corporeal membrane oxygenator. ECMO patients were excluded from a large study on the critically ill with 125 patients (Samoni, *et al.* 2016). In one study (Jones *et al.* 2015) only two of the 61 patients have an ECMO.

Conclusion: This patient is on artificial pulmonary ventilation and vvECMO; we again see a gradual loss of muscle mass and development of ICUAW. The shift in the BIVA plot from the 50th to the 75th percentile ellipse and a gradual decline in PA may indicate poor prognosis.

DISCUSSION

A number of studies in medical/surgical patients confirm the association between elevated bioimpedance-measured hydration status, BIVA measurements and mortality with high statistical significance (Samoni *et al.* 2016; Basso *et al.* 2013). The ECW/ICW ratio allows the discrimination of survivors from non-survivors (Dabrowski *et al.* 2014; Slotwinski *et al.* 2013; Malbrain *et al.* 2014a). A higher ECW/TBW ratio within 24 hours of admission was associated with an increase in the number of ventilator days in 36 mechanically ventilated patients (Slobod *et al.* 2019) The edema index (ECW/TBW ratio) is very sensitive in detecting fluid congestion (Park *et al.* 2018); it can help define cardiorespiratory fitness and functional capacity (Marawan *et al.* 2021) and has been used to guide fluid removal in acute heart failure patients (Yamazoe *et al.*

Tab. 6. BIA results of patient JK
TBW, total body water, ICW, intracellular water, ECW, extracellular water, Overhyd., overhydration, FFM, fat free mass, FM, fat mass, SMM, skeletal muscle mass, BCM, body cell mass, ATH, active body mass; *BIA measurement 1-3; **Reference standard

Patient 3 (JK)	1*	2*	3 *	**
TBW (%)	39.00	36.40	30.30	50-60
ICW (%)	19.10	18.30	14.90	
ECW (%)	19.90	18.10	15.40	
OVERHYD. (%)	2.20	1.00	-0.20	
FFM (%)	18.70	18.00	15.40	17-18
FM (%)	38.20	41.70	45.80	21-27
SMM (kg)	20.60	19.00	13.80	
BCM (kg)	20.00	19.60	14.70	
ATH (%)	61.80	58.30	54.20	73-79

2015). Oxidative stress leads to cell membrane damage, and in BIA measurements we find a decrease in BCM and a drop in the phase angle. A low P.A is associated with increased morbidity, nutritional risk and frailty (Kyle *et al.* 2004; Tanaka *et al.* 2019; Varan *et al.* 2016). Although PA is primarily a predictor of nutritional status, a falling PA indicates fluid loss (Gulatava *et al.* 2021, Scicchiano *et al.* 2020). Low PA can therefore be used as a prognostic marker (Kammar-García *et al.* 2021, Thanapholsart *et al.* 2020).

Our results from COVID 19 patients are consistent with the conclusions of these studies. We confirm that it is feasible to perform repeated BIVA measurements in critically ill patients, as in the study with 344 BIVA measurements on 61 patients (Jones *et al.* 2015). We can see overhydratation, position in the first quadrant, short vector length, gradual decline in phase angle, as can be seen from the graphical records of the typical findings from selected patients. The same results are described by Basso *et al.* (2013) and Cornejo-Pajera *et al.* (2022). We can see muscle loss corelated with the clinical development of polyneuromyopathy in critically ill patients with acute respiratory distress syndrome while they are on long term artificial pulmonary ventilation.

Limitations

The limitation of the method is that the human body is not a homogeneous cylinder. Further, as already mentioned, BIA uses simple or multiple regression equations based on healthy population data to make predictions of masses and volumes of body compartments. Therefore, some caution is needed in assessing BIA parameters in critically ill patients who typically show significant changes in hydration, especially in extreme weight categories and with extracorporeal circulation. The severity of hyperhydration with an increase in ECW due to fluid leak into the interstitium reflects the severity of the systemic inflammatory response (SIRS). In malnourished patients with reduced BCM, this may be masked by edema and an

Tab. 7. Patient IF: BIVA results for the 3 measurements.
R/H, height-adjusted resistance; Xc/H, height-adjusted reactance; PA, phase angle

measurement	R/H	Xc/H	vector length	PA
1	302,74	32,36	304,47	6,1
2	309,35	36,89	311,54	6,8
3	339,76	27,34	340,85	4,6

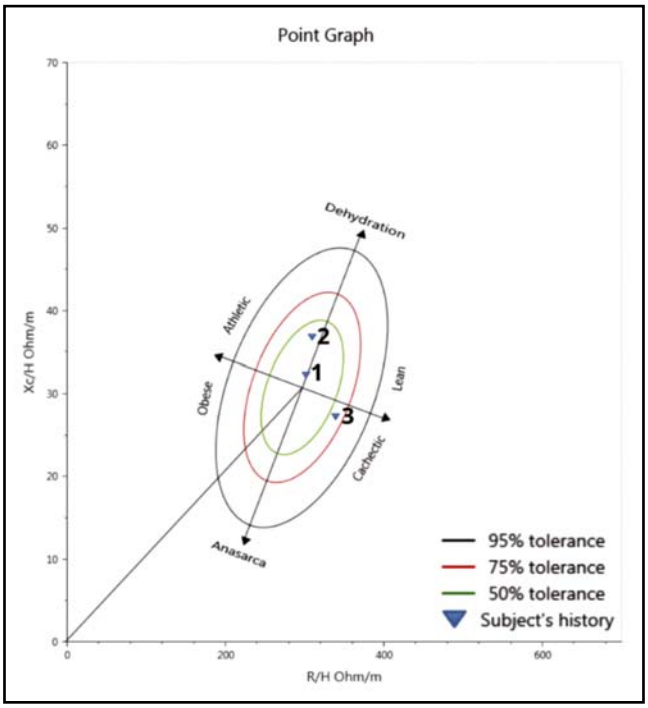

Fig. 8. Patient IF: BIVA results for 3 measurements, point graph
1st BIVA IF: Normal findings, athletic young male, normal PA 6.1
2nd BIVA after one week on artificial ventilation, vvECMO (from 3rd day), remains still O.K.
3rd BIVA. Patient is still under artificial ventilation and ECMO for severe respiratory insufficiency.
We are already seeing muscle loss and development of polyneuromyopathy in critically ill patients on long term artificial pulmonary ventilation and a gradual decline in phase angle (from 6.8 to 4.6), means severity of disease and signifying loss of BCM

Tab. 8. BIA results of patient IF
TBW, total body water, ICW, intracellular water, ECW, extracellular water, Overhyd., overhydration, FFM, fat free mass, FM, fat mass, SMM, skeletal muscle mass, BCM, body cell mass, ATH, active body mass; *BIA measurement 1-3; **Reference standard

Patient 4 (IF)	1*	2*	3 *	**
TBW (%)	48.10	54.90	44.80	55-65
ICW (%)	27.60	34.40	23.70	
ECW (%)	20.40	20.50	21.10	
OVERHYD. (%)	-0.10	-2.50	1.90	
FFM (%)	19.20	19.00	17.70	18-19
FM (%)	22.80	23.20	22.20	13-19
SMM (kg)	31.00	30.20	28.20	
BCM (kg)	34.70	42.90	27.30	
ATH (%)	77.20	76.80	77.80	81-87

accompanying increase in ECW. Greater accuracy in mapping body composition is expected with a multi-frequency approach and the addition of BIVA, which is based on raw impedance data.

Advantages

It is a simple method that can be performed at the bedside and provides information on hydration (TBW, ECW), nutritional status (BCM) and is also a good prognostic tool (using P.A. values) (Kyle *et al.* 2004b). Overall, BIA/BIVA is a more accurate method for body composition analysis compared to basic methods such as BMI, anthropometric measurements, and skin-fold measurements. Bioelectrical impedance is also a cost-effective and less time-consuming alternative to methods that require expensive instruments such as magnetic resonance imaging (MRI), dual-energy X-ray (DXA) (Prasad & Roy, 2020; Füstenberg & Davenport, 2011) and isotope dilution (Simpson *et al.* 2001). Bioimpedance may add useful information about the hydratation status of ICU patients, and combined with the newer bioelectrical impedance vector analysis, which eliminates some of the errors, this is a promising approach for personalized fluid management (Moritz & Ayus, 2015; Dewite *et al.* 2016; Yang *et al.* 2019).

Challenges

Using bioimpedance to monitor patient condition is highly challenging when the patient is unstable. A number of recent studies have aimed to assess the feasibility and validity of BIVA in the critically ill. They show that repeated BIVA to monitor hydration status is feasible in such patients, as it is correlated with cumulative fluid balance, and can have a prognostic role. BIVA hydration may be an additional measure of fluid status to assess treatment in the critically ill (Samoni *et al.* 2016; Pareja *et al.* 2022; Razzera *et al.* 2019; Yao *et al.* 2020).

But the sensitivity of repeated BIVA measurement to detect fluid accumulation, fluid balance or its prognostic role is low in some studies (Jones *et al.* 2015; Curbelo *et al.* 2019). On the other hand there are many studies that strongly validate BIVA for fluid assessment and management (Samoni *et al.* 2016; Yamazoe, *et al.* 2015; Park *et al.* 2018; De Ieso *et al.* 2021), and when PA can be used as a significant prognostic marker (Alves *et al.* 2016; Kammar-Garcia *et al.* 2021; Dabrowski *et al.* 2014; Colin-Ramirez *et al.* 2012; Stapel *et al.* 2018).

There is also a role in nutritional assessment (Hirose S *et al.* 2020; Scicchitano *et al.* 2020) with a strong correlation between dual-energy X-ray absorption (DEXA) and body composition measurement using MF-BIA (Alves at al.,2014; Shah *et al.* 2021).

The discrepancies seen may be due to the use of SF-BIA rather than MF-BIA, or BIS (Jones *et al.* 2015; Samoni *et al.* 2014). BIVA using raw impedance data without depending on regression equations are generally more precise.

CONCLUSION

BIVA is a feasible method for monitoring critically ill patients. We can initially observe overhydration, which signifies low PA. The more severe the inflammation is, the higher the fluid leakage into the interstitium. Upon muscle loss in the critically ill (ICU-AW), there is a shift from the left to the right lower quadrant. A low phase angle indicates degradation of cell membranes and unfavorable prognosis. On the other hand, a move to the upper left quadrant indicates an improvement in patient condition.

Changes in tissue composition in the critically ill, especially during sepsis may produce changes in electrical properties. Correct assessment of fluid status in the critically ill remains crucial for successful personalization of fluid management because both dehydration and overhydration can have detrimental consequences. Early intravascular volume expansion in shock states is vital. Overhydration is prevalent in the onset of acute critical illness as shown by analysis of bioimpedance data. This is due to fluid resuscitation, and depending on the severity of SIRS, mainly crystalloid solutions rapidly leak from the intravascular space into the interstitium. In this initial phase of shock, other methods, such as ultrasound/echocardiography, or methods based on the principle of monitoring stroke volume variability, are more productive in monitoring fluid resuscitation (R). Bioimpedance cannot discriminate between intravascular and interstitial components of extracellular fluid, and it provides no information about volume responsiveness. Nevertheless, it does give us indicators of hydration status, ECW/TBW, vector length and the BIVA quadrant. It turns out that monitoring the hydration status is extremely important also in other phases of shock resuscitation, which take much longer, and here bioimpedance is highly advantageous in monitoring body composition (raw impedance data, use of ECW/TBW ratio, vector length, phase angle) to optimize (O), stabilize (S), and manage fluid evacuation (E) and prevent excessive deresuscitation that can lead to decreased organ perfusion.

Bioelectrical impedance provides data not only about hydration (TBW, ECW, ECW/ICW ratio) but also about cell membranes indicating nutritional status (BCM, P.A.). Using these data shows promise in continuous monitoring of progress in the critically ill – chiefly as it is an inexpensive and easy-to-administer method that can be repeated at the patient's bedside.

Fluid assessment in the critically ill is quite challenging. There are different phases of shock (Resuscitation, Optimization, Stabilization and Evacuation) with different fluid requirements and the patients' cumulative fluid volume status can change. Fluid overload has a known detrimental effect. BIVA can be used as another piece in the hydration puzzle to help guide resuscitation and de-resuscitation during shock (ROSE).

AUTHORS CONTRIBUTIONS

KM, RK, NI, PK, BN, DP: data collection; KM: manuscript writing; KM, PK, BN, DP, RK, NI: final approval.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article. The study was supported by grant SGS09/LF/2022 from the Faculty of Medicine, University of Ostrava.

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