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Comparison of different methods for estimating total body water when describing mass and fluid transfer in dialysis

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Abstract: Over the years, more and more attention has been dedicated to the development of personalized hemodialysis treatment. In order to succeed in this, various mathematical models have been developed, able to estimate, throughout the duration of the dialysis session, the concentrations of solutes and blood volume of the patient. The goal of this work was to investigate how different methods to estimate the total body water of the patient influenced the performance of one of these models, the Casagrande model. The methods considered were Watson anthropometric formula, Chertow anthropometric formula, Daurgidas anthropometric formula and the bioelectrical impedance analysis.

Performance was assessed by the error in the estimation of solute concentrations (sodium, potassium, chloride, calcium, bicarbonate, magnesium, urea, and glucose) at the beginning, end, and at each hour of the duration of the dialysis session.

The results showed that there is not a particular method that is better than the others. While the Chertow anthropometric formula appears to be a slightly worse option than the others, the choice of which method to use

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can be made according to the preferences of the center in which treatments are performed.

It can also be concluded that, in order to further improve the performance of the mathematical model, it will be necessary to focus on other areas, since the choice of the method for estimating total body water does not seem to have a significant impact on performance.

Key-words: Dialysis, Total body water, Mathematical model, Anthropometric formula, BIA

1. Introduction

Hemodialysis (HD) is a therapy administered to patients suffering from end-stage renal disease (ESDR). Although the quality of the treatment has improved over time, there are still multiple comorbidities associated with it. Over the years, there has been a growing need to make this treatment personalized, since the response to hemodialysis can vary greatly from individual to individual, even when it is performed with the same parameters.

In order to achieve this goal, mathematical models have recently been developed whose purpose is to predict fluid volumes and electrolyte concentrations in the patient's body compartments. In particular, recently Casagrande et al. [1] developed a multicompartmental model, which can characterize each patient according to specific parameters, and predict the concentrations of the following solutes:

- sodium (Na^+)
- potassium (K^+)
- calcium (Ca^{2+})
- chloride (CL^-)
- bicarbonate (HCO_3^-)
- urea

The model, developed in Matlab®, is characterized by two stages. In the first stage, solute concentrations are determined by solving a system consisting of mass, fluid and pressure balance equations. In the second phase, instead, through an optimization algorithm, patient-specific parameters are estimated, with the aim of further improving the accuracy of the model.

Initially, the model was run using data from 20 patients at the Regional Hospital of Lugano (Lugano, Switzerland), who were undergoing hemodiafiltration (HDF) 3 times per week. The total number of sessions available was 131.

To assess the quality of the model, the percentage error obtained by comparing the solute concentrations determined using the model and those obtained clinically has been evaluated. For each session, the concentrations after 1,2,3, and 4 (end of session) hours of treatment were used.
Regarding the pre-optimization stage, the mean error was less than 10% for calcium, less than 15% for sodium, potassium, chloride, and bicarbonate, and less than 21% for urea.
As for the optimization step, the results improved further, obtaining an average error of less than 2% for sodium, chloride and calcium, less than 3% for bicarbonate, and less than 8% for potassium and urea.
As can be seen, for some of the solutes the results obtained are very good. On the other hand, it can be seen that the results obtained for urea are not as satisfactory as desired.

With the aim of further improving the performance of the model, the author suggested to focus on the way to estimate the total body water (TBW) of the patient, which in the model is determined using the anthropometric formula of Watson [2], modified by a factor that takes into account the fact that uremic patients carry excess fluid in comparison to health population.
Therefore, the purpose of this work was to investigate what valid alternatives were available to determine TBW. The work was divided into two parts. In the first part we searched the literature for valid alternatives to Watson modified formula. In the second part, the model was tested using these alternatives, and it was evaluated whether the results obtained were superior or inferior to those obtained with the original model. The database available to test the various models was composed of 142 patients, from 4 different hospitals (Como, Lecco, Lugano, Varese), for a total of 881, as shown in Table 1.

Hospital	# Patients	# Sessions
Como	30	180
Lecco	62	371
Varese	30	180
Lugano	20	150
Total	142	881

Table 1: number of patients and sessions by hospital

2. Materials and methods

The work is divided into two parts. In the first one, we searched the literature for viable alternatives to Watson anthropometric formula for estimating TBW. Specifically, Chertow anthropometric formula, Daurgidas anthropometric formula, and estimation of TBW by BIA were chosen. The various methods were compared with each other based on patient data used to validate the Casagrande model to see if the TBWs obtained were statistically different from each other.
Finally, all methods were implemented in the model, and it was analyzed whether their use led to percentage errors regarding solute concentrations that were statistically different from each other.

Total body water estimation methods

In the original model, it is necessary to determine TBW when the initial three body fluid volumes (plasmatic, interstitial and intracellular), which are calculated as shown in Equation 1, hasto be determined.

$$V_{pl}(0) = 0{,}077 \cdot W(0) \cdot \frac{1 - Ht(0)}{100}$$

$$V_{is}(0) = \frac{TBW(0) - V_{pl}(0)}{3.68} \tag{1}$$

$$V_{ic}(0) = 2.68 \cdot V_{is}(0)$$

V_{pl} is the plasma volume, V_{is} is the interstitial volume, V_{ic} is intracellular volume, and Ht is hematocrit.
The equations were taken from the body fluid distributions suggested by (Guyton et Hall, 2006) [3].
In the original model, in order to determine TBW, Watson anthropometric formula are used, modified to account for excess fluid in uremic patients.
In searching for viable alternatives to the latter, only options that did not require additional data to those available clinically were considered. Among the available data, those that could potentially have been useful for our purpose were:

- age
- gender
- height
- Body-weight before the session
- Body-weight after the session
- causes of the Chronic Kidney Disease
- other concurrent diseases (diabetes, heart disease, insulin, etc.)
- prescribed dry weight
- weight loss during the session
- concentration of solutes at the start of the session (sodium, potassium, calcium, urea, chloride, bicarbonate, parathormon, Beta-2 mycoroglobulin, creatinine, magnesium, phosphate, albumin, total calcemia, phosphorus)
- bioelectrical impedance analysis (BIA) data (TBW, intracellular water (ICW), extracellular water (ECW) BMI, etc.). Note that, in general, these data were not measured for each session, but just for the first and last session of each patient.

In searching for viable alternatives to Watson modified formula, three different paths were followed.

First, since Watson formula is an anthropometric formula, we checked to see if there were other anthropometric formula in the literature that had the purpose of determining TBW. It was thus discovered, that in addition to Watson's formula, valid alternatives are the Chertow formula [4] and the Daurgidas formula [5].

The second idea was to focus on the distribution volume of urea. In fact, urea distribution volume and TBW are considered to be identical [6,7]. Urea distribution volume has been extensively investigated in the literature, since it is needed to calculate Kt/V (where K is the effective dialyser urea clearance, t is the duration of hemodialysis, and V is the urea distribution volume), which is one of the most widely used parameters to evaluate the efficacy of dialysis treatment. To calculate the Kt/V, from which the distribution volume can be subsequently derived, two categories of mathematical models have been mainly developed, the Single Pool Urea Kinetic Model (SPUKM), which assumes that TBW consists of a single compartment, and the Double Pool Urea Kinetic Model (DPUKM), which assumes that TBW consists of two compartments.

From these categories of models, equations are derived to calculate Kt/V. To date, the most widely used are those reported in Equation 2 [8,9].

$$_{sp}(Kt/v) = -\ln(R - 0.008 \cdot t) + (4 - 3.5R) \cdot \frac{UF}{W}$$

(2)

$$_{eq}(Kt/v) = _{sp}(Kt/v) - (0.47 \cdot _{sp}(Kt/v))/t + 0.02$$

$_{sp}$(Kt/v) is the Kt/v derived from a SPUKM model, $_{eq}$(Kt/v) is derived from a DBUKM model, R s the ratio between post-dialysis and pre-dialysis BUN (blood urea nitrogen), UF is the ultrafiltration volume in liters, and W is the post-dialysis weight of the patient.

Since post-dialysis BUN is required to calculate BUN, these methods were not considered. The aim of this work is in fact to analyze methods that can estimate TBW before the dialysis session.

The last path focused on the TBW determined by BIA.

Watson anthropometric formula

Watson anthropometric formula was obtained by performing a linear regression on data from 458 men and 265 women, collected from 30 different studies conducted in North America, Europe, and Australia. In general, the study subjects were healthy, and a number of obese subjects respecting the percentage of obesity in Western populations was used. The original TBW was obtained using dilution methods, known to be very accurate (deuterium, tritium, antipyrine, N-acetyl-4-amino antipyrine, urea). Depending on gender, the following two equations were obtained.

For females:

$$TBW = -2.097 + 0.1069 \cdot H + 0.2466 \cdot W \quad (3)$$

For males:

$$TBW = 2.447 - 0.09516 \cdot A + 0.1074 \cdot H + 0.3362 \cdot W \quad (4)$$

H is the height of the individual, W is the weight of the individual, A is the age of the individual.
The strength of these equations is that they allow, in healthy patients, to estimate TBW quite well, using simple anthropometric data, which are easily measurable (height, weight, age).
On the other hand, the biggest limitation in our case is that they were derived from data of non-uremic patients. Since uremic patients tend to accumulate excess fluid, it is not possible to say a priori that Watson formula can be a valid option for predicting their TBW.
To try to solve this problem, a modified version of Watson formula was implemented in the original model, as can be seen in Equation 5 and Equation 6.
For females:

$$TBW = -2.097 + 0.1069 \cdot H + 0.2466 \cdot DW + (W - DW) \quad (5)$$

For males:

$$TBW = 2.447 - 0.09516 \cdot A + 0.1074 \cdot H + 0.3362 \cdot DW + (W - DW) \quad (6)$$

where DW is dry weight.
Although this correction seems reasonable, it is impossible to establish its efficiency, since there is no research in the literature comparing TBW obtained with modified Watson formula to TBW obtained through dilution methods.

Chertow anthropometric formula

Chertow formula was created to overcome the limitations of Watson formulas. In fact, it is derived using data from 3009 patients undergoing dialysis. While in Watson's study TBW was estimated using dilution methods, in this case BIA was used. This is because it is complex, both practically and economically, to apply a dilution method to such a large number of patients. Although probably a less accurate way to derive TBW, BIA has been shown to be a valid way to derive TBW. Moreover, at the end of the study, data from 33 patients whose TBW had been estimated using a

dilution method (deterium oxide dilution) were used to revalidate the formula, obtaining satisfying results.

Data were obtained from centers in the USA, and the sample was composed of 45.4% Caucasian, 46.9% African-American, 6.5% Hispanic, and 1.2% other ethnicities.

To obtain the formula, a linear regression was performed. The following equation was obtained (Equation 7):

$$\begin{aligned} TBW = &-0.07493713 \cdot A - 1.01767992 \cdot G + 0.12703384 \cdot H - 0.04012056 \cdot W \\ &+ 0.57894981 \cdot D - 0.00067247 \cdot W^2 - 0.03486146 \cdot A \cdot G \\ &+ 0.11262857 \cdot G \cdot W + 0.00104135 \cdot A \cdot W + 0.00186104 \cdot H \cdot W \end{aligned} \quad (7)$$

where A is the age of the patient, G is the gender of the patient (1 if male, 0 if female), H is the height, W is the weight of the patient, D is equal to 0 if the patient is not diabetic, 1 otherwise.

When compared to Watson formula, an additional parameter comes into play, namely whether the patient is diabetic or not. This is an information that is easily obtainable and therefore does not add complexity when compared to Watson formula.

Additionally, in the paper is performed a comparison with Watson formula, showing that it tends to significantly underestimate the TBW of patients, confirming that it is not extendable a priori to uremic patients. This is also why Watson anthropometric formula was corrected in the original model.

On a theoretical level, Chertow formula would seem to be an alternative to Watson formula. In this work it is therefore compared with the modified Watson formula.

Daurgidas anthropometric formula

Unlike the previously seen studies, which aimed to derive anthropometric formulas to derive TBW, in this paper the main focus was on comparing urea distribution volumes obtained with mathematical models of urea kinetics to TBW obtained using Watson and Chertow formulas. This investigation originated from the need to further investigate the relationship between distribution volume and TBW. Data from 1124 uremic patients, of African American or Caucasian ethnicity, with a total of 5308 dialysis were used in this study. The results obtained showed that anthropometric formulas tended to give higher TBW values than distribution volumes obtained with any model of urea kinetics. The authors concluded that it is not possible to state whether the difference obtained is

attributable to inaccuracies in the models and methods, or whether there is actually an actual difference between TBW and distribution volume in uremic patients. In this case, there is no direct comparison with either dilution methods or BIA, which makes it difficult to draw conclusions.
However, the authors have proposed correction factors to Watson formula, obtained by performing a linear regression that had as output variable the distribution volume obtained by SPUKM, adjusted to take into account the post-dialysis rebound of urea, and considered by the author an effective way to determine the distribution volume.
The following equation was obtained (Equation 8):

$$V_m = TBW_{Watson} \cdot 0.828 \cdot (1.045\ if\ African\ American) \cdot (1.032\ if\ diabetic) \quad (8)$$

where V_m is the urea distribution volume of the patient, TBW_{Watson} is TBW obtained by applying Watson anthropometric formula. In this formula ethnicity also appears as a variable, which is an easily obtainable parameter. Note that only two ethnicities were considered in the sample, so we would need to consider what would change if the sample were composed of more ethnicities. Since the patients in our model are all of Caucasian ethnicity, we were able to simplify Equation 8, resulting in Equation 9.

$$V_m = TBW_{Watson} \cdot 0.828 \cdot (1.032\ if\ diabetic) \quad (9)$$

As in the Chertow formula, importance is given to the diabetic condition.
Theoretically, the result obtained is a volume of distribution, but since the scientific literature seems to indicate that volume of distribution of urea and TBW coincide, it was taken as a possible method to evaluate TBW.

BIA

BIA is a method used to determine body composition (TBW, fat mass, lean body mass). It gets these results from measuring the impedance of the body to the flow of electric current through the body. In fact, each body structure causes a different drop in intensity by electric current.
BIA has been shown to be a valid method for measuring TBW in healthy subjects [9-11]. It has also been tested in patients with ESDR [12]. In this paper, TBW obtained by BIA was compared with dilution methods (deuterium oxide (D2O) and sodium bromide (NaBr)). Although the number of subjects used was not particularly high (33 patients), the results indicated that also in this case BIA is a valid tool for estimating TBW.
The advantages of BIA are that it turns out to be an easy-to-implement modality, since it is a tool widely available in hospitals and since it requires little time to be performed (some seconds).

Comparison among different TBW estimation methods

As a first step, TBW was calculated for each patient for whom all the necessary data were available, using the 4 different methods (modified Watson formula, Chertow formula, Daurgidas formula), in order to evaluate whether the results obtained were significantly different from one another.
While data from only 20 patients were available when the original model was developed, over the years the database has grown to include 142 patients, for a total of 881 dialysis sessions.
For our analysis, patients for whom all of the following information was available were selected:

- Gender
- Age
- Height
- Bodyweight before the session
- Dry weight
- Diabetes
- TBW estimated by BIA

- Extracellular water and intracellular water estimated by BIA.

After excluding patients in whom one or more of these data were missing, a sample of 102 patients was obtained.

At the statistical level, we first evaluated, through the Lilliefors test, whether the difference between TBW obtained with Watson formula and the various methods followed a normal distribution, considering the results significant for $P < 0,01$. Then, based on the results shown in the "Comparison among different TBW estimation methods" paragraph of the "Results" section, a nonparametric test (Wilcoxon singned rank test) was applied, considering the results significant for $P < 0.01$. Based on the results shown in the paragraph just mentioned, it was decided to test all three alternatives' methods in the model.

Model testing

After having validated the choice of the different methods on a statistical level, we moved on to their implementation in the model.

For each method, solute and session, the normalized root mean squared error (nRMSE) was evaluated (Equation 10), which was the parameter on which the statistical analysis was carried out.

$$nRMSE_y^{sess} = \sqrt{\frac{1}{N} \cdot \sum_i \left(\frac{y_{i,MOD} - y_{i,CLIN}}{y_{i,CLIN}}\right)^2} \quad (10)$$

y is the solute considered, sess the session considered, N the number of concentrations measured per session, $y_{i,MOD}$ the concentrations calculated by the model and $y_{i,CLIN}$ the clinically measured concentrations.

The considered solutes were:

- sodium (Na^+)
- potassium (K^+)
- chloride (CL^-)
- calcium (Ca^{2+})
- bicarbonate (HCO_3^-)
- magnesium (Mg^{2+})
- urea

- glucose

With the exception of potassium, for which N = 2 since concentrations were measured only at the beginning and end of the session, for all other solutes N = 5 since concentrations were measured at the beginning, end, and at each hour of treatment.

With regard to the number of patients and sessions used to run the model, there was a substantial difference in the sample size used for TBW calculated by anthropometric formulas and that used for those calculated by BIA. This is because, as mentioned above, BIA was performed in only two of the usually six sessions, and in some patients TBW data were not available at all.

Table 3 shows the number of patients and sessions on which each formula was tested.

Method	Patients	Sessions
Watson modified	142	881
Chertow	142	881
Daurgidas	142	881
BIA	116	218

Table 3: sample size of patients and sessions by method

For these reasons, the statistical analysis using two samples of different sizes. The first sample (Sample 1) included all sessions that resulted in valid results in all anthropometric formulas, while the second sample (Sample 2) included those that worked with both Watson formulas and BIA.

For each method, the number of sessions for which the model failed to complete the calculation of concentrations, either because of the inability of the algorithm to optimize the data, or because of other coding problems, or due to the lack of some data.

Regarding the statistical analysis, a paired value analysis was performed, using the modified Watson formula as reference. As for the anthropometric formulas, Sample 1 was used, while Sample 2 was used for the comparison with BIA. First, it was tested whether the distributions of the differences between Watson formula and the other methods were normally distributed, through the Lilliefors test, considering the test significant in the case of P value < 0.01. Since based on the test results the distributions can be assumed to be nonnormal, a nonparametric test (Wilcoxon signed rank test) was then applied for each pair, considering the test statistically significant if $P < 0.05$. For each pair, the test was applied 5 times to a random sample consisting of half of the entries in the original sample.

3. Results

Comparison among different TBW estimation methods

The distributions derived for each method are shown in Figure 1, the medians and IRQs in Table 2.

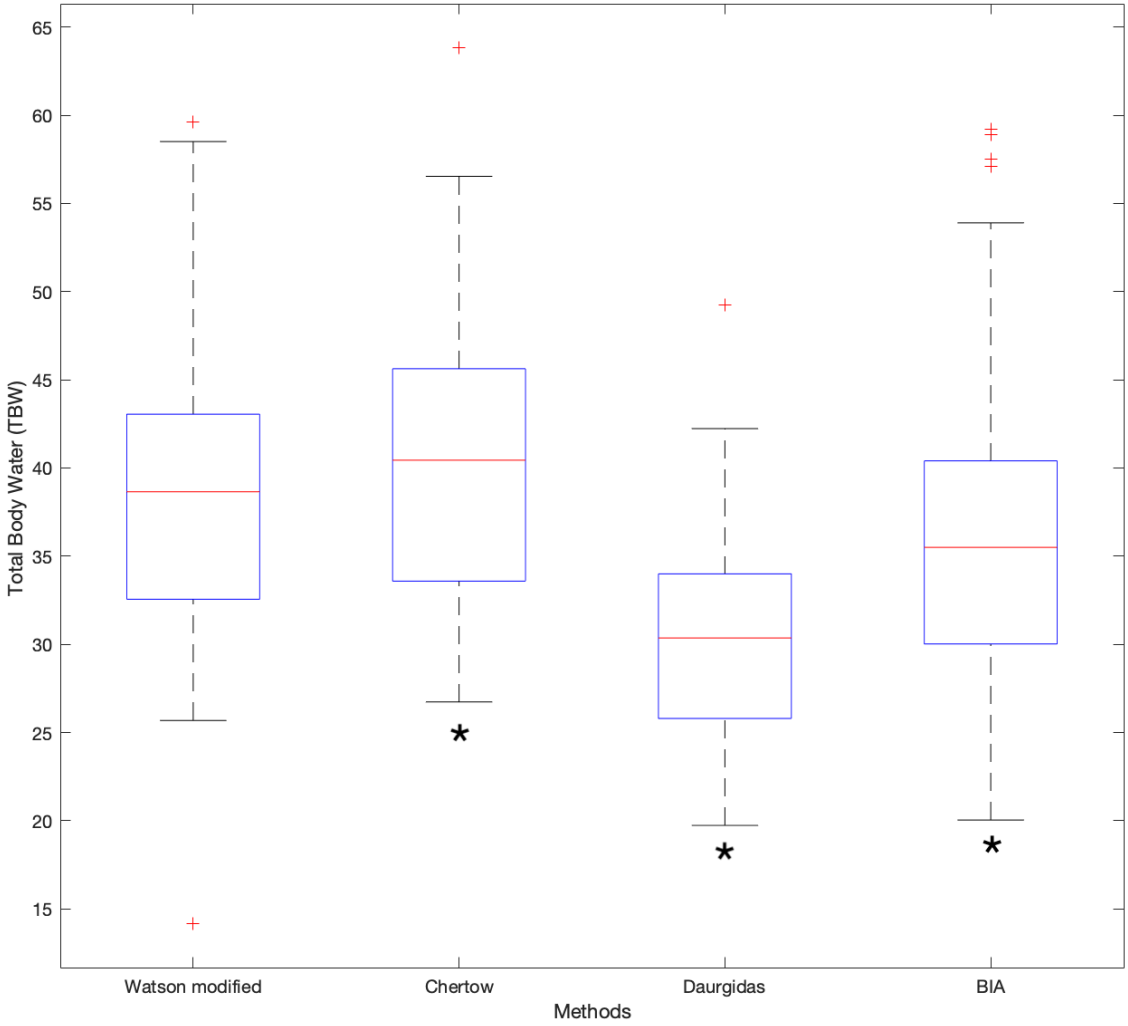

Figure 1: Estimates of total body water by anthropometric formula (Watson modified, Chertow, Daurgidas) and BIA.

* if P < 0,01 compared to Watson modified formula (Wilcoxon signed rank test)

Method	TBW (L)
Watson modified	38.65 (32.56, 43.05)
Chertow	40.44 (33.58, 45.63)
Daurgidas	30.36 (25.79, 33.93)
BIA	35.50 (30.02, 40.40)

Table 2: median and IQR for TBW by method

For what regards the normality test, in all four cases the P value was < 0.01, which is the value for which we considered the test significant.

As for the Wilcoxon signed rank test, all three comparisons were found to be statistically significant, meaning that the populations of TBW values appears to be different.

Analyzing the results, it can be seen that the average TBW obtained with Daurgidas anthropometric formula is the lowest of all. This is in agreement with the research in which it is defined [5], in which the linear regression is carried out considering as output variable the urea distribution volume calculated via SPUKM, adjusted to account for the post-dialysis rebound of urea. In fact, the volumes of distributions calculated by SPUKM and DPUKM turn out to be lower than those determined by any anthropometric formula.

The relationship between BIA and Chertow's formula was already analyzed in [7], resulting in higher TBW in the case of BIA. These results are in disagreement with ours.

Finally, it is interesting to note the relationship between Chertow formula and modified Watson formula. Of all the methods, these are the two in which the results ar(, on average, most similar. This could be a confirmation that the assumption made about Watson formula in the original model is valid, since the Chertow formula was obtained by linear regression from data of uremic patients.

Model testing

Table 4 shows, for each method, the number of sessions for which the model failed to finish the optimization algorithm, and the percentage of these with respect to the total.

Method	Tested sessions	# Not completed
Watson modified	881	266
Chertow	881	286
Daurgidas	881	262
BIA	218	67

Table 4: sample size of patients and sessions by method

Regarding the comparison between the 3 anthropometric formulas, the results are shown in Figure 2 and Table 5.

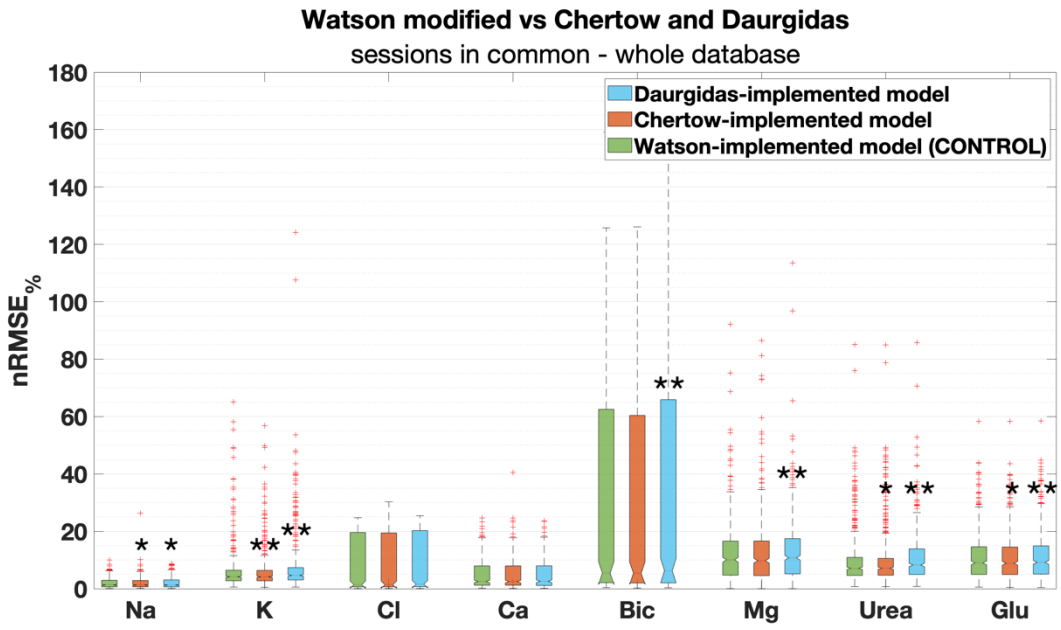

Figure 2: nRMSE by solute for modified Watson formula, Chertow formula and Daurgidas formula

* if 0,01 < P < 0,05, ** if P < 0,01 compared to the RMSE obtained by using the modified Watson formula to estimate TBW into the model

	Na	K	Cl	Ca	Bic	Mg	Urea	Glu
Watson modified	1.30 (0.65,2.95)	4.15 (2.78,6.44)	1.38 (0.64,19.60)	2.50 (1.21,7.95)	5.44 (1.38,62.54)	10.08 (4.72,16.61)	7.12 (4.60,10.91)	8.99 (4.95,14.62)
Chertow	1.29 (0.65,2.87)	4.13 (2.74,6.39)	1.37 (0.11,19.45)	2.49 (1.22,7.96)	5.41 (1.49,60.39)	9.76 (4.56,16.63)	7.14 (4.68,10.59)	8.87 (4.93,14.52)

Daurgidas	1.28 (0.64,3.07)	4.62 (3.05,7.34)	1.57 (0.25,20.26)	2.59 (1.12,7.97)	6.27 (1.99,65.87)	10.77 (5.18,17.44)	8.27 (4.95,13.90)	9.17 (5.09,14.93)

Table 5: median and interquartile range by solutes for modified Watson formula, Chertow formula and Daurgidas formula

Looking at Figure 2, it can be seen that, with regard to the Daurgidas formula, in all cases there was a statistically significant result, except for sodium, but it was leading to a higher nRMSE than the modified Watson formula (potassium, bicarbonate, magnesium, urea, glucose). From this it can be inferred that the Daurgidas formula does not appear to be a viable alternative to the modified Watson formula. On the other hand, with regard to the Chertow formula, in the case of statistically significant results, there was a slight improvement with regard to sodium, potassium, and glucose, and a slight deterioration with regard to urea. Thus, there is no basis for stating that Chertow formula is, overall, a better alternative to Watson modified ones, also considering the fact that it requires one more piece of information than the latter (diabetes).

Looking at Figure 2, we see that, in all cases, bicarbonate, and to a lesser extent chloride, have a significantly higher upper quartile than all other solutes. This result appears to be independent of the type of method used, but related to the hospital facility in which the data were collected. In fact, looking at Figures 3-6, which show the nRMSEs subdivided by hospital structure, it can be seen that, as far as bicarbonate and chlorine are concerned, the data from Lecco present results that are definitely worse than those from Lugano, Como and Varese.

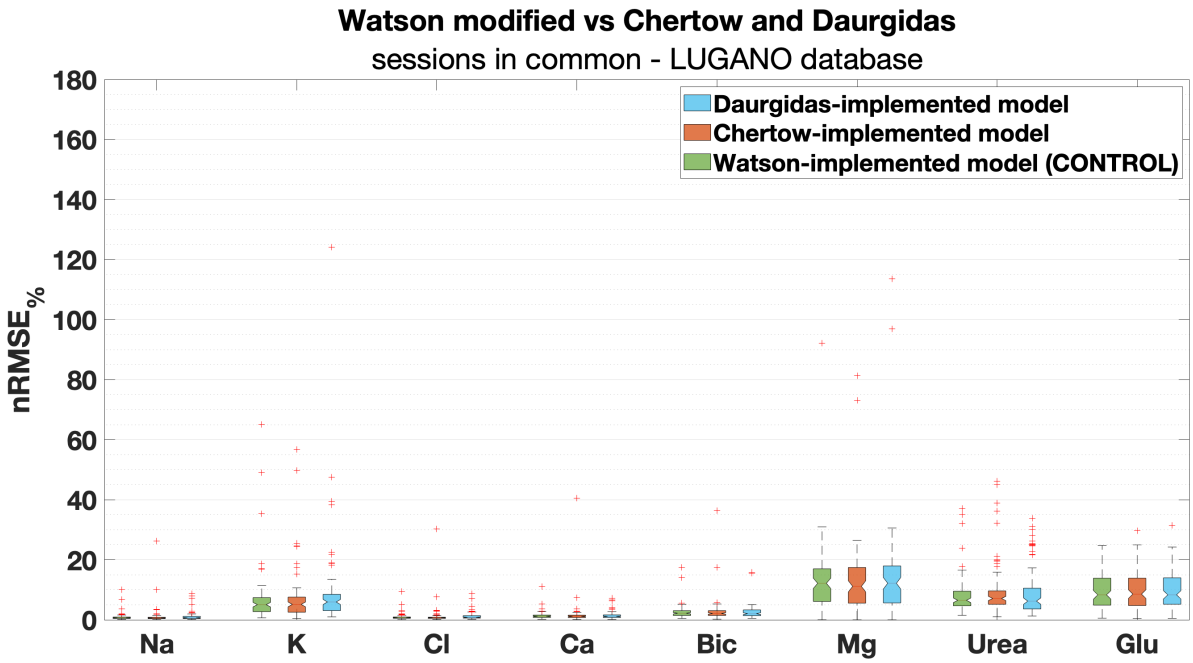

Figure 3: **nRMSE by solute for modified Watson formula, Chertow formula and Daurgidas formula (LUGANO)**

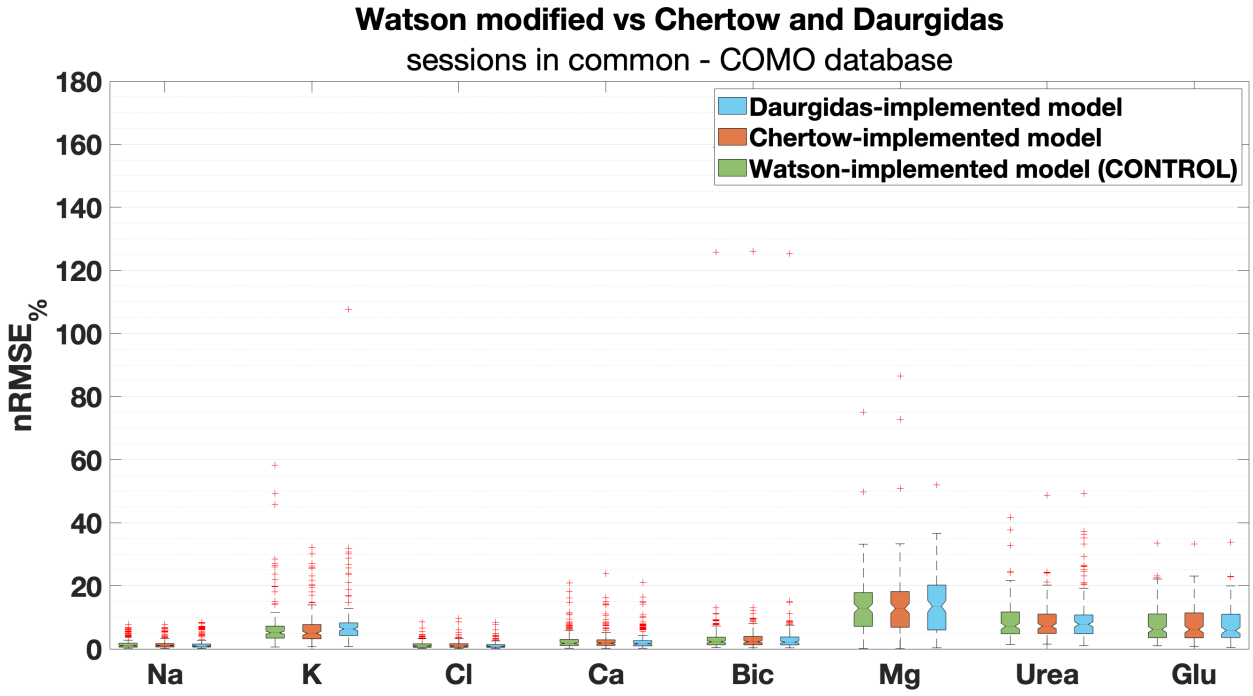

Figure 4: **nRMSE by solute for modified Watson formula, Chertow formula and Daurgidas formula (COMO)**

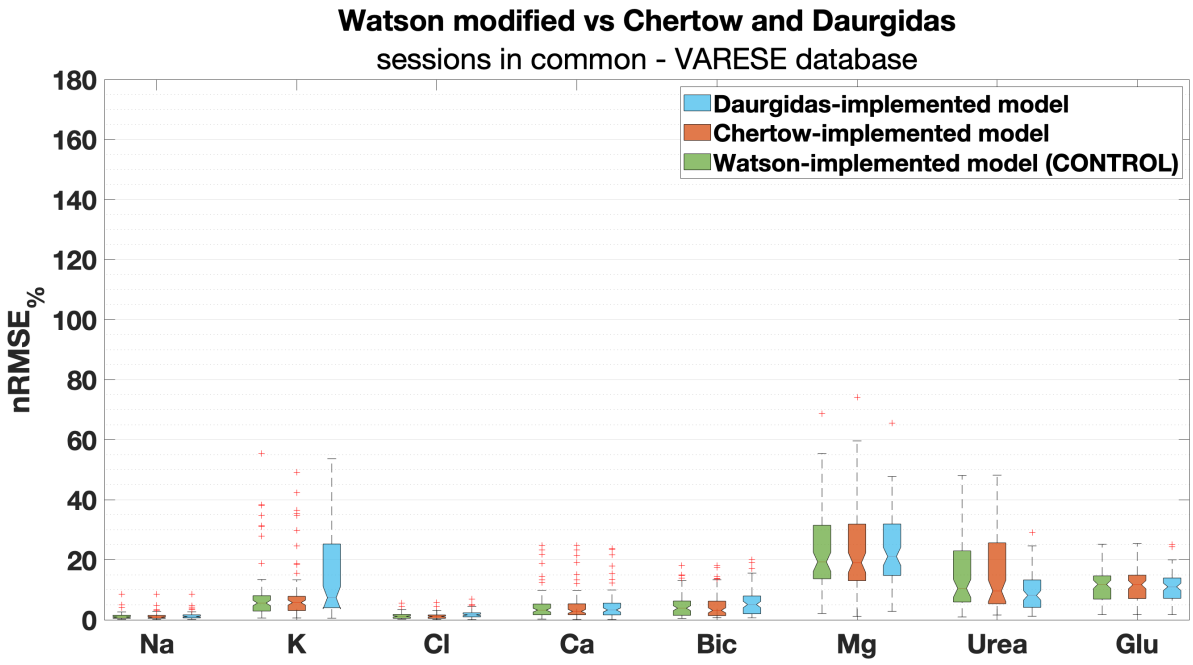

Figure 5: nRMSE by solute for modified Watson formula, Chertow formula and Daurgidas formula (VARESE)

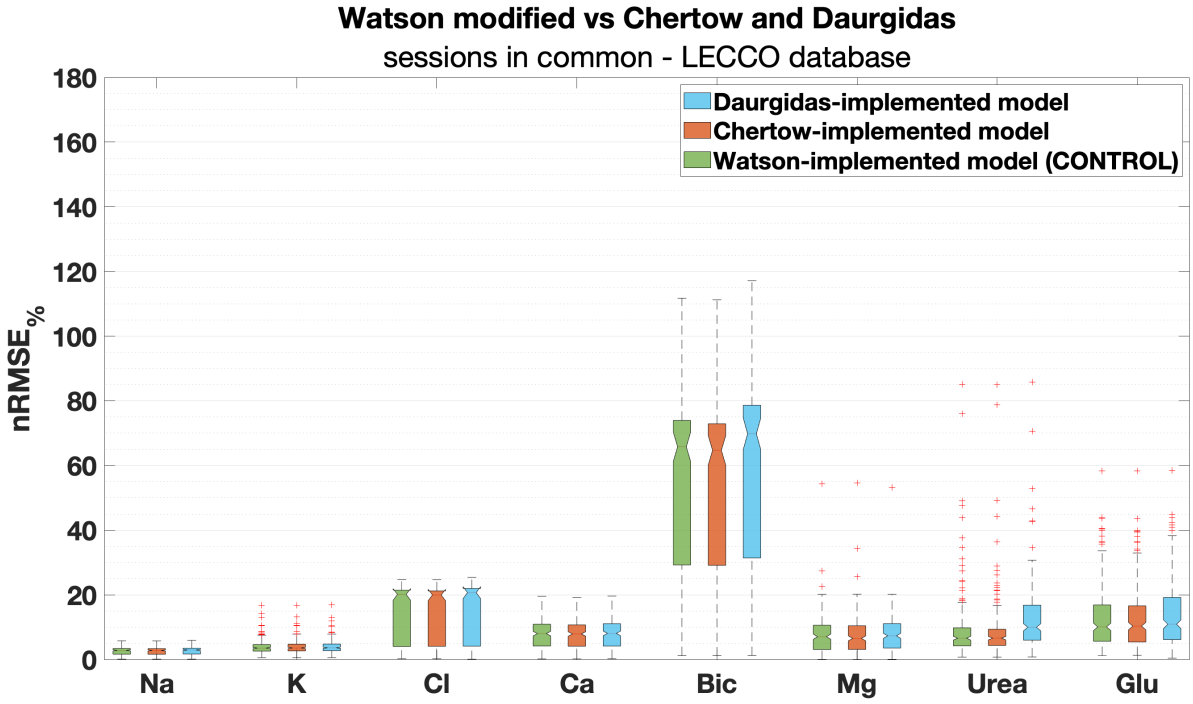

Figure 6: nRMSE by solute for modified Watson formula, Chertow formula and Daurgidas formula (LECCO)

The reason for this difference between the Lecco hospital and the others centers is not clear. Further analysis in this direction is needed.

Regarding the comparison between Watson formula and BIA, the results are shown in Figure 7 and Table 6.

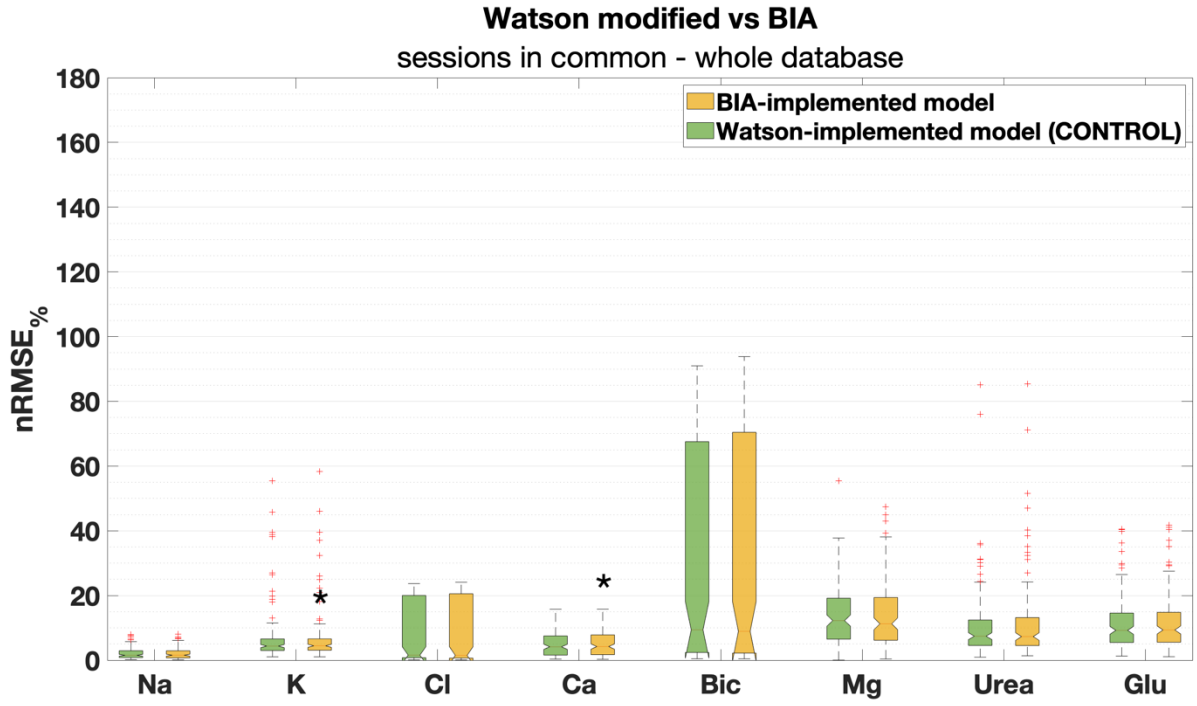

Figure 7: nRMSE by solute for modified Watson formula and BIA

* if 0,01 < P < 0,05, ** if P < 0,01 compared do modified Watson formula

	Na	K	Cl	Ca	Bic	Mg	Urea	Glu
Watson modified	1.53 (0.82,2.95)	4.38 (3.00,6.58)	1.58 (0.80,20.02)	4.15 (1.58,7,52)	9.39 (2.41,67,54)	12.25 (6.52,19.18)	7.44 (4.56,12.44)	9.24 (5.49,14.58)
BIA	1.56 (0.72,2.93)	4.46 (3.09,6.62)	1.50 (0.67,20.55)	4.23 (1.72,7.83)	8.93 (2.21,70.43)	11.26 (6.17,19.40)	7.31 (4.54,13.19)	9.35 (5.56,14.81)

Table 6: median and interquartile range by solutes for modified Watson formula and BIA

Looking at Figure 2, we see that we have statistically significant results for only two solutes (potassium and calcium), and in both cases the TBW estimated via BIA results in a worse nRMSE than Watson formula. Thus, it seems clear that using TBW estimated from BIA instead that from Watson anthropometric formulas does not lead to better results.

Also, in this case we note the problems related to chloride and bicarbonate, but here too these errors are related exclusively to the structure of Lecco, as shown in Figures 8-10. In this case there is not a figure showing data from Lugano's hospital, since there were not sessions in common between the two methods.

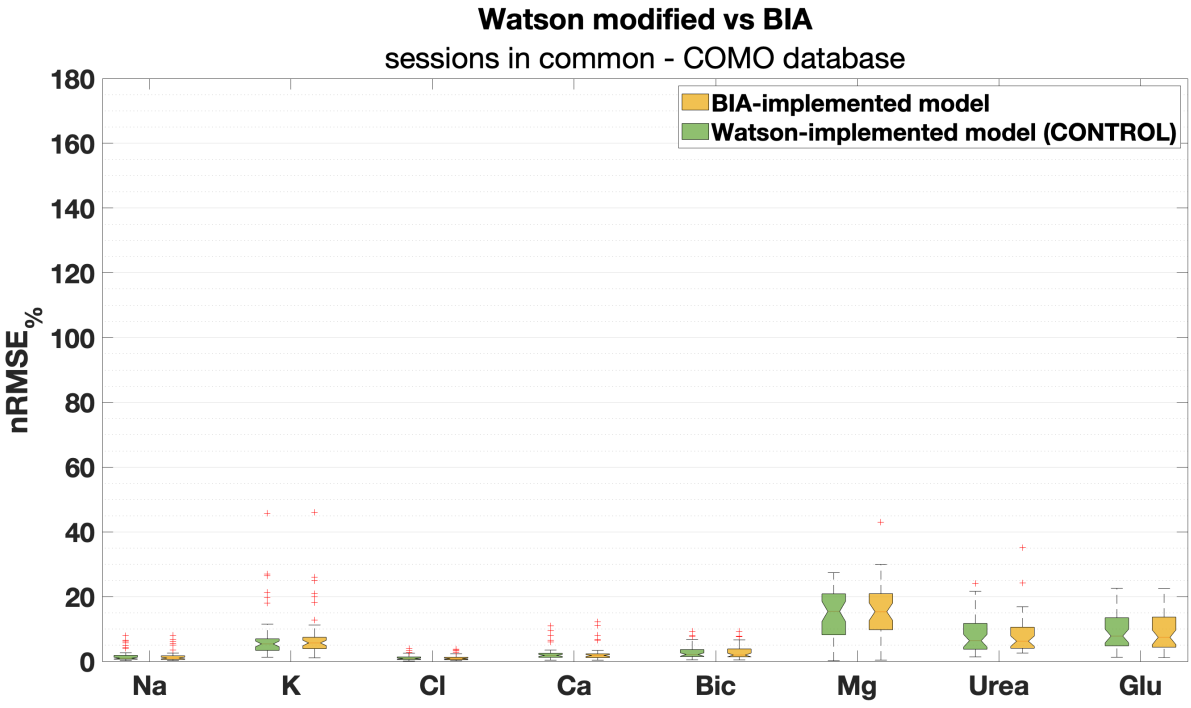

Figure 8: nRMSE by solute for modified Watson formula and BIA (COMO)

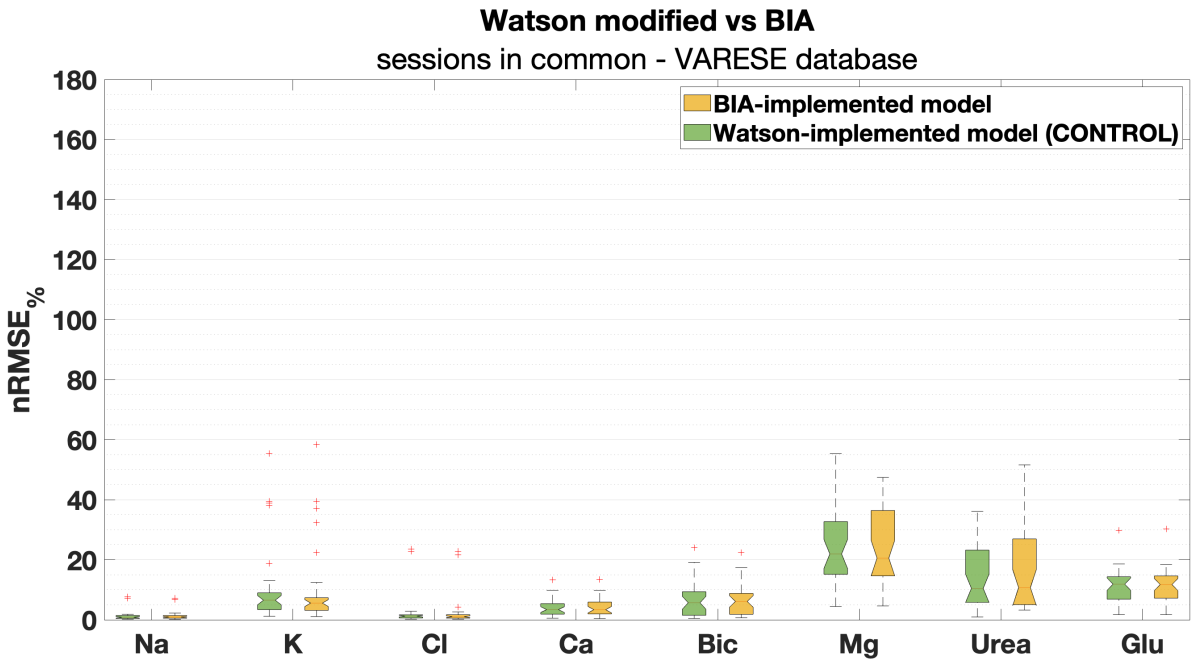

Figure 8: **nRMSE by solute for modified Watson formula and BIA (VARESE)**

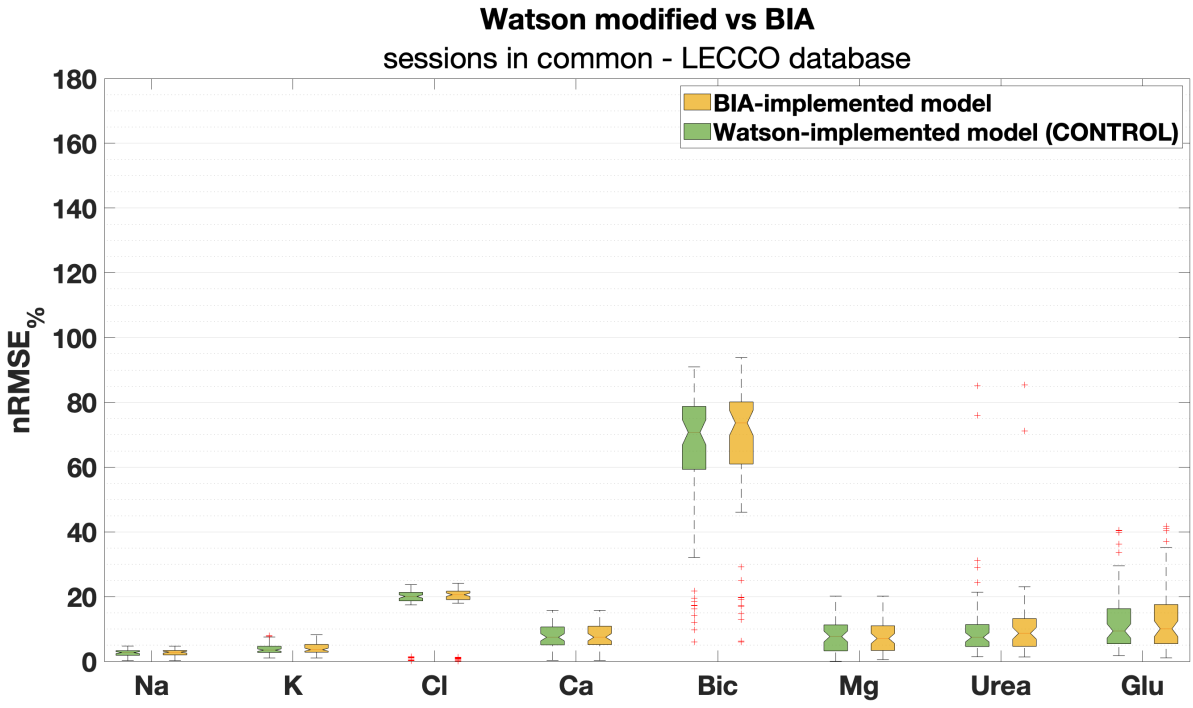

Figure 9: **nRMSE by solute for modified Watson formula and BIA (LECCO)**

For completeness, although a direct comparison was not made before, for the reasons above explained, the distributions of nRMSEs for all methods are shown in Figure 11.

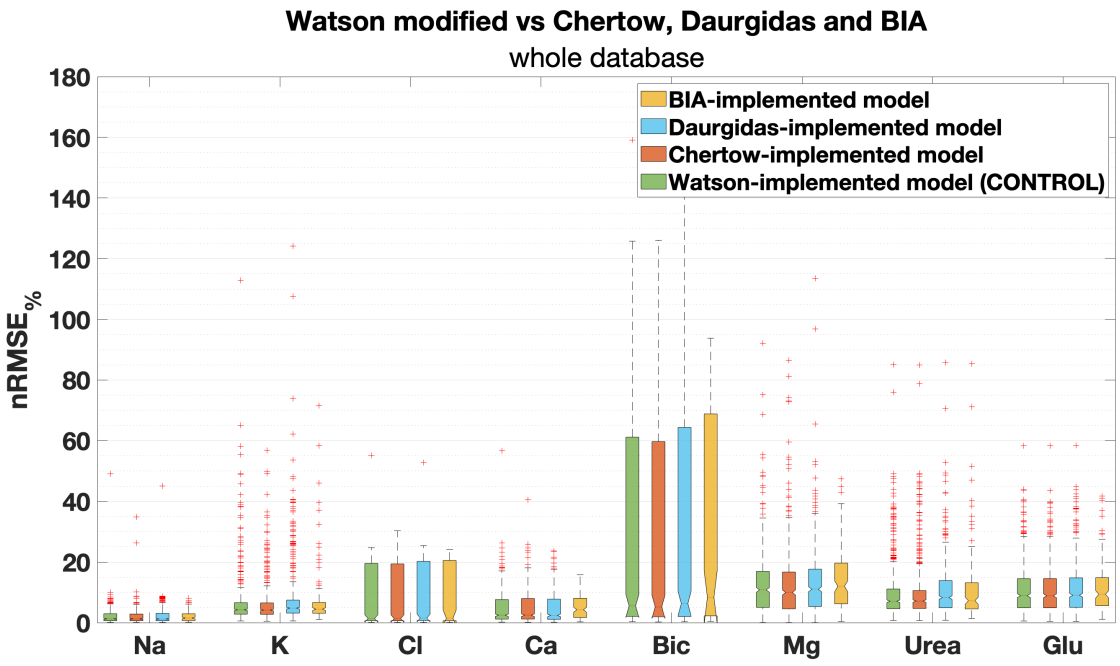

Figure 12: nRMSE by solute for all the tested methods

4. Discussion and Conclusions

The results obtained indicate that none of the alternative methods identified for the formula already implemented in the model (modified Watson) leads to a clear improvement in model performance.

In order to estimate the TBW in the clinical field it is therefore possible to choose which method to adopt according to the demands. As far as the model is concerned, one more reason is added to continue to use the formula already implemented, as it offers comparable performance with the others, but requires less information on comorbidities (diabetes).

Using BIA, on the other hand, is a justified choice, and if the necessary instrumentation is present in the hospital where the patient is performing dialysis, the choice between the latter and using the modified Watson formulas can be made based on staff preference. Regarding BIA a possible future development would be the evaluation of model performance if it were used not only to estimate TBW but also extracellular fluid volume. This is why only sessions for which this information was also available were included in the sub-population chosen to do the first analysis.

To further validate these results, it would be desirable to also have data available from dialysis sessions performed on patients of other ethnicities as well.

Finally, it is interesting to note that although TBW estimates with the various methods are statistically different from each other, the nRMSEs obtained are very similar to each other. This may be due to

the fact that the model optimization algorithm, regardless of the method used to estimate TBW, manages to provide excellent results.

This work has allowed us to highlight that, if we want to try to further improve the performance of the model, it will probably be necessary to analyze aspects other than the way TBW is estimated.

5. References

[1] Casagrande, G., Bianchi, C., Vito, D., Carfagna, F., Minoretti, C., Pontoriero, G., Rombolà, G., Schoenholzer, C., & Costantino, M. L. (2016). Patient-specific modeling of multicompartmental fluid and mass exchange during dialysis. *International Journal of Artificial Organs*, *39*(5). https://doi.org/10.5301/ijao.5000504

[2] Watson, P. E., Watson, I. D., & Batt, R. D. (1980). Total body water volumes for adult males and females estimated from simple anthropometric measurements. *American Journal of Clinical Nutrition*, *33*(1). https://doi.org/10.1093/ajcn/33.1.27

[3] Guyton, Arthur C., C. (2016). Guyton And Hal Textbook Of Medical Physiology 13TH ED. In *Departement of Physiology and Biophysics* (Vol. 4, Issue 3).

[4] Chertow, G. M., Lazarus, J. M., Lew, N. L., Ma, L., & Lowrie, E. G. (1997). Development of a population-specific regression equation to estimate total body water in hemodialysis patients. *Kidney International*, *51*(5). https://doi.org/10.1038/ki.1997.216

[5] Daugirdas, J. T., Greene, T., Depner, T. A., Chumlea, C., Rocco, M. J., & Chertow, G. M. (2003). Anthropometrically estimated total body water volumes are larger than modeled urea volume in chronic hemodialysis patients: Effects of age, race, and gender. *Kidney International*, *64*(3). https://doi.org/10.1046/j.1523-1755.2003.00179.x

[6] San Pietro, A., & Rittenberg, D. (1953). A study of the rate of protein synthesis in humans. I. Measurement of the urea pool and urea space. . *J Biol Chem 201*, 445–455.

[7] Himmelfarb, J., Evanson, J., Hakim, R. M., Freedman, S., Shyr, Y., & Ikizler, T. A. (2002). Urea volume of distribution exceeds total body water in patients with acute renal failure. *Kidney International*, *61*(1). https://doi.org/10.1046/j.1523-1755.2002.00118.x

[8] Daugirdas, J. T. (1995). Simplified Equations for Monitoring Kt/V, PCRn, eKt/V, and ePCRn. *Advances in Renal Replacement Therapy*, *2*(4). https://doi.org/10.1016/S1073-4449(12)80028-8

[9] Ahmad Taher Azar. (2013). *Modelling and Control of Dialysis SystemsAhmad Taher Azar*.

[10] Lukaski, H. C., Johnson, P. E., Bolonchuk, W. W., & Lykken, G. I. (1985). Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *American Journal of Clinical Nutrition*, *41*(4). https://doi.org/10.1093/ajcn/41.4.810

[11] Lukaski, H. C., Bolonchuk, W. W., Hall, C. B., & Siders, W. A. (1986). Validation of tetrapolar bioelectrical impedance method to assess human body composition. *Journal of Applied Physiology*, *60*(4). https://doi.org/10.1152/jappl.1986.60.4.1327

[12] Kushner, R. F., & Schoeller, D. A. (1986). Estimation of total body water by bioelectrical impedance analysis. *American Journal of Clinical Nutrition*, *44*(3). https://doi.org/10.1093/ajcn/44.3.417

[13] Chertow, G. M., Lowrie, E. G., Wilmore, D. W., Gonzalez, J., Lew, N. L., Ling, J., Leboff, M. S., Gottlieb, M. N., Huang, W., Zebrowski, B., College, J., & Lazarus, J. M. (1995). Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *Journal of the American Society of Nephrology*, *6*(1). https://doi.org/10.1681/asn.v6175

6. Abstract in lingua italiana

Negli anni ci si sta concentrando sempre di più sullo sviluppo di trattamenti personalizzati per quanto riguarda l'emodialisi. Per riuscire in questo intento, sono stati sviluppati vari modelli matematici, in grado di stimare, per tutta la durata della seduta dialitica, le concentrazioni dei soluti e del volume ematico del paziente. Obiettivo di questo lavoro è stato quello di indagare come diverse metodiche per stimare il volume complessivo di fluidi del paziente potessero influenzare le prestazioni di uno di questi modelli, il modello Casagrande. Le metodiche prese in considerazione sono state le formule antropometriche di Watson, la formula antropometrica di Chertow, la formula antropometrica di Daurgidas e la bioimpedenziometria.

Le prestazioni descrittive del modello sono state valutate calcolando l'errore nella stima delle concentrazioni dei soluti (sodio, potassio, cloruro, calcio, bicarbonato, magnesio, urea, glucosio) all'inizio, alla fine, e ad ogni ora durante la seduta dialitica.

I risultati hanno mostrato che non vi è una metodica significativamente migliore delle altre. Si può inoltre concludere che, per cercare di migliorare ulteriormente le prestazioni del modello matematico, bisognerà concentrarsi su altri aspetti, dal momento che la scelta della metodica di stima del volume di fluidi totali non sembra avere un impatto significativo sulle prestazioni.

Parole chiave: Dialisi, Total body water, Modello matematico, Formule antropometriche, BIA