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A predictive index of intra-dialysis IDH

A statistical clinical data mining approach

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***Abstract*— Intra-Dialysis Hypotension (IDH) is one of the main hemodialysis related complications, occurring in 25-30% of the sessions. The factors involved in the onset of hypotension in patients undergoing dialysis are due both to clinical conditions (e.g. presence of vascular or cardiac diseases, neuropathology, anemia) and treatment settings such as temperature of the dialysate, sodium concentration, buffer composition, ultrafiltration rate, etc. The patient's peculiar reaction to the treatment implies difficulties in preventing IDH episodes. This work explores the possibility to use a multivariate analysis of clinical data to quantify the risk to develop IDH at the beginning of each session. The study is framed in the DialysIS project (Dialysis therapy between Italy and Switzerland) funded by INTERREG – Italy – Switzerland and Co-funded by European Union. Data referring to a total of 516 sessions performed on 70 adult patients undergoing dialysis treatment (50 patients enrolled at A. Manzoni Hospital Lecco, Italy and 20 patients at Regional Hospital of Lugano, Switzerland) were collected. Clinical prescriptions, hydration status, dialysis machine data and hematochemical data were recorded and stored in a unique flexible structured MySQL® database. A statistical analysis was performed to find the potential risk factor related to IDH onset.**

IDH episodes were automatically detected during the monitored sessions, according to the literature criteria. Patients suffering from IDH in 2 or more sessions were classified as Hypotension Prone (HP), the others as Hypotension Resistant (HR). Initial values of potassium concentration [K+], systolic (SBP) and diastolic (DBP) blood pressure, and weight gain (ΔW) from the end of the previous treatment result to be statistically different between the HP and HR groups.

A new index, J, was defined as a weighted patient-specific combination of these parameters and calculated for each session of each patient. The weight of the index coefficients can be dynamically adjourned based on the longitudinal analysis of [K+], SBP, DBP, and ΔW.

The results reported in this paper were calculated based on a longitudinal analysis of a minimum of three sessions for each patient. The accuracy of the J index in predicting IDH events has been evaluated and quantified in terms of percentage number of predicted IDH events, with respect to the total number of IDHs. Values of J index higher than 1 point out the risk of IDH onset.

J allows the prediction of 100% of IDH episodes using 5 sessions, the 90% using 3 sessions. More specifically, at Lecco Hospital 43 IDH events were detected by the automatic system of which 100% and 95% were respectively predicted by the new index calculated using 5 or 3 sessions. Similarly, at Lugano Hospital 58 IDH were detected by the automatic system of which 100% and 87,5% were predicted using 5 or 3 sessions respectively. A longer longitudinal dataset will allow a higher matching of J to actual IDH episodes.

In conclusion, the evaluation of this new index at the beginning of the dialysis session prior to connecting the patient to the machine can provide the clinician with useful information about the risk for the patient to develop cardiovascular instabilities (IDH) during the treatment and can advise the physician about the need to modify the prescription.

***Keywords*— statistical analysis, data mining, predictive index, intra-dialysis hypotension, hemodialysis.**

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I. Introduction

The factors involved in the onset of hypotension in patients undergoing dialysis (HD) are due both to clinical conditions (e.g. presence of vascular or cardiac diseases, neuropathology, anaemia) and treatment settings such as temperature of the dialysate, sodium concentration, buffer composition, ultrafiltration rate, etc. Intra-HD nausea, vomit and fainting could be symptoms of hypotension that imply discomfort for the patient and extra work for the clinicians. Moreover, when IDH implies a premature interruption of the dialysis session, the patient's blood may not be adequately purified. On the long-term, frequent hypotension episodes may lead to permanent damages to the heart and intestine [2]. In general, clinical procedures to manage IDH include the reduction of blood flow in the extracorporeal circuit, reduction of ultrafiltration rate and recovery of adequate blood volume trough the infusion of fluids, allowing the increase in blood volume and pressure [3]. The question is how to avoid or prevent IDH. In recent years, IDH prevention has been investigated with different approaches, highlighting the multifactoriality of the phenomenon.

One of the open challenges is to determine the probability for the patient to suffer from IDH before the HD session (offline prediction). The patient's peculiar reaction to the treatment may be crucial in reaching this goal. This work explores the possibility to use a multivariate analysis of clinical data to quantify the risk to develop IDH at the beginning of each session.

This study is framed in the DialysIS project (Dialysis therapy between Italy and Switzerland) funded by INTERREG – Italy – Switzerland and Co-funded by the European Union.

II. Materials and methods

A. Data acquisition

The research has been based on the clinical data acquired from 70 patients; 50 patients has been enrolled in Lecco (Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy), and other 20 in Lugano (Nephrology and Dialysis, Regional Hospital of Lugano, Lugano, Switzerland). The enrolled patients were selected with specific criteria: adults undergoing standard or alternative HD therapies performed for at least three months and wearing arteriovenous fistula (native or prosthetic) as vascular access., The age of the enrolled patients (65% males and 45% females) was 70,07±10,89 years with a dialysis age (time from the first treatment) of 61,5±10,89 months, among these patients 31% was affected by diabetic nephropathy and 90% shown heart disease.

The data were collected either from monitor sensors, bio-impedenzimeter, hemogasanalyzer (blood electrolytes and main catabolites), and nurse survey.

Blood volume variation and ultrafiltration rate were continuously monitored; other relevant intra-dialysis parameters (systemic pressure, heart rate, blood parameters, patient weight) were also monitored at scheduled times. Adverse events, fluid infusions and food and beverage consumption during the treatment have been annotated, during each session. Personal and anamnestic data, together with treatment settings were also recorded.

All the acquired data have been cleaned, harmonized and stored in a common database (DB). Six to eight sessions for each patient have been analysed, for a total of 516 sessions.

With specific reference to pre-dialysis conditions, the analysis of this work has been focused on a subset of data: patient weight gain (with respect to the end of the previous session), initial main electrolytes concentration in blood (Ca^{2+}[mmol/l], Mg^{2+}[mmol/l], Na^{+}[mmol/l], K^{+}[mmol/l], Cl^{-}[mmol/l], Urea[mmol/l]), heart rate [bpm], systolic and diastolic pressure [mmHg].

B. Data analysis

The first question to deal with was to automatically find the IDH episodes in the recorded data, so as to evaluate in a second step what parameters differed between hypotension prone and hypotension resistant patients.

The most acknowledged definition of hypotension takes into consideration three criteria: i) if pre-dialysis Systemic Arterial Pressure (SAP_0) is higher than 100 mmHg, then every event with SAP less than 90 mmHg, even without disorders, is considered as IDH episode; ii) if SAP_0 is lower than 100 mmHg, IDH is any reduction of at least 10% SAP_0, related to symptoms; iii) IDH is any reduction in SAP by at least 25% SAP_0, together with symptoms requiring specific interventions (cramps, nausea, vomit) [4].

The patients were classified as IDH prone and resistant, defining Hypotension Prone (HP) a patient who suffered from IDH in 2 or more sessions and Hypotension Resistant (HR) a patient who suffered from 1 IDH episode at most.

Due to the multifactorial nature of IDH, the development of a predictor for these events needs a multivariate analysis of the clinical pre-dialysis values of the parameters. The statistical analysis was performed in different steps: at first, analysing the mean values and the standard deviation of each parameter for each patient and for the entire population, secondly studying the variations in blood pressure, heart rate and blood composition between the beginning of a dialysis session and the end of the previous on (interdialysis period).

The normal distribution of the sample has been verified, then appropriate parametric statistical F-test and t-test analyses has been performed, to determine which among the treatment parameters appears significantly different between HR and HP patients.

C. Development of the new index

A multivariate index "J" has been developed in order to have a unique parameter for the offline prediction of IDH events. This index has been defined as a weighted patient-specific combination of the parameters that showed to be statistically different between HP and HR patients; these parameters were classified as influencing parameters.

The new index, J, was calculated for each session of each patient. A threshold was set to1; a pre-dialysis value higher than 1 warns the clinician about potential IDH onset.

D. J index coefficients calibration

A normalized weight was assigned to each event recognized as a potential risk factor for the onset of IDH. The value of each influencing parameter (IF) was multiplied by the corresponding weighted coefficient (w_c) and each product was added to the others. The result of this sum is the value of the J index.

$$J_t = \sum w_c \cdot IF \qquad (1)$$

The calibration of the weight coefficients has been performed taking into account the incidence (n_{ijk}) of the influencing parameters on the total number of hypotensive events (N) registered on the whole population. The variations of the influencing parameters have been studied to define Basic Pre-Dialysis Conditions (BPDC) that can be related to the variation from the reference value of one or more other influencing parameters. The Reference Patient Profile Condition (RPPC) was defined as the collection of the cumulative mean values of the influencing parameters, iteratively updated for each treatment starting from b to the k-1 treatment, where b is the number of the available treatments for the longitudinal analysis and k is the total amount of the monitored sessions for each patient.

The evaluation of the RPPC has been performed respectively for b equal to 3 and 5 sessions.

A finite set of possible IDH causes (C_{ijk} cases), has been identified. Values of the weight coefficients have been determined for each patient considering the finite set of C_{ijk}. In this way a specific weight was assigned to each BPDC, taking

into account the deviation of each parameter from the average condition.

The expression of J considers also the hypotension proneness (hp), defined as the number of the previous sessions characterized by IDH, for a specific patient.

The hp parameter wants to quantify the effect of the patient-specific clinical history on the potential risk of IDH onset.

A. *J index accuracy evaluation*

The accuracy of the index has been evaluated in terms of number of false positive and negative determined by the index with respect with IDH episodes clinically recorded and automatically identified in the database according to the previous defined criteria.

III. Results

The sample of patients appears representative of the population of dialysis patients [5]. Initial values of potassium concentration [K+], systolic (SBP), diastolic (DBP) blood pressure, mean arterial pressure (MAP) and weight gain (ΔW) from the end of the previous treatment result to be statistically different between the HP and HR patients. Specifically the weight gain and the initial potassium concentration were significantly higher and the blood pressure (SBP, DBP, MAP) significantly lower in HP compared to HR patients ($p<0.01$). The results for weight gain and MAP are shown in Figure 1.

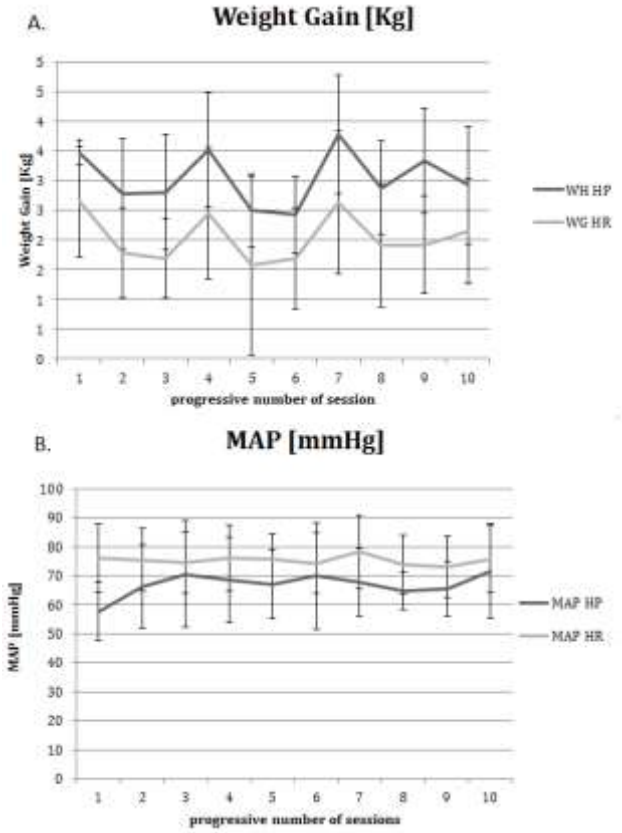

Figure 1. Comparison the averaged weight gain. and MAP in HP and HR patients respectively. The results were represented in terms f average and stanbdard deviaton.

TABLE I. FINITE SET OF POSSIBLE IDH ONSET CONDITIONS

IDH ONSET CONDITIONS			
Occurring BDPC	**C_{ijk}**	**n_{ijk}**	**α,β,γ**
None	C_{000}	n_{000}	$\alpha=\frac{n_{000}}{N}$, $\beta=\frac{n_{000}}{N}$, $\gamma=\frac{n_{000}}{N}$
$BDPC_1$: $K_t^+ \geq \overline{K}^+$	C_{100}	n_{100}	$\alpha=\frac{n_{100}}{N}$, $\beta=0$, $\gamma=0$
$BDPC_2$: $\Delta W_t \geq \overline{\Delta W}$	C_{020}	n_{020}	$\alpha=0$, $\beta=\frac{n_{020}}{N}$, $\gamma=0$
$BDPC_3$: $MAP_t \leq \overline{MAP}$	C_{003}	n_{003}	$\alpha=0$, $\beta=0$, $\gamma=\frac{n_{003}}{N}$
$BDPC_1$&$BDPC_2$: $K_t^+ \geq \overline{K}^+$, $\Delta W_t \geq \overline{\Delta W}$	C_{120}	n_{120}	$\alpha+\beta=\frac{n_{120}}{N}$, $\frac{\alpha}{\beta}=\frac{n_{100}}{n_{020}}$, $\gamma=0$
$BDPC_1$ & $BDPC_3$: $K_t^+ \geq \overline{K}^+$, $MAP_t \leq \overline{MAP}$	C_{103}	n_{103}	$\alpha+\gamma=\frac{n_{100}}{N}$, $\frac{\alpha}{\gamma}=\frac{n_{100}}{n_{030}}$, $\beta=0$
$BDPC_2$ & $BDPC_3$: $\Delta W_t \geq \overline{\Delta W}$, $MAP_t \leq \overline{MAP}$	C_{103}	n_{103}	$\beta+\gamma=\frac{n_{023}}{N}$, $\frac{\beta}{\gamma}=\frac{n_{020}}{n_{003}}$, $\alpha=0$
$BDPC_1$ & $BDPC_2$ & $BDPC_3$: $K_t^+ \geq \overline{K}^+$, $\Delta W_t \geq \overline{\Delta W}$, $MAP_t \leq \overline{MAP}$	C_{123}	n_{123}	$\alpha+\beta+\gamma=\frac{n_{123}}{N}$, $\frac{\alpha}{\beta}=\frac{n_{100}}{n_{020}}$, $\frac{\beta}{\gamma}=\frac{n_{020}}{n_{003}}$

a. List of the finite set of possible factors involved in IDH onset and the equations used to determine the weight coefficients for J.

The normal patient profile condition (NPPC) was defined as the collection of the cumulative mean values $\overline{K}$, $\overline{\Delta W}$ and $\overline{MAP}$ of the influencing parameters. Values of α, β and γ coefficients have been determined for each patient considering the C_{ijk} list. A specific weight was assigned to each BPDC,

taking into account the deviation of each parameter from the average condition. With reference to Table 1, the final formulation of the patient-dependent J index, for each treatment (t), is given in equation (2):

$$J_t = \frac{\alpha}{K} \cdot K_t^+ + \frac{\beta}{\Delta W} \cdot \Delta W_t + \frac{\gamma \cdot \overline{MAP}}{MAP_t} + hp_t \qquad (2)$$

The predictive ability of J are shown in Figure 2, where the different outcomes obtained by using b=3 and b=5 for the NPPC are reported . When b=5, J was able to predict the 100% of treatments characterized by IDH events, with a 38% of false positives (session at risk of IDH, without IDH onset). When b=3 J allowed the prediction of the 90% of sessions characterized by IDH, with the 36% of false positives. More specifically at Lecco Hospital 43 IDH events were detected by the automatic system of which 100% were predicted by the new index based on b=5; while the 90% of IDH was instead predicted when b=3. Similarly, at Lugano Hospital 58 IDH events were detected by the automatic system, 100% of which were predicted by the new index using b=5, the 87,5% using b=3.

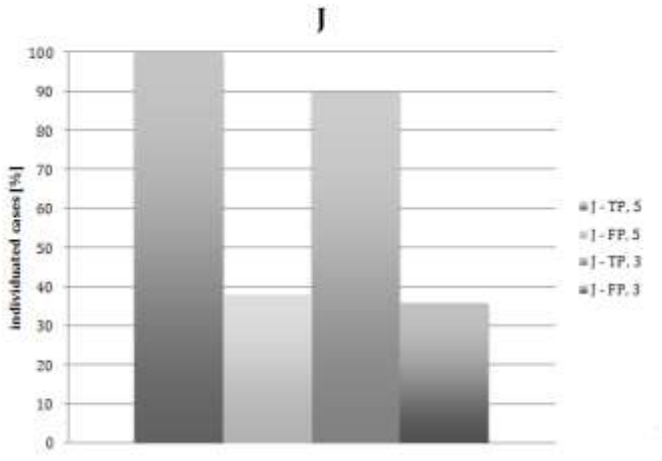

Figure 2. Prediction accuracy of J, evaluated as percentage of predicted IDH (TP=True Positive) and of False Positive sessions (FP). Two different longitudinal datasets (b=3, b=5) were used.

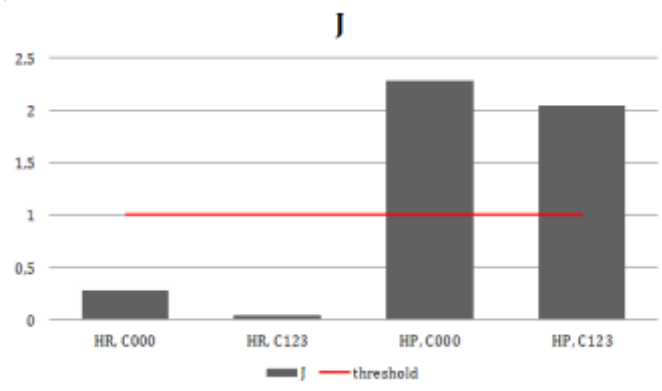

Figure 3. J discrimination thresold and values of J evaluated for different RPPC and BDPC

Figure 3 shows the values of J evaluated for different RPPC and BDPCs. The red line indicates the threshold used for the discrimination of the session at potential risk of IDH onset. Different patients profiles, corresponding to different BPCDs, are shown. The first one corresponds to an HR patient beginning the dialysis treatment without any variation in the influencing parameters pointing out IDH risk. The second one refers to a condition characterized by initial $BPCD_1$, $BPCD_2$, and $BPCD_3$ in a HR patient. In both these cases J is lower than the threshold, thus any alarm of IDH risk would not be highlighted and the sessions has a regular outcome. The third and fourth conditions both refer to HP patients showing no variations in the influencing parameters or BPCD condition respectively. In these situations the values of J surpasses the threshold, thus highlighting IDH risk. The corresponding clinical data confirmed the onset of hypotension during these two specific sessions.

IV. Discussion

The statistical analysis of a large dataset of clinical data allowed extracting a predictive index of hypotension during the dialysis treatment.

J is multifactorial index, based on the weighted combination of the pre-dialysis values of potassium concentration [K+], systolic (SBP) and diastolic (DBP) blood pressure, and weight gain (ΔW) taking into account also the proneness of the specific patient to IDH. It can be calculated at the beginning of each session, through non-invasive measurements and gives the clinician useful information on the probability of IDH onset during the specific treatment, that can be tuned and personalized to avoid IDH onset.

The results highlight that the minimum number of dialysis sessions to be monitored for a reliable evaluation of BPDCs results to be 3. Very good predictability is achieved with b=5. The weight coefficients can be then dynamically adjourned based on the longitudinal analysis of the influencing parameters. The number of false positive keeps quite constant when b varies. This can be ascribed to the action of patient-specific compensatory mechanisms during the therapy. A longer (b>5) longitudinal monitoring of the patient response could imply the automatic correction of the coefficient so as to take into account the ability of these patients to contrast IDH onset.

A further optimization of the index will include the heart rate among the influencing parameters [7].

V. Conclusions

The new index J shows to be capable to determine the probability for a patient to develop hypotension during a specific dialysis session, taking into account his/her peculiar characteristics. It is thus possible to give the clinician useful information about a correct tuning of the therapy.

The index has been tested in its prediction accuracy on a population of patients treated in two different clinical units, located in different countries. The high prediction percentage in both centres highlights the robustness of the index. J index shows to be a useful tool for the evaluation of the patient proneness to IDH in clinical practice.

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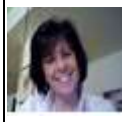

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