Effects and Impact of Fluid Creep in Intensive Care Unit Patients Receiving Intravenous Fluid Therapy After One Week

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Abstract

The management of fluids plays a crucial role in the Intensive Care Unit (ICU) requiring specific customization to meet the needs of the individual patient with the primary goal of restoring cardiovascular stability. We know that excessive fluid administration is associated with increased mortality among hospitalized patients. In this context, we can define the term "fluid creep" as the amount of intravenous fluids used to dilute medications and to maintain catheter patency. Our study focused on fluid creep by conducting a retrospective analysis at a single center using data from the MargheritaTre(M3) database. The aim was to identify variables associated with changes in fluid creep distribution through a linear model (LM), and to implement a classification model to identify patients at risk of receiving a high quantity of creep after one week of ICU admission. The study included 4786 patients receiving an average of 1.6 liters of fluids within the first 24 hours and an average of 2.4 liters during the first week of hospitalization.

For classification, we tested 8 machine learning models using grid search for hyperparameter tuning with 5-fold cross-validation. The hyperparameters were selected to attain the highest average accuracy across the 5 folds. The best machine learning prediction results were obtained with the multilayer perceptron, which showed an accuracy of 0.80 on the hidden test set in predicting patients at risk of receiving high fluid creep.

1. Introduction to Intravenous fluids

During intensive care unit (ICU) admission, patients receive various types of fluids. Treatments in the ICU are subject to customization for each patient, and the absence of clear guidelines makes the management of these fluids very complex [1]. The management of fluids plays a crucial role in the ICU and therefore requires specific customization to meet the needs of the individual patient, primarily aiming to restore cardiovascular stability. While the focus is often primarily on resuscitation fluids, there are other less obvious sources contributing to fluid intake, such as maintenance fluids and "hidden" fluids, also known as fluid creep. In recent years, physicians' awareness of resuscitation fluids has increased. However, these fluids constitute only a minor part of the total fluid intake [2]. We can distinguish three different categories of fluids: maintenance fluids, resuscitation fluids, and fluid creep. Maintenance fluids refer to all fluids aimed at supporting basic bodily functions, such as hydration maintenance. Resuscitation fluids are often the fluids used as the first strategy for patient resuscitation. We define fluid creep as the amount of fluids used for medication dilution and to maintain catheter patency. This study pertains two clinical questions: What variables are associated with an increased distribution of fluid creep in patients admitted to the ICU? Are we able to identify patients at risk of elevated fluid creep after one week? To answer these questions, we investigated on the amount of creep received by patients in the first 7 days of ICU admission by building both a regression and classification model.

2. Materials and methods

The study was conducted on data originating from a single intensive care unit of an Italian hospital from the MargeritaTre (M3) database. The M3 project was approved by the Ethics Committee of the Coordinating Center, Comitato Etico Indipendente di Area Vasta Emilia Centro, as well as each local ethics committee of the hospitals adopting the MargheritaTre software.

2.1. Population selection

We only selected patients who were no longer currently in intensive care, with the restrictive condition that they

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had been discharged or had died by 31 July 2023. Successively, only patients with available comorbidities and admission reasons were included. Next, information was added about to the admission type, distinguishing between patients admitted to the ICU with trauma and those undergoing various types of admission, such as medical, emergency and elective surgery. The next step consists of the extraction of information including weight, height, and the degree of hypoxia in patients. Afterward, the other step consisted of the calculation of fluid creep administered to patients, encompassing both medications and nutrition. We selected specific administration routes for medications, such as intravenous (IV) bolus, IV elastomer, and drugs administered by continuous infusion. Similarly, for nutrition, the following administration routes were included: central vein, peripheral vein, and auxillary peripheral vein. Eventually, the net creep input during the first 24 hours and during the first week was computed for each patient. Our decision to calculate the level of Acute Kidney Injury (AKI) for our population using the Kidney Disease Improving Global Outcomes (KDIGO) score stems from the strong association observed between fluid management strategy, renal functionality, and patient mortality risk. A score of 0 was defined for the absence of AKI, and scores equal to 1, 2, or 3 were assigned for increasing levels of AKI severity. We finally included some variables used to calculate the Simplified Acute Physiology Score (SAPS II) score.

2.2. Classification models

To answer the first clinical question we identified clinically relevant variables that are associated with fluid creep, through a linear model (LM). A second model was developed using a recursive feature selection to identify variables significant for the target prediction. Next, we addressed the second clinical question regarding the ability to predict patients at risk of high FC after one week. To achieve this aim, we constructed a classification model predicting the risk of high creep that relies on information to admission and on information from the first 24 hours in ICU using the entire initial dataset. We considered all possible variables of our dataset including age, gender, reasons for admission, comorbidities, and all other previously calculated parameters. In particular, we examined the distribution of the variable that would become our target, namely the net amount of fluid creep in the first week. We transformed this variable from continuous to binary by setting the threshold for being considered at high risk of fluid creep to the 3rd quartile of the distribution of our variable, which is 3.6 liters. The choice of this threshold is based on analyzing the distribution of the target variable to identify a point where a clear change occurs. As shown in 2, after the 3rd quartile, the trend of the histogram decreases uniformly. Therefore, all patients receiving a quantity of creep greater than 3.6 liters during the first week will be considered as 1, while the remaining will be assigned 0. Thus, we have our new binary target variables. Having chosen the 3rd quartile of the target variable as our threshold, we obtained an imbalanced model with a presence of only 25% for the value 1. Moreover, the SMOTE algorithm was used to balance the dataset. Employing 5-fold cross-validation, we utilized grid search for hyperparameter optimization to evaluate 8 machine learning algorithms for classification. Our goal was to achieve the maximum average accuracy over the 5 folds by selecting appropriate hyperparameters. The tested models were: K-Nearest Neighbors Classifier (KNC), Random Forest (RF), Multilayer Perceptron (MLP), AdaBoost (AB), Quadratic Discriminant Analysis (QDA), Linear Discriminant Analysis (LDA), Decision Tree (DT), and Logistic Regression (LR).

2.3. Other variables of interest

Comorbidities and reasons for admission were collected at the time of admission and, for all other parameters considered (such as weight, height and PaO2/FiO2 ratio (P/F ratio), the first available survey from the first 6 hours after the time of admission was chosen. To calculate the AKI score according to the KDIGO definition, the values measured for each patient's creatinine, urine, and initiation and/or termination of renal replacement therapy in the first 24 hours of admission were used. On the other hand, the variables identified by the SAPS II score definition that we included in our study were: sodium, potassium, heart rate, and mean arterial pressure;for each of them, the most critical value was chosen during the first 24 hours in ICU.

3. Results

3.1. Population

The initial population of this study included 7594 individuals, as we can see in figure 1, with an median age of 65(57-74), 36% female representation, an median ICU length of stay equal to 2,8 days, and an ICU mortality rate of 18.8%. After applying the restrictive condition of discharge from ICU by July 31, 2023, the population shrinks to 7347. The population with available comorbidities result in 6712 patients with similar characteristics to the starting population. The integration of data on ICU admission reduces the population to 6384 patients but general statistics remain aligned. After the addition of admission type data, the patients were reduced to 6361 and also the inclusion of information related to the parameters of weight , height and P/F ratio bring the population to 5437 patients while maintaining consistent demographic characteristics. For the hypoxia level patients were categorized into three levels: zero for the absence of hy-

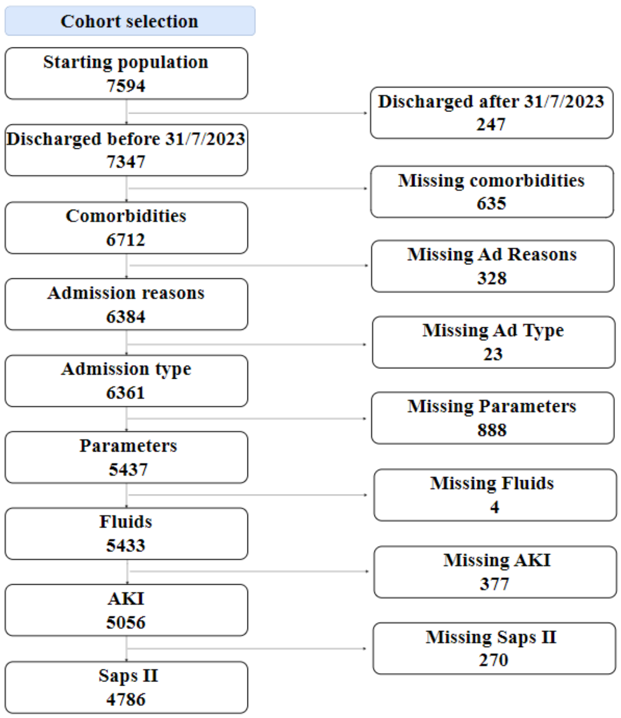

Figure 1. Cohort selection

poxia ($PaO_2/FiO_2 >$ 300mmHg, one for mild hypoxia ($PaO_2/FiO_2 <$ 300mmHg), and two for severe hypoxia ($PaO_2/FiO_2 <$ 150mmHg)[3]. Calculation of fluid creep received by patients brings our study population to 5433 patients with a mean fluid creep in the first 24 hours of 1623 ml (820-2018 ml) and a prevalence of severa hypoxia of 18%. AKI score calculation was possible for 5056 patients. Finally, the addition of certain variables defined by SAPS II results in the final study population, comprising 4786 patients for whom all selected information is available. The SAPS II is a patient severity score that takes into consideration several parameters and examinations of the patient. Our patient population has a median age of about 66(54-74) years. The median levels of the worst values of potassium and sodium are about 3,7 (3,3-4,69) mmol/L and 137 (134-139)mmol/L, respectively. The median length of hospitalization is about 3,1 days, with an average of 1606 ml (849-2000) of creep per patient in the first 24 hours after admission.

3.2. Fluid creep regression model within the first week

In figure 2 we plot the histogram of target distribution. The baseline model highlights that septic shock, mild renal in- sufficiency, intensive treatments, heart rate, amount of creep received in the first day, bicarbonate and sodium exhibit a ($p < 0.05$) and are all positively correlated, with the net fluid creep over the first day, as reported in table 1. From the model using forward feature selection always having as a target the net fluid creep in the first week we note that septic shock ($p < 0.001$), respiratory failure ($p < 0.001$), intensive treatment ($p < 0.001$), creep during the first 24 hours (P-value < 0.001), heart rate (p=0.028), sodium (p=0.032), bicarbonate (p=0.028), respiratory abnormalities (P-value < 0.001), mixed shock (p=0.003), hypovolemic shock (p=0.027) , organic brain coma(p=0.039), and surgery (p=0.044) all emerged as significant variables positively correlated with the target, implying an increase in fluid creep. Conversely, the presence of antiplatelet therapy (p=0.021), COPD (p=0.025), Kidney failure with non-conserved diuresis (p=0.01), mild chronic pulmonary disease (p=0.045), and cerebral vasculopathy (p=0.044) emerged as significant variables negatively correlated with target prediction as we can see in table 1.

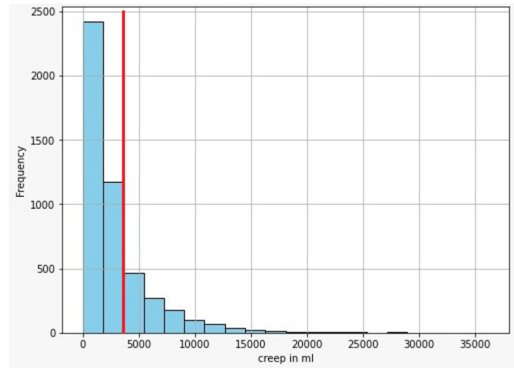

Figure 2. Histogram of the target distribution. The vertical red line indicates the high risk threshold comprising the 3rd quantile of the total FC received by patients.

3.3. Classification model for patients at risk of high fluid creep after one week

Table 2 shows the machine learning models that showed better accuracy metrics. In particular, the support vector machine algorithm was discarded, because it showed a significantly higher computational time than the others. In addition, standardization was applied to numerical variables. The chosen model is the MLP Classifier, with an accuracy of 0.86 and 0.81 on train and test respectively, as we can see in table 2.

4. Discussion

In this study, we analyze the fluid creep within a week and in particular we study which variables are significantly associated with a higher distribution of FC in ICU patients and ask whether we can identify patients at risk of high CF

Variables	Coefficient of the Baseline model	Pvalue of the Baseline model	Coefficient of the recursive model	Pvalue of the recursive model
Age	0.31	0.911	2.762	0.323
Gender (F)	22	0.778	-24.434	0.761
Weight	1.515	0.498	-0.962	0.663
Septic shock	791	**<0.001**	939.634	**<0.001**
AKI developed within the first 24 hours	-76.908	0.140	-53.602	0.300
Severe renal insufficiency	1.86	0.996	-74.140	0.847
Mild renal insufficiency	844	**0.41**	263.887	0.531
P/F ratio	-0.418	0.444	-0.544	0.313
Intensive treatment	1072	**<0.001**	900	**<0.001**
Hypoxia level	92.878	0.358	137.272	0.171
Creep during the first 24 hours	1.458	**<0.001**	1.392	**<0.001**
Mean arterial pressure	1.16	0.663	0.906	0.730
Heart Rate	3.574	**0.015**	3.213	**0.028**
Sodium	19.312	**0.007**	15	**0.032**
Potassium	20.235	0.490	17.421	0.549
Bicarbonate	25.488	**0.006**	25.716	**0.028**
Respiratory failure	-	-	1061	**<0.001**
Respiratory abnormalities	-	-	5917	**<0.001**
Mixed shock	-	-	1610	**0.003**
Surgery	-	-	90	**0.044**
Antiplatelet therapy	-	-	-657	**0.021**
chronic obstructive pulmonary disease	-	-	-429	**0.025**
Kidney failure with non-conserved diuresis	-	-	-1446	**0.029**
Hypovolemic shock	-	-	679	**0.027**
Mild chronic pulmonary disease	-	-	-862	**0.045**
Brain coma	-	-	270	**0.039**
Cerebral vasculopathy	-	-	-316	**0.048**

Table 1. Statistical analysis of baseline variables and with a recursive algorithm using LM

	QDA	KNC	DTC	LDA	MLP	RFC	LR	AB
Acc Train	0.56	0.90	0.99	0.85	0.86	0.86	0.86	0.86
Acc Validation	0.54	0.80	0.81	0.82	0.83	0.83	0.84	0.84
Acc Test	0.32	0.70	0.75	0.78	**0.80**	0.79	0.80	0.80
F1-score	0.39	0.52	0.50	0.50	0.61	0.60	0.59	0.59
AUROC	0.50	0.70	0.68	0.76	0.83	0.82	0.81	0.81
Sens	0.88	0.65	0.50	0.44	0.60	0.62	0.56	0.60
Spec	0.13	0.72	0.84	0.89	0.87	0.86	0.88	0.86
PPV	0.25	0.43	0.51	0.57	0.61	0.59	0.61	0.59
NPV	0.77	0.86	0.83	0.83	0.87	0.87	0.86	0.87
PRC AUC	0.57	0.55	0.57	0.55	0.69	0.59	0.67	0.68

Table 2. Performance metrics

after one week Hypoxia correlates positively with creep, supported by a Japanese ICU study[3]. The observed median fluid creep (1.489 ml) differs from prior studies (661 ml[3] and 645 ml[4]), possibly due to patient severity;indeed, the resulting ICU mortality rate (19%) contrasts with Japan's (7.5%)[3] and Belgium's (11%)[4]. Septic Shock diagnosis significantly predicts high fluid creep, consistent with Sakuraya et al. findings[3]. Moreover the significant positive coefficient of the LM suggests a correlation with increased fluid creep received by patients. To the best of our knowledge, this is the first study to implement a classification algorithm to predict which patients are at risk of high creep and this represent a methodological innovation. Eight machine learning models were evaluated to classify patients at risk of high creep after the first week; MLP classifier performed the best with an accuracy of 0.804 and 0.85 on train and test respectively, showing strong accuracy and good generalization capability. The model also demonstrated high specificity (0.87).

This study presents clinical innovations as it is one of the few studies addressing the issue of fluid creep by using data from an Italian electronic health record. It is also the first study to classify patients at risk of high creep within the first week, using only admission information and data from the initial 24 hours. Moreover considering only FC instead of total fluid received could facilitate the investigation of differences in autonomic and heart rate response after fluid administration, as indicated by other studies[5].

5. Limitations and Future developments

The major limitation of this study is due to its retrospective nature, which influences data availability and quality and the use of data from a single icu. A further limitation is that the final population represents only a part of the entire ICU center, and it results from the selection of patients based on the availability of the variables of interest.

6. Conclusions

In conclusion, our study aims at identifying the most relevant variables that can be observed during a patient's ICU stay and that can predict higher and lower distribution of fluid creep in ICU patients. It is important to note that among the significant variables, shown in bold in the right column in table 1, some such as heart rate, mixed shock, hypovolemic shock and septic shock are closely related to the cardiovascular system. Furthermore, the classification model allows us to better assess the potential risk that a patient may experience high fluid creep during the first week with an accuracy 0.80.

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