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PREDICTING THE CUMULATIVE FLUID INTAKE IN CARDIAC INTENSIVE CARE PATIENTS

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Abstract— *Fluid balance can be considered a valuable biomarker of critical illness. Administering the right dosage over time of fluids, thereby avoiding fluid overload, remains a challenge in intensive care. As a first step towards a fluid management decision support system, this work compared four models for predicting the course of the cumulative fluid intake in 30 cardiac intensive care patients. Analyses of the root mean squared error (RMSE) showed the lowest prediction error for an extrapolation model using a piecewise regression-approach.*

Keywords— *Cumulative fluid intake, prediction, fluid overload, fluid balance, intensive care*

Introduction

Fluid balance can be considered a valuable biomarker of critical illness [1]–[4]. It is calculated by subtracting the fluid outputs from the fluid intakes and documented routinely during a patient's stay in the intensive care unit (ICU). During fluid management in the ICU, fluid overload represents a serious side effect being associated with various comorbidities such as edema, cardiovascular dysfunction or respiratory complications [5]. In addition, fluid overload is an independent risk factor for morbidity and mortality when referring to critically ill surgical patients [6]–[11]. Hence, cumulative fluid balance (CFB), defined as the sum of daily fluid balances over a certain period of time, may provide important information for clinical decision making with respect to fluid management.
The clinical course of a patient's CFB in sepsis has been described by various hit models, such as the "ROSE model" which comprises the resuscitation-, optimisation-, stabilisation- and evacuation-phase [5], [12], [13]. Typical patient trajectories for CFB and cumulative fluid intake (CFI) [5], [12]–[15] with respect to the ROSE model are outlined in Fig. 1. Despite the necessity of administering large amounts of fluids in the resuscitation phase, fluids need to be considered as drugs, emphasising the administration of the right dosage over time within the subsequent phases to meet patient's needs and to avoid fluid overload. However, identifying the transition of a patient from the resuscitation phase to the optimisation phase (and subsequently to the stabilisation phase) is crucial in order to control adequate administration of fluids. Therefore, predicting CFI trajectories might pose the first step towards a fluid management decision support system and could prove beneficial in support intensivists in daily clinical practice. We therefore evaluated and compared four different approaches for estimating the CFI course in cardiac intensive care patients over a clinically reasonable timespan.

Methods

Patient cohort: 30 patients from the FLUIDATEX study (vote EK 30-076 ex 17/18 by the Ethics Committee of Medical University of Graz) were randomly chosen for analysis. The study includes patients in intensive care after cardiac surgery (20 males, 10 females). The mean age of the patients was 68.99 years (sd = 8.38 years). The mean length of stay at the ICU was 5 days (± 1 day). Twelve patients had a coronary artery bypass grafting, 12 patients had heart valve replacement and the remaining 6 patients underwent both interventions.

Materials: Fluid intake for all patients comprised all administered fluids (oral, enteral, parenteral) that were registered in the electronic patient records. For each patient, all intakes were added up cumulatively, resulting in a monotonous time series (expressed by

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the CFI) describing the patient's intake since admission. Data of the first 48 hours of ICU stay was used for generating the model for CFI and data of the subsequent 24 hours were considered to estimate the extrapolation error of prediction.

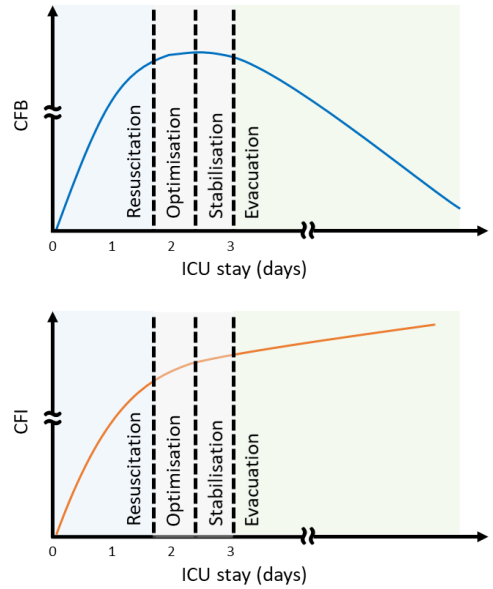

Figure 1: Clinical courses of the cumulative fluid balance (CFB) and the cumulative fluid intake (CFI) throughout a patient's stay at the intensive care unit (ICU) according to the ROSE model.

Statistical modelling and extrapolation: We used the statistical programming language R for Windows 10 (version 4.0.5) [16] for data modelling and analysis. The CFI was modelled using four different methods. As a benchmark we selected linear regression analysis (lm() in base R) as simplest method. Linear models are commonly used to describe and predict a target variable based on one or more independent variables. The general equation of the simple linear regression used in this work is shown in Eq. 1 where y is the observed variable, x is the explanatory variable, β_1 describes the slope and β_0 the intercept. The term e subsumes an unobserved random error.

$$y = \beta_1 x + \beta_0 + e \quad (1)$$

The fitted line can easily be extrapolated using the regression equation provided by the model. Second, we selected a "broken stick" approach, which adds two multiple linear regression lines together [17]. This method provides more freedom after a possible change in patient treatment over time. Based on this approach two subsequent simple linear regression models were fitted to the data. The breakpoint is determined as described in Eq. 2 [17]. The piecewise.linear() function from the R package SiZer was applied to model this approach. Extrapolation was performed using the "predict" function in R.

$$y_i = \begin{cases} \beta_0 + \beta_1 x_i + e_i & for\ x_i \le \alpha \\ \beta_0 + \beta_1 x_i + \beta_2 (x_i - \alpha) + e_i & for\ x_i > \alpha \end{cases} \quad (2)$$

The third method was a time series-based analysis, carried out automatically using the auto.arima() function [18], [19] from the forecast package in R. Time series analysis employs past time-discrete data to predict prospective data points by decomposing patient data into level, trend, seasonality and noise components. This approach may result in a spectrum of models of different degrees of complexity. Note that for prediction we applied the forecast() function from the forecast package as well. The fourth method was a non-linear regression approach, however using polynomial terms of power 2. Adding a polynomial term of this power, such as $\beta_2 * x^2$ to Eq. 1 as can be seen in Eq. 3, describes the final polynomial model.

$$y = \beta_2 x^2 + \beta_1 x + \beta_0 + e \quad (3)$$

Extrapolation was again performed with the predict() function. All model extrapolations were compared against the true course of the CFI using the root mean squared error (RMSE) as evaluation metrics.

Statistical comparison: A within-subjects ANOVA was calculated, comparing the four methods of modelling and extrapolation. The RMSE (in the unit milliliters) over the prediction timespan was entered as the dependent variable, selecting the modelling methods as independent variable (within-subjects factor).

Results

The four different extrapolation methods are depicted exemplarily for a selected patient in Fig. 2. The vertical dotted lines separate the modelling (48h) and prediction (24h) timespans. In this patient linear (2A) and piecewise linear (2B) regressions show a better fit compared to time series analysis (2C) or polynomial regression (2D). The distributions of extrapolation error of the CFI model over all patients is shown in Fig. 3. Piecewise linear modelling ("pw") revealed fewer extreme deviations compared to the other modelling approaches, in particular compared to regression analysis with polynomial terms ("poly") and time series analysis ("tsa"). The methods of modelling were found to be statistically significantly different, $F(2.3,66.71) = 5.51$, $p = 0.004$, generalized eta square = 0.11 (details in Fig. 4). Post-hoc analyses with Bonferroni adjustment revealed that the piecewise linear regression model showed stastically significant reduced extrapolation errors compared to all other models, while there was no difference in-between the three remaining models ($mean_{pw}$ = 631ml, $mean_{linearmodel}$ = 984ml, $mean_{tsa}$ = 1184ml, $mean_{poly}$ =1265ml, $p < 0.05$).

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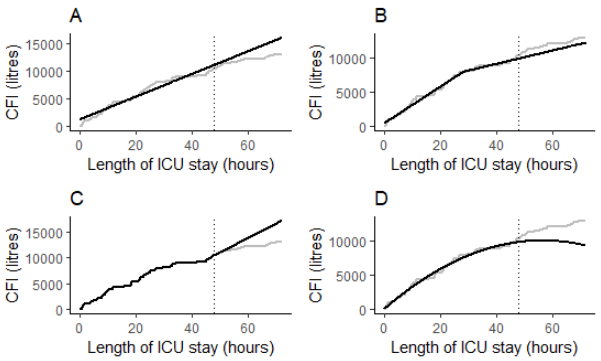

Figure 2: Linear (A), piecewise linear (B), time series analysis (C) and polynomial (D) regression of the cumulative fluid intake (CFI) in an exemplary patient using the first 48h of stay for modelling and the subsequent 24h for prediction.

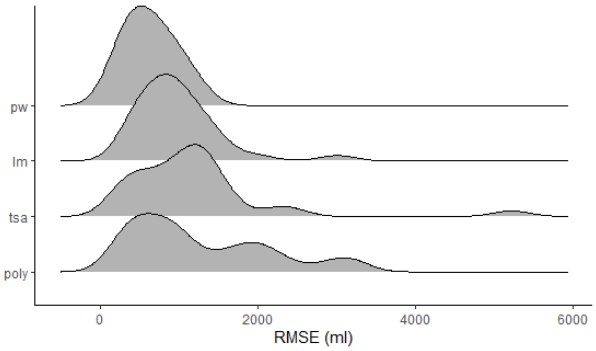

Figure 3: Whole sample extrapolation error of the cumulative fluid intake (48h of modelling, 24h of prediction). Piecewise linear modelling (pw), linear modeling (lm), time series analysis (tsa), polynomial terms (poly), root mean squared error (RMSE).

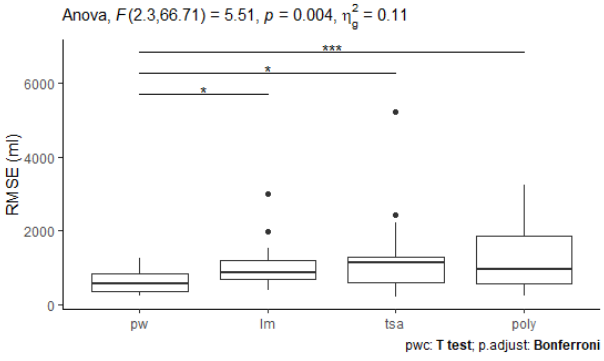

Figure 4: Variance analysis of the cumulative fluid intake extrapolation errors. Piecewise linear modelling (pw), linear modeling (lm), time series analysis (tsa), polynomial terms (poly), root mean squared error (RMSE).

Discussion

In this study we aimed to find a viable model for CFI estimation in cardiac intensive care patients and compared four different statistical methods. Our analysis demonstrated that a piecewise regression model seems to be the most promising model for estimating the CFI trajectory for the 24 hours – which is in good accordance with the common horizon for setting CFB goals – subsequent to the first 48 hours after admission to the ICU.

In this work, the orders of the applied models were restricted. Extrapolations using simple linear regression might be biased too much by the past trajectory, while polynomial regression of power 2 showed large deviations increasing with prediction time. A piecewise regression model using more than two straight lines or a polynomial regression of power 3 or more might outperform our models by allowing a higher degree of freedom. However, this may lead to complicated and overfitted models. Too much complexity might also be a reason for the underperformance of the time series-based model. The applied algorithm compares models of different complexity and chooses based on the best fit. Piecewise linear regression with one breakpoint might just be within a goldilock zone, where the method shows enough freedom to respond to changes in the CFI but not so much as to overestimate small changes. Still, we cannot assume that other statistical models may not perform better at other times of ICU stay or in other patient cohorts.

Although the applicated amount of fluids is usually documented by utilizing either paper-based or computer-assisted tools, especially small amounts of administered fluids (e.g. diluents, fluids used for flushing) are not able to be recorded [20]. Furthermore H. Asfour reported that documentation errors occur in 35% of reported CFBs [21]. These effects might negatively influence the prediction performance of CFI estimation models.

Setting and prescription of fluids to maintain microcirculation, to avoid hypoperfusion respectively, is a major challenge in critically ill patients. In this context fluid overload is common and associated with worse outcomes [5]–[11]. Decision support tools to display the history and prediction of the CFI and CFB might influence the clinical decision at bedside to assist the intensivist when prescribing fluids during the different phases of fluid resuscitation and evacuation.

In summary, predicting the CFI course using a piecewise linear regression model might assist clinicians in guiding fluid therapy, especially when incorporated in future decision support tools. The proposed approach needs to be verified in a larger patient cohort to determine the individual fluid transfer characteristics for CFB prediction.

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