**Prediction of Successful Blood Pressure Response to Fluid Bolus Therapy in Critically Ill Hypotensive Patients**

**Background**

Hypotension in the presence of shock is an urgent event for critically ill patients in the intensive care unit (ICU). Compromised blood supply induced by hypotension can result in multiple organ hypoperfusion and dysfunction. It is essential to rapidly identify the cause of hypotension with immediate treatment. Although it remains controversial whether fluid bolus therapy or vasopressor administration should be the initial approach to reverse blood pressure, fluid bolus therapy has been recommended as the primary-line treatment for most types of the hypotension. However, previous studies have reported that approximately one third of the hypotensive shock patients is not successfully respond to the fluid bolus therapy as their blood pressure remained at a low level {Cecconi:2018hs, Anonymous:2012dy}. This unsuccessful fluid administration could leads to only the increase of fluid balance and excessive positive fluid balance has been proposed as a risk factor for severe organ dysfunction, prolonged mechanical ventilation, longer length of stay in ICU, and increased mortality [citation]. However, little is known about prediction of whether the hypotensive episode will resolve with fluid bolus therapy in critically ill patients.

Patient response to the fluid bolus therapy has been studied as fluid responsiveness, defined as an increase of stroke volume of at least 10-15% in response to the fluid bolus. Several tests and parameters for predicting the fluid responsiveness have been investigated. Among these, passive leg raise test is reported as more generalizable and a less invasive method than dynamic and static circulatory parameters including pulse pressure variation (PPV), stroke volume variation (SVV), central venous pressure, and pulmonary capillary wedge pressure. However, predicting fluid responsiveness dose not always help identify which patients’ blood pressure would increased after the fluid bolus therapy. A previous study reported that if hypotensive patients have a PPV/SVV of less than 0.9, the fluid bolus will not increase patient's blood pressure, although it actually increases stroke volume. Moreover, Cecconi M et al reported that increased blood pressure was likely to be a major positive indicator of fluid challenge. The sufficient blood pressure recovery is an important outcome of fluid bolus therapy in clinical settings. Nevertheless, predicting successful blood pressure response has been poorly investigated.

Machine learning algorithms have been used to predict clinical events in the ICU.

For example, Lonkar et al applied machine learning algorithms to identify factors that are significantly correlated with the future tachycardia in ICU patients. They established a model that could predict future tachycardia that would occur within tens of minutes to a few hours in the future. The area under the receiver operating characteristic curve of this model was 0.86 and the recall rate was 85% at less than a 5% false positive rate. Henry et al developed " targeted real-time early warning score " to identify patients who are likely to develop septic shock in the near future in ICU. The aria under the curve for this model was 0.83 using a supervised machine learning algorithm. The model was capable of identifying future septic shock patients 28.2 hours prior to onset. Although several studies show the applied machine learning successfully developing clinical prediction models for critical events in ICU patient, little is known about whether the machine learning can be applied to build a model that predicts successful blood pressure response to fluid bolus therapy in critically ill patients with hypotension.

The aim of this study is to build a model that predicts sufficient blood pressure increase after the fluid bolus therapy in hypotensive patients in ICU.

**Research hypotheses**

(1) Machine learning algorithms application can identify whether the hypotensive episode in ICU patients will resolve with fluid bolus therapy.

(2) We can use clinical time series, treatment, demographic variables, and diagnosis information to predict the successful clinical response to the first fluid bolus in ICU (defined as the increase of mean arterial pressure (MAP) over 20%) among hypotensive patients (MAP <65mmHg).

(3) There is an association between successful clinical responses to the first ICU fluid bolus and the all-cause in-hospital mortality.

**Research question and objectives**

(1) To build a model that can predict the successful blood pressure response to the first fluid bolus in the ICU for patients with MAP <65mm Hg;

(2) To demonstrate that the successful blood pressure response to the first ICU fluid bolus is associated with hospital mortality among ICU patients with hypotension,.

**Data sources**

**MIMIC-3/MetaVision (from 2008)**

**Study population**

Inclusion criteria:

(1) We included only the first admission to ICU for each patient during the study period

(2) Patients with at least one measurement of MAP <65 mmHg persisting for at least 10 minutes during the first 24 hours of admission to the ICU

(3) Patient who received at least one fluid bolus therapy after the first measurement of MAP < 65mmHg during the first 24 hours after admission to the ICU (Note: Fluid bolus therapy is defined as administration of at least 500 ml pure crystalloid solution within 1 hour)

Exclusion criteria:

(1) Non-ICU stay patients (such as the step-down ICU)

(2) Patients who were aged ≤18 years

**Study outcomes**

Primary outcome:

(1) Successful blood pressure response, defined as ≥20% increase of MAP. The definition of the increase is calculated as (before MAP - after MAP) / before MAP. Before MAP is defined as the median of MAP measured during the 30 minutes prior to starting the fluid bolus therapy. After MAP is defined as the median of MAP measured during the 30 minutes after the end of bolus.

Secondary outcomes:

(1) In-hospital mortality

**Covariates of interest**

Each covariate should be measured before administration of the fluid bolus therapy.

Demographics:

* Age
* Gender
* Race/Ethnicity
* Admission source
* Sequential organ failure assessment (SOFA) score on admission to the medical ICU
* Admission diagnosis

Comorbidities:

* Identified by the Elixhauser ICD-9-CM coding algorithm

Vital signs (using the most current value at the time of bolus administration, plus features derived from up to two hours preceding the bolus):

* Heart rate
* Respiratory rate
* Temperature
* SpO2
* MAP
* Systolic blood pressure
* Diastolic blood pressure

Lab results:

- As the covariates should be measured before the administration of the fluid bolus therapy, we expect missing data; we will use the last observed measurement values before developing hypotension; otherwise, we will exclude them.

Others:

* Patient admission weight
* Urine volume (two hours preceding the bolus)
* Glasgow coma score at admission
* Vasopressor use before developing hypotension (type and rate)

**Conclusions**

This is the first study using MIMIC3 database to establish a prediction model for the blood pressure response to the initial fluid bolus therapy among ICU patients with a hypotensive episode. The prediction model will be in interest for physicians to provide appropriate fluid therapy. Further, we can extend the model to not only the initial fluid bolus therapy but also further fluid therapies in the patients’ ICU stay.

**Acknowledgements**

I would like to thank Professor Jessa Raffa, Ms. Shiya Yi, and Dr. Ryo Uchimido for their great supports to this proposal.

**References**