**ABSTRACT**

**METHODS:**

We retrospectively studied net fluid balance in 10387 patients with sepsis in MIMIC-III (Medical Information Mart for Intensive Care III) database. Based on 24 hours fluid balance, we examined the result of increase in fluid balance on the risk of 28-day mortality, hospital mortality, ICU mortality and length of ICU stay. Patients were divided into 4 groups based on quartile of fluid balance.

**CONTENT**

**METHODS:**

*Study population*

We used the Medical Information Mart for Intensive Care III(MIMIC-III) research database, a large, single-center database comprising information relating to patients admitted to Beth Israel Deaconess Medical Center(BIDMC) [1,2]. The database contains data of high temporal resolution including vital signs, medications, laboratory measurements, observations and electronic documentations for all patients admitted to BIDMC ICUs between 2001 and 2012. Use of the MIMIC-III database has been approved by the institutional review boards of BIDMC and the MIT.

Of all 46520 patients in MIMIC, 12636 were identified sepsis according to Angus criteria [3]. We excluded 188 patients under 16 years old, 1836 who had readmission records, 21 for whom stayed in ICU less than 3 hours and 204 individuals for whom documentation of fluid balance was not available, leaving 10387 unique first admissions.

*Exposure*

The primary exposure was fluid balance in the first 24 hours after ICU admission. It was computed by the bedside electronic record, variables include oral fluid, blood products, medications(input), urine output and other body fluids(output). Total fluid balance was winsorized at the 0.5 and 99.5 percentile to limit the effect of outliers.

*Outcome*

The primary outcome was 28-day mortality after admission. Secondary outcomes were hospital mortality, ICU mortality and length of ICU stay (LOS ICU). Death were identified from the Social Security Death Index.

*Covariates*

Baseline characteristics including age, sex, weight, length of ICU stay and length of hospital stay. Mechanical ventilation duration was calculated in first 24 hours. Medical comorbidities were determined using Elixhauser codes at discharge [4]. We also noted predictors of illness severity including Sepsis-related organ failure assessment score (SOFA), Oxford Acute Severity of Illness Score(OASIS) [5] and Glasgow Coma Scale (GCS) at admission. Values of hemoglobin, creatinine, white blood count(WBC), temperature, respiratory rate, heart rate and mean blood pressure(MBP) at admission were also collected.

*Statistical analysis*

Baseline characteristics were stratified by quartiles of fluid balance. Data are given as mean with standard deviation or median and interquartile ranges for continuous variables and as numbers and percentages for categorical variables. Kruskal-Wallis test, Homogeneity of variance test and fisher tests were employed to determine the significance among non-normal continuous variables, normal continuous variables and categorical variables respectively. Significance was considered at the P < 0.05 level. Continuous variables include Age, weight, length of stay, mechanical ventilation duration, SOFA, vital signs, laboratory values and fluid balance. Comorbidities were considered binary variables. Multivariate logistic regression models were created to defined the association between fluid balance and mortality, and multivariate linear regression models were employed for defined association between fluid balance and LOS ICU.

Fluid balance was examined in quartiles; the lowest quartile was used as reference for all analyses. During the initial investigation of the data, we found that SOFA and OASIS were highly correlated. We chose to use SOFA alone as not to overweight the addition of other covariables in the model.

In subgroup analyses, we examined whether under serval conditions would modified the effect of fluid balance on mortality: (i) patients with pulmonary infections; (ii) patients with chronic kidney disease(CKD); (iii) those with congestive heart failure(CHF); (iiii) patients with hypertension.

All statistical analyses were performed using R 3.4.3.

1. MIMIC-III, a freely accessible critical care database. Johnson AEW, Pollard TJ, Shen L, Lehman L, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, and Mark RG. Scientific Data (2016). DOI: [10.1038/sdata.2016.35](http://dx.doi.org/10.1038/sdata.2016.35). Available at: <http://www.nature.com/articles/sdata201635>
2. Pollard, T. J. & Johnson, A. E. W. The MIMIC-III Clinical Database <http://dx.doi.org/10.13026/C2XW26> (2016)
3. Angus, D C, W T Linde-Zwirble, J Lidicker, G Clermont, J Carcillo, and M R Pinsky. “Epidemiology of Severe Sepsis in the United States: Analysis of Incidence, Outcome, and Associated Costs of Care.” *Critical Care Medicine* 29, no. 7 (2001): 1303–10. https://doi.org/10.1097/00003246-200107000-00002.
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5. Johnson, Alistair E W, Andrew A Kramer, and Gari D Clifford. “A New Severity of Illness Scale Using a Subset of Acute Physiology and Chronic Health Evaluation Data Elements Shows Comparable Predictive Accuracy\*.” *Critical Care Medicine* 41, no. 7 (2013).