Analysis\_plan\_positive balance in fluids in septic patients

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# **1** **OBJECTIVE AND HYPOTHESES**

To assess the association of fluid type and balance + with ICU and hospital mortality among patients admitted to the Intensive Care Unit with sepsis and septic shock,

We hypothesize that

1. A more positive fluid balance is associated with increased hospital outcomes (or ICU outcomes, but hospital outcomes are major outcomes) in patients with sepsis and septic shock[[1]](#footnote-0) [[2]](#footnote-1) [[3]](#footnote-2) [[4]](#footnote-3)
   1. Mortality
   2. Length of ICU stay
   3. Ventilator days
2. The relationship between + fluid balance and hospital outcomes
   1. Can be non-linear, potential optimal cut-off points can be found
   2. the relationship can differ for some subgroups:
3. Pulmonary VS non-pulmonary sepsis
4. Level of inflammation (white blood cells, neutrophil counts): less inflamed VS more inflamed
5. IHD
6. CKD

# **2** **NOTATION AND ABBREVATIONS**

ICU = Intensive Care Unit

BF = Balanced Fluids

UF = Unbalanced Fluids

# **3** **STUDY POPULATION**

## **3.1** **INCLUSION CRITERIA**

Adult patients (aged 16 years and above) with diagnosis of sepsis or septic shock with length of ICU admission > 3 hours.

MIMIC : daily fluid balance - NET balance

eICU :

## **3.2** **EXCLUSION CRITERIA**

## *Patients’ readmission episodes to ICU were excluded*

Definitions:

|  |  |
| --- | --- |
|  |  |
| Sepsis or Septic Shock | Presence of one of the following International Classification of Diseases, 9th Revision (ICD-9) codes: severe sepsis (995.92), septic shock (785.52), or an ICD-9 code for infection plus at least one code of organ dysfunction[[5]](#footnote-4) |
|
| Fluid intake | Intravenous fluid, enteral/parenteral feeding, medication administration, blood products, dialysate |
| Fluid output | Urine output, gastric aspiration/vomitus, drainage (thorax, abdominal), blood loss and ultrafiltration |
| Fluid balance | MIMIC: computed everyday  KC: need to compute the fluid balance at the 24 hour mark upon ICU admission.  Total fluid intake - Total fluid output  TimeZero = Time of Admission  Fluid Balance as measured at  3h, 12h, 24h, 48h, 72h (3d), |
| Intravenous Fluid Type | For hypothesis b) only  Defined as having used balanced or unbalanced fluids in initial 3 days of ICU stay |
| Mean fluid balance | Daily average of total fluid balance during entire ICU stay |

# **4** **MEASUREMENTS AND VARIABLES**

## **4.1** **Outcome variables**

Taken from the spreadsheet

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Tables to extract data | Variables to be extracted in the table | Remarks |
| Hospital Mortality | apachePredVar/ patient | diedInHospital/ hospitalDischargeStatus |  |
| apachePatientResult | actualHospitalMortality |  |
| ICU Mortality | patient | unitDischargeStatus | from unitDischargeLocation = ICU |
| apachePatientResult | actualICUMortality |  |
| Hospital Length of Stay | apachePatientResult | unabridgedUnitLOS |  |
| ICU Length of Stay | apachePatientResult | actualICULOS |  |
| the number of ventilator days within the first admission (optional) | apachePatientResult | unabridgedActualVentdays | Should be intubation days, cause eicu data gives ventilator days, which include non-invasive days  (outcome variable) |
| Ventilator Days within 28 days( to calculate ventilator free days) [KIV] |  |  |  |
| the first period of ventilator days;[KIV] |  |  |  |

## **4.2** **Exposure covariates (or predictor variables)**

Fluid types were extracted from infusion drug table, please see here for the list of fluid types (KIV for secondary objective)

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Tables to extract data | Variables to be extracted in the table | Remarks |
| **Crystalloids** | | | |
| Balanced Solutions | | | |
| Hartmann’s Solution (Compound sodium lactate) |  |  |  |
| Lactated Ringer’s (LR) Solution |  |  |  |
| NORMOSOL-R 7.4%(Hospira) |  |  |  |
| D5% LR |  |  |  |
| PLASMA-LYTE 148 (Baxter) |  |  |  |
| Unbalanced Solutions | | | |
| Normal saline / Isotonic Saline (IS) (0.9% Saline) |  |  |  |
| ½ Normal Saline |  |  |  |
| D5% IS |  |  |  |
| D5% ½ Normal Saline |  |  |  |
| 0.9% NACL+KCL 20MEQ |  |  |  |
| **Colloids** | | | |
| HES; 6% Pentastarch;  10% Pentastarch |  |  |  |
| Gelofusine (4% succinylated gelatin  solution) |  |  |  |
| Albumex (4% albumin in Sodium chloride) |  |  |  |
|  |  |  |  |
| Mean Fluid Balance |  |  |  |

## **4.3** **Mandatory covariates, known confounders**

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | Tables to extract data | Variables to be extracted in the table | Remarks |
| APACHE IV score | apacheApsVar | ApacheApsVarID |  |
| apachePatientResult | apacheScore |  |
| patients who received Dialysis during ICU stay |  |  | (need to exclude ESKD patients) |
| Age | patient | age | Age |
| apachePredvVar | Age |  |
| Gender | patient | gender | Gender |
| apachePredVar | gender |  |
| ethnic group | patient | ethnicity | Interesting findings: one study find that minor ethnic groups have worse outcomes, suspect related to social demographics, poorer people have worse outcomes |
| height | patient | admissionHeight | Obesity paradox: u-shape relationship |
| weight | patient | admissionWeight, dischargeWeight | weight |
| infusionDrug | patientWeight | infusionDrug |
| Source of Admission (e.g. EMD, General Ward, Operating Theatre) | apachePredVar | admitSource | Currently a numeric variable, need to know how it is defined |
| patient | unitAdmitSource |  |
| ICU type |  |  |  |
| Source of infection(Pulmonary or Non-pulmonary)(from admission diagnosis) |  |  |  |
| Comobidities |  |  |  |
| diabetes mellitus (DM) | apachePredVar | diabetes |  |
| pastHistory | pastHistoryValueText |  |
| Hypertension (HTN) | pastHistory | pastHistoryValueText |  |
| Ischemic heart disease (IHD) | pastHistory | pastHistoryValueText |  |
| Recent Myocardial Infarction | apachePredVar | midur |  |
| pastHistory | pastHistoryValueText |  |
| Chronic kidney disease (CKD) | pastHistory | pastHistoryValueText |  |
| Chronic liver disease (CLD) | pastHistory | pastHistoryValueText |  |
| apachePredVar | cirrhosis |  |
| apachePredVar | hepaticFailure |  |
| Cancer | pastHistory | pastHistoryValueText |  |
| apachePredVar | lymphoma |  |
| apachePredVar | leukemia |  |
| apachePredVar | metastaticCancer |  |
| Immunosuppression | apachePredVar | immunosuppresion |  |
| pastHistory | pastHistoryValueText |  |
| Chronic obstructive pulmonary disease (COPD) | pastHistory | pastHistoryValueText |  |
| AIDS | apachePredVar | aids |  |
| pastHistory | pastHistoryValueText |  |
| Admission vitals |  |  |  |
| temperatue | vitalPeriodic | Temperature |  |
| lab | labName, minimum labresultoffset |  |
| respiratory rate | vitalPeriodic | Respiration |  |
| lab | labName, minimum labresultoffset |  |
| heart rate | vitalPeriodic | Heartrate |  |
| systolic blood pressure | vitalPeriodic | systemicsystolic |  |
| diastolic blood pressure | vitalPeriodic | systemicdiastolic |  |
| mean arterial pressure | vitalPeriodic | systemicMean |  |
| oxygen saturations (SpO2) | vitalPeriodic | SaO2 |  |
| Glasgow coma scale (GCS) | apacheApsVar | eyes, motor, verbal |  |
| Fraction of inspired oxygen (FiO2) | apacheApsVar | FiO2 |  |
| lab | labName, minimum labresultoffset |  |
| Basic labs |  |  |  |
| Lactate | lab | labName, minimum labresultoffset |  |
| Hemoglobin |  |  |  |
| Creatinine |  |  |  |
| White blood cells |  |  |  |
| Neutrophils |  |  |  |

## **4.4** **Additional covariates, potential confounders**

\*\*\*Reasons for including these covariates if applicable \*\*\*\*

## **4.5** **Effect Modification**

[[6]](#footnote-5)\*\*\*Reasons for including these covariates if applicable \*\*\*\*

**[[7]](#footnote-6)**

# **5** **DATA MANAGEMENT**

\*\*\* raw data files, program files etc. and documentation files if applicable\*\*\*

# **6** **STATISTICAL ANALYSES**

We will perform a retrospective analysis of adult patients (aged 16 years and above) admitted to intensive care units in continental United States between 2014-2015, based on the Philips eICU Collaborative Research Database v1.1. All patients had a diagnosis of sepsis, severe sepsis or septic shock, or an ICD-9 code fo infection plus at least one code of organ dysfunction [[8]](#footnote-7) [[9]](#footnote-8) ~~which required a diagnosis of infection and organ dysfunction.~~ Repeat ICU admissions and ICU stays <XXh were excluded. Hospital and ICU mortality were the primary outcomes. Multilevel multiple logistic regression of positive balance in fluids, and types of fluids on the primary outcomes were done, controlling for variables found to be significant (P<0.05) on univariate analysis.

# **7** **STAFF LIST**

# **8** **APPENDIX 1 – Meeting Minutes**

First Meeting in Tower Block 12-01 on 11/07/2017 4-5pm

Attendees: Mornin, KC, Sandra, Zaw and Chen Ying

Summary-Several questions of major interest

1. What volumes of fluids are expected for sepsis patients? And what types of fluids are better for sepsis patients? (Current project)
   1. Mentioned that for sepsis patients, conservative recommendations are 4 Litre /24 hrs, for better patients, 2 Litre/ 24 hrs.
   2. As to how to measure amount of fluids, we decided to use total amount of fluids used in first 24 hours admitted in icu or first 48 hours admitted in icu, which other studies have been using.
   3. Major outcomes include: hospital/icu mortality, LOS, intubation days. Mornin mentioned that for intubation days, mortality could be a competing risk for intubation days, three approaches can be taken
      1. Competing risk analysis for intubation days
      2. Normalized intubation days by LOS
      3. Study intubation days only among survivors.
2. How timings to antibiotics related to clinical outcomes of septic patients?
   1. Timings to antibiotics, eicu data only have antibiotics used in eicu?? Need to check dataset
3. Relationship between teaching status and clinical outcomes could also be one of the project
4. Relationship between drug usage and clinical outcomes: dosage and duration
   1. Zaw mentioned in the meeting: different drugs have different weights, how to compare?? To be found in reference
   2. Need to come up with a list of drugs
5. Relationship between steroids usage with mortality

# **9** **APPENDIX 2 – Results**

1. "Fluid resuscitation in septic shock: A positive fluid balanc... : Critical ...." <http://journals.lww.com/ccmjournal/Abstract/2011/02000/Fluid_resuscitation_in_septic_shock__A_positive.3>. Accessed 26 Jul. 2017. [↑](#footnote-ref-0)
2. "Higher Fluid Balance Increases the Risk of Death From Sepsis ...." <https://www.ncbi.nlm.nih.gov/labs/articles/27922878/>. Accessed 26 Jul. 2017. [↑](#footnote-ref-1)
3. "Study protocol for the Balanced Solution versus Saline in Intensive ...." <https://www.ncbi.nlm.nih.gov/pubmed/28651514>. Accessed 26 Jul. 2017. [↑](#footnote-ref-2)
4. (n.d.). Impact of positive fluid balance on mortality and length of stay in septic .... Retrieved July 26, 2017, from <https://www.ncbi.nlm.nih.gov/pubmed/26813080> [↑](#footnote-ref-3)
5. (n.d.). Sepsis Coding Decision Tree in ICD-9 and ICD-10 - DecisionHealth. Retrieved July 26, 2017, from <http://decisionhealth.com/ICD-10/Homehealth/pdf/PVT-0715-Tool.pdf> [↑](#footnote-ref-4)
6. [↑](#footnote-ref-5)
7. [↑](#footnote-ref-6)
8. (n.d.). Epidemiology of severe sepsis in the United States: analysis of - NCBI. Retrieved July 26, 2017, from <https://www.ncbi.nlm.nih.gov/pubmed/11445675> [↑](#footnote-ref-7)
9. (2017, April 21). Resuscitation With Balanced Fluids Is Associated With Improved .... Retrieved July 26, 2017, from <https://www.ncbi.nlm.nih.gov/pubmed/28437373> [↑](#footnote-ref-8)