Capillary leak Index as a Prognostic Indicator for Post-Operative Abdominal Sepsis in Critically ill Patients

Protocol with Statistical Analysis Plan of Thesis

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What is already known on this subject? AND

What does this study add?

Intra-abdominal infections are a major cause of morbidity and mortality in hospital settings worldwide. However, data from most published clinical trials under- estimate the true mortality risk for several reasons**. (Meng et al., 2024).**

Major surgery may induce an inflammatory response, which results in an increased level of C-reactive protein (CRP) and represented in albumin loss to the extravascular area due to increased capillary permeability. Our study will be done to evaluate the association between capillary leak index (CLI) and intensive care unit related mortality in patients underwent major abdominal surgery **(Susanti et al., 2021)**.

1. INTRODUCTION

Sepsis has been recognized as a life-threatening organ dysfunction caused by a dysregulated host response to infection **(Clements, 2021).** Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for continuous research **(JAMA, 2016).**

Peritonitis can be classified by the anatomical integrity of the abdominal cavity. Primary peritonitis is associated with undamaged intra-abdominal cavity organs. It is also known as spontaneous bacterial peritonitis and is treated without surgical intervention. The source of infection is often hard to establish and is usually found occurring in infants and cirrhotic patients **(Mureșan et al., 2018)**.

Secondary peritonitis is an infection of the peritoneal cavity after hollow viscus perforation, anastomotic leak, ischemic necrosis, or other injuries of the gastrointestinal tract **(Montravers et al., 2015).** Tertiary peritonitis is defined as a serious recurrent or persistent intra-abdominal infection after the successful control of secondary peritonitis. Irrespective of the cause, several measures are available and accepted as improving the survival rate, the most important being the early recognition of intra-abdominal infection. Efforts to achieve fluid balance should be initiated immediately to replace any intravascular insufficiency. Vasoactive agents

may be necessary to augment and assist fluid restoration **(Vincent JL and De Backer 2013)**.

The treatment strategy for peritonitis primarily aims at the stabilization of possible organ dysfunction by routine intensive care medicine. Low risk secondary peritonitis (localized peritonitis), Ampicillin/Sulbactam or Carbapenem can be used as a monotherapy, however in combination therapy 2nd generation Cephalosporin + Metronidazole or 3rd generation Cephalosporin + Metronidazole can be used **(Sartelli et al., 2016)**. High risk Secondary peritonitis Piperacillin/Tazobactam or Carbapenem or Tigecycline can be used as a monotherapy. A combination therapy 4th generation Cephalosporin + Metronidazole are usually used. Tertiary peritonitis antifungal therapy in high-risk patients and empirical therapy should cover the probable micro flora and should be changed according to the culture results **(Morrissey et al., 2013).**

Capillary leak syndrome (CLS) refers to a syndrome of deranged fluid homeostasis, often observed in critically ill patients, CLS is frequently defined by excessive fluid shift from the intravascular to the extravascular space, resulting in intravascular hypovolemia, extravascular edema formation, and hypo perfusion necessitating further fluid resuscitation. In health, fluid exchange between intravascular and extravascular spaces is vital for maintaining the body's homeostasis. However, disturbances in this delicate equilibrium, can lead to the clinical picture of CLS **(Saravi et al., 2023).**

CLI is measured by dividing CRP level by albumin level. Systematic response to tissue injury, including major surgery, is marked by increased pro inflammatory cytokines, which promotes CRP production and capillary leakage. If the injury still exists, inflammatory process will continue **(Susanti et al., 2021).**

Our study will be done to evaluate the association between capillary leak index (CLI) and intensive care unit (ICU) related mortality in patients underwent major abdominal surgery.

2. AIM/OBJECTIVES

In this study we are going to evaluate the "CLI" as an early prognostic indicator for post-operative abdominal sepsis in critically ill patients.

3. METHODOLOGY:

Patients and Methods

- **Type of Study:** Prospective Cohort study.
- **Study Setting**: Surgical intensive Care Unit, Ain Shams University Hospitals.
- **Study Period:** 6 months.
- **Inclusion criteria:**

- Age: ≥18 years old presented with Post-operative intra-abdominal sepsis due to secondary peritonitis in the form of fever, increase TLC more than $12x10^3$ and increase procalcetonin > 0.5 microgram per liter.
- Sex: Both sexes.
- Post-Operative secondary peritonitis eg. Perforated viscus and abdominal abscess.
- Estimated length of ICU stays ≥48 hrs.

- **Exclusion criteria:**

- Patient refusal.
- Advanced Liver diseases According New MELD score ≥ 20 **(Kamath et al.,2001)**
- Renal diseases (Moderate decrease in GFR 30-59 ml/min/1.73m²--Severe decrease in GFR 15-29 ml/min/1.73m²--Kidney failure less than 15 ml/min/1.73m² or on Hemodialysis).
- Pregnancy.
- Primary peritonitis.
- Tertiary peritonitis
- Mortality within first 48hrs of ICU admission.
- Advanced malignancy (Stage III localized malignancy with spreading lymph nodes Stage IV spreading to Other parts of the body such as to the liver, lungs and bones)

Sampling Method:

Simple randomization.

Sample Size: Using the PASS 15 program for sample size calculation, reviewing results from the previous study **(Susanti et al, 2021)** showed that the mortality rate among

the study group was 14.5%11/67) and, that the CLI a t day three is a good predictor for mortality with ROC-AUC=0.892, based on these findings and after 15% adjustment for dropout rate a sample size of at least 50 patient achieves 95% power to detect a difference of 0.3920 between t h e a r e a under t h e ROC curve (AUC) under the null hypothesis of 0.5000 and an AUC under the alternative hypothesis of 0.8920 using a two-sided z-test at a significance level of 0.050. The data are continuous responses.

Ethical considerations:

- An informed consent according to rules of ethical committee in Ain Shams University will be obtained from the patients or guardians after being informed about the research procedure and any potential risks suspected.
- All patients' data are highly confidential.

Study Tools:

After an informed consent, the enrolled patients will be subjected to:

- Full clinical assessment and history taking.
- Laboratory investigations including random blood sugar, arterial blood gases (ABG), complete blood count (CBC), serum albumin and C re-active Protein "CRP", liver function test, Kidney function test and procalcitonin.
- Imaging studies including Pelvi-abdominal U/S and Pelvi-abdominal multi-slice (CT) with or without contrast.
- Other investigations include Electrocardiogram (ECG), Echocardiography.

Study Procedures:

All patients will be subjected to the following in the first post-operative day in the ICU:

1. Full history taking including

- Demographic Data: there include age, sex and BMI.
- Medical history: this includes diabetes mellitus (DM), cardiopulmonary diseases, renal or hepatic diseases.
- APACHE II Score.

- SOFA Score.

2. Patients will be divided into two groups according to CLI

- Group I: Low CLI < 85.55
- Group II: High CLI > 85.55 **(PALACIOS et al., 2018).**

3. History of previous operations.
4. Drug history & special habits.
5. Complain of the patient:
   - Abdominal pain: This included onset, course, duration, site, radiation.
6. Associated symptoms: e.g.: Vomiting, change in bowel habits (constipation or diarrhea), Fever, tachycardia and tachypnea.
7. Investigations:

- Laboratory investigations: Complete blood count (CBC). Liver function tests (LFT). Renal Function test (RFT). Coagulation profile. Daily assessment.
- Specific laboratory investigations: CRP and Serum albumin Daily assessment.
- Radiological investigations: Plain abdomen X-ray erect x-ray, Pelvi-abdominal ultrasonography, Computed Tomography (CT) abdomen as needed.

8. Management of sepsis and septic shock and will be done according to surviving sepsis campaign guidelines 2021.

9. Continuous monitoring of Temp, NIBP, IBP, HR, RR, intra-abdominal pressure, sPO2, UOP and GCS.

Sampling:

Blood sampling: About 5.0 ml venous blood sample was taken from each patient. 2.0 ml blood was put into vacutainer Ethylene-diaminetetra-acetic acid (EDTA) tube for CBC. The reminder of blood sample was put into plain tube for serum separation and estimation of LFT, RFT, The CRP level was measured using ABX Pentra 400 (HORIBA, Germany), whereas the albumin level was measured using HumaStar 80 (HUMAN, Germany).Reference values for serum albumin is 35 to 55 g/l and for CRP is less than 6 mg/dl CLI will be calculated as CRP divided by serum albumin and multiplied by 100 in the first day post-operative and daily for 5 days with a cut-off

point < 85.55 **(PALACIOS et al., 2018)**.

Measurements

Primary outcome measure:

Correlation between CLI and 28 days Mortality.

Secondary outcomes measure:

- Mechanical Ventilation days.
- Incidence of organ failure.
- Length of ICU stays.

Statistical Analysis:

All data will be recorded, tabulated, analyzed and statistically compared between patients to identify any significant difference between them

The finding will be discussed with regard to the achievement of the aim, their significance and their comparison with other available data in medical literature.

4. REFERENCES

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Statistical analysis Plan

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Statistical analysis was done by SPSS v27 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test. A two-tailed P value < 0.05 was considered statistically significant.

Evaluation of Diagnostic Performance:

a) Diagnostic sensitivity: It measures the incidence of true positive results in patients' groups. (TP)/(TP+FN)×100.Where:

TP (true positive): number of diseased patients accurately classified by the test and FN (false negative): number of diseased patients accurately misclassified by the test.

b) Diagnostic specificity: It measures the incidence of true negative results in a non-diseased group. (TN)/(TN+FP)×100. Where:

TN (true negative): number of non-diseased subjects correctly classified by the test FP (false positive): number of non-diseased patients misclassified by the test.

c) Positive Predictive value (PPV): It is the percentage of true positive results among total positive results. (TP)/(TP+FP)×100.

d) Negative Predictive value (NPV): It is the percentage of true negative results among total negative results. (TN)/(TN+FN)×100.

e) Receiver Operating Characteristic curve (ROC-curve) analysis:

The overall diagnostic performance of each test was assessed by ROC curve analysis, a curve that extends from the lower left corner to the upper left corner then to the upper right corner is considered a perfect test. The area under the curve (AUC) evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance

for the test). A value below 0.5 indicates a very poor model. A value of 0.5 means that the model is no better than predicting an outcome than random chance. Values over 0.7 indicate a good model. Values over 0.8 indicate a strong model. A value of 1 means that the model perfectly predicts those group members who will experience a certain outcome and those who will not.