High capillary leak index is associated with increased risk of ICU-related mortality after major abdominal surgery

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Abstract

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

***Design*: This was a prospective study with cohort analytic design.**

***Patients and participants*: We included adult patients aged 18 and older who were treated in ICU after underwent major abdominal surgery. Patients who were pregnant, having menstruation, relaparotomy, diabetes mellitus, and idiopathic systemic capillary leak syndrome were excluded from this study. Blood was collected before surgery and at 48 and 72 hours after surgery. Patients were observed for mortality incidence during treatment in the unit. The CRP level was measured using ABX Pentra 400 (HORIBA, Germany), whereas the albumin level was measured using HumaStar 80 (HUMAN, Germany). CLI was measured by dividing CRP level by albumin level. Data were analyzed using SPSS Statistics version 21.0 (IBM, New York, U.S.).**

***Results*: CLI at hour 72 was associated with increased risk of ICU-related mortality (RR 21.667; 95% CI 2.938-159.763; p<0.001).**

***Discussion*: Acute inflammation normally resolved within three days. Systematic response to tissue injury, including major surgery, is marked by increased proinflammatory cytokines, which promotes CRP production and capillary leakage. CRP production will increase to its peak level 36-50 hours after inflammation. However, if the injury still exists, inflammatory process will continue.**

***Conclusions*: High CLI at hour 72 can be considered as the risk factor to ICU-related mortality.**

Key words: CLI, major abdominal surgery, mortality.

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Introduction

Major abdominal surgery is a major surgical process and carries a high risk to the patient's life. (1) Surgical trauma will induce a physiological stress response in the form of cytokine release and inflammatory cascade. Consequently the body enters a catabolic phase and requires adequate perioperative fluid management. (2,3)

The production of C-reactive protein (CRP) will increase from 4-6 hours of the onset of the inflammatory trigger and will increase every 8 hours reaching its peak level 36-50 hours after inflammation. (4) In surgical intensive care unit (ICU) patients, traumatic injuries and septic conditions can be simultaneously or subsequently present. In the early phase of injury, the response is

regulated by acute phase reactants, proinflammatory mediators (tumour necrosis factor alpha [TNF-α], interleukin [IL]-1, IL-6, IL-8, IL-8) and the activation of endothelial cells (intercellular adhesion molecule [ICAM]-1, vascular cell adhesion molecule [VCAM]-1) leading to systemic inflammatory response syndrome (SIRS). (5) After major abdominal surgery, glycocalyx markers in human plasma are at levels comparable to septic patients. In sepsis, level of IL-6 correlates with syndecan-1, ICAM-1, VCAM-1, and lactate, while ICAM-1 furthermore correlates with CRP and lactate levels. High level of glycocalyx marker indicates that significant shedding of endothelial glycocalyx occurres in patients with sepsis and major abdominal surgery, which lead to capillary leak syndrome. (6) Capillary leak can occur during severe inflammatory process caused by infection or due to excessive fluid in resuscitation. (7) Increased capillary permeability is an important cause of decreased albumin concentration in patients. (8)

There are three things that trigger excess perioperative fluid administration: provision of fluid replacement for fasting, replacement of unseen fluid loss due to exposure to body tissues during surgical procedures, and third space fluid loss. (3) This excessive fluid can cause global increased permeability syndrome (GIPS), followed by impaired organ function or even organ failure characterized by an increase in the capillary leak index (CLI). The end result is an increase in interstitial fluid in 4 major compartments of the body: head, chest, abdomen, and extremities. (9) Capillary leak index is defined as the ratio of CRP in milligrams per deciliter over albumin in grams per liter, multiplied by 100. (10,11)

Recent studies have shown that hypervolemia in critically ill patients can cause many complications such as acute kidney injury (AKI), electrolyte imbalance, respiratory disorders, heart failure, gastrointestinal disorder, impaired wound healing, and even increased mortality. (11-20)

Theoretically, hypervolemia will trigger the release of atrial natriuretic peptide (ANP), which is proven to cause glycocalyx endothelial damage resulting in increased capillary permeability. (21) Progressive capillary leakage characterized by an increase of CLI will induce organ dysfunction and has poor prognosis. (11)

This study was to evaluate the association between CLI and ICU-related mortality in patients underwent major abdominal surgery. This was the first study to evaluate the association between CLI and ICU-related mortality in major abdominal surgery patients.

Materials and method

This was a prospective study with cohort analytic design in a period from December 2019 till March 2020. The study was conducted after ethical clearance from Health Research Ethics Committee of Raden Mattaher Hospital and Jambi University of Medicine, Jambi (No: S42/SPE/X/2019).

Participant were adult patients aged 18 or older who were treated in ICU after undergoing major abdominal surgery. Patients who were pregnancy, having menstruation cycle, anuria, macroscopic haematuria, acute kidney injury, chronic kidney injury, relaparotomy, diabetes mellitus, and idiopathic systemic capillary leak syndrome were excluded from this study. Participants were dropped if the data were incomplete and could not be followed up in 3 days. Participants were recruited with non-probability sampling through consecutive sampling after fulfilling inclusion and exclusion criteria. Sample size were determined by paired t-test formula. For two groups to be able to analyze CLI, a minimum of 36 samples was needed.

Blood was collected before surgery, and at 48 and 72 hours after surgery. Patients were observed for mortality incidence during treatment in the unit. The CRP level was measured using ABX Pentra 400 (HORIBA, Germany) while albumin level was measured using HumaStar 80 (HUMAN, Germany). CLI was measured using the following formula: CRP level (mg/dl) / albumin level (g/l) x 100. Patients with CLI below 60 would be included in the study. CLI was divided into three groups based on the timing: CLI1 (before surgery), CLI2 (48 hours after surgery), and CLI3 (72 hours after surgery). Participant characteristics that were recorded include: age, gender, sequential organ failure assessment (SOFA) score, surgery type, and duration of surgery. The independent variable in this study was the patient outcome, whether the participants survived or did not.

Data were analyzed using SPSS Statistics version 21.0 (IBM, New York, US). Patient baseline characteristic was presented according to the specified type of variable. Categorical variable was displayed as a percentage (number). Numeric variables were tested for normality using the Kolmogorov-Smirnov test. If the data was normally distributed, it would be presented with mean±SD, otherwise it would be presented with median (min-max).

The cut-off point, sensitivity, and specificity of CLI1, CLI2, and CLI3 were determined by using the receiver operating characteristic (ROC) curve. After obtaining the cut-off point, the CLI variable was divided into high and low categories based on the cut-off point value. The relationship and relative risk

between CLI and patient outcomes were analyzed by chi-square or Fisher's exact test. The 28-day survival probability affected by CLI1, CLI2, and CLI3 were analyzed using the Kaplan-Meier method with the Mantel-Haenszel log-rank test analysis.

Results

From 76 participants included in this study, the mortality rate of major abdominal surgery was quite high at 14.5%. Age, gender, surgery type, surgery duration, preoperative CRP, and albumin level at 48 hours postoperative did not have significant relationship with patient outcome ($p>0.05$). Patients with higher SOFA score, CRP level and CLI value had worse outcomes, while patients with low albumin level had an increase in mortality risk ($p<0.05$) (**Table 1**).

A graph model using ROC curve found that CLI at 72 hours postoperative was the best parameter (**Figure 1**). The cut-off point of CLI at 72 hours postoperative was 278.35 and had high sensitivity level (90.9%) and specificity level (78.5%) to predict mortality rate in major abdominal surgery patients. The area under the ROC curve (AUC) value of 0.892 indicated that CLI at 72 hours had good accuracy as a mortality predictor (**Table 2**). Bivariate analysis showed that CLI at 72 hours was associated with increased risk of ICU-related mortality (RR 21.667; 95% CI 2.938-159.763; $p<0.001$) (**Table 3**). Only CLI at 72 hours had a significant effect on the major abdominal surgery survival probability after being analyzed statistically using the Mantel-Haenszel log-rank test. The significance number was 0.000 ($p<0.05$) (**Figure 2**).

Discussion

This study found that the cut-off point of CLI at 72 hours postoperative was 278.35 and had a high sensitivity level (90.9%) and specificity level (78.5%) to predict mortality rate in major abdominal surgery patient. In contrast with this study, a previous study in critically ill patients with mechanical ventilation found that the cut-off point of CLI was ≥61 with sensitivity of 62% and specificity of 68%. (11) Another study on sepsis and septic shock patients found that CLI cut-off point was >85.55 with 100% sensitivity and 89% specificity, and AUC of 0.88. This study found that CLI had a good accuracy to predict capillary leakage in septic shock. (10)

The higher cut-off point in this study versus previous studies might be due to the circumstance that major abdominal surgery induced various inflammation processes and altered the structure and function of endothelial capillaries. This catalyzed haemostatic dysregulation and deterioration in tissue perfusion. Surgery trauma will increase proinflammatory cytokine such as IL-6, IL-8, and IL-16. Perioperative proinflammatory cytokine will alter the endothelial capillaries and induce microvascular problems. (22,23) Endothelial dysfunction in patients worsened by excessive fluid administration will induce hazardous capillary leakage.

In this study, CLI at 72 hours had the most significant relationship with patient outcome compared to other timings. Capillary leakage may be attributed to inflammatory reaction by surgical trauma. (24) Major surgery will induce stress and acute inflammation. The inflammation process is normally resolved within three days. Systematic response to tissue injury, including major surgery, is marked by increased proinflammatory cytokines, which promotes CRP production and capillary leakage. CRP production will increase to its peak level 36-50 hours after inflammation. Peak albumin leakage hypothetically occurs at the same time. A recent study found that two days after major abdominal surgery the plasma albumin concentration decreased by 33%. The time course of the capillary leakage could be synchronous with the level of inflammation. (4,25) Lastly, capillary leakage during severe inflammatory process could be worsened by infection or due to excessive fluid in resuscitation. Major abdominal surgery tends to have excessive fluid administration and induce more capillary leakage. (7) Rapid intravenous infusion causes hypervolemia and damages the endothelial surface layer causing increased albumin leakage and other plasma constituents. (24) If the injury still exists, the inflammatory process will continue. Therefore, if the CLI at 72 hours is still high, this indicates severe inflammatory process is still occurring and could lead to worsen patient outcome.

Conclusion

High CLI 72 hours postoperatively can be considered as the risk factor to ICU-related mortality. The limitations of this study were that it was conducted in a single-center hospital and only observed CLI in patients. Future studies can be carried out by prospective multicentre studies and determine the intervention performed in patients with risk factors for capillary leakage and intervention to prevent the complication of capillary leakage.

Competing interests

The author(s) declared no potential competing interest with respect to any patents, patent applications, or products in development or for market.

Table 1. Subject characteristics

Variable	Outcome		p
	Non-survive, n (%) 11 (14.5%)	Survive, n (%) 65 (85.5%)	
Age (year), mean±SD	57.36±12.65	48.82±14.38	0.068*
Gender - Male, n (%) - Female, n (%)	 8 (16.7%) 3 (10.7%)	 40 (83.3%) 25 (89.3%)	0.362**
Surgery type - Emergency, n (%) - Elective, n (%)	 5 (20.0%) 6 (11.8%)	 45 (88.2%) 20 (80.0%)	0.265**
Surgery duration (minute), median (min-max)	120 (60-180)	90 (45-360)	0.750***
SOFA score, median (min-max)	2 (0-9)	0 (0-4)	0.003***
CRP level - Preoperative, median (min-max) - 48h postoperative, median (min-max) - 72h postoperative, median (min-max)	 48 (6-96) 96 (24-384) 96 (48-768)	 24 (0-192) 24 (0-192) 24 (0-192)	 0.123*** 0.007*** 0.001***
Albumin level - Preoperative, median (min-max) - 48h postoperative, mean±SD - 72h postoperative, median (min-max)	 3.10 (2.3-3.6) 3.37±0.58 3.10 (2.3-3.5)	 3.6 (1.9-4.6) 3.28±0.66 3.5 (2.0-5.3)	 0.013*** 0.67* 0.003***
Capillary leak index (CRP/albumin) - Preoperative, median (min-max) - 48h postoperative, median (min-max) - 72h postoperative, median (min-max)	 133.30 (18.20-417.40) 218.20 (75.0-1324.1) 384.0 (165.5-3072.0)	 48.0 (0-662.1) 106.70 (0-662.0) 117.00 (0-923.0)	 0.048*** 0.026*** <0.001***

Legend: SD=standard deviation; SOFA=sequential organ failure assessment; CRP=C-reactive protein. *Independent t-test; **Fisher's exact test; ***Mann-Whitney test.

Table 2. Area under ROC curves (AUC) to predict mortality

Variable	AUC	Cut-off value	Sensitivity	Specificity	95% CI	
					Lower	Upper
CLI1	0.687	65.75	63.6%	53.8%	0.531	0.843
CLI2	0.711	174.60	63.6%	70.8%	0.576	0.846
CLI3	0.892	278.35	90.9%	78.5%	0.817	0.966

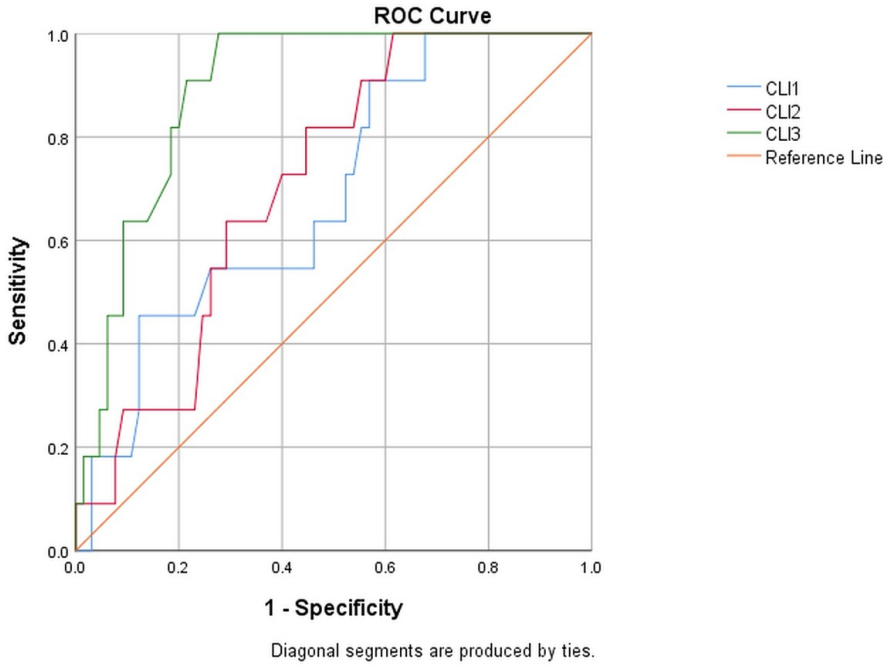
Legend: ROC=receiver operating characteristic; CLI=capillary leak index; CI=confidence interval.

Table 3. Relationship between CLI and ICU-related mortality

Variable	Outcome		p	RR	CI 95%
	Non-survivor, n (%)	Survivor, n (%)			
CLI1 - High (≥65.75) - Low (<65.75)	 7 (18.9%) 4 (10.3%)	 30 (81.1%) 35 (89.7%)	0.283*	1.845	0.588-5.786
CLI2 - High (≥174.60) - Low (<174.60)	 7 (26.9%) 4 (8.0%)	 19 (73.1%) 46 (92.0%)	0.033**	3.365	1.083-10.453
CLI3 - High (≥278.35) - Low (<278.35)	 10 (41.7%) 1 (1.9%)	 14 (58.3%) 51 (98.1%)	0.000**	21.667	2.938-159.763

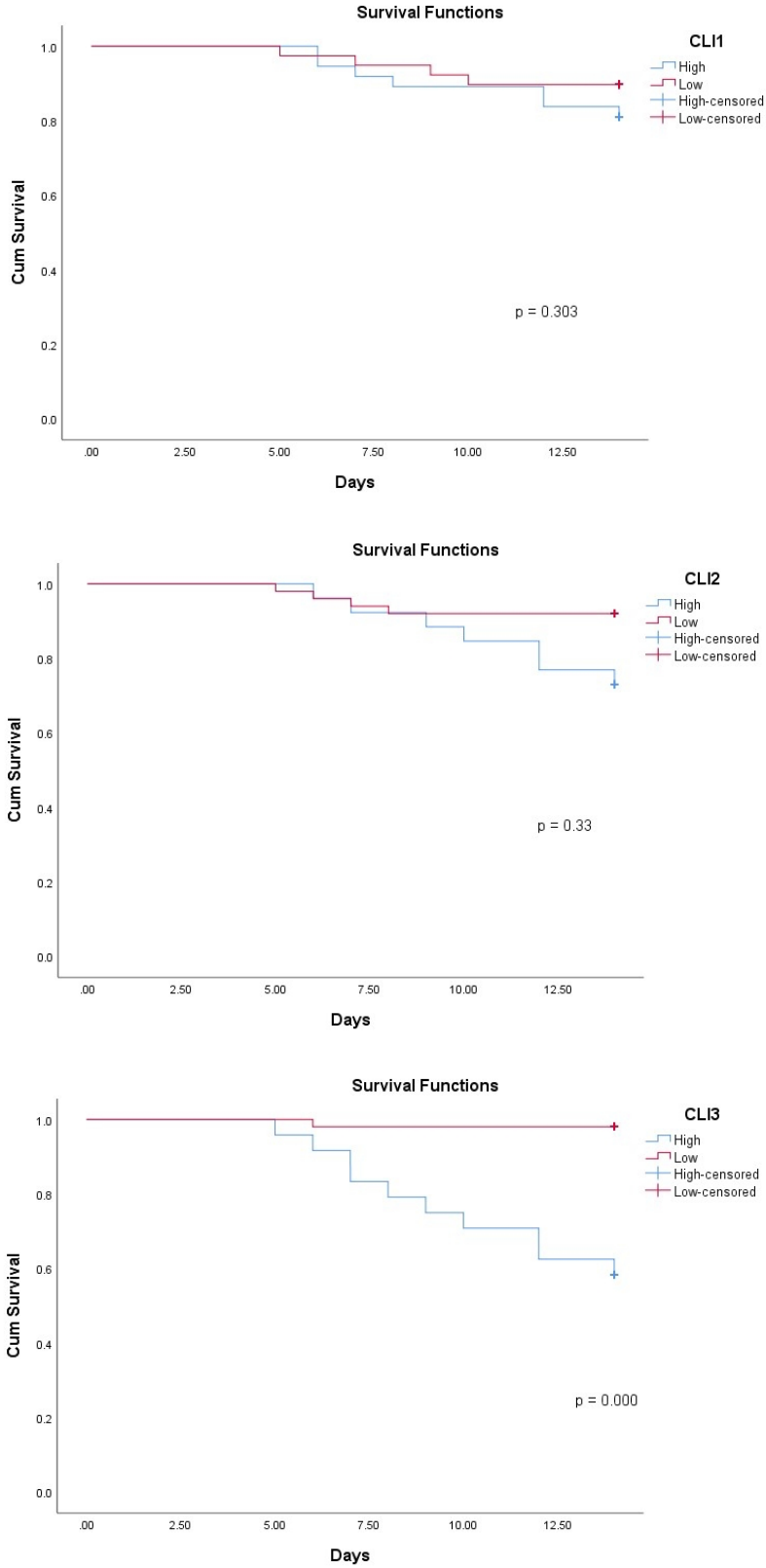
Legend: CLI=capillary leak index; ICU=intensive care unit; RR=relative risk; CI=confidence interval. *Chi-square test; **Fisher's exact test.

Figure 1. ROC of CLI and ICU-related mortality



Legend: CLI=capillary leak index; ROC=receiver operating characteristic; ICU=intensive care unit.

Figure 2. Survival analysis high CLI



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