Platelet To Lymphocyte Ratio As A Predictor Of SIRS In Patients With Peptic Ulcer Perforation Underwent Surgery

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Abstract

Background: The high incidence of postoperative Systemic Inflammatory Response Syndrome (SIRS) in patients with peptic ulcer perforation motivates researchers to search for inexpensive, convenient, simple, and non-invasive preoperative biomarkers that can be used to predict SIRS.

Aim: To assess the Platelet Lymphocyte Ratio (PLR) as a predictor of SIRS in patients with peptic ulcer perforation who underwent surgery at Sanglah General Hospital Denpasar.

Methods: This study used a retrospective cohort design involving 94 respondents of Peptic Ulcer Perforation patients who underwent surgery at Sanglah Hospital Denpasar from January 2016 to December 2019. The parameters in this study were age, gender, nutritional status, PLR, and occurrence of SIRS.

Results: Of all the research variables, only PLR was significant. The statistical tests obtained a p-value <0.001 and OR 37.3 (CI: 2.71-9.02). The best cut-off point is 348.5, with an AUC value of 87.5%. The OR value of 37.3 means that PLR348.5 causes SIRS to occur 37.3 times.

Conclusion: There is a significant relationship between PLR with the incidence of SIRS, and PLR can be a predictor of SIRS incidence in PUP patients undergoing surgery

Keywords: Peptic Ulcer Perforation, Platelet Lymphocyte Ratio, SIRS

Introduction:

Peptic ulcer disease refers to injuries that occur to the gastric mucosa resulting in ulceration of the mucosal layer to the submucosal layer.[1] Peptic ulcer disease occurs due to an imbalance between gastric acid, pepsin, and the mucosal barrier. This disease occurs in about 4 million people worldwide every year. The incidence of peptic ulcer disease has been estimated to be around 1.5% to 3%.[2]

A systematic review from developed countries estimated that the annual incidence of peptic ulcer disease is 0.10% -0.19% of outpatient data and 0.03% -0.17% of inpatient data. Although 10%-20% of patients with peptic ulcer disease will develop complications, only 2%-14% of ulcers will have perforation leading to an acute abdomen.[3]

The most common complications of peptic ulcer disease include bleeding, perforation, and obstruction. Perforation is a serious complication of peptic ulcer disease. Patients with perforated peptic ulcer (PUP) often present with acute abdominal symptoms with a high risk of morbidity and mortality. PUP carries a mortality rate ranging from 1.3% to 20%. It has been reported that the 30-day postoperative mortality rate is up to 20%, and the 90-day postoperative mortality rate is up to 30%.[3]. Oktay Aydin et al. stated that PUP could cause local and generalized peritonitis, sepsis, and death with a morbidity rate of 50% and mortality ranging from 4% to 30%.[4]

The stomach has a high level of acidity. Therefore, most individuals with perforated peptic ulcers are not at risk for immediate bacterial growth. However, leakage of acidic fluid into the abdominal cavity can cause severe chemical peritonitis, and within hours of perforation, the patient will develop an acute abdomen and signs of peritonitis. When food leaks into the abdominal cavity, an inflammatory reaction occurs and can lead to multiple pockets of an abscess. If left untreated, the patient will develop SIRS and progress to multiorgan failure.[5]

SIRS is an inflammatory condition that affects all body parts, resulting from a response to an infectious or non-infectious process through various pathways. Some risks that cause SIRS can be trauma, infection, impaired immunity, invasive procedures such as intravenous line installation, or surgery. One-third of SIRS patients may progress to sepsis. Complications can cause the failure of one or more organs, which can further lead to death.[6]

The prevalence of SIRS is quite high, about 1/3 of the total hospitalized patients and >50% of all ICU patients, and in the surgical ICU, it can cover >80% of hospitalized patients.[7]

Churpeck et al. conducted a study of 269,951 hospitalized patients, where it was found that 15% of patients had SIRS at the time of hospital admission. As many as 47% were found

during the patient's stay, where the mortality rate is significantly in patients with SIRS (4.3%) compared to patients without SIRS (1.2%).[8]

In Indonesia, several studies provide an overview of the incidence of SIRS. Burnan Hedi et al. found that the incidence of SIRS in the ICU Lahat Hospital was 66% of the number of patients treated, and 61.7% were surgical cases.[7]

Early diagnosis of SIRS is very important to reduce patients' high morbidity and mortality rates. However, there is often a delay in diagnosis because specific signs and symptoms are not always found, such as changes in the leukocyte count, fever, tachycardia, and tachypnea.[9]

Several biomarkers have been studied for the early diagnosis of SIRSSuch as C-reactive protein (CRP), procalcitonin, mean platelet volume (MPV), and platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR), to predict the prognosis in inflammatory diseases.These markers can be divided into risk prediction, diagnosis, monitoring, and outcome. In this group of biomarkers, we can see the success of several biomarkers such as procalcitonin and CD14 as markers of SIRS and sepsis. However, examining C-reactive protein (CRP) and procalcitonin requires additional testing costs and is sometimes unavailable in some hospitals and ordinary clinical practices.[1]

Platelet Lymphocyte Ratio (PLR) is an inflammatory biomarker used to indicate systemic inflammation. PLR is defined by the absolute number of platelets divided by the absolute number of lymphocytes. This is a simple procedure obtained from a complete blood count and does not add to the cost of a blood count laboratory examination. The complete blood count is an examination carried out routinely in hospitals, especially for patients who will undergo surgery. PLR has been tested as a guide for the prognosis of various diseases, such as cancer, community pneumonia, and sepsis.[9]

Oktay Aydin et al. stated that sepsis and death in PUP patients who had surgery were higher in women of old age, long hospitalization, NLR values, high PLR, and low lymphocyte counts. The sensitivity and specificity of the PLR values of the groups used by the research subjects were 75% and 98.50%, respectively.[4]

There are still few studies on the usefulness of the platelet-to-lymphocyte ratio in predicting the occurrence of postoperative SIRS in surgically treated peptic ulcer perforations [4] and at Sanglah Hospital, no research has been conducted on the use of Platelet Lymphocyte Ratio in predicting the occurrence of postoperative SIRS in patients with peptic ulcer perforation.

On the other hand, cases of peptic ulcer perforation at Sanglah Hospital are quite high, and it was reported that between 2015 and 2016, there were 50 cases of peptic ulcer perforation.[10] Of the 116 cases of generalized peritonitis at Sanglah Hospital between 2016 and 2018, 53 cases (45.7%) were caused by peptic ulcer perforation.[11]

Platelet Lymphocyte Ratio is a marker of inflammation that is inexpensive, convenient, simple, and non-invasive that can be measured on routine complete blood counts performed on patients in hospitals and regular clinical practice.[12] Currently, an examination is needed to support a diagnosis that is fast and easy to do, especially in areas that have limited tools. This is what underlies the researcher to conduct a study of the platelet lymphocyte ratio in predicting the occurrence of SIRS in PUP patients who were operated on at Sanglah Hospital, Denpasar.

Methods:

This study is an analytical observational study using a retrospective cohort design to determine the predictors of SIRS in PUP patients operated on at Sanglah Hospital. The predictor tested was Platelet Lymphocyte Ratio. The study was conducted using medical record data of all patients with PUP operated on at Sanglah Hospital Denpasar from January 2016 to December 2019. The Ethics Committee approved this research of Udayana University/ Sanglah Hospital Denpasar Bali with No. 2352/UN14.2.2.VII.14/LT/2020.

Inclusion criteria: All PUP patients who had surgery at Sanglah Hospital Denpasar from 2016 until this study was conducted. Exclusion criteria: (1) Patients aged less than 18 years (2) Patients with perforation related to trauma, such as stab trauma or perforation due to tumor or malignancy. (3) Patients with congenital immune disease or immunodeficiency. (4) Incomplete medical records. (5) Missing medical records. Free Variable: Platelet Lymphocyte Ratio, dependent variable: SIRS, and control variable: age, gender, nutritional status.

Statistical tests were carried out using the Statistical Package for Social Sciences (SPSS) program, version 25.0. Statistical data analysis consists of(1)Univariable Analysis, (2) Bivariate analysis with chi-square test, and (3) multivariate using logistic regression.

Results:

This study used a retrospective cohort design involving 96 respondents of PUP patients who underwent surgery at Sanglah Hospital. Characteristics of respondents were described by age, gender, and nutritional status (Table 1).

Table 1 Characteristics of Respondents

Variable	SIRS incident		p
	SIRS	No SIRS	
Age (n,%)			
60 years	32 (33.3%)	24 (25%)	0.240
< 60 years old	18 (18.8%)	22 (22.9%)	
Gender (n,%)			
Man	38 (39.6%)	32 (33.3%)	0.478
Woman	12 (12.5%	14 (14.6%)	
Nutritional status			
BMI (≥ 25 kg/m2)	19 (19.8%)	15 (15.6%)	0.581
BMI (18.5-25 kg/m2)	31 (32.3%)	31 (32.3%)	

The bivariate analysis aims to determine the relationship of risk factors to the occurrence of SIRS in PUP patients who have been operated on at Sanglah Hospital. The first step in the bivariate analysis was to determine the cut-point of PLR on the occurrence of SIRS in PUP patients using the ROC curve (Figure 1).
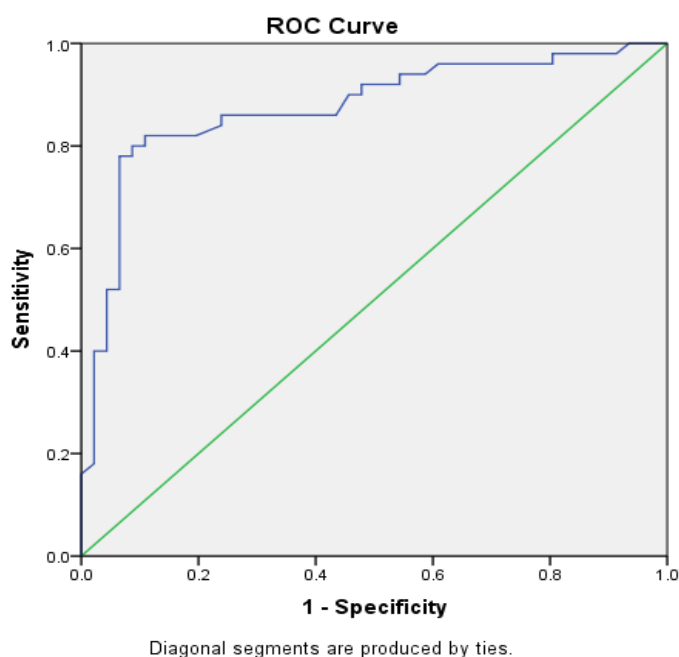
Figure 1 PLR ROC curve to the occurrence of SIRS

The ROC curve image shows the PLR sensitivity with an AUC value of 87.5%. Statistically, the AUC value of 87.5% is high. If PLR is used to diagnose SIRS in 96 respondents, the correct conclusion is obtained in 84 patients. Clinically, the AUC PLR value is satisfactory because it is greater than the minimum AUC value expected by the researcher, 70%. The best cut-off point is 348.5. Bivariate analysis was then carried out by making a 2x2 cross-tabulation and calculating the association's size in the form of an Odds Ratio (OR). The statistical test used is the Chi-Square Test (table 2).

Table 2 Bivariate Analysis

Variable	SIRS incident		OR	CI95%	p
	SIRS	**No SIRS**			
Age					
60 years	32 (33.3%)	24 (25%)	1.6	0.84-1.91	0.240
< 60 years old	18 (18.8%)	22 (22.9%)			
Gender					
Man	38 (39.6%)	32 (33.3%)	1.3	0.73-1.87	0.478
woman	12 (12.5%	14 (14.6%)			
Nutritional status					
BMI (≥ 25 kg/m2)	19 (19.8%)	15 (15.6%)	1.2	0.75-1.64	0.581
BMI (18.5-25 kg/m2)	31 (32.3%)	31 (32.3%)			
PLR					
348.5	41 (42.7%)	5 (5.2%)	37.3	2.71-9.02	<0.001
< 348.5	9 (9.4%)	41 (42.7%)			

Significant results were obtained only on PLR values with p-value <0.001 and OR 37.3 (IK: 2.71-9.02), meaning that there was a relationship between PLR and the incidence of SIRS in this study. The OR value of 37.3 means that PLR 348.5 causes SIRS to occur 37.3 times.

The multivariate analysis aims to determine the most dominant risk factors influencing the occurrence of SIRS in PUP patients who have been operated on at Sanglah Hospital. Multivariate analysis in this study using logistic regression test includes all variables. The results of the omnibus test obtained a p-value of <0.001, and the results of the Hosmer and Leme show test obtained a p-value of 0.709 > 0.05, meaning that this test model is fit to be used. The classification table obtained 85.4%, which means that the test model used in predicting the independent variable to the dependent variable is 85.4%, and the final result of the variables in the equation (Table 3).

Table 3. Multivariate Analysis Results

Variable	B	Adj OR	CI95%	P
PLR	3,609	36.9	11.28-120.81	<0.001

Table 3 shows the PLR variable with a p-value of <0.001 with a positive B value, which means there is a positive relationship between PLR and the occurrence of SIRS. So it can be concluded that a high PLR can predict the occurrence of SIRS in PUP patients as much as 36.9 times and is the most dominant variable causing SIRS.

Discussions:

The results of the research on the characteristics of respondents based on age obtained that the age of respondents 60 years with the occurrence of SIRS as many as 32 respondents (33.3%) while the age < 60 years with the occurrence of SIRS as many as 18 respondents (18.8%) with p-value> 0.05 means there was no association between age and the incidence of SIRS in this study. The results of this study differ from a study in Korea using the National Health Insurance claims database, which reported that the majority of patients with PUP were younger than 60 years, with a male predominance. In another South Korean study, male predominance was observed (85.1%), and the mean age and BMI of the subjects were 50.6 ± 18.3 years and 21.7 ± 2.9 kg/m2.[13] Thorsen K, Soreide JA, et al. reported that most peptic ulcer perforations occurred in the middle age group between 30-and 50 years.[14]

Peptic ulcer disease is common, with a lifetime prevalence in the general population of 5–10% and an incidence of 0.1–0.3% per year. Despite a sharp decline in the incidence and rates of hospital admission and death over the past 30 years, complications are still encountered in 10-20% of these patients. Peptic ulcers remain a significant health care problem that can consume many financial resources.[15]

Sukit M Chakma et al. reported that most patients with peptic perforated peritonitis were among the middle age group in Northeast India.[16] Hedi et al.'s research conducted an evaluation involving 47 respondents, and it was found that data aged > 61 years had more SIRS than those aged < 61 years. Males were found to be more in this study, namely 63.8%.[7] Physiologically the body's ability to maintain immune system function decreases at the end of the life span. In old age, the ability to produce an immune response decreases. Old age is a time

of changes in body functions, and physical and psychological abilities experience a very rapid decline.[17]

The research results on the characteristics of respondents based on gender were found to be male, with the occurrence of SIRS in as many as 38 respondents (39.6%). In comparison, the female sex with SIRS occurrence were 12 respondents (12.5%) with a p-value of 0.478 > 0.05. There was no association between gender and the incidence of SIRS in this study. Study Aydin et.al involved 23 respondents from PUP patients. 18 respondents were male (78.3%).[4] Research results differ in Hedi et al. (2017) concluded that age and sex had a relationship with SIRS occurrence. Thorsen et al. found that the female sex found more peptic ulcers (59%) in the age group 60 years.[18]

Based on BMI obtained BMI of 25 kg/m2 with the occurrence of SIRS as many as 19 respondents (19.8%) and no SIRS as many as 15 respondents (15.6%) while BMI (18-24.9 kg/m2) with the occurrence of SIRS as many as 31 31 respondents (32.3%) and no SIRS (32.3%) with p-value 0.581 > 0.05 and OR 1.2 (IK: 0.75-1.64) means that there is no relationship between BMI with the incidence of SIRS in this study. In women, higher Body Mass Index was associated with higher PLR levels, and there was also evidence of an interaction between age × BMI that significantly affected PLR scores. The positive relationship between obesity and PLR is often associated with a chronic inflammatory state.[19]

Studylie et al. investigated the impact of obesity (projected as Body Mass Index (BMI)) on short-term and long-term mortality of septic patients in the ICU. They found an association between BMI and 30-day mortality. Obese and younger patients (P <0.001) had worse SOFA scores and received more aggressive treatment than normal-weight patients. Obese patients had longer use mechanical ventilation, which was associated with length of hospital stay (LOS). Obesity is a growing problem in industrialized countries. The study results with different respondents by Mica et al., involving 651 in a retrospective study, found the incidence of sepsis was significantly higher in the high BMI group.[20]

The Relation of PLR with the occurrence of SIRS in PUP patients undergoing surgery

PLR sensitivity in this study was obtained with an AUC value of 87.5%. Statistically, the AUC value of 87.5% was high. If PLR is used to diagnose SIRS in 96 respondents, the correct conclusion is obtained in 84 patients. The best cut-off point is 348.5. PLR with SIRS data obtained PLR 348.5 with SIRS occurrence in as many as 41 respondents (42.7%). In comparison, PLR <348.5 with the occurrence of SIRS in as many as 9 respondents (9.4%) with a p-value of <0.001 and OR 37.3 (IK: 2.71-9.02) means that there is a relationship between PLR and the incidence of SIRS in this study. The OR value of 37.3 means that the PLR 348.5 predicts the occurrence of SIRS 37.3 times.

The results of Aydin & Pehlivanll's study found that the results of the Receiver Operating Characteristics (ROC) curve analysis showed that the PLR cut-point was 322.22 and the lymphocyte count was <0.67 microliters (p = 0.035), and concluded that PLR has a diagnostic value for mortality in patients who were operated. Because of PUPs. PLR, NLR, and lymphocyte count values can be used as new biomarkers to identify the risk of death in patients with peptic ulcer perforation operated on.[4]

Shen, Huang, and Zhang found that the normal PLR values ranged from 130-to 150. A high PLR (>250) is associated with increased in-hospital mortality. Higher PLR levels are predictive of

inflammation with higher severity, and low lymphocyte counts may represent a suppressed immune and inflammatory response. The increase in PLR may reflect the degree of inflammatory and immune response to infection associated with a poor prognosis.[21]

Different research results were found in Gulbagci et al., involving 906 respondents. NLR and PLR values were calculated and interpreted statistically. A significant difference was found between the NLR groups (p = 0.048), but no significant difference was found for the PLR (p = 0.422).[22] Peptic ulcer perforation is a surgical emergency with manifestations in the form of localized peritonitis or generalized peritonitis with a high risk of developing SIRS and sepsis associated with mortality and morbidity.[23]

In a study with different respondents conducted by Jo et al. on trauma patients, the AUC PLR value of 0.82 at a 95% confidence interval: 0.74-0.89) was greater than the lymphocyte count of 0.72 (95% CI: 0, 63-0.81) and a platelet count of 0.67 (95% CI: 0.57-0.76). PLR is significantly associated with an increased risk of in-hospital death in patients treated for traffic accidents.[24]

The Most Influential Factors In The Occurrence Of SIRS In PUP Patients Who Have Surgery

Platelets play an important role in immunomodulatory and inflammatory processes by inducing the release of inflammatory cytokines and interacting with various types of bacteria and immune cells, including neutrophil cells, T lymphocytes, natural killer (NK), and macrophages, which contribute to the initiation or exacerbation of the inflammatory process.[21]

The results showed that PLR had a p-value of <0.001 with a positive B value, which means there is a positive relationship between PLR and the occurrence of SIRS. A high PLR can predict the occurrence of SIRS in PUP patients as much as 36.9 times and is the most dominant variable causing SIRS. Low lymphocyte counts, to some extent, represent suppressed immune and inflammatory responses and have also been reported to be associated with inflammatory disease. Lymphocytes in the blood are dysfunctional during sepsis, which can be seen significantly in lymphopenia and decreased levels of CD4+ T lymphocytes, CD8+, and NK cells.[21]

A potential mechanism for immunosuppression in sepsis is lymphocyte apoptosis, in which death of the receptor or mitochondrial-mediated pathway may occur.[25] The research results by Lin and Hottenga (2016) stated that differences influence PLR in gender, age, and lifestyle. Studies have shown that the PLR is lower in men than in women, and older age is associated with increased PLR.[19] Higher PLR is associated with lower lymphocytes and higher platelet counts. Platelets play an important role in angiogenesis, thrombosis, and hemostasis, and an increase in platelet count has been implicated in cardiovascular disease and cancer development.[19] SIRS results from a process involving the immune-inflammatory and anti-inflammatory systems triggered by infectious agents. The host response is complex and variable, with both pro-inflammatory and anti-inflammatory mechanisms contributing to eradicating infection and tissue recovery in organ injury. Early and appropriate intervention is very important to improve patient outcomes to reduce morbidity and mortality.[26]

In PUP, the first phase appears within 2 hours after the perforation is clinical symptoms such as acute abdominal pain, tachycardia, and severing. The perforation then causes gastric contents to leak into the peritoneal cavity, causing chemical peritonitis. Severe pain stimulates the sympathetic nerves, and the tachycardia and acral become cold. Within 2 to 12 hours of

onset, the inflammation extends to a larger peritoneum area, and the pain is localized to pain throughout the abdomen. After the onset of more than 12 hours, the patient becomes hemodynamically unstable. SIRS, sepsis, and death can be a consequence of this event.[27]

SIRS is common in patients with perforated peptic ulcers. About 30-35% of patients have sepsis on arrival in the operating room, and it is the leading cause of death in about 40-50%. Within 30 days postoperatively, more than 25% of patients develop septic shock, which carries a 50-60% mortality rate. Thus, investigations and interventions aimed at preventing, detecting, and treating sepsis in patients with perforated peptic ulcers can reduce mortality and morbidity. This goal can be achieved by systematically assessing the signs of sepsis and treating the patient according to the principles of the Sepsis Campaign, including fluid resuscitation, culture, empirical broad-spectrum antibiotics, and source control of infection.[28]

SIRS incidence is higher at age > 61 years, and SIRS is more common than at age < 61 years. Physiologically the body's ability to maintain immune system function decreases at the end of the life span. In old age, the ability to produce an immune response decreases. Old age is a time of changes in body functions, and physical and psychological abilities experience a very rapid decline[17].

Lin and Hottenga stated that differences influence PLR in gender, age, and lifestyle. Studies have shown that the PLR is lower in men than in women, and older age is associated with increased PLR.[19]

In women, a higher Body Mass Index is associated with higher PLR levels, and evidence for an age × BMI interaction significantly affects PLR scores. The positive relationship between obesity and PLR is often associated with chronic inflammatory states.[19]

Conclusion:

There is a significant relationship between PLR obtained, a cut of point 348.5 with an AUC value of 87.5% with the incidence of SIRS and PLR is a predictor of SIRS incidence in PUP patients undergoing surgery 37.3 times.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

None-declared.

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