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High c-reactive protein level as risk factors of complications in upper gastrointestinal bleeding

I Ketut Mariadi,[1,3] Karismayusa Sudjana[2], I Dewa Nyoman Wibawa[1]

ABSTRACT

Purpose: Upper gastrointestinal bleeding is the major medical emergency case in the field of gastroenterology. The complications of UGI bleeding are recurrent bleeding and death. Identifying risk factors for the complications is expected to prevent or reduce recurrent bleeding complications and deaths from UGI bleeding. This study aims to know the risk of UGI bleeding complications in patients with a high level of C reactive protein (CRP).

Patients and methods: A prospective observational analytic study was performed, including all UGI bleeding patients (variceal and nonvariceal). CRP level was used to determine the high-risk cohort. High-risk cohort if the CRP level 5 mg/L and above, and low risk if CRP level less than 5 mg/L. The outcome of the study was the incidence of complication, both rebleeding and death during follow up for six weeks.

Results: Based on the characteristic data of the sample, the high-risk group appears to have a slightly older age, higher leucocyte count, lower hemoglobin levels, and higher serum creatinine than the low-risk group. The incidence rate of complication in the high-risk group was 85.3% while in the low-risk group was 37.5%, and the relative risk (RR) was 2.27 (95% CI: 1.43-3.67). There were significant differences in the incidence of complications between the group, X^2: 16; p <0.001. The RR for rebleeding in the high-risk to low-risk cohort was 2.68 (95% CI: 1.31-5.47); this difference is statistically significant (X^2:9.3; p=0.02). The RR for death complication was 1.70 (95% CI: 0.63-4.53), and the difference is not statistically significant (X^2: 1.2; p=0.28).

Conclusion: In this study, we found the CRP level ≥ 5 mg/L as a significant risk factor for rebleeding complications but not mortality in a patient with UGI bleeding.

Keywords: CRP, GI bleeding, complication

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[1]Gastroenterohepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali, Indonesia
[2]Internal Medicine Residency Program, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital.
[3]Doctoral program, Faculty of Medicine, Universitas Udayana

*Corresponding to:
I Ketut Mariadi;
Gastroenterohepatology Division, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesi; Doctoral program, Faculty of Medicine, Udayana University
ketutmariadi@yahoo.com

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INTRODUCTION

Upper gastrointestinal (UGI) bleeding is defined as GI blood loss having an origin proximal to the ligament of Treitz. The manifestation of Acute UGIB is hematemesis, "coffee ground" emesis, the return of red blood via a nasogastric tube, and or melena with or without hemodynamic compromise. Hematochezia may occur in patients with extremely brisk UGIB.[1]

Upper gastrointestinal bleeding is the most frequent medical emergency case in gastroenterology, which is about 74.3% of all cases that come to the emergency room.[2] The rate of hospitalization due to UGI bleeding ranges from 250.000 to 400.000 per year.[3]

Based on the cause, UGI bleeding can be grouped into variceal bleeding and nonvariceal bleeding. Nonvariceal hemorrhage is the most common cause of UGI bleeding in Western countries. It is about 80-90%, mainly due to peptic ulcers.[4,5] But Another study by Moledina found variceal bleeding is the most common cause of UGI bleeding, which is around 50-60%.[6]

The complications of UGI bleeding are recurrent bleeding and death.[7,8] These complications generally occur within 4-6 weeks after UGI bleeding occurs.[9] several factors influence the occurrence of these complications, such as old age and the presence of comorbid diseases.[10] The mortality and morbidity due to UGI bleeding in Indonesia are still high, where complications of death and recurrent bleeding are around 60-65%.[11]

C-reactive protein (CRP) has been recognized as a nonspecific marker for inflammation. An increment of CRP level is used as a prognostic factor in various medical conditions. Elevated CRP has been associated with a high risk of in-hospital mortality in critically ill patients in ICU.[12] CRP has been used as a prognostic marker in variceal

and nonvariceal UGI bleeding. Risk stratification can aid clinical decision-making regarding the timing of endoscopy and hospital discharge. It is recommended to use a validated risk stratification tool to stratify patients into high and low-risk groups.[13] This study aims to know the risk of UGI bleeding complications in patients with a high CRP level. By understanding the risk of complications, we can prevent or reduce recurrent bleeding complications and deaths from UGI bleeding.

MATERIAL AND METHODS

This study is a prospective observational analytic study. The study was conducted at Sanglah General Hospital (RSUP) Denpasar from August 2017 to July 2018. The selection of samples in this study was consecutive sampling, which included all UGI bleeding patients who met the subject's eligibility criteria to reach the planned number. The cohort group was all UGI bleeding patients aged 18 years or more, except patients who were unwilling to participate and UGI bleeding patients who asked to discharge from the hospital before being allowed to go home by the treating doctor. The number of samples is 68 patients. The patient was stratified as high risk if the CRP level 5 mg/L and above and low risk if the CRP level smaller than 5 mg/L. Several variables were previously assumed to be related to complications from UGI bleeding was also recorded in this study, such as leukocytes, thrombocytes, hemoglobin levels, serum creatinine, Blood Urea Nitrogen (BUN), Alanine Aminotransferase (ALT) levels, albumin, international normalized ratio (INR), the presence of comorbid diseases, and the degree of bleeding. Rebleeding was defined as UGI Bleeding after a stable clinical period of 24 hours, resulting in admission, blood transfusion, or intervention to stop the hemorrhage.[8] The degree of bleeding was classified based on the classification of hypovolemic shock according to blood loss,[14] we reclassified into 2 degrees, class I and II as mild-moderate and class III and IV as severe bleeding. UGI bleeding complication defines by the presence of rebleeding and death during follow up six weeks.

This study was approved by the Ethics Commission of the Medical Faculty of Udayana University, and all participants provided written informed consent before enrollment. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Clinical laboratory examinations were carried out in the clinical laboratory of Sanglah General Hospital, Denpasar. The endoscopy procedure was performed on all subjects to determine the source of UGI bleeding, classified as variceal or nonvariceal bleeding. Subsequently, subjects were followed for six weeks to see any repeated bleeding or death as complications. Subjects or families of subjects were contacted by telephone to be asked for repeated bleeding and or death in the subject. If the subject or family of the subject cannot be contacted by telephone after being tried twice on the same day, it will be tried again to contact the subject or family of the subject three times later in 2 times, and if there is still no answer the subject is considered a loss to follow up. Statistical analysis is performed with computer software SPSS V23.0. P-values of 0.05 or less were considered statistically significant. Chi-square test for all variables was done to determine the risk factor and relative risk

RESULTS

There were 68 patients who met the criteria as samples in this study. Two people out of a total of 68 samples were excluded due to loss to follow up. We use CRP level 5 mg/dl to divide the cohort sample into high-risk (CRP ≥ 5 mg/dl) and low-risk group (CRP< 5mg/dl) for complication. The characteristics of the cohort groups can be seen in Table 1. The subjects characteristic data in the high-risk group appears to have a slightly older age, higher leucocyte count, lower hemoglobin levels, higher serum creatinine, and Glasgow Blatchford Score than the low-risk group.

The occurrence of complications in high-risk vs. low-risk cohort can be seen in Table 2. Complications that occur in high-risk groups are more frequent than in the low-risk group, where the incidence rate of complication in the high-risk group was 85.3% while in the low-risk group, the incidence of complication was 37.5%, and with the relative risk (RR) 2.27 (95% CI: 1.43-3.67) for high-risk cohort group. a Chi-square test was used to test the incidence rate difference, and there were significant differences in the incidence of complications, X^2: 16; p <0.001.

In a specific type of complication, rebleeding was more frequent in a high-risk cohort group, but death complication was the same. For rebleeding complications, the high-risk cohort incidence was 58.8% and 21.9% in the low-risk cohort. This difference is statistically significant (X^2:9.3; p=0.02), and the relative risk for rebleeding in the high-risk to low-risk cohort was 2.68 (95% CI: 1.31-5.47).

For death complications, the incidence of death in the high-risk cohort and low-risk cohort was 26.5% and 15.6%. The difference is not statistically significant (X^2: 1.2; p=0.28), and the RR was 1.70 (95% CI: 0.63-4.53).

Based on this cohort study, patients with UGI bleeding (variceal or nonvariceal) who have CRP

Table 1. Characteristics of the sample base on CRP group

Characteristics	CRP < 5 mg/L (n=32)	CRP ≥ 5 mg/L (n=34)	p value
Age (year, mean±SD)	50.1 ±12.3	56.9 ±12.6	0.029*
Gender (n, %)			
Male	20 (62.5)	26 (76.5)	0.27
Female	12 (37.5)	8 (23.5)	
Type of bleeding (n, %)			
Non variceal	14 (43.8)	20 (58.8)	0.22
Variceal	18 (56.3)	14 (41.2)	
Shock (n, %)	8 (25.0)	11 (32.4)	0.51
Degree of bleeding (n, %)			
I-II (mild-mod)	23 (71.8)	22 (64.7)	0.52
III-IV (severe)	9 (28.2)	12 (35.3)	
Lab results (mean±SD)			
Leucocyte (10^3/uL)	10.5 ± 6.4	13.9 ± 5.2	0.01*
HgB (gr/dL)	10.1 ± 2.9	8.4 ± 2.7	0.021*
Thrombocyte (10^3/uL)	215.4 ± 150.4	214.2 ± 118.7	0.97
ALT (U/L)	29.4 ± 15.6	35.8 ± 29.9	0.27
Creatinine (mg/dL)	1.13 ± 1.23	2.24 ± 2.77	0.041*
BUN (mg/dL)	28.9 ± 30.4	41.9 ± 37.2	0.12
INR	1.4 ± 0.4	1.4 ± 0.3	0.63
Glasgow Blatchford Score	7.09 ± 4.35	9.79 ± 3.82	0.008*

*significant at p<0.05

Table 2. The occurrence of complication in high risk vs low risk cohort

Outcome Variable		High risk N (%)	Low risk N (%)	p value	RR (95% CI)
Complication	Yes	29 (85.3)	12 (37.5)	< 0.001*	2.27
	No	5 (14.7)	20 (62.5)		(1.43-3.67)
Rebleeding	Yes	20 (58.8)	7 (21.9)	0.02*	2.68
	No	14 (41.2)	25 (78.1)		(1.31-5.47)
Death	Yes	9 (26.5)	5 (15.6)	0.28	1.70
	No	25 (73.5)	27 (84.4)		(0.63-4.53)

*significant at p < 0.05

level 5 mg/L and above during admission have a 2.3-time risk for complication and a 2.7-time risk for rebleeding compare with low-risk group. Alternatively, the probability of patient who presents with UGI bleeding and CRP ≥ 5 mg/L for complication was 70%, and the probability for rebleeding was 73%.

DISCUSSION

Upper gastrointestinal bleeding is the major medical emergency case in the field of gastroenterology. It has been known that the clinical predictors of increased risk for rebleeding or mortality include old age, poor overall health status, shock condition, comorbid illnesses, low levels of initial hemoglobin,[15] and individuals who present with hematemesis or bright red blood per nasogastric tube aspirate are at particularly high risk for rebleeding within the first 72 h.[16] There are some prognostic scales to predict rebleeding and mortality, such as the Rockall and Blatchford scores.[17,18] Although these scoring systems have been validated in some studies, these scoring systems need a better discriminative ability for mortality and rebleeding.[19] Adding another marker is one approach for increasing these abilities.

An increment of CRP level is used as a prognostic factor in various medical conditions. Elevated CRP has been associated with a high risk of in-hospital mortality in critically ill patients in ICU.[12] CRP has been used as a prognostic marker in variceal and nonvariceal UGI bleeding. The CRP level was an independent risk factor for rebleeding for all nonvariceal UGI bleeding patients as well as those patients with peptic ulcer bleeding.[20] The CRP level also has a prognostic value in other diseases, such as ruptured esophageal varices.[21]

It is known that IL-1β and tumors necrosis factor-alpha (TNF-α) stimulates CRP production.[22] Therefore, we assume that one possible mechanism of this study finding is that the release of the proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8 from macrophages and monocytes in the further lead to an increase the CRP production and release, results in an active inflammatory state as the cause of rebleeding.

Few studies have evaluated CRP as a prognostic factor for GI bleeding. One study reported an increase in the CRP level by≥100%, in 3–6 months before endoscopy predicts bleeding from the upper GI tract.[23] This study evaluated only a small number of patients with UGI bleeding. Other studies in variceal bleeding found low levels of CRP (<0.5 mg/dl) were significantly associated with longer survival.[24]

CONCLUSION

In this study, CRP appears as a risk factor for worse outcomes in patients present with UGI bleeding. We found CRP level ≥ 5 mg/L as a risk factor for rebleeding complications but not for mortality in both variceal and nonvariceal bleeding. Further studies are warranted, and incorporating CRP into known prognostic scales, such as the Blatchford or Rockall scores, might give rise to a better outcome predictor for patients with UGI Bleeding.

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DISCLOSURE

The authors declare that they have no conflicts of interest in this work.

AUTHORS CONTRIBUTION

All authors have contributed equally to all processes in this research, including preparation, data gathering, and analysis, drafting, and approval for publication of this manuscript.

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