

The Relationship between Obesity, Intraoperative Blood Loss, NLR, and CRP with Perioperative Complications in Colorectal Cancer Surgery

Lambertus Josef F. Buga^{1*}, Gede Eka Rusdi Antara², Made Agus Dwianthara Sueta², I Made Mulyawan², Ida Bagus Made Suryawisesa³, Ida Bagus Budiarta⁴

¹General Surgery Training Programme, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia.

²Digestive Surgery Department, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia.

³Oncology Surgery Department, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia.

⁴Vascular Surgery Department, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Bali, Indonesia.

*Correspondence author: yosephbuga@gmail.com.

ABSTRACT

Aim: This study examines the relationship between obesity, intraoperative blood loss, and systemic inflammatory responses (NLR and CRP) concerning perioperative complications in colorectal cancer surgery. **Methods:** A retrospective analytical observational study was conducted on 96 patients who underwent colorectal cancer surgery from January 1 to August 31, 2023. The analysis included obesity history, intraoperative blood loss, NLR, and CRP levels, using descriptive statistics, Chi-Square tests for Odds Ratios (OR), and logistic regression for adjusted odds ratios. **Results:** The study found a 38.5% complication rate in patients with BMI ≥ 25 kg/m² (OR=35) and a 29.5% rate in those with CRP >150 mg/L (OR=7). Patients with NLR >3 had a 21.1% complication rate (OR=1.3), while those with intraoperative blood loss >800 mL faced an 83.3% complication rate (OR=36). Logistic regression indicated that obesity and CRP are independently associated with major complications. **Conclusion:** Obesity, intraoperative blood loss, NLR, and CRP collectively influence major perioperative complications, with obesity and CRP being the most significant independent factors in colorectal cancer surgery.

Keywords: Colorectal cancer, obesity, CRP, NLR, intraoperative blood loss, major perioperative, complications.

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INTRODUCTION

Colorectal cancer (CRC) is a malignant tumor that arises from the epithelial tissue of the colon and rectum.¹ CRC is a highly heterogeneous malignancy caused by the interaction between genetic and environmental factors. The incidence of CRC is approximately 1.2 million each year worldwide. CRC is the second most common malignancy in women (614,000 cases/year) and the third most common in men (746,000 cases/year).²

According to the American Cancer Society, CRC is the third most commonly

diagnosed cancer and also the third leading cause of cancer-related mortality in both men and women.³ In Indonesia, CRC ranks as the third most prevalent cancer and has shown a significant increase in incidence, about 12.8 per 100,000 adults, with a mortality rate of 9.5% of all cancer cases.⁴ The incidence in men is comparable to women and tends to occur more frequent in the productive age group. In contrast, data from Western countries reported that CRC is mostly diagnosed in elderly patients.³

A study by Gunasekaran et al.⁵ reported 121 cases of CRC at Prof. I.G.N.G Ngoerah

General Hospital between 2013 and 2017. The highest number of cases occurred in the 50–60 years age group (39.7%), followed by the 61–70 years group (23.1%), while those aged over 70 had the lowest number (14.9%). Regarding gender, CRC was more prevalent in males (59.5%) than females (40.5%). The most common type was adenocarcinoma not otherwise specified (NOS) (97.5%) and diagnosed at stage II (53.7%).⁵ Surgical resection is the best curative therapy for CRC. However, it carries a high risk of recurrence. Furthermore, CRC surgery is not free of postoperative morbidity and mortality concerns.²

This study aims to investigate the association between obesity, intraoperative blood loss in colorectal cancer surgery, and systemic inflammatory response represented by neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) with the occurrence of major perioperative complications in colorectal cancer surgery.

METHODS

Retrospective observational analytic study was conducted at Prof. Dr. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia.

Subjects were selected using systematic random sampling. The inclusion criteria were as follows: (1) Patients aged ≥ 18 years who had been clinically diagnosed with colorectal cancer based on histopathological examination; (2) Patients with clinical staging of colorectal cancer classified as stage 0, I, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, or IVb; (3) Patients who underwent surgical treatment including local excision/simple polypectomy, wide surgical resection with anastomosis, or resection of the primary tumor in cases of resectable metastatic disease, at Prof. Dr. dr. I.G.N.G. Ngoerah Hospital between January 1 and August 31, 2023.

The independent variables in this study included:

- Obesity, assessed based on body mass index (BMI), categorized as $<25 \text{ kg/m}^2$ or $\geq 25 \text{ kg/m}^2$;
- Intraoperative blood loss, categorized as $\leq 800 \text{ mL}$ or $>800 \text{ mL}$;
- Neutrophil-to-lymphocyte ratio (NLR), classified as low (≤ 3) or high (>3);
- C-reactive protein (CRP) level, categorized as $\leq 150 \text{ mg/L}$ or $>150 \text{ mg/L}$.

The dependent variable was the presence of major or minor perioperative complications related to colorectal cancer surgery. All study data were derived from electronic medical records system.

Descriptive analysis was conducted to summarize the characteristics of the study subjects. Comparative analysis was conducted using 2x2 cross-tabulations and the Chi-square (χ^2) test, reporting odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, logistic regression analysis was performed to evaluate the independent association between each variable and the occurrence of perioperative complications. This analysis reported adjusted odds ratios (aORs) with corresponding 95% CIs and p-values ($\alpha = 0.05$).

RESULTS

A total 96 subjects included to this study (**Table 1**). Most of the subjects were male (59.4%) with mean age was 54.82 ± 10.845 years. Patients with a body mass index (BMI) of $<25 \text{ kg/m}^2$ (59.4%) were more prevalent than those with a BMI of $\geq 25 \text{ kg/m}^2$ (40.6%). Most patients have stage IVA (46.9%) and low grade (60.4%) tumor. The most frequently performed surgical procedures were wide surgical resection with anastomosis, resection of the primary tumor along with resectable metastases for colon cancer (38.5%) and

transabdominal resection for rectal cancer (33.3%).

Table 1. Characteristics of Subjects

Variable	Category	Frequency (N=96)	Percentage (%)
Sex	Male	57	59.4%
	Female	39	40.6%
Age	Mean \pm SD	54.82 \pm 10.845	–
Obesity (BMI)	<25 kg/m ²	57	59.4%
	\geq 25 kg/m ²	39	40.6%
Cancer Stage	I	1	1.0%
	IIA	10	10.4%
	IIIA	1	1.0%
	IIIB	19	19.8%
	IIIC	12	12.5%
	IVA	45	46.9%
	IVB	8	8.3%
Histopathological Grading	Well differentiated	6	6.3%
	Moderately differentiated / Low grade	58	60.4%
	Poorly differentiated / High grade	32	33.3%
Surgical Technique	Wide surgical resection + anastomosis, resection of primary tumor + resectable metastasis (colon cancer)	37	38.5%
	Transabdominal resection (AR or APR, LAR, TME) (rectal cancer)	32	33.3%
	Resection, stoma, or colonic stenting for unresectable metastatic tumors	27	28.1%
CRP Level	\leq 150 mg/L	52	54.2%
	>150 mg/L	44	45.8%
NLR	\leq 3	20	20.8%
	>3	76	79.2%
Intraoperative Blood Loss	\leq 800 mL	90	93.8%
	>800 mL	6	6.3%
Perioperative Complications	Minor	80	83.3%
	Major	16	16.7%

Regarding inflammatory markers and surgical outcomes, most patients had a CRP level of \leq 150 mg/L (54.2%) and NLR values were predominantly high (>3) in 79.2% patients. A total of 90 patients (93.8%) experienced intraoperative blood loss \leq 800 mL. Major complications occurred in (16.7%). The incidence of major perioperative complications was significantly higher among patients with a BMI \geq 25 kg/m², CRP levels >150 mg/L, NLR >3 , and intraoperative blood loss >800 mL (**Table 2**).

The results of multivariate analysis revealed that obesity (BMI \geq 25 kg/m²) and elevated CRP levels were significantly associated with major complications.

DISCUSSION

In this study, most of the CRC patients were male. This finding is consistent with research conducted by Nikijuluw et al.⁶ and Gunasekaran et al.⁵ who reported a higher prevalence of CRC in males than females. The higher CRC incidence in males is associated with estradiol levels. Normal estradiol plays a

role in spermatogenesis and fertility; however, excessive estradiol inhibits gonadotropin secretion such as LH, which then reduces testosterone secretion. High testosterone levels are proven to be protective against CRC.⁷ Additionally, alcohol consumption and smoking habits more common among men also trigger CRC. Excessive alcohol intake alters the normal condition of the

gastrointestinal mucosa, promoted by the oxidation of acetaldehyde (a metabolite of ethanol), which promotes inflammation in the gastrointestinal tract mucosa and abnormal cell growth. Acetaldehyde also disrupts DNA repair by inhibiting enzymes involved in the process, binds with other molecules, and causes DNA mutations that can lead to carcinogenesis.⁶

Table 2. Comparison of Obesity, CRP, NLR, and Intraoperative Blood Loss and The Incidence of Perioperative Complications

Variable	Perioperative Complications		Bivariate Analysis			Multivariate Analysis		
	Minor (N=80)	Major (N=16)	OR	95% CI	P-value	Adjusted OR	95% CI	Adjusted p-value
Obesity (kg/m ²)								
<25	56 (98.2%)	1 (1.8%)	35.000	4.373-	0.000	21.665	2.558-	0.005
≥25	24 (61.5%)	15 (38.5%)		280.140			183.475	
C-Reactive Protein (CRP) (mg/L)								
≤150	49 (94.2%)	3 (5.8%)	6.849	1.805-	0.002	4.722	1.027-	0.046
>150	31 (70.5%)	13 (29.5%)		25.990			21.706	
Neutrophil-Lymphocyte Ratio (NLR)								
≤3	20 (100%)	0 (0%)	1.267	1.128-	0.025			
>3	60 (78.9%)	16 (21.1%)		1.432				
Intraoperative Blood Loss (mL)								
≤800	79 (87.8%)	11 (12.2%)	35.900	3.831-	0.000	9.322	0.875-	0.064
>800	1 (16.7%)	5 (83.3%)		336.500			99.290	

The average age of patient in this study was 54.82 ± 10.845 years, This finding is consistent with the American Cancer Society which states that the incidence of CRC is higher in individuals aged 50 years and older compared.⁸ Similarly, Gunasekaran et al., in their study at Prof. Ngoerah General Hospital, found that the highest number of cases occurred in the 50–60 year age group.⁵

Colorectal cancer arises as the accumulation of various genetic and epigenetic alterations that transform normal epithelium into adenocarcinoma. Several causes include mutations in tumor suppressor genes such as APC, TP53, and DCC, as well as activating mutations in oncogenes like K-RAS. According to Sakai et al. in addition to mutations in tumor suppressor genes, aberrant DNA methylation also occurs, which can

inactivate the signaling pathways of tumor suppressor genes. These aberrant methylation patterns and gene mutations increase with aging. Aging is associated with a decline in cellular and tissue function, impairing structural maintenance and repair processes, leading to the accumulation of cellular damage. Consequently, the body's overall resilience gradually diminishes, resulting in various metabolic distortions that give rise to degenerative and age-related diseases, such as CRC.⁷

Obesity (BMI ≥ 25 kg/m²) is a risk factor of major perioperative complication in CRC surgery. This finding aligns with research conducted by Chung et al. (2021), which showed that obesity increases the risk of postoperative complications in colorectal cancer patients undergoing surgery. Obesity-

induced dysregulation of the immune system, or obesity-related deficiencies in immune response-mediating cells, is a likely mechanism explaining the increased risk of complications.⁹ Other study also support the conclusion that obesity increases the risk of perioperative complications, particularly major complications.¹⁰

In this study, intraoperative blood loss (IBL) >800 mL was not an independent risk factor of major perioperative complications in CRC surgery. There is still a lack of research explaining the association between intraoperative blood loss and the occurrence of perioperative complications in CRC surgery. Tamagawa et al.¹¹ in their study analyzing data from over 1,500 cases, reported that IBL ≥ 200 mL was an independent risk factor for poor overall survival (OS), disease-free survival (DFS), and postoperative morbidity in stage II/III CRC patients undergoing radical surgery. In the TNM classification, T-stage affects the amount of blood loss, as surgery for advanced T-stage cancer likely requires more extensive dissection.¹¹

Intraoperative blood loss (IBL) induce suppression in the activity or cytotoxicity of natural killer (NK) cells. This reduction correlates with the volume of blood loss. Several studies have found that perioperative blood transfusions can also suppress immune function and increase the risk of recurrence and metastasis. Perioperative transfusions resulting from blood loss can accelerate tumor progression by inducing inflammatory responses and immunosuppression. Allogeneic blood products release inflammatory factors during storage and can lead to immunosuppression, including inhibition of NK cell activity and reduction in the Th1/Th2 ratio, thereby increasing the risk of infectious complications after transfusion.¹²

Systemic inflammatory responses play a role in the development of various cancers

through genetic mutations, genomic instability, epigenetic modifications, cancer cell proliferation at different stages, and tumor metastasis. Macrophages are abundant in the lamina propria of the intestine, and tumor-associated macrophages (TAMs) are linked to tumor progression. Type I macrophages (M1) produce pro-inflammatory cytokines involved in pathogen defense and tumor cell killing mechanisms, such as tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), and create an oxidative environment through the production of inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS). Type I macrophages also produce IL-23, which stimulates IL-17. IL-17 in turn induces the production of IL-1, IL-6, IL-8, chemokine ligand 1, and TNF- α in stromal, epithelial, endothelial cells, and monocyte subsets. These pro-inflammatory cytokines collectively recruit neutrophils to peripheral tissues for phagocytosis and apoptosis. Neutrophil apoptosis reduces IL-23 secretion and thus decreases IL-17, granulocyte-colony stimulating factor (G-CSF), and granulopoiesis. In chronic inflammatory conditions such as colorectal cancer, this process is disrupted. IL-23 continues to be produced, promoting IL-17 expression and increasing the presence of neutrophils and monocytes in peripheral tissues. These changes result in the accumulation of neutrophils during chronic inflammation, which promotes tumor growth. Unremoved apoptotic neutrophils release intracellular granules that cause further tissue damage. This explains why NLR levels tend to be elevated in patients with colorectal cancer.^{16,19,23}

Putera et al.¹⁹ in their study, explained that a high NLR is associated with more advanced stages of colorectal cancer. In this study, high NLR increase the risk of major complication, although it is not considered an independent factor. The finding of a significant association

between NLR and perioperative complications in CRC surgery supports the role of NLR as a prognostic marker in assessing the risk of perioperative complications.

C-reactive protein (CRP) level was associated the occurrence of major perioperative complications in this study. This finding is consistent with studies by Lee *et al.* and Nisa which explained that higher CRP levels were associated with an increased risk of cancer recurrence and mortality from colorectal cancer in patients undergoing surgery.^{13,22} McSorley *et al.* also suggested CRP threshold values of 190 mg/L on postoperative day (POD) 2, 170 mg/L on POD 3, and 145 mg/L on POD 4. They recommended that CRP concentrations above the 150 mg/L between POD 3–5 should prompt immediate investigation and/or management of potential postoperative complications in CRC surgery.¹⁴

Inflammatory pathways can contribute to tumor development by enhancing cell movement, increasing blood vessel permeability, and stimulating the formation of new blood vessels. Cancer cells may secrete various cytokines and chemokines, attracting inflammatory cells into the tumor microenvironment (TME) and elevating levels of C-reactive protein (CRP) in the bloodstream. CRP can attach to the surface of dying cells and trigger the classical complement pathway, promoting the tagging and removal of these cells by phagocytes. It also has the ability to attract C4b-binding protein, an important inhibitor of the classical complement pathway, and influence the function of immune cells like macrophages, neutrophils, and monocytes. As such, CRP functions not only as a marker of inflammation but also plays a role in regulating innate immune responses.²⁴

CONCLUSION

Obesity, intraoperative blood loss, NLR, and CRP are simultaneously associated with the occurrence of major perioperative complications. However, only obesity and CRP are identified as independent factors with major perioperative complications in CRC surgery.

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DISCLOSURE

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