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Original Research Article

Oncologic Impact of Conservative Treatment Compared with Surgical Treatment of Anastomotic Leakage Following Colorectal Cancer Surgery: A Retrospective Study

Junichi Sakamoto, Atsuko Tsutsui, Chie Hagiwara and Go Wakabayashi

Department of Surgery, Ageo Central General Hospital, Ageo, Japan

Abstract

Objectives: Differences in oncological outcomes between conservative and surgical treatments for anastomotic leakage (AL) in patients undergoing colorectal cancer surgery remain unclear.

Methods: From July 2011 to June 2020, 385 patients underwent curative resection with double-stapling anastomosis for left-sided colon and rectal cancers. Among them, 33 patients who experienced AL were retrospectively evaluated and categorized into two groups: conservative (n = 20) and surgical (n = 13). In the surgical group, abdominal lavage using a sufficient amount of normal saline was performed during reoperation. The primary endpoint was the 3-year cumulative incidence of local recurrence (LR).

Results: Seven (21.2%) patients in the conservative group experienced LR, while none in the surgical group. Survival analysis indicated no differences in overall and recurrent-free survival. However, the 3-year cumulative incidence of LR was significantly lower in the surgical group than in the conservative group (0% versus 31.3%, p=0.045).

Conclusions: Differences in AL management were associated with oncological outcomes, specifically a decreased LR. Therefore, surgeons should consider our findings when determining the most appropriate AL treatment to improve oncological outcomes.

Keywords

anastomotic leakage, colorectal cancer, local recurrence, oncological outcome

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Introduction

Anastomotic leakage (AL) is a serious complication following colorectal cancer (CRC) surgery. The incidence of AL post-rectal surgery ranges from 3.2% to 11.1%[1-5], depending on several factors such as tumor location, anastomostic technique, patient characteristics, and AL definition. AL has been widely associated with poor long-term oncologic outcomes[6-8]. Several studies have reported that AL increased local recurrence (LR) rates[9-11].

However, the mechanism through which AL causes LR remains unclear. A defect in the bowel lumen at the anastomosis site may allow the escape of viable neoplastic cells implanted within the peritoneal cavity. Previous studies have demonstrated the presence of viable CRC cells within the bowel lumen[12,13] and reported implantation metastasis in patients with CRC[14,15].

AL management options can be classified into conservative and surgical approaches, including abdominal lavage, resection, or anastomosis repair; drainage tube placement near the AL site; and diverting stoma construction. However, few studies have evaluated whether differences in AL management impact oncological outcomes.

Against this background, this novel study aimed to assess

Corresponding author: Junichi Sakamoto, Btaq1659@gmail.com
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the difference in oncological outcomes between conservative and surgical treatments for AL in patients undergoing left-sided colon or rectal cancer surgery with double-stapling technique (DST) anastomosis.

Methods

Design

This was a single-center, retrospective, observational study. The study protocol was conducted in accordance with the Declaration of Helsinki. The need for written consent from study subjects was waived by the institutional review board. This retrospective study was approved by the Ethical Advisory Committee of Ageo Central General Hospital before study initiation.

Patients

We reviewed data of all patients who underwent restorative surgery for left-sided colon and rectal cancers with DST anastomosis at Ageo Central General Hospital in Saitama, Japan. We identified 385 patients between July 2011 and June 2020, of whom 33 (8.6%) experienced AL. We excluded patients with noncurative resection, secondary malignancies, or double cancer. Curative resection was defined as complete tumor resection with all margins being negative. Patients who underwent surgical intervention after noncurative endoscopic resection were excluded from the study.

Definitions

This study defined AL as the leakage of bowel content or abscess formation at the anastomosis requiring therapeutic intervention, such as reoperation, radiological intervention, and antibiotics based on the International Study Group of Rectal Cancer (ISGRC) criteria[16]. AL was diagnosed if the emission of gas, pus, or feces from the drainage fluid or wound was confirmed. In patients with clinically suspicious symptoms, such as fever, peritonitis, or turbid drain discharge, AL was confirmed through radiologic investigation, such as CT scan. Soluble contras medium enema radiography was performed for clinically suspicious patients without definite evidence of AL by physical findings or CT scan.

The selection criteria for lateral lymph node dissection were as follows: (1) the main lesion of the tumor located in the rectum, with the lower tumor margin below the peritoneal reflection; (2) suspected metastasis on preoperative imaging, such as abdominal CT or magnetic resonance imaging (i.e., lymph nodes with a short-axis diameter of 7 mm or more were regarded as lymph node enlargement). Intraoperative rectal lavage before intestinal resection depended on the attending surgeon. In the case of low anterior resection, transanal drainage was indicated.

Although the attending surgeon ultimately judged the type of AL management, the criteria for choosing conservative or surgical treatment was based on the ISGRC recommendations. Specifically, reoperation was performed for all patients with AL, except those who already had covering stoma and were considered to have minor leakage. The conservative group constituted 20 patients, and the surgical group constituted 13 patients. All reoperations in this study were performed within 24 hours of AL diagnosis. Regarding intraoperative abdominal lavage (IAL), the abdominal cavity was first washed with at least 5000 mL of normal saline at the beginning of the reoperation. After careful abdominal exploration and definitive diagnosis of AL, an additional lavage of at least 5000 mL of normal saline was performed, primarily in the pelvic cavity. Anastomosis resection or repair was performed only when necrosis or circumferential dehiscence was observed.

Primary tumor staging was performed according to the classification system of the Union for International Cancer Control (UICC) 8^{th} edition. Postoperative complications were categorized according to the Clavien-Dindo classification. LR was defined as the occurrence of recurrent tumors located within the pelvis, whereas distant metastasis from the anastomosis was defined as distant recurrence (peritoneal dissemination). Recurrence patterns were evaluated by reviewing operative and pathological reports and classified as axial (anastomotic), anterior, posterior (presacral), or lateral (pelvic sidewall).

Main outcome measure

The primary endpoint was the 3-year cumulative incidence of LR.

Follow-up

The patients underwent standardized follow-ups every 3 months for the first 3 years. At each visit, a physical examination and laboratory tests were performed. A computed tomography scan was performed every 6 months. Additionally, a colonoscopy was performed 1 year after surgery and repeated at least every 2 years thereafter.

Statistical analyses

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria)[17]. EZR is a modified version of the R Commander, designed to add statistical functions frequently used for biostatistics.

Differences in categorical and continuous variables were analyzed using the chi-squared test (or Fisher's exact test) and Student's *t*-test. Survival analyses were evaluated using the Kaplan-Meier method and the log-rank test. Each outcome was calculated from the initial surgery date to the event date (local or distant recurrence, death, or last follow-

Table 1. Patients Characteristics and Pathological Details of Tumors.

Variable	Conservative group (n=20)	Surgical group (n=13)	p-value
Age at surgery, years[a]	66 (48-77)	73 (65-84)	0.013
Sex, n (%)			
Male	13 (65%)	10 (76.9%)	0.70
Female	7 (35%)	3 (23.1%)	
Tumor location, n (%)			
Sigmoid colon	4 (20%)	2 (15.4%)	0.72
Upper rectum	8 (40%)	4 (30.1%)	
Middle rectum	5 (25%)	6 (46.2%)	
Lower rectum	3 (15%)	1 (7.7%)	
ASA physical status, n (%)			
Score 1-2	17 (85%)	10 (76.9%)	0.66
Score 3-4	3 (15%)	3 (23.1%)	
Charlson comorbidity index[a]	3.5 (1-8)	5 (3-8)	0.020
CROSS classification, n (%)			
score 0-1	9 (45%)	2 (15.4%)	0.13
score 2-4	11 (55%)	11 (84.6%)	
UICC stage, n (%)			
I	5 (25%)	3 (23.1%)	0.16
II	5 (25%)	8 (61.5%)	
III	7 (35%)	2 (15.4%)	
IV	3 (15%)	0	
Tumor stage, n (%)			
pT1/T2	5 (25%)	3 (23.1%)	1
pT3/T4	15 (75%)	10 (76.9%)	
Nodal status, n (%)			
pN0	10 (50%)	11 (84.6%)	0.067
pN1/pN2	10 (50%)	2 (15.4%)	
Number of harvested lymph nodes[a]	21 (3-47)	16 (5-34)	0.093
Distal margin, mm[a]			
Sigmoid colon	85 (55-110)	65 (60-70)	0.39
Upper rectum	45 (20-55)	37.5 (30-70)	0.95
Middle rectum	20 (15-40)	32.5 (20-100)	0.23
Lower rectum	25 (10-30)	15	0.64
Additional therapy, n (%)			
Neoadjuvant therapy	0	0	-
Adjuvant chemotherapy	9 (45%)	3 (23.1%)	0.28

[a]Data are presented as medians (ranges).
ASA, American Society of Anesthesiologists;
CROSS, ColoRectal Obstruction Scoring System;
UICC, Union for International Cancer Control

up). The level of significance was set at $p<0.05$.

Results

Patient characteristics and pathological details of the tumors are presented in Table 1. The median age at surgery was 69 years (range: 48-84 years). Tumors were located in the rectum in 27 (81.8%) patients. The patients were equally distributed between the groups according to sex, tumor location, American Society of Anesthesiologists physical status, and ColoRectal Obstruction Scoring System classification. However, a significantly higher proportion of older patients was observed in the surgical group ($p = 0.013$), whereas the Charlson Comorbidity Index was higher than that in the conservative group ($p = 0.020$). No significant differences were observed in the pathological details of the tumors, such as the UICC stage, T-stage, N-stage, and the number of harvested lymph nodes. No patients received preoperative or

Table 2. Description of Initial Surgery for the Tumors.

Variable	Conservative group (n=20)	Surgical group (n=13)	p-value
Surgical procedure, n (%)			
Sigmoidal resection	4 (20%)	2 (15.4%)	0.89
High anterior resection	2 (10%)	3 (23.1%)	
Low anterior resection	14 (70%)	8 (61.5%)	
LLND, n (%)	3 (15%)	0	0.26
Surgical approach, n (%)			
Open surgery	8 (40%)	9 (69.2%)	0.16
Minimally invasive surgery	11 (55%)	4 (30.8%)	
Conversion	1 (5%)	0	
Operation time, min[a]	293.5 (170-665)	256 (184-387)	0.11
Estimated blood loss, g[a]	75 (3-1155)	346 (3-1488)	0.48
Perioperative blood transfusion, n (%)	1 (5%)	2 (15.4%)	0.55
Covering stoma construction, n (%)	12 (60%)	0	0.00051
Transanal drainage, n (%)	10 (50%)	3 (23.1%)	0.16
Intraoperative rectal lavage, n (%)	9 (45%)	6 (46.2%)	1

[a]Data are presented as medians (ranges).
LLND, Lateral Lymph Node Dissection

Table 3. Postoperative and Oncological Outcomes.

Variable	Conservative group (n=20)	Surgical group (n=13)	p-value
Time to AL diagnosis, days[a]	6 (2-13)	4 (0-26)	0.77
Length of hospital stay, days[a]	28 (14-76)	53 (25-89)	0.011
Hospital death related to complications, n (%)	0	1	0.39
Follow-up time, days[a]	1418 (484-3298)	1580 (68-3034)	0.50
Systemic recurrence, n (%)	10 (50%)	3 (23.1%)	0.16
Local recurrence, n (%)	7 (35%)	0	0.027

[a]Data are presented as medians (ranges).
AL, anastomotic leakage

postoperative chemoradiotherapy or radiotherapy.

A description of the initial surgery for the tumors is presented in Table 2. No significant differences were observed between the groups regarding surgical procedure, surgical approach, operative time, estimated blood loss, or perioperative blood transfusion. The number of patients requiring covering stoma construction during the initial surgery was significantly higher in the conservative group than in the surgical group ($p < 0.001$). Intraoperative anal rectal lavage was performed in 15 patients (45.5%), with no significant difference observed between the groups.

The postoperative and oncological outcomes are summarized in Table 3. The median follow-up time was 48.2 months (range: 2.3-109.9 months). No significant difference was observed in the time to AL diagnosis between the groups (6 versus 4 days, p = 0.77). The length of hospital stay was significantly shorter in the conservative group than in the surgical group (28 versus 53 days, p = 0.011). No perioperative deaths occurred. However, one patient in the surgical group passed away in the hospital after experiencing complications. Seven (35%) patients in the conservative group experienced LR, while none did in the surgical group (p = 0.027). Recurrence patterns were classified as posterior type in five (71.4%), axial type in one (14.3%), and anterior type in one (14.3%) patient (Table 4).

The 3-year overall survival (OS) rates were not significantly different between the conservative and surgical groups (95.0 and 59.2%, respectively; p=0.082) (shown in Figure 1a). Similarly, the 3-year recurrence-free survival (RFS) rates were not significantly different between the groups (54.0 and 38.5%, respectively; p=0.61) (shown in Figure 1b). However, the 3-year incidence of LR was significantly higher in the conservative group (31.3 versus 0%; p = 0.045) (shown in Figure 2).

Discussion

This study demonstrated that surgical management of patients with AL was associated with a decreased incidence of LR. The incidence of LR was significantly higher in the conservative group than in the surgical group. This is one of the few characteristic studies that have evaluated the effects of different management strategies for AL on oncological outcomes.

AL is among the most feared and serious complications of CRC surgery. Despite improvements in the prevention strategies for AL, such as indocyanine green near-infrared fluorescence bowel perfusion assessment[18], mechanical and oral antibiotic bowel preparation[19], and use of poly-

Table 4. Details of LR in All Patients.

Variable	Non-AL group (n=352)	AL group (n=33)
LR, n (%)	12 (3.4%)	7 (21.2%)
Tumor location, n (%)		
Sigmoid colon	6/143 (4.2%)	3/6 (50%)
Upper rectum	0/104 (0%)	1/12 (8.3%)
Middle rectum	4/78 (5.1%)	2/11 (18.2%)
Lower rectum	2/27 (7.4%)	1/4 (25%)
UICC stage, n (%)		
0/I	2/111 (1.8%)	1/8 (12.5%)
II	3/110 (2.7%)	2/13 (15.4%)
III	7/120 (5.8%)	4/9 (44.4%)
IV	0/9 (0%)	0/3 (0%)
X[a]	0/2 (0%)	0 (0%)
LR pattern, n (%)		
Axial (anastomotic)	6 (50%)	1 (14.3%)
Anterior	0	1 (14.3%)
Posterior (presacral)	2 (16.7%)	5 (71.4%)
Lateral (pelvic sidewall)	4 (33.3%)	0

[a]Cases with complete response after neoadjuvant chemoradiotherapy.
AL, Anastomotic leakage;
LR, Local recurrence;
UICC, Union for International Cancer Control

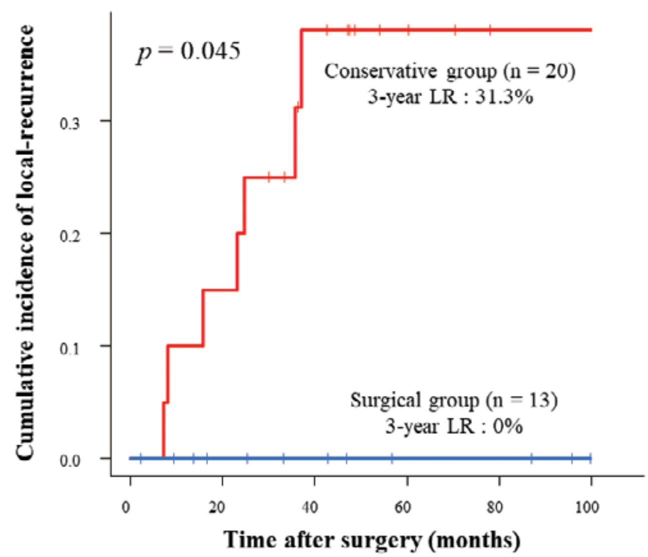

Figure 2. Kaplan-Meier cumulative incidence of local recurrence curve for patients in each group (red, Conservative group; blue, Surgical group). LR, local recurrence

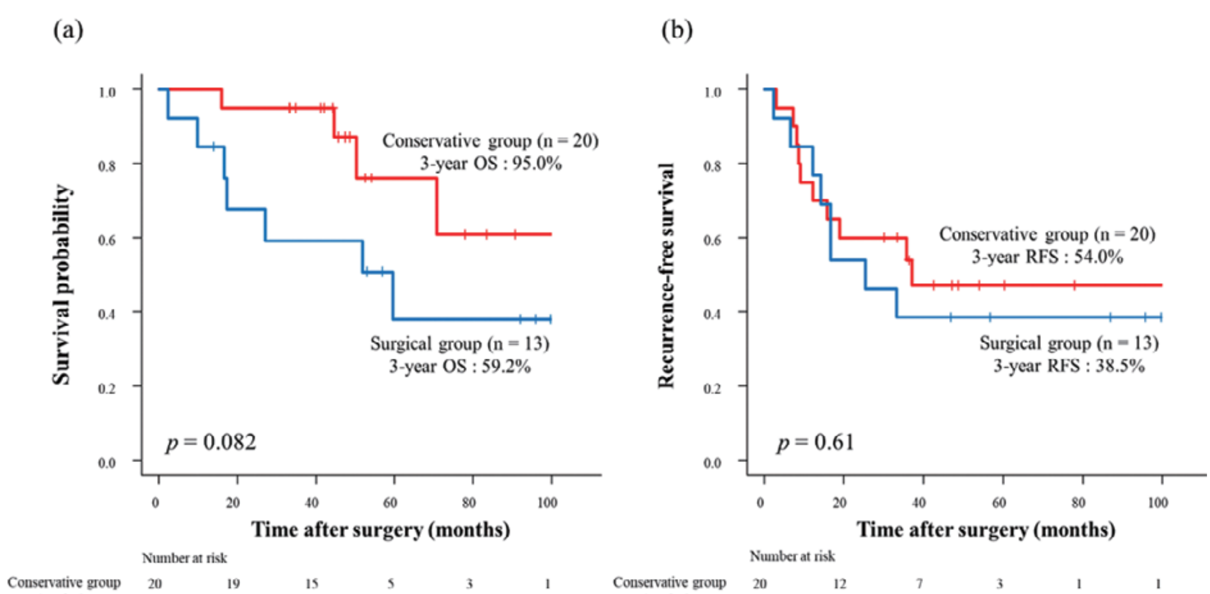

Figure 1. (a) Kaplan-Meier OS curve for patients in each group (red, Conservative group; blue, Surgical group). (b) Kaplan-Meier RFS curve for patients in each group (red, Conservative group; blue, Surgical group). OS, overall survival; RFS, recurrence-free survival

glycolic acid sheet[20], AL still occurs in a fair percentage of patients. Once AL occurs, it negatively affects short-term outcomes, increasing morbidity and mortality and higher hospitalization and costs. Furthermore, AL occurrence worsens long-term oncological outcomes[21]. In the current study, the 5-year OS rate was 59.4%, which was similar to the results of Ramphal et al[9]. As several studies have reported, AL may lead to a delay in initiating postoperative adjuvant chemotherapy and may affect the oncological outcomes of patients.

Recent studies have reported that AL was associated with a significant risk of LR after CRC surgery[9,10]. In the present study, seven patients with AL (21.2%) and twelve without AL (3.4%) developed LR. According to a multicenter case-control study[11], the LR rate increased by 18.6% after AL, with an odds ratio of 4.58 (95% confidence interval, 2.05-10.24; $p < 0.001$). The presence of exfoliated viable CRC cells within the bowel lumen has been demonstrated with a reported percentage of 70%[22]. Yu et al. reported implantation metastasis from a molecular point of view using whole-exome sequencing and lineage inference for cancer heterogeneity and evolution analysis[15]. In the present study, LR in the AL group was different from LR in the non-AL group (Table 4). In other words, both groups had a common tendency for LR to increase with disease stage, but the characteristics of the tumor location differed between the AL and non-AL groups. The reason for the high incidence of LR in sigmoid colon cancer in the non-AL group was that half of the cases were from the early period when minimally invasive surgery was introduced at our institution, leading to poor surgical techniques. In addition, there were cases in which the distal margin was not sufficiently secured during implantation at the initial surgery. Furthermore, the LR patterns were significantly different between the two groups ($p = 0.038$). In the non-AL group, LR was mostly axial type or lateral type, whereas in the AL group, the posterior type was the most common. Extraluminal infiltration of viable CRC cells due to AL and implantation into the widely opened retrorectal space might have caused a higher prevalence of posterior LR in the AL group.

Curative resection is the mainstay of LR treatment. However, surgical treatment of LR, particularly when located around the pelvis, could be highly invasive, with a high occurrence of postoperative complications[23,24]. Furthermore, a second recurrence may occur even if curative resection was achieved[25]. Therefore, identifying AL management strategies to reduce the risk of LR is clinically important.

Surgical treatment is often selected for AL, except in patients with minor leakage or effective drainage and who already have a covering stoma. IAL was performed using a sufficient amount of normal saline during reoperation. We hypothesized that IAL may reduce LR by washing out viable CRC cells disseminated into the peritoneal cavity owing to AL.

In this study, survival analysis indicated no differences in the 3-year OS and RFS, whereas the 3-year cumulative incidence of LR was significantly lower in the surgical group than in the conservative group. Furthermore, no LR was observed in the surgical group. We evaluated the relationship between the cumulative incidence of LR and several clinicopathological factors, including the type of AL management, age, tumor location, tumor stage, nodal status, surgical procedure, intraoperative rectal lavage, and adjuvant treatment. However, we observed no significant difference in the cumulative incidence of LR with any of the aforementioned factors, except for the type of AL management. These results indicate that AL management could be a vital prognosticator of LR.

To the best of our knowledge, no studies similar to the present study have evaluated the effects of different management strategies for AL on oncological outcomes. Additionally, the significance of intraoperative peritoneal lavage cytology in colorectal cancer remains unconfirmed[26]. In contrast, several studies have reported the efficacy of extensive IAL in advanced gastric cancer[27,28]. Song et al. reported that extensive IAL was beneficial for the RFS and OS of advanced gastric cancer[29]. Furthermore, reverse transcriptase-polymerase chain reaction analysis showed that viable cancer cells were not detected in the washing fluid[27]. Thus, we concluded that sufficient IPL can remove free cancer cells, and efforts to eliminate free cancer cells could be an effective treatment for AL patients. Additionally, we encountered an unfortunate case of rectal cancer where conservative treatment was selected for AL that occurred during the early development of unresectable LR in the pelvis with extensive pelvic sidewall involvement, which was early-stage cancer. Consequently, the decision on whether AL should be treated conservatively must be carefully considered.

Our study has several limitations, including its single-center and retrospective design. The small number of patients was a major limitation. The small sample sizes led to differences in patient backgrounds, specifically age, and were insufficient to analyze survival outcomes such as disease recurrence and OS. The survival curves revealed that the surgical group was below the conservative group. This was because the surgical group, including many elderly patients, had more deaths from other diseases. Second, a histological assessment of the peritoneal lavage was not performed in our study. Peritoneal cytology should have been performed before and after abdominal lavage to determine the optimal lavage volume. Third, while the patients who underwent R1/R2 resection were not included in the study, the quality of the initial surgery, including the circumferential resection margin, was not assessed. Fourth, radiological examination was not performed in all patients without clinically suspicious AL. Hence, there is a possibility that not all asymptomatic leakages were identified. Finally, a more severe grade of AL was included in the surgical group. This severe inflammation was considered the reason for the longer hospital stay observed in the surgical group. In addition, we could not exclude the possibility that a systemic inflammatory response would have been associated with the oncological outcomes.

Although there were these limitations, our data indicates that AL management was associated with a decreased incidence of LR. Further multi-institutional and large-scale studies are required to overcome these limitations and establish the clinical relevance of our findings.

Summarily, the difference in AL management was associated with oncological outcomes; specifically, abdominal lavage for AL may reduce the number of viable CRC cells released into the peritoneal cavity, leading to a decreased incidence of LR. Therefore, to improve oncological outcomes, surgeons should consider our findings when determining the most appropriate treatment for AL.

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Conflicts of Interest
There are no conflicts of interest.

Author Contributions
Conceptualization: JS.
Data curation: JS, CH.
Formal analysis: JS.
Funding acquisition: JS.
Investigation: JS.
Methodology: JS.
Project administration: JS.
Resources: JS.
Software: JS.
Supervision: JS.
Validation: JS.
Visualization: JS.
Writing - original draft: JS.
Writing - review & editing: AT, GW.

Approval by Institutional Review Board (IRB)
Approval was obtained from the Ethical Advisory Committee of the Ageo Central General Hospital before initiating the study (no.1075). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to Participate
The institutional review board waived the need for written informed consent.

Consent to Publish
Not applicable.

Data Availability Statement
The datasets analyzed in the current study are available from the corresponding author upon request.

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