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PROCALCITONIN AS A TOOL FOR TIMELY DIAGNOSIS OF ANASTOMOTIC LEAK IN ELDERLY COLORECTAL CANCER SURGERY: A DIAGNOSTIC ACCURACY STUDY.

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Abstract

Background: The diagnostic utility of procalcitonin for detecting anastomotic leaks (AL) in older adults following colorectal cancer surgery remains unclear. Age-related immune system changes may influence baseline procalcitonin levels and its diagnostic performance in this population. This study aimed to evaluate the diagnostic accuracy of postoperative day 3 procalcitonin levels for AL detection in older adults with colorectal cancer.

Methods: A delayed cross-sectional diagnostic test study was conducted in patients aged ≥65 years undergoing colorectal cancer surgery. Postoperative day 3 procalcitonin levels were assessed against the reference standard of clinically confirmed AL. Receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) were calculated.

Results: The AL incidence was 7.7%. The ROC analysis for procalcitonin on postoperative day 3 yielded an AUC of 0.68 (95% CI: 0.58-0.78) for AL prediction. The optimal cutoff point (Youden index) was 0.61 ng/mL, with a sensitivity of 0.69, specificity of 0.62, positive likelihood ratio of 1.86, and negative likelihood ratio of 0.48. Excluding ileostomies improved the AUC to 0.78, and focusing on grade C ALs resulted in an AUC of 0.81.

Conclusion: Procalcitonin on postoperative day 3 demonstrated limited diagnostic accuracy for AL detection in older adults with colorectal cancer. However, performance improved when excluding ileostomies and was notably better for detecting severe (grade C) ALs, suggesting a potential role in identifying high-risk leaks in this population.

Introduction

Colorectal cancer (CRC) represents a significant global health burden, ranking as the third most common cancer worldwide and the second leading cause of cancer-related mortality. Surgical resection remains the cornerstone of curative treatment for localized CRC, offering the potential for long-term survival. However, this intervention is not without its risks, and postoperative complications significantly impact patient outcomes, healthcare costs, and overall quality of life. Among these complications, anastomotic leak (AL) stands out as a particularly devastating event, associated with increased morbidity, prolonged hospital stays, reoperation, and even mortality. Anastomotic leak, defined as the failure of a surgical anastomosis to contain intraluminal contents, occurs in a variable proportion of patients following colorectal resection, with reported rates ranging from 3% to 20%. The incidence of AL is influenced by numerous factors, including patient-related characteristics, surgical technique, and the complexity of the procedure. In particular, older adults, who constitute a growing proportion of CRC patients, are at an elevated risk of postoperative

complications, including AL. This heightened susceptibility can be attributed to age-related physiological changes, such as diminished immune function, reduced tissue perfusion, and increased prevalence of comorbidities. The aging immune system undergoes significant alterations, a phenomenon known as immunosenescence, which contributes to a weakened response to surgical trauma and an increased vulnerability to infection. This altered immune landscape can potentially mask or delay the clinical presentation of AL in older adults, leading to delayed diagnosis and treatment. Furthermore, the presence of comorbidities, such as cardiovascular disease, diabetes mellitus, and chronic kidney disease, further complicates the postoperative course and increases the risk of AL in this vulnerable population. Early detection of AL is critical for optimizing patient outcomes. Timely diagnosis allows for prompt intervention, including surgical revision, percutaneous drainage, or conservative management, thereby minimizing the severity of complications and improving patient survival. However, the clinical presentation of AL can be nonspecific and often mimics other postoperative complications, such as surgical site infection or ileus. Traditional diagnostic methods, including clinical assessment, imaging studies (e.g., CT scan), and contrast enemas, have limitations in terms of sensitivity and specificity, particularly in the early postoperative period. In recent years, the use of biomarkers for the early detection of AL has gained increasing attention. Procalcitonin (PCT), a precursor of the hormone calcitonin, has emerged as a promising biomarker for bacterial infections and sepsis. PCT levels rise rapidly in response to bacterial infection and systemic inflammation, making it a potentially valuable tool for detecting AL, which is often associated with bacterial contamination of the peritoneal cavity. However, the diagnostic performance of PCT for AL detection in older adults with CRC remains poorly understood. While several studies have investigated the utility of PCT in predicting postoperative complications following colorectal surgery, the majority of these studies have included heterogeneous patient populations, with limited representation of older adults. Given the unique physiological and immunological characteristics of this population, it is crucial to evaluate the diagnostic accuracy of PCT specifically in older adults undergoing CRC surgery. The rationale for investigating PCT as a diagnostic marker for AL in older adults stems from the hypothesis that age-related changes in the immune system may influence the kinetics and diagnostic performance of PCT. In older adults, the baseline PCT levels may be elevated due to chronic inflammation or subclinical infections, potentially affecting the interpretation of postoperative PCT levels. Furthermore, the attenuated inflammatory response in older adults may result in a delayed or blunted rise in PCT levels in the presence of AL, potentially reducing its sensitivity as a diagnostic marker. Therefore, this study aims to evaluate the diagnostic performance of PCT on postoperative day 3 for detecting AL in older adults (≥65 years old) with CRC. By focusing on this specific population, we seek to provide valuable insights into the clinical utility of PCT as a diagnostic tool for AL in older adults, who are at an increased risk of this complication. The postoperative day 3 was selected as a key time point for PCT measurement based on the understanding that AL typically manifests within the first few days following surgery. This timing allows for the assessment of PCT levels during the critical period when early detection of AL is most crucial.

The findings of this study have the potential to significantly impact clinical practice by providing evidence-based guidance on the use of PCT for AL detection in older adults with CRC. If PCT demonstrates adequate diagnostic accuracy, it could serve as a valuable tool for early identification of AL, enabling timely intervention and improving patient outcomes. Conversely, if PCT proves to be a poor diagnostic marker in this population, alternative strategies for AL detection will need to be explored. Furthermore, this study will contribute to the growing body of literature on the use of biomarkers for postoperative complications following CRC surgery. By elucidating the diagnostic performance of PCT in older adults, we can advance our understanding of the complex interplay between age, immunity, and surgical outcomes. In conclusion, this research is designed to address a critical knowledge gap regarding the utility of PCT for AL detection in older adults with CRC. By providing evidence-based insights into the diagnostic performance of PCT, this study aims to improve the management of postoperative complications in this vulnerable population and ultimately enhance patient outcomes.

Materials and Methods:

Study design: - We conducted a diagnostic test study using a delayed-type cross-sectional design.11 All patients admitted to the institution between 2002 and 2004 who met the eligibility criteria were included in the study. Data for all variables were collected in an anonymous database using REDCap electronic data capture tools. The study was reviewed and approved by our institution's ethics committee. Ethical compliance and the International Committee of Medical Journal Editors were ensured under our Ethics and Research Institutional Committee approval. Upon admission, patients or their caregivers provided written informed consent for the use of their clinical information in research. The study adhered to the list of essential items for reporting diagnostic accuracy studies (Standards for Reporting of Diagnostic Accuracy).13

Study population: - Eligible study participants included older adults (65 year old) who underwent surgical resection of the colon or rectum for colorectal cancer. The exclusion criteria were as follows: (1) no anastomosis performed during the same surgical procedure, (2) lack of procalcitonin measurement on postoperative day 3, (3) insufficient follow-up to determine the presence of an anastomotic leak, (4) patients with active infection before surgery, and (5) inability to provide informed consent. The following variables were analyzed: demographic characteristics of the patients, body mass index, American Society of Anesthesiologists (ASA) Physical Status Classification, presence of diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, chronic kidney disease, preoperative laboratory results, neoadjuvant treatments, including radiotherapy and/or chemotherapy, surgical approach (open or laparoscopic), tumor location, TNM classification, intraoperative bleeding and the need for transfusion, procalcitonin levels on postoperative day 3, surgical complications (categorized according to the Clavien-Dindo classification), and hospital stay duration. During the postoperative period, all patients were examined daily to assess their clinical condition, including assessment of pain, fever, hemodynamic status, abdominal examination, return of bowel function, and any wound drainage.

Index test:- Serum procalcitonin levels were analyzed in the institution's clinical laboratory using a chemiluminescence assay. Baseline procalcitonin values were not available because they are not part of the institutional protocol; however, blood levels were measured on postoperative day 3 for all patients as part of routine care. Procalcitonin values gathered by the attending surgeons were considered in clinical decision-making for each patient.

Reference standard: - An anastomotic leak was defined as any deviation from the expected postoperative recovery associated with the anastomosis. This includes the presence of pus or enteric fluid in surgical drains or wounds, detection of an abdominal or pelvic collection near the anastomosis on a computed tomography scan, or identification of anastomotic dehiscence during reoperation. This includes anastomotic leakage grade A, B, or C according to The International Study Group of Rectal Cancer.14

Statistical analysis: - A description was made with demographic, clinical, and surgical variables. Categorical variables were described as proportions and continuous variables as medians with their respective interquartile range (IQR). A bivariate analysis was performed with MannWhitney U tests or c2 tests, as appropriate, in order to compare differences between the variables according to whether anastomotic leak was present. A linear regression analysis was performed to explore the factors that may influence procalcitonin levels. We calculated the receiver operating characteristic (ROC) curve and its AUC with the corresponding 95% confidence interval (95% CI). The optimal cutoff point with the greatest diagnostic performance was determined using the Youden index method, and we calculated its sensitivity, specificity and likelihood ratios (LRþ and LR). In addition, we conducted subgroup analyses, excluding patients with a defunctioning ileostomy and those with anastomotic leakage grade A and B. This was done because these patient groups might exhibit a less-severe

inflammatory response. The percentages of missing data for the variables were as follows: body mass index 0.9%, albumin 16%, approach 0.9%, and intraoperative bleeding 4.4%; these were imputed using multiple imputation by predictive mean matching. All analyses were carried out using R (version 2023.12.1 þ 402; R Foundation for Statistical Computing, Vienna, Austria).

Sample size calculation:- All patients who met the selection criteria during the study period were included in the analysis. A post-hoc sample power calculation was performed.

Results:

A total of 338 patients were included in the study, and a flowchart shows the selection process. The incidence of anastomotic leak was 7.7%, with 2 cases classified as grade A, 9 as grade B, and 15 as grade C. The median age of the patients was 72.0 years (IQR, 69.0e78.0 years), with the majority being female (53.8%). Tumors were most commonly located in the right colon, followed by the sigmoid colon and rectum. The most frequent tumor stages were II and III (41.4% and 35.2%, respectively). When comparing characteristics on the basis of the presence or absence of an anastomotic leak, we found that the ASA physical status classification was greater in patients with leaks. In addition, tumor location in the rectum and the use of neoadjuvant therapy were more common in patients with leaks, with statistically significant differences observed. Further demographic, clinical, and surgical characteristics are detailed in The median procalcitonin level was 0.40 ng/mL (IQR, 0.17e0.99 ng/mL). When comparing procalcitonin levels between the groups, patients with anastomotic leaks had significantly greater levels (0.36 ng/mL, IQR, 0.17e0.92 vs 0.90 ng/mL, IQR, 0.38e1.78; P ¼ .002). In terms of surgical outcomes, patients with an anastomotic leak exhibited a significantly greater proportion of major complications and mortality. Similarly, they experienced a longer duration of hospital stay (Table II). On postoperative day 3, the ROC curve demonstrated an AUC of 0.68 (95% CI, 0.58e0.78) for the prediction of an anastomotic leak using procalcitonin levels. The cutoff point with the greatest diagnostic performance, according to the Youden index, was 0.61 ng/ mL, with a sensitivity of 0.69, specificity of 0.62, a LRþ of 1.86, and a LR of 0.48 for predicting an anastomotic leak. In the subgroup analysis, we found that excluding patients with a defunctioning ileostomy increased the AUC to 0.78 (95% CI, 0.68e0.88). The optimal cutoff remained the same, with a sensitivity of 0.86, specificity of 0.62, a LRþ of 2.30, and a LR of 0.21 for predicting an anastomotic leak. In the other subgroup analysis, excluding patients with grade A and B anastomotic leaks increased the AUC to 0.81 (95% CI, 0.73e0.89). The optimal cutoff remained unchanged, with a sensitivity of 0.93, specificity of 0.62, an LRþ of 2.51, and an LR of 0.10 for predicting an anastomotic leak. Finally, when analyzing the factors that may influence procalcitonin levels on postoperative day 3, we found that age was significantly associated with greater levels (P ¼ .027), whereas a laparoscopic approach was associated with lower procalcitonin levels compared with an open approach (P < .001). In contrast, neoadjuvant therapy, Charlson comorbidity index, and rectal tumor location were not associated with procalcitonin levels. This indicates that age and surgical approach are independent factors influencing procalcitonin levels, regardless of the presence of anastomotic leakage (Table III). Using the obtained AUC value, the number of cases and controls, and a significance level of 0.05, a post-hoc power analysis calculated a power of 0.88 for the sample.

Discussion:

This study aimed to evaluate the diagnostic performance of procalcitonin (PCT) on postoperative day 3 for detecting anastomotic leak (AL) in older adults (≥65 years) undergoing colorectal cancer surgery. Our findings revealed that PCT, while showing some discriminatory ability, demonstrated limited diagnostic accuracy for AL detection in this population, with an area under the receiver operating characteristic curve (AUC) of 0.68. However, the performance improved when ileostomies were excluded (AUC 0.78) and was notably better for detecting severe (grade C) ALs (AUC 0.81), suggesting a potential role in identifying high-risk leaks. The overall limited diagnostic accuracy of PCT in our study contrasts with some previous reports that have suggested a higher predictive value

for postoperative complications, including AL, following colorectal surgery. This discrepancy may be attributed to several factors, including differences in study populations, surgical techniques, and the timing of PCT measurements. Notably, our study specifically focused on older adults, a population known for its altered immune response and increased susceptibility to complications. The age-related changes in the immune system, characterized by immunosenescence, may have influenced the kinetics and diagnostic performance of PCT in our study. Older adults often exhibit a blunted inflammatory response, which could have resulted in a less pronounced rise in PCT levels in the presence of AL. Furthermore, the presence of comorbidities, such as cardiovascular disease and diabetes mellitus, which are prevalent in this population, may have further complicated the interpretation of PCT levels. The observed improvement in PCT performance when ileostomies were excluded suggests that the presence of an ileostomy might introduce confounding factors. Ileostomies can lead to increased intestinal permeability and bacterial translocation, potentially elevating PCT levels independently of AL. This observation highlights the importance of considering surgical techniques and their potential impact on biomarker levels when evaluating diagnostic performance. The significantly higher AUC for detecting grade C ALs indicates that PCT may be more useful in identifying severe leaks, which are associated with greater clinical significance and morbidity. This finding suggests that PCT could serve as a valuable tool for risk stratification, allowing clinicians to prioritize patients at high risk for severe AL for closer monitoring and aggressive intervention. The optimal cutoff point for PCT in our study was 0.61 ng/mL, with a sensitivity of 0.69 and a specificity of 0.62. These values indicate that while PCT can identify a substantial proportion of patients with AL, it also has a considerable false-positive rate. The positive likelihood ratio of 1.86 and the negative likelihood ratio of 0.48 further support the notion that PCT has limited diagnostic accuracy as a standalone marker for AL detection. Our study has several limitations. First, the delayed cross-sectional design, while efficient for evaluating diagnostic performance, does not allow for the assessment of PCT kinetics over time. Serial PCT measurements may have provided a more comprehensive understanding of its diagnostic utility. Second, the sample size, while adequate for the primary analysis, may have limited the power to detect subtle differences in PCT performance across subgroups. Third, the study was conducted at a single center, which may limit the generalizability of the findings. Despite these limitations, our study provides valuable insights into the diagnostic performance of PCT for AL detection in older adults with colorectal cancer. Our findings suggest that while PCT may not be a reliable standalone marker, it could serve as a useful adjunct to clinical assessment and imaging studies, particularly for identifying patients at high risk for severe AL. Future research should focus on evaluating the diagnostic performance of PCT in combination with other biomarkers and clinical parameters. Multicenter studies with larger sample sizes and serial PCT measurements are needed to validate our findings and develop more robust diagnostic algorithms. Furthermore, the impact of surgical techniques, such as laparoscopic versus open surgery, and the use of enhanced recovery after surgery (ERAS) protocols, on PCT levels and AL detection should be explored. In conclusion, our study demonstrates that PCT on postoperative day 3 has limited diagnostic accuracy for AL detection in older adults with colorectal cancer. However, its performance improves for severe ALs, suggesting a potential role in identifying high-risk leaks. Further research is needed to optimize the use of PCT in this population and develop more effective strategies for early AL detection.

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