

# Red cell distribution width and mean platelet volume as predictors of anastomotic dehiscence in colorectal surgery

## A pilot multicenter case-match study.



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## Red cell distribution width and mean platelet volume as predictors of anastomotic dehiscence in colorectal surgery. A pilot multicenter case-match study.

**AIM:** *One of the most serious complications in modern colorectal surgery is the occurrence of an anastomotic dehiscence. The aim of this study was to evaluate the role of preoperative red cell distribution width (RDW) and mean platelet volume (MPV) as predictors of anastomotic dehiscence in elective surgery for colorectal cancer.*

**MATERIALS AND METHODS:** *Forty-two patients with a clinically manifested anastomotic dehiscence after oncological colorectal surgery, and 42 controls matched for age, sex, pathological stage and tumor localization were enrolled. Correlations between the preoperative RDW and MPV values and anastomotic dehiscence were investigated.*

**RESULTS:** *Both the median RDW value (14.4 % vs 13.1%;  $p=0.007$ ) and the median MPV value (8.0 fL vs 7.5 fL;  $p=0.037$ ) were significantly higher in patients with anastomotic dehiscence than in those without. In multiple regression analysis only the RDW remained significantly associated with anastomotic dehiscence.*

**CONCLUSIONS:** *The preoperative values of RDW may be useful in predicting anastomotic damage in elective oncological surgery.*

**KEY WORDS:** Anastomotic Dehiscence, MPV, RDW

## Introduction

Colorectal cancer (CRC) is one of the most incident malignancies worldwide <sup>1</sup>. Currently, a multidisciplinary approach is used for its evaluation and treatment, including surgeons, gastroenterologists, pathologists, oncologists, radiotherapists and others <sup>2</sup>. Surgery is the only treatment that can guarantee the complete cure in

patients with early stage disease, non endoscopically removable, and in cases of locally advanced disease treated in a multidisciplinary fashion <sup>3-5</sup>. Nevertheless, oncological colorectal surgery is weighted by complications. One of the most serious complications in modern colorectal surgery is the occurrence of an anastomotic dehiscence (AD) in those patients in whom the continuity of the gross intestine is restored after the removal of the diseased tract.

AD has been reported to occur in 3% to 27% of colorectal surgical operations, causing considerable postoperative morbidity and mortality rates <sup>6-7</sup>. Cong et al. reviewed recently 39 studies reporting on 24,232 patients who underwent anterior resection for rectal cancer; they observed AD in 8.6% of the cases, 5.4% of whom required re-operation and 0.4% died<sup>8</sup>. In other reports

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AD has been demonstrated to be the most common cause of unplanned reoperation in colorectal surgery, and has been also associated with greater short-term mortality, poorer oncological outcomes and overall survival, as well as higher costs for the health care systems<sup>9-12</sup>. Early diagnosis is essential for contrasting the adverse effects of AD; a delay in antibiotic administration from the onset of septic shock causes a decrease in survival of 7.6% per hour<sup>13</sup>. Unfortunately, the early diagnosis is often difficult, based in extremely variable clinical parameters, which additionally can mimic other complications and clinical conditions<sup>14</sup>. For this reason, the discovery of biomarkers which can accurately predict the occurrence of postoperative AD is of imperative importance in order to improve the outcomes of colorectal surgery. The red cell distribution width (RDW) and the mean platelet volume (MPV) have been demonstrated to correlate with the intensity of several chronic and acute inflammatory diseases<sup>15-20</sup>, as well as with the features and outcomes of several malignancies including CRC<sup>21,22</sup>. The aim of the present study was to evaluate the role of preoperative RDW and MPV values as predictors of AD in patients undergoing elective surgery for colorectal cancer.

## Materials and Methods

Forty-two patients who underwent elective surgery for colorectal cancer in the surgical units involved in the study from January 2012 through January 2017 and had a postoperative clinically manifested anastomotic dehiscence were enrolled. Subsequently, a control group of 42 patients with matching characteristics in terms of sex, age, stage and localization of the disease, American Society of Anesthesiologists (ASA) score, body mass index (BMI), and surgical approach was retrieved. In both the cases and controls surgery was performed by scheduled surgical procedures, in which an intestinal anastomosis was performed without a protective stoma of any kind (real or virtual ileostomy, caecostomy etc.). All patients included in this retrospective study gave their informed consent for each single procedure, and for the use of their anonymous clinical data for research purposes; the study was carried out in accordance with the principles of the Declaration of Helsinki.

Cases operated on in emergency, those who had red cell or platelet supplements before surgery, those who had a protective stoma or a previous Hartman operation, and those with unavailable clinical, surgical, pathological and laboratory data were excluded. All the operations were performed by senior surgeons or trainees under adequate supervision, with an open or laparoscopic approach. Traditional right and left hemicolectomies and anterior resections were the surgical procedures performed in accordance to the localization of the lesions; larger or lesser resections were excluded to reduce bias. All the

anastomoses were made up with stapling devices; the choice of the type and dimension of the stapling device was made by the surgeon based on the localization of the disease, the anatomical conditions of the patients, and its proper experience. Among the patients with AD, five were observed between the 1<sup>st</sup> and 3<sup>d</sup> postoperative day, 32 between the 4<sup>th</sup> and 10<sup>th</sup> postoperative day, and the five remaining cases occurred from the 11<sup>th</sup> postoperative day on. The latter cases were managed conservatively, as the pelvic collections were evacuated through radiologically guided drainages.

Demographic, clinical and laboratory data were retrieved from the clinical records of the patients. The blood samples were obtained within a week before surgery with standard procedures and methodologies dictated by the current international and national guidelines, adopted by the institutions involved in the study; the samples were processed and analyzed in two certified laboratories. Normal ranges for RDW and MPV are respectively 11 - 13.5% and 7.2 - 11.1 fL in the laboratories involved. All results are expressed as mean (mean  $\pm$  standard deviations, SD) or median values (median and interquartile range, IQR). Variables distribution was assessed by the Shapiro-Wilk test. Statistical differences between groups were compared using unpaired Student's t-test or Mann-Whitney rank sum test, as appropriate. Correlations between variables were assessed by Pearson's correlation or Spearman's correlation as appropriate. Logistic regression analysis with AD absence vs. presence as dependent variable was conducted to determine associations between variables potentially involved in anastomotic dehiscence. The ability of studied parameters to predict AD event was analyzed using receiver operating characteristics curve (ROC) analysis. Optimal cut-off maximizing sensitivity and specificity was selected. Sensitivity and specificity were reported using the optimal ROC curve value according to the Youden Index. Logistic regression analysis was run to calculate the probability of AD using combined RDW and MPV; ROC curves for such combination were plotted, with calculation of the area under the curve (AUC) and the best cut-off values. The results of the AUC represented the global accuracy of the tests performed: 0.91-1.00 (excellent), 0.81-0.90 (good), 0.71-0.80 (fair), 0.61-0.70 (poor), and 0.51-0.60 (fail). Statistical analyses were performed using MedCalc for Windows, version 15.4 64 bit (MedCalc Software, Ostend, Belgium) and SPSS for Windows, version 14.0 32 bit (IBM Corporation; Armonk, NY, USA).

## Results

As expected, no statistically significant differences were found in the demographic and clinical features summarized in Table I, between patients with and without AD. Statistically significant correlations were searched between the values of the indexes under investigation and the

TABLE I - Main clinical features of cases and controls included into the study.

|   | Dehiscence                    | Non-dehiscence                |
|---|-------------------------------|-------------------------------|
| Sex   | 26M – 16F                     | 26M – 16F                     |
| Age (mean ± SD, years)                      | 68.9 ± 10                     | 69.2 ± 8.9                    |
| Disease localization                        | R:6 L:9 Sigmoid: 7 Rectal: 22 | R:6 L:9 Sigmoid: 7 Rectal: 22 |
| ASA score (mean ± SD)                       | 2.2 ± 0.58                    | 2.1 ± 0.36                    |
| BMI (mean)                                  | 25.5 ± 4.0                    | 24.8 ± 4.5                    |
| Distance from AV (rectal tumors, mean ± SD) | 10.2 cm ± 4.0                 | 10.7 cm ± 3.9                 |
| AJCC stage                                  | I:6, II:15, III:14, IV:4      | I:8, II:7, III:18, IV:6       |
| Laparoscopy                                 | 7                             | 8                             |

BMI: body mass index, AV: anal verge, AJCC: American Joint Committee on Cancer, ASA: American Society of Anesthesiology, M: males, F: females, R: right colon, L: left colon, SD: standard deviation.

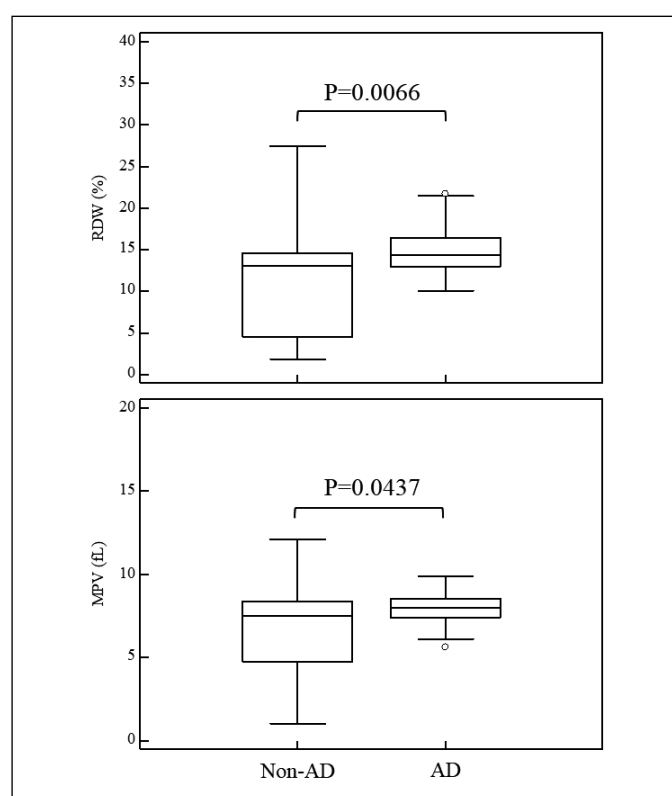


Fig. 1: Red cell distribution width (RDW) and mean platelet volume (MPV) levels in anastomotic dehiscence (AD) and non-AD groups. The central horizontal line on each box represents the median, the ends of the boxes are 25 and 75 percentiles and the error bars 5% and 95. P-values derived from Krustal-Wallis test.

main demographic and clinical features of the patients enrolled, globally and separately as dehiscence and non-dehiscence cases. We found that RDW was significantly associated with the site of the disease in the global cohort and in both the groups of patients with and without AD; in particular, it was higher in proximal tumors, in relation to more distal lesions. There were not detected other statistically relevant associations. Statistically significant differences were found in the

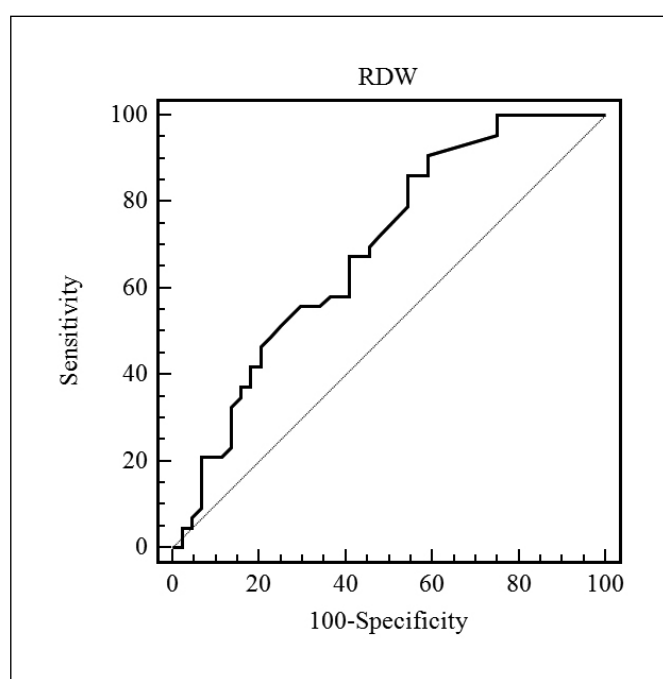


Fig. 2: Receiver operating characteristics (ROC) curve analysis of the RDW values in predicting anastomotic dehiscence in oncological colorectal surgery. The area under the curve (AUC) was 0.673 (95% CI: 0.561 - 0.772).

median preoperative values of RDW and MPV between patients with and without AD. The median RDW value was 14.4 % (IQR: 13.0 - 16.4 %) in patients with AD (Fig. 1), and 13.1 % (IQR: 4.5 to 14.6 %) in patients without AD (p=0.007), while the MPV median values were respectively 8.0 fL (IQR: 7.6 - 8.2 fL) and 7.5 fL (IQR: 6.4 - 7.7 fL) (p=0.037). In univariate logistic regression analysis RDW (crude odds ratio, OR=1.197, 95% CI: 1.059 - 1.353, p=0.004) and MPV (crude OR=1.361, 95% CI: 1.053 - 1.759, p=0.001), were associated with AD. In multiple logistic regression analysis, after adjusting for age, gender, BMI, ASA, site of disease and surgical approach, only RDW (OR: 1.194,

TABLE II - Multiple logistic regression analysis (including age, gender, BMI, ASA, site of disease, surgical approach, MPV and RDW) showing ORs for anastomotic dehiscence.

| Factor            | AD    |             | P-value |
|-------------------|-------|-------------|---------|
|                   | OR    | 95%CI       |         |
| Age               | 0.995 | 0.928-1.067 | 0.884   |
| Gender            | 1.088 | 0.264-4.479 | 0.907   |
| BMI               | 1.050 | 0.894-1.233 | 0.553   |
| ASA score         | 0.820 | 0.141-4.756 | 0.825   |
| Site of disease   | 1.026 | 0.344-3.062 | 0.963   |
| Surgical approach | 2.351 | 0.24-22.770 | 0.460   |
| MPV               | 1.280 | 0.888-1.845 | 0.185   |
| RDW               | 1.194 | 1.013-1.407 | 0.035   |

BMI: body mass index, ASA: American Anesthesiology Society, MPV: mean platelet volume, RDW: red blood cell distribution width, AD: anastomotic dehiscence, OR: odds ratio, CI: confidence interval.

95% CI: 1.013 - 1.407,  $p=0.035$ ) remained significantly associated with AD (Table II).

We performed ROC curve analysis for both RDW and MPV. The Area Under the Curve (AUC) was 0.673 (95% CI: 0.561 - 0.772,  $p=0.004$ ), and 0.633 (95% CI: 0.520 - 0.736,  $p=0.036$ ), respectively (Fig. 2). Considering a cut-off RDW value at 11%, sensitivity was 90.2% (95% CI: 76.9 - 97.3) and specificity 38.1% (95% CI: 23.6 - 54.4). Sensitivity and specificity were 92.7% (95% CI: 80.1 - 91.5) and 38% (95% CI: 23.6 - 54.4) respectively, when an MPV cut-off value at 6.5 fL was tested. We also evaluated the combination of these indexes, but no improvements were detected in their predictive value.

## Discussion

Anastomotic dehiscence is one of the most feared complications in colorectal surgery. It can occur early after surgery, commonly caused by a technical error or defect, causing severe general peritonitis, and imposing a re-laparotomy for abdominal cleaning and fashioning a diverting stoma<sup>23-24</sup>. Most frequently, AD occurs during the 5<sup>th</sup> or 6<sup>th</sup> postoperative days, due to impaired anastomotic healing, and may be managed conservatively when minor self-limited leakages are clinically and/or radiologically observed<sup>14,23</sup>. In the latter case, impaired healing may be caused by an excessive inflammatory reaction or reduced blood supply to the anastomotic rims, due to micro-ischemic or thrombotic events<sup>25</sup>. RDW has been demonstrated to be influenced by increased systemic inflammation that not only hinders the survival of erythrocytes, but also deforms their membranes<sup>26</sup>; higher RDW levels have been, indeed, associated to increased activity in several inflammatory diseases

<sup>15,16,19,20</sup>. Additionally, RDW and MPV have been found to be increased in intestinal ischemia and thrombosis<sup>27,28</sup>. These evidences suggest that both indexes might be useful in detecting AD in colorectal surgery.

RDW and MPV have been already evaluated as markers of surgical outcomes and complications in several types of surgical or invasive procedures. Aydinli et al. evidenced in a recent study that several parameters making part of the hemogram, namely RDW, MPV, PLR, and NLR, can predict the outcomes in open heart surgery patients; in particular, they found that the combination of three parameters, including the neutrophil to lymphocyte ratio (NLR), RDW, and MPV, is to be considered as a sensitive, high-quality, low-cost outcome prediction marker<sup>29</sup>. Cheung et al. showed that preoperative RDW independently predicted 30-day mortality in patients who underwent major- or ultra-major non-cardiac surgery, but with low sensitivity and specificity<sup>30</sup>. Furthermore, Korantzopoulos et al. showed that RDW is associated with the development of atrial fibrillation after elective on-pump cardiac surgery, and Mizuno et al. reported the usefulness of RDW in addition to the Mehran risk core in predicting contrast induced acute renal injury in patients who underwent percutaneous coronary intervention for ST-myocardial infraction<sup>31,32</sup>. These studies reflect the increasing relevance of blood count markers in monitoring surgical outcomes, and detecting postoperative complications.

To our knowledge, we are the first to study the role of RDW and MPV in predicting anastomotic dehiscence in oncological colorectal surgery. A statistically significant difference has been found in the preoperative levels of both indexes in patients with AD in comparison with the controls. These results were further supported by univariate logistic regression, but after adjusting for some confounders like age, gender, BMI, ASA, site of disease and surgical approach in a multiple logistic regression model, only RDW resulted independently associated with AD event. (Table II). The cause of such a difference is not clear. It is well known that malignancies cause a permanent inflammatory status which may impact on the involvement, activation and morphological modification of blood cells and platelets. The difference in RDW values may reflect an excessive inflammatory response, which subsequently causes an impaired healing of the anastomosis, and thus AD. Furthermore, additional comorbidities can be responsible for RDW alterations, like anemias, cardiovascular diseases, and diabetes, and can reduce intestinal healing leading to AD<sup>33</sup>. In our cohort, the patients enrolled had no haematological disorders and were matched in accordance to their ASA score.

Using ROC analysis for the detection of an optimal cut-off value for both the indexes under evaluation, and the study of their performance in detecting AD, we found again that RDW was superior to MPV. Considering an RDW cut-of value at 11%, the AUC was poor (0.673),

negatively influenced by an extremely low specificity of the test. This was to be expected, considering that 11% is the inferior limit of the reference range used in our laboratory to determine the RDW status. This means that the role of this index in predicting AD in colorectal surgery must be better evaluated, especially in the light of a potential clinical application. The importance of our findings remain, considering that only a few indicators, like C-reactive protein (CRP) and procalcitonin (PC), have demonstrated a certain usefulness in the diagnosis and management of intestinal AD<sup>34</sup>. The use of simple, low-cost, and widely available indexes, like those contained in the hemogram, has raised particular interest in recent years also in this setting; recently the value of the NLR before surgery and at the fourth postoperative day has been tested with promising results, despite some methodological concerns<sup>35-37</sup>. We did not investigate the role of the postoperative values of RDW and MPV in the present study, because we wanted to avoid bias due to red cell and/or platelet transfusions; nevertheless, this issue is interesting and should be evaluated in the future.

Exploring the associations of the indexes under investigation and the main demographic and clinical features of the patients, we found that RDW was related to the proximity of the tumors within the gross intestine. This finding is difficult to interpret. However, it is known that the lesions of the right colon, especially those of the caecum, can reach greater dimensions, ulcerate and bleed before getting clinically manifested, in comparison with those of the left and sigmoid colon, and the rectum<sup>38</sup>. This depends on the larger dimensions and the specific anatomy of the caecum and the right colon. The increment of RDW in the tumors of the proximal gross intestine may be related to the iron deficiency anemia deriving from the bleeding which characterize these tumors, persisting for a variable period of time before the diagnosis.

Our study has some limitations. First of all, data were collected retrospectively. Furthermore, the number of cases is relatively limited, but is higher than that presented in other studies evaluating other biomarkers of AD. On the other hand, this is the first report, designed with a rigorous case-match methodology, exploring the role of RDW and MPV in detecting AD in patients undergoing colorectal surgery for cancer.

## Conclusions

In conclusion, our findings suggest that an elevation of the preoperative values of RDW may be a useful predictor of intestinal AD in elective oncological surgery. The clinical utility of this finding should be further investigated, considering the scarcity of other specific markers of AD, the wide diffusion and the cost-effectiveness of complete blood tests.

## Riassunto

La deiscenza anastomotica rappresenta una delle complicanze più temibili in chirurgia oncologica colo-rettale. Si verifica nel 3-27% dei casi, in genere occorre tra la 5a-6a giornata postoperatoria ed è caratterizzata da un considerevole aumento della morbilità e mortalità. Per questo motivo, la disponibilità di biomarcatori umorali che possano predire la sua insorgenza sarebbe di grande utilità per i chirurghi, che con il loro utilizzo sarebbero in grado di diagnosticare e trattare precocemente la deiscenza, riducendo morbilità e mortalità. In questo studio pilota abbiamo esaminato per la prima volta il ruolo di due parametri ematologici preoperatori, l'ampiezza di distribuzione della popolazione eritrocitaria (red blood cell distribution width, RDW) e il volume piastrinico medio (mean platelet volume, MPV), come indici predittivi di deiscenza anastomotica. Sono stati inclusi nello studio 42 pazienti operati per carcinoma colo-rettale e i relativi controlli, selezionati accuratamente sulla base di età, sesso, ASA score, BMI, stadio e localizzazione del tumore, e tipo di procedura chirurgica eseguita. I valori medi di RDW (4.4 % vs 13.1%; p=0.007) e MPV (8.0 fL vs 7.5 fL; p=0.037) nel preoperatorio erano significativamente superiori nei casi che nei controlli. In seguito ad analisi di regressione multipla, solo il RDW è rimasto associato significativamente con l'insorgenza di deiscenza anastomotica. I nostri risultati suggeriscono che il RDW può essere utile nel predire l'insorgenza di deiscenza anastomotica in chirurgia colo-rettale. Questo risultato è estremamente interessante considerando che è un indice a basso costo e facilmente accessibile da tutti i chirurghi nel territorio. Ciononostante, la sua effettiva utilità clinica deve essere ulteriormente valutata in futuri studi prospettici.

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