ESR and CRP are better predictors of colorectal anastomotic dehiscence than blood cell count indexes of systemic inflammation: a multinational study on 1,432 patients

By
Abdrabou N. Mashhour
Assistant professor of General and Colorectal surgery
Faculty of medicine
Cairo university
2019

18 Authors

Panagiotis Paliogiannis[1], Simona Deidda[2], Svilen Maslyankov[3], Tsvetelina Paycheva[3], Ahmed Farag[4], Abdrabou Mashhour[4], Evangelos Misiakos[5], Dimitrios Papakonstantinou[5], Michal Mik[6], Joanna Losinska[6], Fabrizio Scognamillo[7], Fabio Sanna[7], Claudio Francesco Feo[8], Giuseppe Cherchi[8], Andreas Xidas[9], Angelo Zinellu[10], Angelo Restivo[2], Luigi Zorcolo[2]

Authors

The authors are from Italy, Bulgaria, Egypt, Greece and Poland

Introduction

- Anastomotic dehiscence (AD) is one of the most severe complications in modern colorectal surgery.
- It has been reported to occur in 3% to 27% of the cases in relation to specific risk factors

Introduction

- despite recent improvements in the preoperative selection and preparation of the patients,
- the evolution of minimally invasive surgical techniques,
- the stapling devices used to fashion the anastomoses,
- and the postoperative management of the patients

Introduction

- Anastomotic dehiscence represent the most common cause of unplanned reoperation in large colorectal surgery cohorts
- AD is associated with greater short-term mortality, poorer oncological outcomes and overall survival, and higher costs for the health care systems

Introduction

- Anastomotic dehiscence can be clinically manifested in several ways, in relation to:

1. The grade of the anastomotic breakdown
2. The anatomical site (colon or rectum)
3. The type of the surgical procedure
4. The general condition of the patient
5. The presence of a protective stoma.

Introduction

Generally, early AD is caused by technical errors or defects, has a major clinical impact, and a reoperation is often needed to treat it.

Introduction

- Most commonly, AD occurs between the 5th and 8th postoperative days
- It has a variable clinical presentation
- Minor leaks can be treated conservatively using drains to evacuate possible infectious collections,
- While major defects require re-intervention to clean the abdomen and restore the intes integrity or exteriorize the bowel.

Introduction

- In all cases, a prompt diagnosis is crucial, because a delay in antibiotic administration from the onset of septic shock has been associated with a decrease in survival of 7.6% per hour.
- The discovery of biomarkers which predict AD early after colorectal surgery, would bring consistent advantages in the management and outcomes of this complication.

Biomarkers

- Several biomarkers have been evaluated so far, most of them related with the inflammatory response to surgical manipulation, and the consequent reparative events in resected tissues.

Biomarkers

- Factors like interleukins, C Reactive Protein (CRP), Procalcitonin (PCT), Na^+, Tissue Plasminogen Activator (TPA), soluble fibrin and others have been evaluated in blood samples, as well as indexes including the cells participating in the inflammatory process, like the neutrophil to lymphocyte ratio (NLR)

Biomarkers

- NLR has been demonstrated to be a prognostic factor in numerous diseases, including primary and metastatic colorectal cancer and other malignancies.
- Furthermore, it has been associated with the outcomes of several types of surgical procedures, and with the onset of postoperative complications.
- However, poor data are currently available regarding its role in predicting anastomotic dehiscence in colorectal surgery.

Aim of the work

In the present study we investigated the role of NLR and derived neutrophil to lymphocyte ratio (dNLR) as predictive markers of anastomotic dehiscence, along with the role of the lymphocyte to monocyte (LMR) and the platelet to lymphocyte (PLR) ratios, in 1,432 patients with colorectal cancer who underwent elective surgical resection in nine different centers, and we compared them with the predictive performances of CRP and erythrocyte sedimentation rate (ESR).

Methods

- Data of all consecutive patients with histologically proven colorectal cancer, and undergoing elective surgery at the surgical units involved in the study from 1st January 2013 through 31th December 2017 were collected in an electronic database.

Methods

- Demographic and clinical data, including sex, age, BMI, ASA score, Charlson comorbidity index, localization and histology of the disease, the stage of the disease were registered.
- Tumor distance from the anal verge was included for patients with rectal cancer.
- The surgical procedure, postoperative course, morbidity, and 30-day mortality were collected.

The inclusion criteria

a) Patients with histologically proven colorectal cancer
b) Patients undergoing elective surgical procedure with an open or minimally invasive (laparoscopic or robotic) approach
c) Cases with available clinical, surgical, and pathological data
d) Cases with available blood cell counts before surgery, and at the 1st and 4th postoperative days
e) Patients who signed an informed consent for each procedure performed.

The exclusion criteria

a) Patients younger than 18
b) Those operated on in emergency setting
c) Those who did not have an anastomosis.

Methods

All the operations were performed by senior surgeons, and 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 his experience.

Methods

- Regarding laboratory tests, fasting blood samples were obtained with standard procedures
- Complete blood counts before the operation, on the 1st postoperative day, and on the 4th postoperative day were retrieved, and the NLR, dNLR, LMR, and PLR were calculated. In addition, the values of CRP (mg/dL) and ESR (mm />hr) were registered.

Methods

Cases who had a clinically manifested anastomotic dehiscence (Extended Clavien-Dindo Classification stage III or V) within 30 days form surgery were included in the AD group

Methods

The study was carried out in accordance with the principles of the Declaration of Helsinki, and was approved by the ethics committee of University Hospital (AOU) of Cagliari.

Results

- The global number of patients enrolled in the study was 1,432; among them 817 (57%) were male, and the mean age was 65.8 (± 13,7).
- Globally, 106 (7.4%) cases of AD fulfilling the selection criteria were registered.

Results

	All cases 1,432	Dehiscence 106	No-dehiscence 1,326	p-value
Male sex, n (%)	822 (57.4)	65 (56.6)	757 (57.1)	ns
Age (mean ± SD), years	65.8 ± 13.7	67.4 ± 11.4	65.7 ± 13.9	ns
BMI (mean ± SD))	25.1 ± 4.2	23.5 ± 4.2	25.2 ± 4.1	0.0002
ASA score (mean ± SD)	2.2 ± 0.8	2.2 ± 0.8	2.2 ± 0.8	ns
Charlson comorbidity index (mean ± SD)	5.5 ± 2.3	6.5 ± 3.0	5.4 ± 2.3	0.0017
Disease localization				
- **Right colon, n (%)**	451 (31.5)	23 (21.7)	428 (32.3)	ns
- **Transverse colon, n (%)**	99 (6.9)	7 (6.6)	92 (6.9)	ns
- **Left colon, n (%)**	149 (10.4)	15 (14.1)	134 (10.1)	ns
- **Sigmoid, n (%)**	331 (23.1)	19 (17.9)	312 (23.5)	ns
- **Rectum, n (%)**	395 (27.6)	40 (37.7)	355 (26.8)	ns
- **Multiple, n (%)**	7 (0.5)	2 (1.9)	5 (0.4)	ns
AJCC stage				
- **0, n (%)**	13 (0.9)	2 (1.9)	11 (0.8)	ns
- **I, n (%)**	242 (16.9)	16 (15.1)	226 (17)	ns
- **II, n (%)**	470 (32.8)	21 (19.8)	449 (33.9)	0.0353
- **III, n (%)**	526 (36.7)	55 (51.9)	471 (35.5)	0.0368
- **IV, n (%)**	167 (11.7)	12 (11.3)	155 (11.7)	ns
- **NA, n (%)**	14 (1)	0 (0)	14 (1.1)	ns
Tumor grading				
- **G1, n (%)**	193 (13.5)	9 (8.5)	184 (13.9)	ns
- **G2, n (%)**	1018 (71.1)	68 (64.1)	950 (71.6)	ns
- **G3, n (%)**	211 (14.7)	29 (27.4)	182 (13.7)	0.0027
- **NA, n (%)**	10 (0.7)	0 (0)	10 (0.7)	ns
Distance from AV, rectal tumors (mean ± SD), cm	9.5 ± 3.3	9.2 ± 3.3	9.5 ± 3.3	ns
Resection type (total procedures)	1438	106	1332	
- **Right hemicolectomy, n (%)**	474 (33)	21 (19.8)	453 (34)	0.0337
- **Left hemicolectomy, n (%)**	151 (10.5)	18 (17)	133 (10)	ns
- **Anterior resection, n (%)**	566 (39.4)	56 (52.8)	510 (38.3)	ns
- **Segmental resection, n (%)**	197 (13.7)	7 (6.6)	190 (14.3)	ns
- **Total colectomy, n (%)**	25 (1.7)	4 (3.8)	21 (1.6)	ns
- **Other, n (%)**	25 (1.7)	0 (0)	25 (1.9)	ns
Surgical approach				
- **Open, n (%)**	1060 (74)	70 (66)	990 (74.7)	ns
- **Laparoscopic, n (%)**	372 (26)	36 (34)	336 (25.3)	ns
Dehiscence postoperative day, median (95% CI)	-	6 (5 – 7)	-	
Dehiscence treatment				
- **Open, n (%)**	-	77 (72.6)	-	
- **Conservative, n (%)**	-	25 (23.6)	-	
- **NA, n (%)**	-	4 (3.8)	-	
Other complications, n (%)	1152 (80.4)	53 (50)	227 (17.1)	
Lenght of stay, (mean ± SD), days	11.7 ± 7.5	24.1 ± 17.3	10.6 ± 4.4	
30-days mortality	18 (1.3)	11(10.4)	7 (0.5)	

AD group

- significantly lower mean BMI value (23.5 ± 4.2 vs 25.2 ± 4.1, p=0.0002)
- significantly higher mean Charlson comorbidity index (6.5 ± 3.0, p=0.0017).
- significantly higher percentage of TNM stage III cases (51.9% vs 35.5%, p=0.0368)
- significantly higher percentage of concomitant complications (50% vs 17.1%, p=0.0042)
- greater length of stay (24.1 ± 17.3 vs 10.6 ± 4.4, p< 0,0001)
- significantly worse 30-day postoperative mortality (10.4% vs 0.5%, p< 0,0001).

Results

- There was no significant differences between patients with and without AD in the median values of white blood cells, neutrophils, monocytes, lymphocytes and platelets before surgery;
- Similarly the red cell distribution width (RDW), CRP, and ESR, as well as cell ratios were not statistically different, with the only exception of PLR (200 vs 178, p=0.038) which showed a limited statistically significant difference.

Results

- ***first postoperative day,*** some further differences in blood cell populations and indexes were observed, but the greatest statistical differences were registered on the 4^{th} postoperative day.
- ***On the 4^{th} postoperative day***, patients with AD had significantly greater mean WBC (10 vs 7.9, $p<0.0001$) and neutrophil (8 vs 5.7, $p<0.0001$) values, but lower mean lymphocyte (0.9 vs 1.10, $p<0.0001$) values.

Results

- In addition, the mean NLR (9.6 vs 5.3, $p<0.0001$), dNLR (4.7 vs 2.9, $p<0.0001$), and PLR (254 vs 218, $p<0.0001$)
- values were consistently greater in patients who developed an AD
- Nevertheless, the CRP (163.5 vs 72.1, $p<0.0001$) and ESR (105 vs 64, $p<0.0001$) values were consistently higher in AD patients.

Parameter	Patients	Preop	1st postop day	4th postop day
WBC median (IQR)	Non-AD	6.50 (5.40-8.30)	10.40 (8.30-12.90)	7.90 (6.30-9.90)
	AD	6.25 (5.20-7.60)	9.10 (7.30-12.10)	10.00 (7.65-12.72)
	P-value	***ns***	***ns***	***<0.0001***
Neutrophils median (IQR)	Non-AD	4.10 (3.20-5.50)	8.40 (6.50-10.70)	5.70 4.40-7.52
	AD	4.00 (3.10-5.03)	7.50 (6.05-10.10)	8.00 5.92-10.10
	P-value	***ns***	***ns***	***0.0001***
Monocytes median (IQR)	Non-AD	0.50 (0.40-0.60)	0.60 (0.50-0.90)	0.50 (0.40-0.70)
	AD	0.50 (0.40-0.60)	0.50 (0.30-0.60)	0.50 (0.40-0.60)
	P-value	***ns***	***<0.0001***	***ns***
Lymphocytes median (IQR)	Non-AD	1.50 (1.10-1.90)	1.00 (0.70-1.40)	1.10 (0.80-1.40)
	AD	1.30 (1.00-1.82)	0.80 (0.60-1.10)	0.90 (0.70-1.17)
	P-value	***ns***	***0.0002***	***<0.0001***
Platelets median (IQR)	Non-AD	258 (211-319)	220 (179-271)	231 (184-285)
	AD	267 (216-323)	216 (175-263)	240 (182-306)
	P-value	***ns***	***ns***	***ns***
RDW median (IQR)	Non-AD	14.8 (13.8-16.6)	14.9 (13.8-16.8)	15.0 (13.8-17.0)
	AD	15.1 (13.7-17.2)	16.0 (13.7-17.5)	15.9 (13.9-17.6)
	P-value	***ns***	***ns***	***ns***
CRP median (IQR)	Non-AD	3.3 (2.0-6.7)	63.0 (13.4-90.0)	72.1 (27.2-101.5)
	AD	4.4 (2.5-8.3)	87.3 (54.1-106.4)	163.5 (112.0-213.7)
	P-value	***ns***	***0.0023***	***<0.0001***
ESR median (IQR)	Non-AD	13.0 (5.0-34.0)	29.0 (23.0-47.0)	64.0 (36.0-79.0)
	AD	8.0 (6.3-13.8)	31.5 (28.0-45.0)	105.0 (82.0-132.0)
	P-value	***ns***	***ns***	***<0.0001***
NLR median (IQR)	Non-AD	2.90 (2.10-3.90)	8.35 (6.00-11.80)	5.30 (3.60-7.40)
	AD	3.30 (2.28-4.13)	9.80 (7.12-12.30)	9.60 (6.55-10.98)
	P-value	***ns***	***0.007***	***<0.0001***
dNLR median (IQR)	Non-AD	1.90 (1.50-2.40)	4.60 (3.58-6.10)	2.90 (2.10-3.90)
	AD	2.10 (1.60-2.50)	5.00 (4.10-6.22)	4.70 (3.40-5.50)
	P-value	***ns***	***0.025***	***<0.0001***
LMR	Non-AD	3.00 (2.20-4.00)	1.60 (1.10-2.10)	2.00 (1.50-2.80)
	AD	2.70	1.80	2.00

Results

- ROC curve analysis for the indexes which showed statistically significant differences between the two groups of patients on the 4^{th} postoperative day
- Among the blood cell indexes, the NLR at a cutoff point of 7.1 showed the best AUC (0.744, 95% CI: 0.719-0.768) with a sensitivity and specificity of 72.7% and 73.4%, respectively, followed by the dNLR (0.732, 95% CI: 0.707-0.757) at a cutoff point of 3.8. PLR showed a poor result in ROC analysis.
- Both the CRP and ESR showed better AUCs than the blood cell ratios under evaluation (0.803 and 0,843, respectively).

Discussion

- Anastomotic dehiscence is one of the most serious postoperative adverse events in colorectal surgery.
- This was confirmed also in the present study considering the rate of postoperative concomitant complications, length of stay and 30-day mortality, which were significantly higher in patients with AD than in those with an uncomplicated postoperative course

Discussion

- The rate of ADs in our series (7.4%) was similar to that reported in other recent articles.
- AD patients in our study had lower mean BMI values in comparison to those without AD; this result is somewhat unexpected, considering that obesity is traditionally considered one of the main risk factors of AD.

Discussion

- On the other hand, these patients had a worse Charlson comorbidity index, as well as higher tumor TNM stage and histological grade.
- This may be associated with a greater level of systemic inflammation, which in one hand determine the increased AD rates, and on the other alters several hematological biomarkers, like those investigated herein.

Discussion

- To our knowledge, this is the first study to evaluate the role of the dNLR, LMR and PLR in predicting AD.
- These simple blood count indexes, together with the NLR and RDW, have been demonstrated to have a prognostic potential in several chronic pathological conditions, including colorectal cancer and colorectal liver metastas and a potential role in predicting outcomes in surgical procedures.

Discussion

- NLR is the most studied index to this purpose.
- Josse et al. retrospectively investigated its role in predicting complications in 583 patients who underwent surgical resection for suspected or confirmed colorectal cancer.

Discussion

- The authors found that a preoperative NLR greater or equal to 2.3 was significantly associated with a major perioperative complication rate; on multivariate analysis, a high NLR and Charlson Comorbidity Index ≥3 were significantly related to major morbidity.
- Nevertheless, they did not detect any relationship between an elevated preoperative NLR and specific complication types, although there was a trend towards higher NLR values in patients with AD

Discussion

- Miyakita et al. published a study on 260 patients with rectal cancer who underwent radical surgery to examine the relations between complications and 5 types of risk scores, including the preoperative NLR.
- Complications developed in 56 patients (21.5%), and 18 cases of AD where encountered

Discussion

- The authors evidenced that the levels of the NLR calculated in blood samples obtained at initial presentation and before chemo-radiotherapy were significantly associated to surgical complications in general, and especially to AD.

Discussion

- Another study recently published by Mik et al. included 724 patients who underwent elective open colorectal surgery, and (among them) the rate of AD was 4.6%[10]. In this study blood samples were obtained also on the 1st and 4th postoperative days, and both CRP and NLR were evaluated. The authors found a statistically significant difference of the mean value of NLR on the 4th postoperative day, between patients

Discussion

- In our cohort, the AUC was greater (0.744), the sensitivity was slightly higher (73%) and the specificity lower (73%) at a NLR cutoff point of 7.1 on postoperative day 4. This value was relatively close to the NLR cutoff value in patients with AD found in the study of Mik et al.; in addition, the median NLR value found in our series (9.60) was close to the median value found by Mik et al. (9.03) in this subset of patients.

Discussion

- Furthermore, Mik et al. compared the performance of CRP, which is the most accurate blood test of inflammation currently available, with that of NLR; they found that the former, measured on the 4th postoperative day, performs better than NLR in predicting AD, with an AUC of 0.83, sensitivity 75%, and specificity 91% at a cutoff point of 180 mg/L[10]. We found similar results in our study; the CRP AUC at a cutoff point of 127mg/L (consistently lower than that calculated by Mik et al.) was 0.803, with 71% sensitivity and 86% specificity
- .

Discussion

- In addition, we evaluated the role of ESR, which was demonstrated to be the best predictor of AD, with an AUC to 0.843, sensitivity 68% and specificity 93%. This is a particularly interesting finding not reported so far in other studies, and deserves to be further investigated in future prospectively designed studies

Discussion

- Our study has some limitations, mainly its retrospective design, the lack of information about treatments which may alter the indexes under evaluation (like steroids etc.), as well as potential variability in the perioperative management of the patients and laboratory testing.

Discussion

- On the other hand, it includes the larger cohort employed so far for the study of the role of specific inflammatory indexes in predicting AD, some of them tested for the first time.
- Further prospectively designed trials are necessary to confirm the better predictive ability of ESR in comparison with other markers

Discussion

- In conclusion, our data evidenced that both the ESR and the CRP perform better than the blood cell count indexes, representing the best markers available in early diagnosing, and thus, reducing the morbidity and mortality of AD in colorectal surgery.
- ESR was the marker that showed the greatest predictive ability.
- NLR, a simple, inexpensive, and widely available index performs better than other blood cell ratios

Thank you