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Lymphocyte count and platelet volume predicts postoperative complications in esophagectomy for cancer: a cohort study

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ABSTRACT – **Background** – Biomarkers from routine complete blood count are known predictive factors of long-term outcomes in cancer patients. The value of these biomarkers in the setting of trimodal therapy for esophageal cancer in predicting early postoperative outcomes is not studied. **Objective** – The present study evaluated the value of cellular blood components changes during neoadjuvant chemoradiotherapy followed by curative intent esophagectomy for cancer in predicting postoperative mortality and morbidity. **Methods** – A cohort of 149 consecutive patients that underwent chemoradiotherapy using platinum- and taxane-based regimens followed by esophagectomy was analyzed. Cellular components of blood collected before neoadjuvant therapy (period A) and before surgery (period B) were assessed for postoperative mortality and complications. Univariate and multivariate Cox regression models were applied to evaluate the independent prognostic significance of blood count variables. **Results** – Postoperative morbidity was present in 46% of the patients. On multiple regression analysis platelet volume (B) (OR: 1.53; 95% CI: 1.2–2.33) was an independent predictor of general complications. Severe postoperative surgical complications were present in 17% of the patients. On multiple regression analysis, lymphocyte decrease between B-A periods (OR: 0.992; 95% CI: 0.990–0.997) was related to higher risk for severe complications. Cervical anastomotic leakage was present in 25.6% of the patients. On univariate analysis eosinophil count in A and B periods was related to cervical anastomotic leakage. For this outcome, multivariate joint model could not identify independent risk variables of cellular components of blood. The 30-day mortality rate was 7.4%. On univariate analysis, platelet count in period B was associated to higher risk for mortality. The multivariate joint model could not accurately predict mortality due to the few number of patients in the mortality group. **Conclusion** – This is the first study to assess the relationship between peripheral blood count variables changes during neoadjuvant chemoradiotherapy using a platinum- and taxane-based regimen followed by curative intent esophagectomy for cancer in predicting postoperative complications. The platelet volume prior to surgery is related to postoperative complications and the lymphocyte count change prior to surgery predicts severe postoperative complications in the setting of trimodal therapy for esophageal cancer.

HEADINGS – Esophageal neoplasms. Neoadjuvant therapy. Blood cells. Leukocytes. Blood platelets. Lymphocytes. Neutrophils.

INTRODUCTION

Esophageal cancer treatment is based on neoadjuvant chemoradiotherapy followed by surgery in most potentially curable esophageal cancer[1,2]. Esophagectomy usually presents high postoperative morbidity and mortality, and certain complications may even influence long-term survival[3].

Accumulating evidence shows that preoperative hematological biomarkers from routine complete blood count, such as red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean corpuscular volume (MCV) may predict long-term outcomes in cancer[4-14]. For esophageal cancer, preoperative NLR before surgery predicts overall survival (OS) and disease-free survival (DFS)[15]. Postoperative NLR elevation after surgery may also predict early postoperative outcomes in esophageal cancer[16].

The value of cellular blood components prior to neoadjuvant therapy and prior to surgery in the setting of trimodal therapy for esophageal cancer in predicting early postoperative complications and mortality has not been reported, and is the aim of this study.

METHODS

A retrospective cohort was performed, assessing the correlation of cellular components of blood and their changes during trimodal therapy for esophageal carcinoma with postoperative mortality and postoperative complications. Consecutive patients of a single institute with completion of neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens, followed by curative intent esophagectomy, were selected. Peripheral blood was obtained in two different moments: before neoadjuvant therapy (A); and before surgery (1-7 days) (B). Blood test was not collected during acute infectious disease, neither during targeted antitumor therapy.

Recruitment included 2009 to 2019 period. Patients were staged with endoscopy, CT-scan, and PET-scan prior to neoadjuvant therapy and classified accordingly to the 8th edition of UICC staging[17]. Patients were followed with clinical evaluation, peripheral blood analysis, CT-scan and endoscopy. Complications were classified accordingly to the international consensus on standardization of data collection for complications associated

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with esophagectomy[18] and Clavien-Dindo classification[19]. Pathological response to neoadjuvant therapy was graded accordingly to Ryan score[20]. The local ethics committee approved the study.

Statistical analysis

For absolute and relative variable, chi-square test, Fisher test or likelihood-ratio test were used for each outcome. Multivariate Cox proportional hazard analysis was performed to determine independent risk factors for the outcomes. Only variables that were significant (P<0.1) on univariate analysis were included as co-variables in the multivariable analyses. Data were assessed with IBM-SPSS software version 20.0, and a significance level of 0.05 was adopted.

Ethics approval and consent to participate

This study was approved by local Ethics Committee (CAPEPesq).

RESULTS

Patients' baseline characteristics

One hundred and forty-nine consecutive patients underwent neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens followed by esophagectomy and were included. The mean age was 60.9 years (SD±8.6), with male predominance (75.8%). There were 117 transthoracic (video-assisted thoracoscopic) procedures and 32 transhiatal procedures, all of them with cervical anastomosis. The median time from completion of neoadjuvant chemoradiotherapy to surgery was 13 weeks (IQR 8). The two chemotherapy regimens adopted were carboplatin and paclitaxel (75.2%), and cisplatin and paclitaxel (24.8%). The radiation therapy dosage was 41.4 cGy (75%), 45 cGy (13.5%), and 50.4 cGy (11.5%).

General postoperative complications

The postoperative morbidity was present in 46% of the patients. Clinical postoperative complications, such as pneumonia, cardiovascular events, respiratory failure, thromboembolic events, were present in 22% of the patients. Surgical complications, such as bleeding, chylothorax, cervical anastomotic leak, were present in 35.5% of the patients.

On univariate analysis age was related to general postoperative complications. Before surgery (period B), platelet volume was also related to general complications. On multiple regression analysis, age (OR: 1.05; 95% CI: 1.01-1.1; P=0.019) and platelet volume (B) (OR: 1.53; 95% CI: 1.2-2.33; P=0.045) were independent predictors of general complications (TABLE 1 and FIGURE 1). The predictive model for general complications can be expressed by the following equation: equation = *exp* (-7.3+0.049 x Age+0.423 x Platelet Volume (B)) / (1+*exp* (-7.3+0.049 x Age+0.423 x Platelet Volume (B))).

Severe postoperative complications

Severe postoperative complications (Clavien-Dindo ≥ IIIa) were present in 17% of the patients.

On univariate analysis transhiatal access was related to severe postoperative complications. The decrease of lymphocytes between B-A periods was correlated to severe complications. On multiple regression analysis, surgical access (thoracoscopy: OR: 0.23; 95% CI: 0.088-0.602; P=0.003) and lymphocyte change between B-A periods (OR: 0.992; 95% CI: 0.990-0.997; P=0.046) were related to higher risk for severe complications (TABLE 2 and FIGURE 2). The predictive model for severe complications can be expressed by the following equation = *exp* (-1.12–0.001 x Lymphocyte (B-A) – 1.47 (if thoracoscopy)) / (1+*exp* (-1.12–0.001 x Lymphocyte (B-A) – 1.47 (if thoracoscopy)).

Cervical anastomotic leakage

Cervical anastomotic leakage was present in 25.6% of the patients, and mostly was easily manageable and classified as grade[18] I or II (90%).

On univariate analysis grade of cellular differentiation was related to cervical anastomotic leakage. Eosinophil count in A (OR: 1.001; 95% CI: 1-1.002; P=0.011), and B (OR: 1.001; 95% CI: 0.999–1.002; P=0.038) periods was also related to cervical anastomotic leakage (TABLE 3). The multivariate joint model was performed and the risk for cervical anastomotic leakage was constant, independently of the blood cellular variables.

Postoperative mortality

The 30-day mortality rate was 7.4%.

On univariate analysis, age, histology, clinical stage, Ryan pathological response score, and complications were related to 30-days postoperartive mortality. For cellular components of blood, all variables were not related to postoperartive mortality, but platelet count in period B (OR: 1.007; 95% CI: 0.999–1.017; P=0.017) (TABLE 4). The multivariate joint model could not accurately predict postoperative 30-day mortality due to the few number of patients in the mortality group.

DISCUSSION

Results of this cohort of 149 consecutive esophageal cancer patients that underwent neoadjuvant chemoradiotherapy using a platinum- and taxane-based regimen followed by curative intent esophagectomy suggest that mean platelet volume and lymphocyte decrease during neoadjuvant therapy are independent variables that can predict postoperative complications.

It has been well established that there is a complex relationship among tumor, systemic inflammation, and nutritional and immune status[5,11,21-23] that may influence in surgical complications risks[24-26].

Cancer cells release growth factors and inflammatory mediators that stimulate production and activation of peripheral blood platelets[27,28]. Increased mean platelet volume is an early index of activated platelets[29]. In our study, mean platelet volume was related to higher risk for general complications, although the peripheral platelet count was not related to higher risk for complications.

Lymphocyte decrease in cancer patients reflects host immune function due to hormonal change, malnutrition, antitumor immune response, or may be due to chemotherapy induced depletion[30-36]. Lymphopenia has strong relationship with lower heart ejection fraction postoperatively[37], major adverse cardiac outcomes[38-40] and infectious complications[36]. In the present study, lymphocyte decrease between B and A periods increases the risk for severe postoperative complications. Despite lymphopenia may also reflect radiation therapy side effect[41], in the present radiation dose did not influence morbidity.

Although previous studies reported that preoperative NLR might predict severe postoperative complications for colorectal, head and neck, and gastric surgery[26,42-46], in the present study NLR and PLR were not related to postoperative complications in esophageal carcinoma.

TABLE 1. General postoperative complications. Univariate analysis. Cellular components of blood are expressed in mean ± standard deviation (SD).

Variable	Postoperative complications		OR	95% CI		*P*
	No (N=78)	Yes (N=71)		Lower	Upper	
Age (yr)			1.049	1.008	1.091	**0.007****
Mean ± SD	59.3±8.3	62.7±8.6				
Sex, n (%)						0.276
Male	62 (54.9)	51 (45.1)	1.00			
Female	16 (44.4)	20 (55.6)	1.52	0.72	3.23	
Histology, n (%)						0.940*
Adenocarcinoma	24 (54.5)	20 (45.5)	1.00			
SCC	52 (51.5)	49 (48.5)	1.13	0.56	2.30	
Undifferentiated carcinoma	2 (50)	2 (50)	1.20	0.16	9.30	
cStage, n (%)						0.345#
I	1 (20)	4 (80)	1.00			
II	20 (60.6)	13 (39.4)	0.16	0.02	1.62	
III	48 (52.2)	44 (47.8)	0.23	0.03	2.13	
IV	9 (47.4)	10 (52.6)	0.28	0.03	2.97	
Radiation, n (%)						0.606
41.4	56 (50)	56 (50)	1.00			
45	12 (60)	8 (40)	0.67	0.25	1.76	
50.4	10 (58.8)	7 (41.2)	0.70	0.25	1.97	
Chemotherapy, n (%)						0.889
Cisplatin, Paclitaxel	19 (51.4)	18 (48.6)	1.00			
Carboplatin, Paclitaxel	59 (52.7)	53 (47.3)	0.95	0.45	2.00	
Interval CRT-Surgery (days)			1.006	0.999	1.013	0.113**
Mean ± SD	97.5±41.3	110.1±50.8				
Surgical access, n (%)						0.484
Transhiatal	15 (46.9)	17 (53.1)	1.00			
Trasthoracic	63 (53.8)	54 (46.2)	0.76	0.35	1.66	
Ryan score, n (%)						0.637
1	43 (55.1)	35 (44.9)	1.00			
2	14 (51.9)	13 (48.1)	1.14	0.48	2.74	
3	13 (44.8)	16 (55.2)	1.51	0.64	3.56	
Margins, n (%)						0.910
Free	71 (52.2)	65 (47.8)	1.00			
Compromised	7 (53.8)	6 (46.2)	0.94	0.30	2.93	
Grade of cellular differentiation, n (%)						0.054
1	8 (61.5)	5 (38.5)	1.00			
2	43 (44.3)	54 (55.7)	2.01	0.61	6.59	
3	24 (66.7)	12 (33.3)	0.80	0.22	2.98	
Hb (g/dL) (A)	13.2±2	13.4±1.7	1.061	0.889	1.267	0.951**
Ht (%) (A)	39.4±5.2	40.2±4.8	1.036	0.968	1.107	0.549**
MCV (fL) (A)	87.6±7	88.6±7	1.020	0.973	1.069	0.734**
RDW (%) (A)	14.1±1.9	14.1±1.6	0.995	0.827	1.196	0.906**
Neut (/uL) (A)	5168.6±2219.6	5069.9±2421.1	1.000	1.000	1.000	0.633**
Eos (/uL) (A)	224.3±329	273.4±328	1.000	0.999	1.002	0.068**
Lymp (/uL) (A)	1863.4±617.7	2007.6±713.1	1.000	1.000	1.001	0.327**
Plat (nL) (A)	280.4±79.2	269±103.6	0.999	0.995	1.002	0.151**
MPV (fL) (A)	10.2±1.4	10.5±0.9	1.213	0.890	1.653	0.338**
NLR (A)	3.5±4	2.9±1.9	0.919	0.799	1.057	0.267**
PLR (x1000) (A)	0.19±0.2	0.15±0.08	0.104	0.003	3.174	0.081**
Hb (g/dL) (B)	12.6±1.5	12.4±1.7	0.946	0.771	1.161	0.521**
Hb (g/dL) (B-A)	-0.61±1.83	-0.96±1.83	0.899	0.749	1.079	0.408**
Ht (%) (B)	37.5±3.9	37.3±4.6	0.988	0.916	1.067	0.692**
Ht (%) (B-A)	-1.83±5.14	-2.93±5.04	0.957	0.896	1.023	0.246**
MCV (fL) (B)	92.3±6.4	92.1±6.2	0.993	0.944	1.046	0.624**
MCV (fL) (B-A)	4.72±4.66	3.34±5.04	0.942	0.879	1.010	0.053**
RDW (%) (B)	14.4±1.9	14.9±3	1.083	0.940	1.247	0.652**
RDW (%) (B-A)	0.32±1.88	0.83±2.81	1.106	0.944	1.296	0.500**
Neut (/uL) (B)	3722.3±1529.9	3741.9±2019.1	1.000	1.000	1.000	0.513**
Neut (/uL) (B-A)	-1432.4±2174.3	-1291±2448.1	1.000	1.000	1.000	0.654**
Eos (/uL) (B)	175.1±195	246.3±299.8	1.001	1.000	1.003	0.234**
Eos (/uL) (B-A)	-50.7±332.6	-27.9±237.9	1.000	0.999	1.001	0.367**
Lymp (/uL) (B)	1090.5±391.4	1132.1±434.2	1.000	0.999	1.001	0.671**
Lymp (/uL) (B-A)	-769.6±688	-873.7±562.7	1.000	0.999	1.000	0.411**
Plat (nL) (B)	211.6±57.1	210.9±67.7	1.000	0.995	1.005	0.610**
Plat (nL) (B-A)	-68.5±72.9	-56.5±108.4	1.001	0.998	1.005	0.261**
MPV (fL) (B)	9.83±0.74	10.11±0.92	1.524	1.015	2.287	**0.045****
MPV (fL) (B-A)	-0.41±1.42	-0.4±0.82	1.008	0.762	1.332	0.518**
NLR (B)	4.04±3.14	3.74±2.47	0.962	0.854	1.084	0.414**
NLR (B-A)	0.53±4.97	0.89±2.57	1.023	0.941	1.114	0.713**
PLR (x1000) (B)	0.22±0.09	0.21±0.11	0.65	0.02	19.86	0.439**
PLR (x1000) (B-A)	0.03±0.22	0.06±0.1	3.65	0.35	37.98	0.545**

(A): before neoadjuvant therapy; (B): before surgery. Chi-squared test; *Fisher's exact test; #Likelihood ratio test; ** Mann-Whitney test.

TABLE 2. Clavien-Dindo classification of surgical complications. Univariate analysis. Cellular components of blood are expressed in mean ± standard deviation (SD).

Variable	Clavien-Dindo		OR	95% CI		*P*
	< IIIa (N=122)	≥ IIIa (N=27)		Lower	Upper	
Age (yr)			1.033	0.982	1.088	0.314**
Mean ± SD	60.5±8.5	62.8±8.7				
Sex, n (%)						0.463
Male	94 (83.2)	19 (16.8)	1.00			
Female	28 (77.8)	8 (22.2)	1.41	0.56	3.57	
Histology, n (%)						0.197#
Adenocarcinoma	33 (75)	11 (25)	1.00			
SCC	85 (84.2)	16 (15.8)	0.57	0.24	1.34	
Undifferentiated carcinoma	4 (100)	0 (0)	&			
cStage, n (%)						0.151#
1	5 (100)	0 (0)	1.00			
2	30 (90.9)	3 (9.1)	&			
3	73 (79.3)	19 (20.7)	&			
4	14 (73.7)	5 (26.3)	&			
Radiation, n (%)						0.575#
41.4	92 (82.1)	20 (17.9)	1.00			
45	15 (75)	5 (25)	1.53	0.50	4.71	
50.4	15 (88.2)	2 (11.8)	0.61	0.13	2.90	
Chemotherapy, n (%)						0.105
Cisplatin, Paclitaxel	27 (73)	10 (27)	1.00			
Carboplatin, Paclitaxel	95 (84.8)	17 (15.2)	0.48	0.20	1.18	
Interval CRT-Surgery (days)			1.007	0.999	1.015	0.099**
Mean ± SD	100.5±44	117.1±54.4				
Surgical access, n (%)						0.007
Transhiatal	21 (65.6)	11 (34.4)	1.00			
Trasthoracic	101 (86.3)	16 (13.7)	0.30	0.12	0.74	
Ryan score, n (%)						0.775
1	65 (83.3)	13 (16.7)	1.00			
2	21 (77.8)	6 (22.2)	1.43	0.48	4.23	
3	23 (79.3)	6 (20.7)	1.30	0.44	3.83	
Margins, n (%)						0.464*
Free	110 (80.9)	26 (19.1)	1.00			
Compromised	12 (92.3)	1 (7.7)	0.35	0.04	2.83	
Grade of cellular differentiation, n (%)						0.633#
1	11 (84.6)	2 (15.4)	1.00			
2	77 (79.4)	20 (20.6)	1.43	0.29	6.97	
3	31 (86.1)	5 (13.9)	0.89	0.15	5.25	
Hb (g/dL) (A)	13.3±1.9	13.2±1.4	0.971	0.778	1.212	0.349**
Ht (%) (A)	39.8±5.2	39.8±3.8	1.000	0.919	1.088	0.717**
MCV (fL) (A)	88±7	88.4±6.8	1.007	0.947	1.069	0.974**
RDW (%) (A)	14±1.9	14.2±1.3	1.048	0.842	1.305	0.195**
Neut (/uL) (A)	5088.8±2316.5	5263.3±2328.3	1.000	1.000	1.000	0.695**
Eos (/uL) (A)	251.3±351	233.3±203.1	1.000	0.998	1.001	0.583**
Lymp (/uL) (A)	1886.4±650.4	2140.4±712.6	1.001	1.000	1.001	0.102**
Plat (nL) (A)	276.9±92.5	266±88.3	0.999	0.994	1.004	0.498**
MPV (fL) (A)	10.4±1.2	10.3±0.9	0.956	0.682	1.338	0.509**
NLR (A)	3.3±3.4	2.8±2.1	0.934	0.765	1.140	0.280**
PLR (x1000) (A)	0.18±0.17	0.14±0.08	0.020	0.000	11.410	0.058**
Hb (g/dL) (B)	12.5±1.6	12.6±1.7	1.024	0.786	1.335	0.821**
Hb (g/dL) (B-A)	-0.81±1.86	-0.65±1.71	1.049	0.836	1.315	0.493**
Ht (%) (B)	37.4±4.2	37.7±4.7	1.019	0.923	1.125	0.747**
Ht (%) (B-A)	-2.42±5.23	-2.08±4.57	1.013	0.934	1.099	0.637**
MCV (fL) (B)	92.1±6.4	92.7±6.1	1.016	0.950	1.087	0.770**
MCV (fL) (B-A)	3.99±4.94	4.37±4.66	1.016	0.932	1.107	0.980**
RDW (%) (B)	14.7±2.6	14.7±2.1	1.007	0.854	1.188	0.882**
RDW (%) (B-A)	0.58±2.5	0.5±1.76	0.985	0.821	1.182	0.803**
Neut (/uL) (B)	3689.6±1678.7	3919.6±2168.1	1.000	1.000	1.000	0.887**
Neut (/uL) (B-A)	-1369.3±2226.3	-1343.7±2660	1.000	1.000	1.000	0.912**
Eos (/uL) (B)	209.8±247.5	204.1±274.7	1.000	0.998	1.002	0.778**
Eos (/uL) (B-A)	-42.1±292.2	-29.3±287	1.000	0.999	1.002	0.289**
Lymp (/uL) (B)	1101.7±394.9	1148.2±484.5	1.000	0.999	1.001	0.972**
Lymp (/uL) (B-A)	-780.3±627.3	-992.2±630.2	0.999	0.999	1.000	**0.049****
Plat (nL) (B)	213.6±62	200.3±62.2	0.996	0.989	1.004	0.243**
Plat (nL) (B-A)	-62.1±94.7	-65.7±76	1.000	0.995	1.004	0.945**
MPV (fL) (B)	9.93±0.83	10.1±0.88	1.269	0.780	2.067	0.462**
MPV (fL) (B-A)	-0.46±1.24	-0.2±0.78	1.160	0.854	1.576	0.069**
NLR (B)	3.94±2.96	3.71±2.27	0.970	0.824	1.142	0.839**
NLR (B-A)	0.66±4.2	0.88±2.98	1.015	0.909	1.133	0.846**
PLR (x1000) (B)	0.22±0.1	0.2±0.09	0.106	0.001	15.242	0.337**
PLR (x1000) (B-A)	0.04±0.19	0.06±0.1	2.106	0.102	43.565	0.757**

(A): before neoadjuvant therapy; (B): before surgery. Chi-squared test; *Fisher's exact test; #Likelihood ratio test; ** Mann-Whitney test.

TABLE 3. Cervical anastomotic leakage. Univariate analysis. Cellular components of blood are expressed in mean ± standard deviation (SD).

Variable	Cervical anastomotic leak		OR	95% CI		*P*
	No (N=109)	Yes (N=40)		Lower	Upper	
Age (yr)			0.993	0.952	1.036	0.927**
Mean ± SD	61.1±8.4	60.6±9.2				
Sex, n (%)						0.313
Male	85 (75.2)	28 (24.8)	1.00			
Female	24 (66.7)	12 (33.3)	1.52	0.67	3.43	
Histology, n (%)						0.096#
Adenocarcinoma	37 (84.1)	7 (15.9)	1.00			
SCC	70 (69.3)	31 (30.7)	2.34	0.94	5.83	
Undifferentiated carcinoma	2 (50)	2 (50)	5.29	0.64	44.03	
cStage, n (%)						0.812#
I	3 (60)	2 (40)	1.00			
II	25 (75.8)	8 (24.2)	0.48	0.07	3.40	
III	66 (71.7)	26 (28.3)	0.59	0.09	3.74	
IV	15 (78.9)	4 (21.1)	0.40	0.05	3.27	
Radiation, n (%)						0.579#
41.4	82 (73.2)	30 (26.8)	1.00			
45	16 (80)	4 (20)	0.68	0.21	2.21	
50.4	11 (64.7)	6 (35.3)	1.49	0.51	4.39	
Chemotherapy n (%)						0.648
Cisplatin, Paclitaxel	26 (70.3)	11 (29.7)	1.00			
Carboplatin, Paclitaxel	83 (74.1)	29 (25.9)	0.83	0.36	1.88	
Interval CRT-Surgery (days)			1.005	0.997	1.012	0.214**
Mean ± SD	100.7±45.2	111.1±49.1				
Surgical access, n (%)						0.854
Transhiatal	23 (71.9)	9 (28.1)	1.00			
Trasthoracic	86 (73.5)	31 (26.5)	0.92	0.39	2.21	
Ryan score, n (%)						0.829
1	56 (71.8)	22 (28.2)	1.00			
2	21 (77.8)	6 (22.2)	0.73	0.26	2.04	
3	21 (72.4)	8 (27.6)	0.97	0.37	2.51	
Margins, n (%)						0.515*
Free	98 (72.1)	38 (27.9)	1.00			
Compromised	11 (84.6)	2 (15.4)	0.47	0.10	2.22	
Grade of cellular differentiation, n (%)						0.019#
1	10 (76.9)	3 (23.1)	1.00			
2	64 (66)	33 (34)	1.72	0.44	6.68	
3	32 (88.9)	4 (11.1)	0.42	0.08	2.18	
Hb (g/dL) (A)	13.1±1.9	13.7±1.5	1.216	0.969	1.526	0.142**
Ht (%) (A)	39.3±5.2	41.1±4.2	1.088	0.998	1.185	0.053**
MCV (fL) (A)	87.9±6.9	88.6±7.1	1.016	0.963	1.071	0.863**
RDW (%) (A)	14.2±1.9	13.7±1.2	0.804	0.600	1.076	0.066**
Neut (/uL) (A)	4997.4±2218.4	5451.3±2544.6	1.000	1.000	1.000	0.304**
Eos (/uL) (A)	229.2±340.9	298.5±289.9	1.001	1.000	1.002	**0.011****
Lymp (/uL) (A)	1864.9±653.9	2115.3±676.1	1.001	1.000	1.001	0.062**
Plat (nL) (A)	273.4±79.7	279.1±119.3	1.001	0.997	1.005	0.594**
MPV (fL) (A)	10.3±1.3	10.6±0.8	1.311	0.898	1.915	0.145**
NLR (A)	3.4±3.6	2.7±1.3	0.901	0.742	1.094	0.643**
PLR (x1000) (A)	0.18±0.17	0.14±0.07	0.021	0.000	4.146	0.088**
Hb (g/dL) (B)	12.4±1.6	12.9±1.6	1.212	0.957	1.534	0.137**
Hb (g/dL) (B-A)	-0.75±1.87	-0.86±1.74	0.966	0.790	1.181	0.907**
Ht (%) (B)	37.1±4.2	38.5±4.3	1.087	0.995	1.189	0.083**
Ht (%) (B-A)	-2.27±5.31	-2.59±4.56	0.988	0.919	1.062	0.930**
MCV (fL) (B)	92.4±6.2	91.8±6.8	0.984	0.930	1.042	0.548**
MCV (fL) (B-A)	4.42±4.76	3.12±5.12	0.945	0.875	1.021	0.105**
RDW (%) (B)	14.6±2	14.8±3.5	1.037	0.903	1.192	0.677**
RDW (%) (B-A)	0.36±1.91	1.12±3.27	1.143	0.966	1.353	0.126**
Neut (/uL) (B)	3594.3±1511.5	4102.3±2317.9	1.000	1.000	1.000	0.531**
Neut (/uL) (B-A)	-1370.5±2172	-1349±2647.9	1.000	1.000	1.000	0.977**
Eos (/uL) (B)	194±255.5	248.8±239.6	1.001	0.999	1.002	**0.038****
Eos (/uL) (B-A)	-35.9±320.8	-49.8±190.1	1.000	0.999	1.001	0.216**
Lymp (/uL) (B)	1085.4±431.7	1177.3±346.6	1.001	1.000	1.001	0.088**
Lymp (/uL) (B-A)	-774.8±655.7	-938±550.8	1.000	0.999	1.000	0.330**
Plat (nL) (B)	210.9±62	212.4±62.8	1.000	0.995	1.006	0.948**
Plat (nL) (B-A)	-61.3±79.5	-66.7±119	0.999	0.995	1.003	0.705**
MPV (fL) (B)	9.88±0.83	10.18±0.82	1.525	0.986	2.358	0.054**
MPV (fL) (B-A)	-0.41±1.27	-0.4±0.85	1.006	0.738	1.371	0.900**
NLR (B)	3.94±2.97	3.78±2.46	0.980	0.856	1.121	0.733**
NLR (B-A)	0.57±4.44	1.03±2.45	1.032	0.934	1.140	0.826**
PLR (x1000) (B)	0.22±0.1	0.2±0.08	0.051	0.001	3.957	0.218**
PLR (x1000) (B-A)	0.04±0.2	0.05±0.09	1.74	0.15	19.60	0.979**

(A): before neoadjuvant therapy; (B): before surgery. Chi-squared test; *Fisher's exact test; #Likelihood ratio test; ** Mann-Whitney test.

TABLE 4. Postoperative mortality (30-days). Univariate analysis. Cellular components of blood are expressed in mean ± standard deviation (SD).

Variable	Mortality (30-days)		Total (N=149)	OR	95% CI		*P*
	No (N=138)	Yes (N=11)			Lower	Upper	
Age (yr)				1.113	1.017	1.218	**0.034****
Mean ± SD	60.5±8.4	66.9±8.6	60.9±8.6				
Sex, n (%)							0.462*
Male	106 (93.8)	7 (6.2)	113	1.00			
Female	32 (88.9)	4 (11.1)	36	1.89	0.52	6.88	
Histology, n (%)							0.043#
Adenocarcinoma	37 (84.1)	7 (15.9)	44	1.00			
SCC	97 (96)	4 (4)	101	0.22	0.06	0.79	
Undifferentiated carcinoma	4 (100)	0 (0)	4	&			
cStage, n (%)							0.011#
I	5 (100)	0 (0)	5	1.00			
II	33 (100)	0 (0)	33	&			
III	81 (88)	11 (12)	92	&			
IV	19 (100)	0 (0)	19	&			
Radiation, n (%)							0.882#
41.4	104 (92.9)	8 (7.1)	112	1.00			
45	18 (90)	2 (10)	20	1.44	0.28	7.36	
50.4	16 (94.1)	1 (5.9)	17	0.81	0.10	6.94	
Chemotherapy, n (%)							>0.999*
Cisplatin, Paclitaxel	34 (91.9)	3 (8.1)	37	1.00			
Carboplatin, Paclitaxel	104 (92.9)	8 (7.1)	112	0.87	0.22	3.47	
Interval CRT-Surgery (days)				1.011	1.000	1.022	0.107**
Mean ± SD	101.3±43.6	130.8±70	103.5±46.3				
Surgical access, n (%)							0.251*
Transhiatal	28 (87.5)	4 (12.5)	32	1.00			
Trasthoracic	110 (94)	7 (6)	117	0.45	0.12	1.63	
Ryan score, n (%)							0.024#
1	75 (96.2)	3 (3.8)	78	1.00			
2	21 (77.8)	6 (22.2)	27	7.14	1.65	31.00	
3	27 (93.1)	2 (6.9)	29	1.85	0.29	11.69	
Margins, n (%)							>0.999*
Free	126 (92.6)	10 (7.4)	136	1.00			
Compromised	12 (92.3)	1 (7.7)	13	1.05	0.12	8.92	
Grade of cellular differentiation, n (%)							0.865#
1	12 (92.3)	1 (7.7)	13	1.00			
2	89 (91.8)	8 (8.2)	97	1.08	0.12	9.40	
3	34 (94.4)	2 (5.6)	36	0.71	0.06	8.51	
Postoperative complications, n (%)							0.003
No	77 (98.7)	1 (1.3)	78	1.00			
Yes	61 (85.9)	10 (14.1)	71	12.62	1.57	101.33	
Cervical anastomotic leak, n (%)							0.728*
No	100 (91.7)	9 (8.3)	109	1.00			
Yes	38 (95)	2 (5)	40	0.59	0.12	2.83	
Clavien Dindo, n (%)							<0.001*
< IIIa	121 (99.2)	1 (0.8)	122	1.00			
≥ IIIa	17 (63)	10 (37)	27	71.18	8.57	591.43	
Hb (g/dL) (A)	13.3±1.9	12.7±1.5	13.3±1.9	0.847	0.636	1.129	0.103**
Ht (%) (A)	39.9±5	38.2±4.5	39.8±5	0.939	0.843	1.047	0.177**
MCV (fL) (A)	88±6.9	89.6±7.5	88.1±7	1.036	0.944	1.137	0.604**
RDW (%) (A)	14.1±1.8	14.1±1.1	14.1±1.8	1.005	0.712	1.419	0.450**
Neut (/uL) (A)	5086.7±2319.8	5543.6±2270.8	5120.9±2311.6	1.000	1.000	1.000	0.515**
Eos (/uL) (A)	253±336	186.4±212.7	248±328.3	0.999	0.996	1.002	0.443**
Lymp (/uL) (A)	1926.8±633	2010.5±1039.9	1933±667.1	1.000	0.999	1.001	0.860**
Plat (nL) (A)	275.6±94.1	266.3±46.5	274.9±91.6	0.999	0.991	1.006	0.911**
MPV (fL) (A)	10.4±1.2	10.3±0.6	10.4±1.2	0.959	0.589	1.560	0.667**
NLR (A)	3.1±3	4.3±4.8	3.2±3.2	1.074	0.949	1.216	0.866**
PLR (x1000) (A)	0.17±0.15	0.22±0.23	0.17±0.15	3.387	0.245	46.9	0.852**
Hb (g/dL) (B)	12.5±1.5	12.3±2	12.5±1.6	0.918	0.621	1.357	0.778**
Hb (g/dL) (B-A)	-0.81±1.82	-0.36±2.02	-0.78±1.83	1.136	0.826	1.562	0.329**
Ht (%) (B)	37.5±4.1	37.2±5.9	37.4±4.3	0.984	0.852	1.138	0.849**
Ht (%) (B-A)	-2.47±5.06	-0.98±5.72	-2.36±5.11	1.055	0.943	1.180	0.337**
MCV (fL) (B)	92.2±6.3	92.5±6.4	92.2±6.3	1.008	0.913	1.112	0.942**
MCV (fL) (B-A)	4.16±4.93	2.91±4.24	4.06±4.88	0.948	0.835	1.077	0.467**
RDW (%) (B)	14.6±2.6	15±1.6	14.7±2.5	1.056	0.862	1.293	0.219**
RDW (%) (B-A)	0.54±2.42	0.96±1.83	0.57±2.38	1.064	0.861	1.315	0.339**
Neut (/uL) (B)	3704.9±1763.7	4063.6±1927.9	3731.6±1771.9	1.000	1.000	1.000	0.532**
Neut (/uL) (B-A)	-1355.2±2305.7	-1480±2372.3	-1364.6±2302.7	1.000	1.000	1.000	0.630**
Eos (/uL) (B)	206.3±239.2	240±389.7	208.8±251.7	1.000	0.998	1.003	0.852**
Eos (/uL) (B-A)	-47.3±279.4	53.6±407.2	-39.7±290.3	1.002	0.999	1.004	0.476**
Lymp (/uL) (B)	1089.9±380	1363.6±668.7	1110.2±411.3	1.001	1.000	1.003	0.281**
Lymp (/uL) (B-A)	-833.6±600.3	-646.8±953.7	-819.5±631.1	1.000	0.999	1.001	0.654**
Plat (nL) (B)	208.9±62.8	243.1±40.9	211.3±62	1.007	0.999	1.017	**0.017****
Plat (nL) (B-A)	-65.7±93.4	-23.2±42.5	-62.8±91.4	1.007	0.998	1.017	0.058**
MPV (fL) (B)	9.97±0.83	9.87±0.95	9.96±0.84	0.870	0.408	1.854	0.282**
MPV (fL) (B-A)	-0.41±1.2	-0.43±0.76	-0.41±1.17	0.984	0.568	1.706	0.837**
NLR (B)	3.94±2.9	3.38±2	3.89±2.84	0.907	0.672	1.223	0.504**
NLR (B-A)	0.84±3.87	-0.97±5.21	0.7±3.99	0.925	0.826	1.035	0.352**
PLR (x1000) (B)	0.21±0.09	0.23±0.12	0.21±0.1	4.632	0.010	2202.1	0.752**
PLR (x1000) (B-A)	0.05±0.17	0.01±0.25	0.04±0.17	0.436	0.029	6.669	0.851**

(A): before neoadjuvant therapy; (B): before surgery. Chi-squared test; *Fisher's exact test; #Likelihood ratio test; ** Mann-Whitney test.

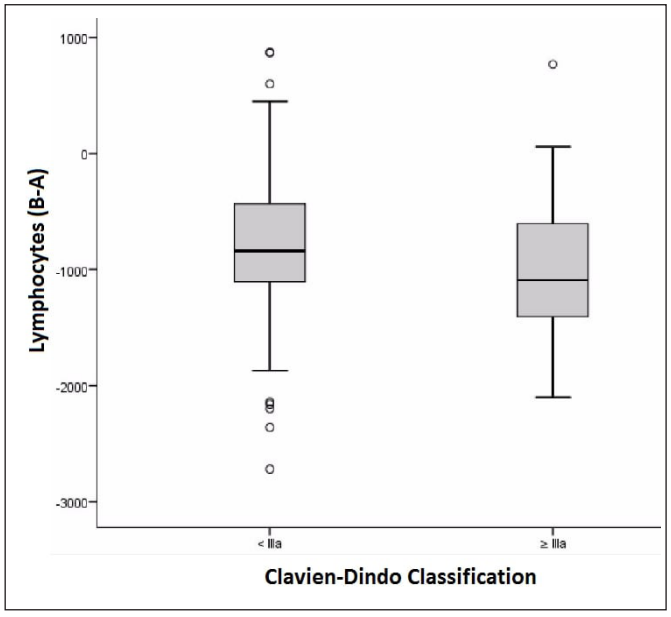

FIGURE 1. Box-plot of lymphocyte change between before surgery period (B) and before neoadjuvant therapy period (A), accordingly to Clavien-Dindo classification. Lymphocytes are expressed in units/μL.

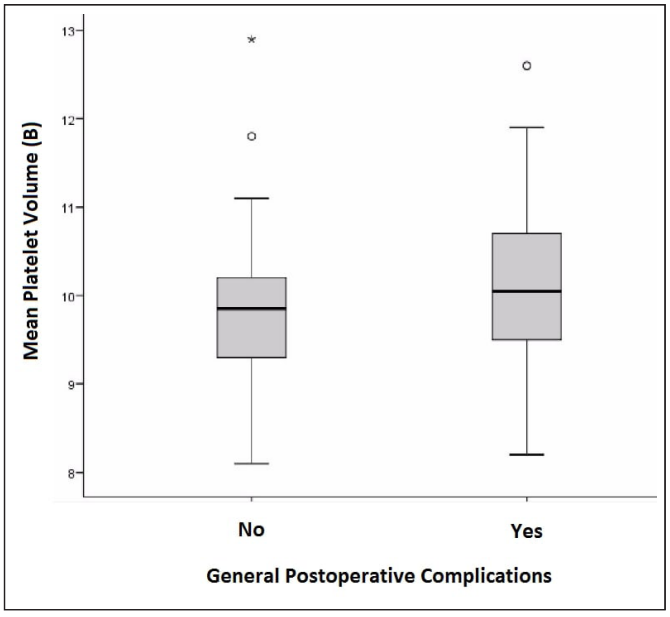

FIGURE 2. Box-plot of mean platelet volume (MPV) before surgery and its relationship with postoperative complications. MPV are expressed in fL.

The role of eosinophils in solid tumors is unclear, and may favor an antitumor inflammatory response, depending on the surrounding stimuli[47-50]. Eosinophils also might contribute to thrombophilia in patients with cancer[51,52]. In the present study, higher eosinophil level, either prior to neoadjuvant therapy or prior to surgery, was related to higher chance of esophageal anastomotic leak on univariate analysis. The effect was not retained on multivariate analysis. This may be attributable to the small sample size of cervical anastomotic leakage.

The results of this study should be interpreted in the context of certain inherent limitations. It is a single-center retrospective study with a relatively small sample size. The low number of complication events and mortality limited the statistical power of the analysis of the results. Also, cellular blood components levels are dynamic and may vary in the same patient from day-to-day. Future controlled prospective studies are warranted to validate the predictive risk models.

Despite these limitations, this is the first study to assess the relationship between peripheral blood count variables changes during neoadjuvant chemoradiotherapy using a platinum- and taxane-based regimen followed by curative intent esophagectomy for esophageal cancer in predicting postoperative complications. Variables of routine blood count are already in use as part of the patient's routine laboratory work for esophageal cancer patients, and are easily assessable, cost-effective, readily available, and can be used as predictive risk factors for postoperative outcomes.

CONCLUSION

The platelet volume prior to surgery is related to postoperative complications and the lymphocyte count change prior to surgery predicts severe postoperative complications in the setting of trimodal therapy for esophageal cancer.

Authors' contribution

Tustumi F: analysis and interpretation of data. Takeda FR: acquisition of data. Brandão AAGS: drafting the article. Sallum RAA: revising the article critically for important intellectual content. Ribeiro Junior U: conception and design of the study. Cecconello I: final approval of the version to be submitted.

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Tustumi F, Takeda FR, Brandão AAGS, Sallum RAA, Ribeiro Junior U, Cecconello I. Linfócitos e volume plaquetário estão associados a complicações pós-esofagectomia por câncer: um estudo de coorte. Arq Gastroenterol. 2019;56(4):377-85.

RESUMO – **Contexto** – Os biomarcadores obtidos do hemograma completo são fatores prognósticos a longo prazo em pacientes com câncer. No entanto, o valor desses biomarcadores no contexto da terapia trimodal para o câncer de esôfago na predição de resultados pós-operatórios precoces não é estudado. **Objetivo** – O presente estudo avaliou o papel dos componentes celulares do sangue na predição de mortalidade e morbidade pós-operatória. **Métodos** – Uma coorte de 149 pacientes consecutivos submetidos à quimiorradioterapia usando esquemas baseados em platina e taxano seguidos por esofagectomia foi analisada. Os componentes celulares do sangue coletados antes da terapia neoadjuvante (período A) e antes da cirurgia (período B) foram avaliados quanto à mortalidade e complicações pós-operatórias. Modelos de regressão de Cox univariada e multivariada foram aplicados para avaliar a significância prognóstica independente das variáveis da contagem sanguínea. **Resultados** – A morbidade pós-operatória esteve presente em 46% dos pacientes. Na análise de regressão múltipla, o volume plaquetário (B) (OR: 1,53; IC95%: 1,2–2,33) foi um preditor independente de complicações gerais. Complicações cirúrgicas pós-operatórias graves estavam presentes em 17% dos pacientes. Na análise de regressão múltipla, a diminuição de linfócitos entre os períodos B-A (OR: 0,992; 95% CI: 0,990–0,997) esteve relacionada ao maior risco de complicações graves. Fístula da anastomose cervical esteve presente em 25,6% dos pacientes. Na análise univariada, a contagem de eosinófilos nos períodos A e B relacionou-se com a fístula da anastomose cervical. Para este resultado, o modelo multivariado de articulação não conseguiu identificar variáveis de risco independentes entre os componentes celulares do sangue. A taxa de mortalidade em 30 dias foi de 7,4%. Na análise univariada, a contagem no período B foi associada a maior risco de mortalidade. O modelo multivariado de articulação não pôde predizer mortalidade devido ao pequeno número de pacientes no grupo de mortalidade. **Conclusão** – Este é o primeiro estudo a avaliar o papel das variáveis do hemograma durante a quimiorradioterapia neoadjuvante para câncer na predição de complicações pós-operatórias. Volume plaquetário e variação da contagem de linfócitos séricos antes da cirurgia podem ser utilizados como biomarcadores preditivos de complicações pós-operatórias nos pacientes com neoplasia de esôfago submetidos a terapia trimodal.

DESCRITORES – Neoplasias esofágicas. Terapia neoadjuvante. Células sanguíneas. Leucócitos. Plaquetas. Linfócitos. Neutrófilos.

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