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Survival and prognostic analysis of preoperative indicators in patients undergoing surgical resections with rhabdomyosarcoma

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Abstract

Several preoperative blood and biochemical parameters are associated with postoperative survival in many kinds of tumors. The aim of this study is to study the predictive value of several routine preoperative blood and biochemical parameters on the prognosis patients with rhabdomyosarcoma (RMS).

We retrospectively recruited 55 patients diagnosed with RMS and had surgery at West China Hospital, Sichuan University between January 2010 and December 2018. Baseline characteristics of the patients, tumor features, surgery details, and values of several examinations were extracted. A long-term follow-up was conducted by phone call. A novel statistical analysis was subsequently carried out to look for the relationship of preoperative parameters and patients' prognosis.

The ROC analysis showed an area under curve (AUC) of 0.608, 0.620, 0.626, 0.591, and 0.518 for neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), lactic dehydrogenase (LDH), and alkaline phosphatase (ALP) respectively, and the cut-off value of 2.843, 162.961, and 0.239 for NLR, PLR, and MLR respectively. The survival analysis showed that certain blood and biochemical parameters could cause differences in overall survival (OS) ($P = .005$ for NLR, $P = .005$ for PLR, and $P = .007$ for MLR) and progression free survival (PFS) ($P = .029$ for NLR, $P = .008$ for PLR, and $P = .013$ for MLR).

Several preoperative blood and biochemical parameters are novel prognostic factors in RMS patients. Specifically, a higher NLR, PLR, and MLR value will predict a statistically shorter OS and PFS.

In the future, surgeons should care more about NLR, PLR, and MLR values and several other parameters in patients' preoperative normal blood and biochemical tests to predict the postoperative conditions.

Abbreviations: AJCC = American Joint Committee on Cancers, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ARMS = alveolar rhabdomyosarcoma, AST = aspartate transferase, AUC = area under curve, ERMS = embryonal rhabdomyosarcoma, HR = hazard ratio, LDH = lactic dehydrogenase, MLR = monocyte to lymphocyte ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression-free survival, PLR = platelet to lymphocyte ratio, RMS = rhabdomyosarcoma, ROC = receiver operating characteristics, SD = standard deviation, WBC = white blood cell.

Keywords: blood and biochemical parameters, overall survival, prognostic factors, progression free survival, rhabdomyosarcoma

1. Introduction

Rhabdomyosarcoma (RMS) is recognized as the most universal sarcoma in children under 15 years old, which takes up over 50% of all soft tissue sarcoma and 4.5% of all malignancies in children.[1,2] Meanwhile, it's reported that an approximate 350 children are eventually diagnosed with RMS in the United States alone.[3] Due to the severity and vulnerability of RMS, wide attention has been focused on its pre-clinical research, diagnosis, treatment, and prognosis.[4] In 2013, the World Health Organization (WHO) pathologically divided RMS into several subgroups, including spindle cell/sclerosing, pleomorphic, alveolar rhabdomyosarcoma (ARMS), and embryonal rhabdomyosarcoma (ERMS).[5] Types of RMS were correlated with distinct and different prognosis. Another report suggested that high variability in site, size, histology, differentiation, and clinical behavior of the original tumors contributed to the complexity of long-term management.[6] Fortunately, with the advancement in molecular biology, risk stratification, and targeted appropriate tailor therapy, it became easier to enact a well-rounded, targeted, personal, and highly-effective therapy.[7]

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HJ and MZ contributed equally to this work.

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Thanks to the advancement of diagnostic technologies, precise classification of the tumor's biological features, and subsequent standard treatment can be obtained.[8] Therefore, a couple of standard technologies in treatment have also been developed. To be specific, chemotherapy, new adjuvant therapy, radiology and biotherapy immunotherapy are the most highly-recommended non-surgical strategies.[9] Still, surgery remains the best possible way to manage early- and medium-stage and regionally limited malignancies, especially in tumors located in the upper and lower extremities and the retroperitoneal cavity are best recommended.[10,11] Hence, a standard perioperative management schedule should be established, therefore special attention to certain prognosis-related procedures should be paid. In other words, prognostic factors which can be obtained preoperatively are ought to be found and evaluated.

To our regret, insufficient parameters which could predict postoperative outcomes have been determined, which prevented surgeons to take necessary measurements and predict prognosis before surgery. Among these, some parameters reflecting the inflammatory response and biochemical values have been proved to have such correlation with prognosis in several types of tumors.[12–14] The most widely known correlation is the one between the value of lactic dehydrogenase (LDH) and prognosis of patients with most types of lymphoma.[15] As is all known, inflammatory response plays an important role in tumor activity, since this process attracts and releases inflammatory cells and secrets significant chemicals.[16] In the meantime, tumorigenesis and tumor development depend on a certain degree of inflammatory response and needs to be mediated by immune cells and molecules.[17] Therefore, core cells in the immune system, such as neutrophils, monocytes, platelets, white blood cells (WBC), lymphocytes, and other cells can largely have an impact on tumor behavior and thus influence disease outcome. Previous studies on other tumors have pointed out several ratios were correlated with tumor prognosis, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte (PLR), and monocyte to lymphocyte (MLR), etc.[18,19] Thus, our study recruited 55 patients diagnosed with RMS at West China Hospital, Sichuan University from January 2010 to December 2018 to identify the correlation between these important blood and biochemical parameters.

2. Methods

2.1. Patient selection

In order to recruit as many patients as we could, we retrospectively analyzed the clinical records of 87 patients diagnosed with RMS and treated at West China Hospital, Sichuan University between January 2010 and December 2018. Strict inclusion and exclusion criteria were subsequently proposed to limit the heterogeneity of patients. Three investigators were assigned to carefully analyze patients' clinical records to meet the set inclusion and exclusion criteria. The inclusion criteria included: having at least 1 surgery; the surgical records as well as the pathological records could be traced whether at West China Hospital, Sichuan University or at other hospitals; patients with pathologically diagnosed evidence. The main exclusion criteria included: having surgeries elsewhere and surgical records were not able to be collected; patients who did not receive surgery; patients with incomplete follow-up so that their living status could not be determined. After a strict selection process, a total of 55 patients were enrolled into this study. All the 55 patients were from China, with 35 men and 20 women. Our study strictly conformed to the Declaration of Helsinki (2013) of the World Medical Association. Our study was approved by the Ethics Committee of West China Hospital, Sichuan University. The authors had no access to information that could identify individual participants during or after data collection

2.2. Clinical data collection

After defining the exact number of patients to be recruited, we collected the parameters from the clinical records system. In general, the baseline characteristics of the patients (age, sex, etc), the features of the tumor, the information concerning the surgery, the results of important clinical blood and biochemical tests were extracted. The T-stage, N-stage, M-stage, TNM-stage by AJCC (American Joint Committee on Cancers) were extracted to reflect the features of the tumors. The date, pathway of surgery, whether there was a combined chemotherapy, radiotherapy, adjuvant therapy, biochemical therapy, and immunotherapy were extracted to reflect the treatment options. The values of alanine aminotransferase (ALT), aspartate transferase (AST), LDH, alkaline phosphatase (ALP), neutrophil count, platelet count, lymphocyte count, monocyte count, hemoglobin, albumin of the last examination before the surgery were collected.

2.3. Postoperative follow-up

Since discharge, we conducted a long-term follow-up for 8 years at most by phone call. The follow-up was performed to every patient each month. The follow-up collected the patient's general condition, postoperative recovery, tests' results during reexamination in hospitals, suspected symptoms, life quality, etc. Subsequently, we determined the date of progression and date of death.

2.4. Statistical analysis

We calculated the OS and PFS according to the date of diagnosis, date of progression, and date of death. The OS and PFS were recorded by months. Then we generated a receiver operating characteristic (ROC) curve based on survival data and NLR, PLR, MLR, LDH, and ALP values to determine a cut-off point for these parameters. Then we applied the Kaplan–Meier method and the log-rank test to come up with the survival curves by both OS and PFS. We subsequently compared the differences in survival data between groups. Finally, we used cox proportional hazards regression to calculate the hazard ratios (HRs) by multivariate and univariate analyses respectively to look for potential validated indicators. We also did a Chi-squared-analysis to determine the heterogeneity of NLR, PLR, and MLR values in subgroups divided by age, sex, T-stage, N-stage, M-stage, TNM-stage by AJCC, ALT, AST, LDH, ALP, neutrophil count, platelet count, lymphocyte count, monocyte count, hemoglobin value, and albumin value.

The results were all standardly presented as mean ± SEM, *P*-value was considered statistically significant when $P < .05$. We then evaluated their clinical significance according to specific circumstances. All data analyses were performed using SPSS22.0 (IBM, the USA).

3. Results

3.1. Patients characteristics

We finally recruited 55 patients diagnosed with RMS and had at least 1 surgery at West China Hospital, Sichuan University. In the

55 patients, 35 were men and 20 were women. Among them, 39 patients were under 30 years old and 16 were over 30 years old. In T-stage classification, 26 patients were stage T_{1a} or T_{1b}; 23 patients were stage T_{2a} or T_{2b}, and only 6 patients were stage T_3. In N-stage classification, 27 patients were stage N_0 indicating no lymph node metastasis and 28 patients were stage N_1. In M-stage analysis, 34 patients were M_0 indicating no distant metastasis and 21 patients were M_1. In AJCC classification, 12 patients were determined as stage Ia or Ib; 13 patients were determined as stage IIa or IIb; 12 patients were stage III; and 17 patients were IV. The detailed information of the patients recruited were shown in Table 1.

The mean of NLR, PLR, and LMR of non-survival group were 4.12, 192.30, and 3.25 respectively. The standard deviation (SD) of NLR, PLR, and LMR of non-survival group were 2.84, 108.81, and 1.55 respectively. The mean of NLR, PLR, and LMR of survival group were 2.82, 139.10, and 5.23 respectively. The SD of NLR, PLR, and LMR of survival group were 3.12, 95.39, and 5.23 respectively. The mean of NLR, PLR, and LMR of progression-free group were 3.33, 154.78, and 4.84 respectively. The SD of NLR, PLR, and LMR of progression-free group were 3.92, 112.06, and 2.74 respectively. The mean of NLR, PLR, and LMR of progression group were 3.33, 154.78, and 4.84 respectively. The SD of NLR, PLR, and LMR of progression group were 3.92, 112.06, and 2.74 respectively.

In Chi-squared analysis, heterogeneity of NLR between subgroups was not influenced by age ($P=.808$), sex ($P=.520$), T-stage ($P=.826$), N-stage ($P=.452$), M-stage ($P=.663$), TNM-stage by AJCC ($P=.829$), ALT ($P=.159$), AST ($P=.395$), LDH ($P=.586$), platelet count ($P=.247$), lymphocyte count ($P=.473$), monocyte count ($P=.178$), and hemoglobin ($P=.156$). Heterogeneity of NLR between subgroups was influenced by ALP ($P=.023$), neutrophil count ($P<.001$), and albumin value ($P=.028$). Heterogeneity of PLR was not affected by age ($P=.123$), sex ($P=.218$), T-stage ($P=.826$), N-stage ($P=.853$), M-stage ($P=.109$), TNM-stage by AJCC ($P=.085$), ALT ($P=.449$), AST ($P=.119$), LDH ($P=.449$, ALP ($P=.263$), neutrophil count ($P=.495$), platelet count ($P=.247$), lymphocyte count ($P=.088$), monocyte count ($P=.722$), and albumin value ($P=.115$). Heterogeneity of PLR was affected by hemoglobin ($P=.026$). Meanwhile, MLR heterogeneity was not influenced by age ($P=.303$), sex ($P=.959$), T-stage ($P=.612$), N-stage ($P=.076$), M-stage ($P=.171$), TNM-stage by AJCC ($P=.113$), ALT ($P=.692$), AST ($P=.498$), LDH ($P=.692$), ALP ($P=.058$), neutrophil count ($P=.162$), platelet count ($P=.912$), lymphocyte count ($P=.231$), monocyte count ($P=.140$), and hemoglobin

Table 1

Baseline characteristics and preoperative values of clinical examinations.

			NLR			PLR			MLR		
N=55		Total n (valid percentage)	<2.843	>2.843	P	<162.96	>162.96	P	<0.239	>0.239	P
Age	< 30	39	24	15	P=.808	28	11	P=.123	23	16	P=.303
	≥30	16	12	4		8	8		7	9	
Gender	Male	35	24	11	P=.520	25	10	P=.218	19	16	P=.959
	Female	20	12	8		11	9		11	9	
T	1a, 1b	26	18	8	P=.826	18	8	P=.826	16	10	P=.612
	2a, 2b	23	14	9		14	9		11	12	
	3	6	4	2		4	2		3	3	
N	0	27	19	8	P=.452	18	9	P=.853	18	9	P=.076
	1	28	17	11		18	10		12	16	
M	0	34	23	11	P=.663	25	9	P=.109	21	13	P=.171
	1	21	13	8		9	10		13	12	
TNM-stage	Ia, Ib	12	9	3	P=.812	9	3	P=.088	8	4	P=.109
	IIa, IIb	13	9	4		9	4		10	3	
	III	9	6	3		8	1		5	4	
	IV	21	12	9		9	12		8	13	
ALT	≤40	41	29	12	P=.159	28	13	P=.449	23	18	P=.692
	>40	14	7	7		13	6		7	7	
AST	≤40	44	30	14	P=.395	31	13	P=.119	25	19	P=.498
	>40	11	6	5		5	6		5	6	
LDH	≤245	41	26	15	P=.586	28	13	P=.449	23	18	P=.692
	>245	14	10	4		8	6		7	7	
ALP	≤110	32	17	15	P=.023	19	13	P=.263	14	18	P=.058
	>110	23	19	4		17	6		16	7	
Neutrophil cell count	≤7.5	46	35	11	P<.001	31	15	P=.495	27	19	P=.162
	>7.5	9	1	8		5	4		3	6	
Platelet count	≤300	40	28	12	P=.247	28	12	P=.247	22	18	P=.912
	>300	15	8	7		8	7		8	7	
Lymphocyte count	≤4	50	32	18	P=.473	31	19	P=.088	26	24	P=.231
	>4	5	4	1		5	0		4	1	
Monocyte count	≤0.8	48	33	15	P=.178	31	17	P=.722	28	20	P=.140
	>0.8	7	3	4		5	2		2	5	
Hemoglobin	≤150	47	29	18	P=.156	28	19	P=.026	23	24	P=.043
	>150	8	7	1		8	0		7	1	
Albumin	≤55	39	22	17	P=.028	23	16	P=.115	18	21	P=.051
	>55	16	14	2		13	3		12	4	

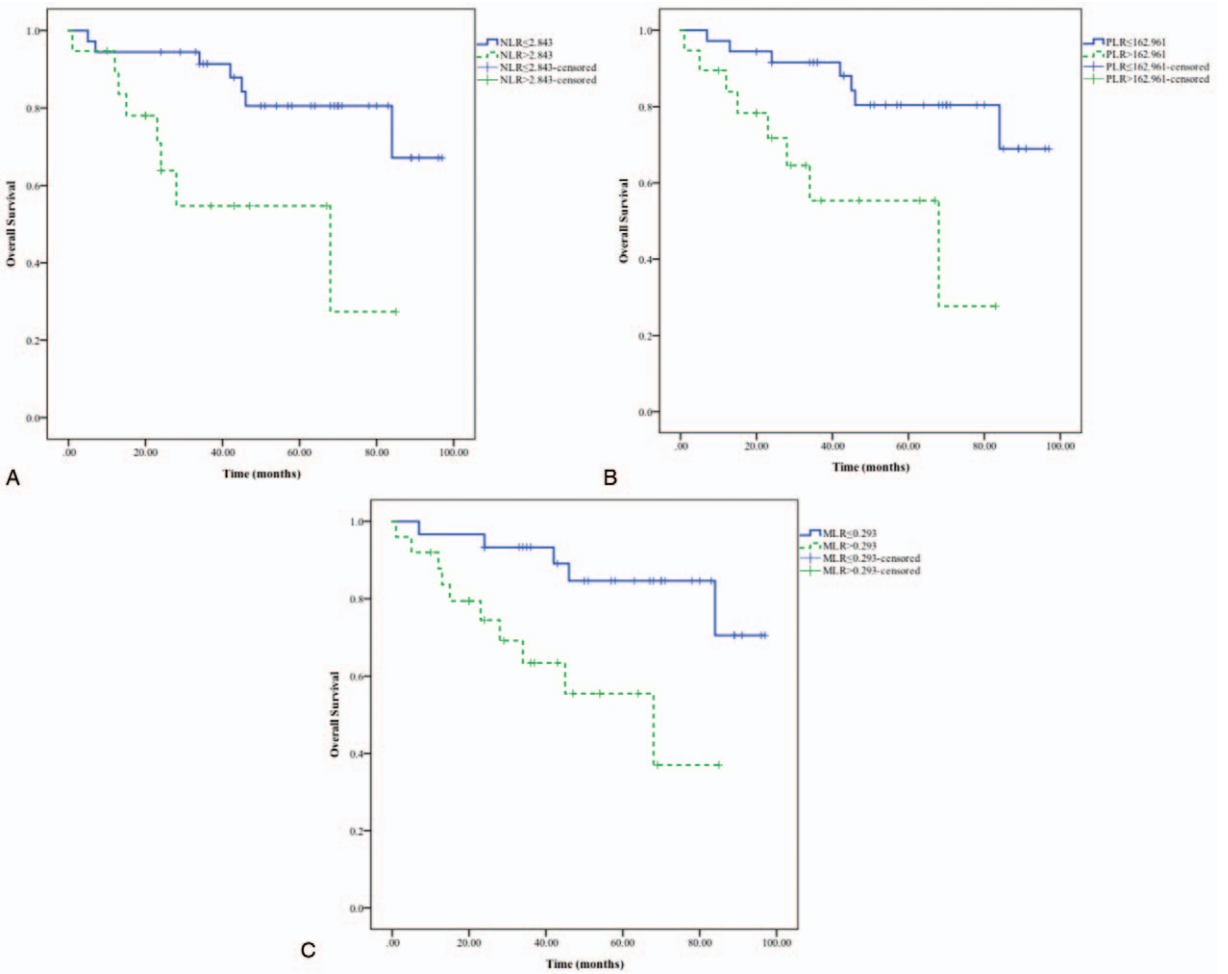

Figure 1. (A). Overall survival of NLR ≤2.843 and NLR >2.843 group (36 and 19 patients, respectively). (B). Overall survival of PLR ≤162.961 and PLR >162.961 group (36 and 19 patients, respectively). (C). Overall survival of MLR ≤0.293 and MLR >0.293 group (30 and 25 patients, respectively).

(P=.051). MLR heterogeneity was affected by hemoglobin (P=.043).

3.2. ROC analysis

In order to examine the proper cut-off values of NLR, PLR, MLR, LDH, and ALP, the exact values of NLR, PLR, MLR, LDH, and ALP and the living status were incorporated in order to generate the ROC curves. During the process, we deemed the cancer related deaths as the end point. Statistically, the area under curve (AUC) of NLR, PLR, MLR, LDH, and ALP were 0.608, 0.620, 0.626, 0.591, and 0.518. We found the AUCs of NLR, PLR, MLR, LDH, and ALP were all over 0.5, therefore theoretically, they could serve as satisfactory potential biomarkers. However, the AUCs of LDH and ALP were just above 0.5, thus we did not treat these 2 parameters as potential biomarkers to avoid unconscious mistakes. Subsequently, the appropriate cut-off values were calculated, which were 2.843, 162.961, 0.239 for NLR, PLR, and MLR respectively according to the maximum specificity and sensitivity.

3.3. Prognostic indicator analysis

After confirming the optimal cut-off values of NLR, PLR, and MLR, we generated Kaplan–Meier curve for both OS and PFS. The Kaplan–Meier curves of NLR (≤2.843, >2.843), PLR (≤162.961, >162.961), and MLR (≤0.239, >0.239) for OS were shown in Fig. 1A–C. Accordingly, we calculated statistical P values which reflected the statistical differences of OS between subgroups, which were .005, .005, and .007 for NLR, PLR, and MLR respectively. In other words, subgroups with different values of NLR, PLR, and MLR led to a statistically distinct OS. Therefore, to some extent, NLR, PLR, and MLR could serve as potential biomarkers for the prediction of OS and general postoperative performance.

With the same means, the Kaplan–Meier curves of NLR (≤2.843, >2.843), PLR (≤162.961, >162.961), and MLR (≤0.239, >0.239) for PFS were also generated and shown in Fig. 2A–C. Accordingly, we calculated statistical P values which reflected the differences of PFS between subgroups, which were .029, .008, and .013 for NLR, PLR, and MLR respectively. In other words, subgroups with different values of NLR, PLR, and MLR contributed to a statistically distinct PFS. Hence, NLR, PLR, and MLR could also serve as promising biomarkers for the postoperative PFS and general postoperative outcomes.

So, we supposed that preoperative blood indicators including NLR, PLR, and MLR were satisfactory and efficient factors to predict prognosis reflected by OS. Meanwhile, we also believed that preoperative blood indicators including NLR, PLR, and

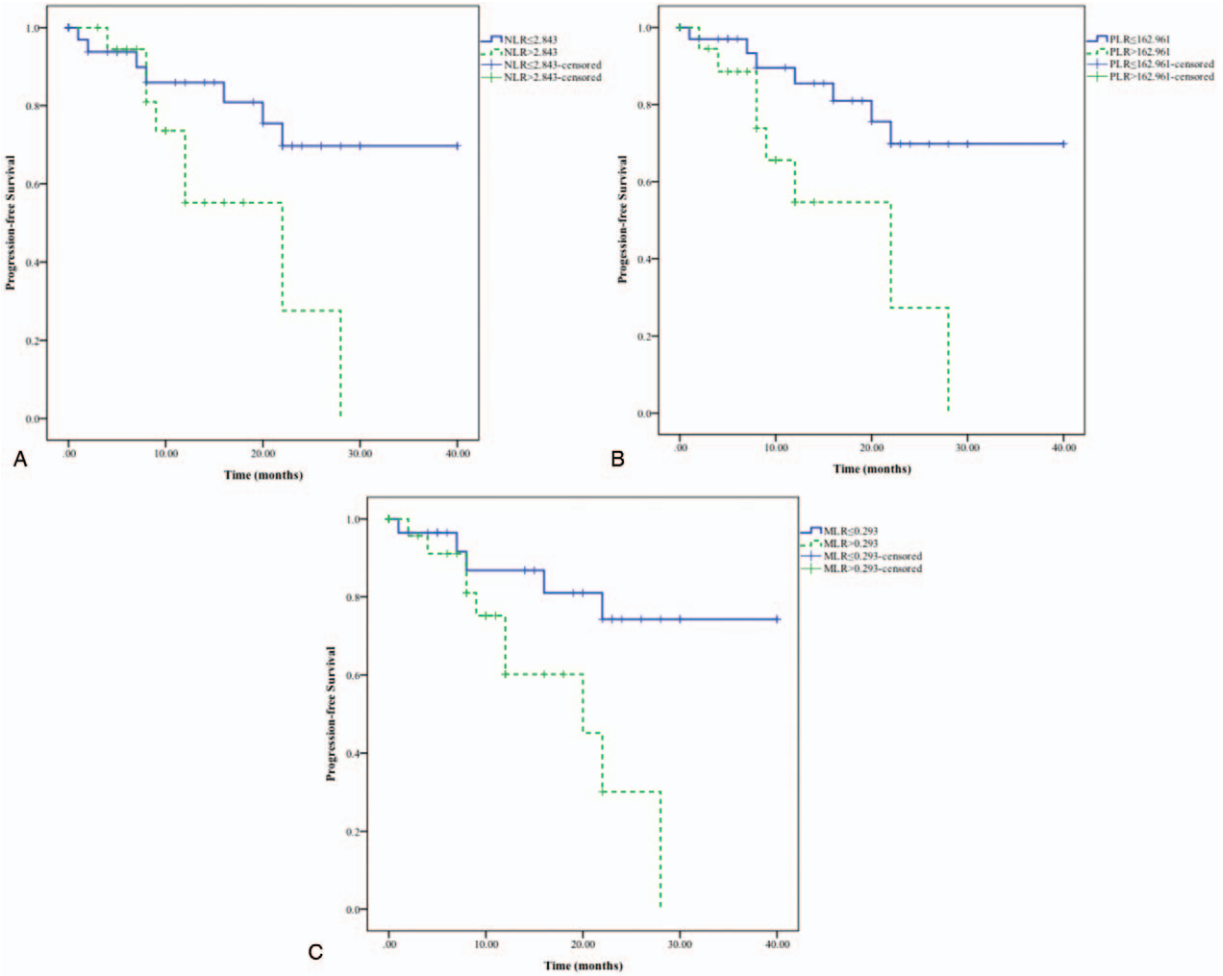

Figure 2. (A). Progression free survival of NLR ≤2.843 and NLR >2.843 group (36 and 19 patients, respectively). (B). Progression-free survival of PLR ≤162.961 and PLR >162.961 group (36 and 19 patients, respectively). (C). Progression-free survival of MLR ≤0.34 and MLR >0.34 group (30 and 25 patients, respectively).

MLR were also satisfactory and efficient factors to predict prognosis reflected by PFS.

3.4. Prognostic values of other parameters

Besides the abovementioned parameters in blood tests, we speculated that there might be other parameters that could have an impact on postoperative OS. Therefore, we applied Cox analysis to calculate the HRs by both multivariate and univariate analytic methods. The outcomes of the Cox analysis were shown in Table 2.

In univariate analysis, no statistical correlation was found between age (HR = 0.943, *P* = .920), sex (HR = 0.985, *P* = .978), TNM-stage by AJCC (HR = 1.578, *P* = .073), ALT (HR = 1.090, *P* = .884), LDH (HR = 1.860, *P* = .240), APT (HR = 1.266, *P* = .653), neutrophil count (HR = 1.266, *P* = .653), platelet count (HR = 1.871, *P* = .263), monocyte count (HR = 0.652, *P* = .682), hemoglobin (HR = 0.771, *P* = .734), albumin (HR = 1.549, *P* = .407), and postoperative OS. Statistical association was determined between WBC count (HR = 3.269, *P* = .035), NLR (HR = 4.017, *P* = .009), PLR (HR = 4.156, *P* = .010), MLR (HR = 4.106, *P* = .012), and postoperative OS.

In multivariate analysis, no statistical correlation was found between age (HR = 2.107, *P* = .481), sex (HR = 0.403, *P* = .298), TNM-stage by AJCC (HR = 1.911, *P* = .198), ALT (HR = 0.112, *P* = .127), AST (HR = 0.677, *P* = .737), LDH (HR = 2.741, *P* = .311), APT (HR = 15.393, *P* = .081), platelet count (HR = 0.900, *P* = .918), WBC count (HR = 0.334, *P* = .502), hemoglobin (HR = 5.911, *P* = .280), NLR (HR = 11.729, *P* = .134), PLR (HR = 2.235, *P* = .420), and postoperative OS. Statistical association was determined between neutrophil count (HR = 66.710, *P* = .008), monocyte count (HR = 0.023, *P* = .016), albumin (HR = 9.043, *P* = .037), MLR (HR = 11.218, *P* = .019), and postoperative OS.

4. Discussion

RMS is the most common soft tissue sarcoma among children, having a great impact on childhood development. With the development of diagnostic and treatment technologies, several brand-new options have been put forward for the long-term and whole-length management of RMS. These emerging technologies included combined chemotherapy, radiotherapy, adjuvant therapy, molecular therapy, biotherapy, and immunotherapy as well as separated ones. Despite the advancement of these assistant therapies, surgery still remains the best first-line treatment for early diagnosed RMS and in patients with low- or medium-stage

Table 2

Influence of age, gender, TNM-stage, ALT, AST, LDH, APT, neutrophil count, platelet count, WBC count, monocyte count, hemoglobin, albumin, NLR, PLR, MLR on overall survival by univariate and multivariate analysis.

		Univariate analysis		Multivariate analysis	
Variables	**Parameter**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age	≤30	1.00		1.00	
	>30	0.943 (0.298–2.982)	.920	2.107 (0.265–16.715)	.481
Gender	Female	1.00		1.00	
	Male	0.985 (0.335–2.898)	.978	0.403 (0.073–2.235)	.298
TNM-stage	Ia, Ib	1.00		1.00	
	IIa, IIb				
	III				
	IV	1.578 (0.958–2.599)	.073	1.911 (0.712–5.126)	.198
ALT	≤40	1.00		1.00	
	>40	1.090 (0.346–3.431)	.884	0.112 (0.007–1.871)	.127
AST	≤40	1.00		1.00	
	>40	1.948 (0.608–6.242)	.261	0.677 (0.070–6.581)	.737
LDH	≤245	1.00		1.00	
	>245	1.860 (0.660–5.245)	.240	2.741 (0.389–19.302)	.311
APT	≤110	1.00		1.00	
	>110	1.266 (0.452–3.541)	.653	15.393 (0.716–330.954)	.081
Neutrophil count	≤7.5	1.00		1.00	
	>7.5	1.266 (0.452–3.541)	.653	66.710 (2.934–1516.896)	.008
Platelet count	≤300	1.00		1.00	
	>300	1.871 (0.625–5.602)	.263	0.900 (0.122–6.661)	.918
WBC count	≤9.5	1.00		1.00	
	>9.5	3.269 (1.088–9.820)	.035	0.334 (0.014–8.207)	.502
Monocyte count	≤0.8	1.00		1.00	
	>0.8	0.652 (0.085–5.009)	.681	0.023 (0.001–0.500)	.016
Hemoglobin	≤150	1.00		1.00	
	>150	0.771 (0.173–3.438)	.734	5.911 (0.236–148.110)	.280
Albumin	≤55	1.00		1.00	
	>55	1.549 (0.551–4.358)	.407	9.043 (1.137–71.912)	.037
NLR	≤2.843	1.00		1.00	
	>2.843	4.017 (1.415–11.407)	.009	11.729 (0.470–292.880)	.134
PLR	≤162.961	1.00		1.00	
	>162.961	4.156 (1.413–12.228)	.010	2.235 (0.295–18.643)	.420
MLR	≤0.239	1.00		1.00	
	>0.239	4.106 (1.366–12.340)	.012	11.218 (1.478–85.112)	.019

ALT = alanine aminotransferase, APT = alkaline phosphatase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase, MLR = monocyte to lymphocyte ratio, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio.

RMS or with RMS limited to a constricted region.[20] Moreover, new approaches and routes have also been developed in tumors located at different parts of the body.[11] Therefore, the contraindications for surgery have decreased over the years. With this regard, more RMS patients were provided with the opportunity and possibility of a radical surgery.[21] Hence, it is emergent to continuously develop the surgical capacity and innovative surgical approaches as well as to better the perioperative care and management. This management includes the choice of aided treatment with surgery and the preoperative prediction of postoperative outcome and body condition.

Our research recruited 55 pathologically diagnosed RMS patients and explored the possibility of defining several preoperative parameters that could have predictive values on postoperative survival outcome. By this means, our conclusion made it possible to predict the patients' status relying on simple and inexpensive preoperative examination results. By generating the Kaplan–Meier curves, we found that preoperative NLR, PLR, and MLR values had the tendency to affect postoperative OS. The higher the NLR, PLR, and MLR values were, the shorter OS were more likely to be observed, with a statistically concrete satisfactory *P*-value of .005, .005, and .007 respectively. In the meantime, the Kaplan–Meier curves on PFS also showed that NLR, PLR, and MLR values were likely to predict postoperative PFS. In detail, a higher NLR, PLR, and MLR value had the tendency to witness a shorter postoperative PFS with a statistical *P*-value of .029, .008, and .013 respectively. Since NLR, PLR, and MLR can be calculated based on the exact value of neutrophil count, platelet count, monocyte count, and lymphocyte count, it is easy to assess the abovementioned parameters with high prognostic stability and reliability. Thus, we recommended that not only values reflected by common blood routine examination but also the calculation of NLR, PLR, and MLR should be considered as the routine preoperative procedures of such patients.

Besides, we used Cox analysis to generate the HRs of independent preoperative risk factors which were likely to have the potential to predict the postoperative OS in RMS patients. Our statistical analysis found that WBC count, NLR value, PLR value, and MLR value were independent prognostic factors for RMS patients. Detailed analysis indicated that a higher WBC, NLR, PLR, and MLR value were more likely to predict a

statistically shorter OS. On the contrary, in univariate analysis, age, sex, TNM-stage by AJCC, ALT, AST, LDH, ALP, neutrophil count, platelet count, monocyte count, hemoglobin count, and albumin count were not regarded as independent risk factors. And in multivariate analysis, we found neutrophil count, monocyte count, albumin value, and MLR value were prognostic factors for postoperative OS. Specifically, a higher neutrophil count, albumin and MLR value and a lower monocyte count contributed to a statistically significant shorter OS. Hence, these significant preoperative indicators by univariate and multivariate analysis should also be considered to be done preoperatively as routine examination.

Inflammatory response has long been correlated with tumorigenesis and tumor development and the cells and molecular mediators have also been studied to look for their roles in inflammatory reaction and subsequent tumor activity.[22] So far, quite a number of tumors have been proved to have an inflammatory cell- and molecule-related prognosis manifested by OS and PFS.[23] In 2016, a team suggested that a comprehensive role of PLR, NLR, MLR, and tumor size were valuable to predict the survival status for gastrointestinal stromal tumors.[24] In 2017, some physicians found that NLR value was an independent preoperative prognostic factor in bladder cancer patients undergoing transurethral resection.[25] In the same year, another study confirmed that NLR, MPV, and platelet count were correlated with postoperative survival.[26] In the meantime, a couple of animal research and review articles also paid great attention to similar relationships and the inner mechanism.[27]

Neutrophils, monocytes, and lymphocytes are regarded as important elements in both the innate and adaptive immune response, playing a big role in the direct elimination of harmful substances, the secretion and mediation of chemokines and molecules, and the cascade activation of a series of cells and activities.[28,29] Platelets were previously understood as a core element in blood coagulation and thrombus formation process, but presently platelets are also considered to release several kinds of pro-inflammatory or inflammatory molecules which are essential in the cascade reaction.[30] In other words, besides coagulation, platelets also interact with various elements in the immune systems.

Neutrophils are believed to work in the first-line reaction of innate immune response by direct elimination.[31] Some studies pointed out neutrophil were able to form a specific tumor microenvironment by secreting various molecules and activating a series of cells.[32] Neutrophils are believed to get attracted by chemicals secreted by tumors and therefore manifest tropism to tumor regions.[33] After accumulating at tumor sites, the neutrophils provided suitable growing ground for tumor cells, thus extending the life span of tumor cells.[34] Moreover, neutrophils were able to help tumor cells to detach on organs and tissues and also help tumor cells to disseminate. Platelet and platelet-related parameters have also been proved to be novel prognostic indicators.[35] Increasing evidence pointed out platelets were able to attach on the tumor cells thus forging a protective sheath around the tumor so that it became relatively difficult for surveillance cells to detect tumor signals released by receptors and ligands on the surface of tumor cells.[36] In another aspect, monocytes were also reported to be engaged in tumor development. As was reported, monocytes were able to differentiate into tumor-associated macrophages which mediated the tumorigenesis and tumor developing process.

As far as we are concerned, an elevated NLR value refers to either an elevated neutrophil count or a decreased lymphocyte count. Since lymphocytes play important roles in immune elimination and surveillance, both of the conditions will lead to a more fitting condition for tumorigenesis and tumor progression. Similarly, an increasing PLR indicates either an increasing platelet count or a diminished lymphocytes count. These conditions are also preferable for tumorigenesis and tumor progression. Equally, an elevated MLR reflected an elevated monocyte count or a decreased lymphocyte count, which still contributed to tumor development.

To the best of our knowledge, this is the first study to investigate the predictive values of several preoperative blood and biochemical parameters on the prognosis in patients with RMS. Our study found out that several routine preoperative blood and biochemical parameters were novel indicators for the prediction of postoperative OS and PFS, including NLR, PLR, and MLR. This could help better the perioperative and whole-length management of RMS patients. Moreover, our results could remind researchers who investigate the inner mechanisms of the inflammatory cells in tumors alike.

Nevertheless, we did acknowledge that there were several shortcomings in our study. Firstly, we recruited a rather small number of patients, which might have contributed to unconscious bias. Secondly, our research was only a single-center study, most patients we included were southwest inhabitants in China. Therefore, we believe studies recruiting larger number of patients especially patients from different regions would be more convincing to verify the prognostic role of such parameters.

5. Conclusion

NLR, PLR, and MLR are novel prognostic factors in RMS patients. To be specific, a higher NLR, PLR, and MLR value are likely to predict a statistically shorter OS and PFS. At the same time, WBC count, NLR, PLR, MLR, neutrophil count, monocyte count, albumin and MLR are also associated with the long-term survival outcome.

Author contributions

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References

[1] Gosiengfiao Y, Reichek J, Walterhouse D. What is new in rhabdomyosarcoma management in children? Paediatr Drugs 2012;14:389–400.

[2] Borinstein SC, Steppan D, Hayashi M, et al. Consensus and controversies regarding the treatment of rhabdomyosarcoma. Pediatr Blood Cancer 2018;65:
[3] Soffer S, Amitai MM, Shimon O, et al. Rhabdomyosarcoma disease spread evaluation on CT scans: association with primary tumor size and Ki-67 proliferation marker. Clin Imaging 2019;56:41–6.
[4] Liu YT, Wang CW, Hong RL, et al. Prognostic factors and treatment outcomes of adult patients with rhabdomyosarcoma after multimodality treatment. Anticancer Res 2019;39:1355–64.
[5] Ballinger ML, Goode DL, Ray-Coquard I, et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. Lancet Oncol 2016;17:1261–71.
[6] Childhood Rhabdomyosarcoma Treatment (PDQ(R)): Patient Version. *PDQ Cancer Information Summaries*. Bethesda, MD; 2002.
[7] Pal A, Chiu HY, Taneja R. Genetics, epigenetics and redox homeostasis in rhabdomyosarcoma: emerging targets and therapeutics. Redox Biol 2019;25:110–24.
[8] Ahmad TY, Al Houri HN, Al Houri AN, et al. Aggressive recurrent orbital rhabdomyosarcoma in adulthood. Avicenna J Med 2019;9: 37.
[9] Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. Nat Rev Dis Primers 2019;5:1.
[10] Phelps HM, Lovvorn HN3rd. Minimally invasive surgery in pediatric surgical oncology. Children (Basel) 2018;5:158.
[11] Koivusalo AI, Rintala RJ, Pakarinen MP. Combined management of perianal rhabdomyosarcoma with chemotherapy, radical surgery, and irradiation: a series of three consecutive children. J Pediatr Surg 2019;54:285–7.
[12] Amaral SR, Casal Moura M, Carvalho J, et al. 6PPrognostic significance of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors. Ann Oncol 2019;30:i3.
[13] Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, et al. Combined diagnostic efficacy of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) as biomarkers of systemic inflammation in the diagnosis of colorectal cancer. Dis Markers 2019;2019:1–7.
[14] Sun Y, Zhang L. The clinical use of pretreatment NLR, PLR, and LMR in patients with esophageal squamous cell carcinoma: evidence from a meta-analysis. Cancer Manag Res 2018;10:6167–79.
[15] Terragni R, Morselli-Labate AM, Vignoli M, et al. Is serum total LDH evaluation able to differentiate between alimentary lymphoma and inflammatory bowel disease in a real world clinical setting? PLoS One 2016;11:e0151641.
[16] Shibutani M, Maeda K, Nagahara H, et al. The prognostic significance of the advanced lung cancer inflammation index in patients with unresectable metastatic colorectal cancer: a retrospective study. BMC Cancer 2019;19:241–9.
[17] Beatty GL. Overcoming therapeutic resistance by targeting cancer inflammation. Am Soc Clin Oncol Educ Book 2016;35:e168–73.
[18] Peng HX, Yang L, He BS, et al. Combination of preoperative NLR, PLR and CEA could increase the diagnostic efficacy for I-III stage CRC. J Clin Lab Anal 2017;31:e22075.
[19] Ying HQ, Deng QW, He BS, et al. The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014;31:305–13.
[20] Yunteng W, Xuhui M, Guoxin R, et al. Radical surgery for head and neck rhabdomyosarcoma failed primary chemotherapy. J Craniofac Surg 2019;30:e113–6.
[21] Komasara L, Stefanowicz J, Bryks-Laszkowska A, et al. Reconstructive option after radical mutilating surgery in children with genitourinary rhabdomyosarcoma: when sparing the bladder is not an option. Int J Urol 2016;23:679–85.
[22] Kolb R, Sutterwala FS, Zhang W. Obesity and cancer: inflammation bridges the two. Curr Opin Pharmacol 2016;29:77–89.
[23] Koestler DC, Usset J, Christensen BC, et al. DNA methylation-derived neutrophil-to-lymphocyte ratio: an epigenetic tool to explore cancer inflammation and outcomes. Cancer Epidemiol Biomarkers Prev 2017;26:328–38.
[24] Feng F, Tian Y, Liu S, et al. Combination of PLR, MLR, MWR, and tumor size could significantly increase the prognostic value for gastrointestinal stromal tumors. Medicine (Baltimore) 2016;95:e3248.
[25] Tazeh NN, Canter DJ, Damodaran S, et al. Neutrophil to lymphocyte ratio (NLR) at the time of transurethral resection of bladder tumor: a large retrospective study and analysis of racial differences. Bladder Cancer 2017;3:89–94.
[26] Yilmaz E, Coskun EI, Sahin N, et al. MPV, NLR, and platelet count: new hematologic markers in diagnosis of malignant ovarian tumor. Eur J Gynaecol Oncol 2017;38:346–9.
[27] Wang J, Zhu QW, Cheng XY, et al. Assessment efficacy of neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio in preeclampsia. J Reprod Immunol 2019;132:29–34.
[28] Losada B, Guerra JA, Malon D, et al. Pretreatment neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/monocyte ratios and outcome in elderly breast cancer patients. Clin Transl Oncol 2018;21:855–63.
[29] Kimyon Comert G, Turkmen O, Kar I, et al. Independent predictors of survival in endometrium cancer: platelet-to-lymphocyte ratio and platelet/neutrophil/monocyte-to-lymphocyte ratio. J Turk Ger Gynecol Assoc 2018;19:78–86.
[30] Huang X, Hu H, Zhang W, et al. Prognostic value of prognostic nutritional index and systemic immune-inflammation index in patients with osteosarcoma. J Cell Physiol 2019;234:18408–14.
[31] Lee JW, Shin NR, Park JW, et al. Callicarpa japonica Thunb. attenuates cigarette smoke-induced neutrophil inflammation and mucus secretion. J Ethnopharmacol 2015;175:1–8.
[32] Wang H, Fan J, Li NL, et al. A subanesthetic dose of isoflurane during postconditioning ameliorates zymosan-induced neutrophil inflammation lung injury and mortality in mice. Mediators Inflamm 2013;2013:479–93.
[33] Szabady RL, McCormick BA. Control of neutrophil inflammation at mucosal surfaces by secreted epithelial products. Front Immunol 2013;4:220–6.
[34] Clark AJ, Diamond M, Elfline M, et al. Calicum microdomains form within neutrophils at the neutrophil-tumor cell synapse: role in antibody-dependent target cell apoptosis. Cancer Immunol Immunother 2010;59:149–59.
[35] Chippindale AJ, Patel B, Mamtora H. A case of necrobacillosis. Thorax 1990;45:74–5.
[36] Pande RL, Brown J, Buck S, et al. Association of monocyte tumor necrosis factor alpha expression and serum inflammatory biomarkers with walking impairment in peripheral artery disease. J Vasc Surg 2015;61:155–61.