Biomarkers in Medicine

Economical and easily detectable markers of digestive tumors: platelet parameters

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Aim: This study aimed to evaluate the clinical values of platelet parameters in patients with digestive tumors. **Patients & methods:** A total of 974 people were classified into three groups: malignant group, patients with digestive malignant tumors; benign group, patients with benign tumors; and normal group: healthy individuals. **Results:** Compared with the benign and normal groups, the malignant group showed significantly increased platelet count (PLT) and plateletcrit (PCT) and significantly reduced mean platelet volume (MPV) and platelet-large cell rate (P-LCR, $p < 0.001$). Elevated PLT and PCT and reduced MPV and P-LCR indicated poor overall survival in patients with digestive tumors. **Conclusion:** PLT, PCT, MPV and P-LCR were proven to be predictive biomarkers for patients with digestive malignant tumors. Elevated PLT and PCT or decreased MPV and P-LCR indicated poor overall survival.

Despite the improvement of medical technology and the progress of research on new approaches to cancer treatment, cancer remains a major public health problem in the world. Cancer was the first or second leading death before the age of 70 years in 91 of 172 countries based on the estimates from the WHO in 2015 [1]. Digestive system tumors have high morbidity and mortality [1]. Tumors have been a worldwide problem for centuries, due to not only their complex biological characteristics but also the difficulty of early diagnosis [2–4]. Although many biochemical and immune indicators, such as α-fetoprotein [5,6], oncofetal antigen [7], prostate-specific antigen [8,9], thymidine kinase 1 [10] and squamous cell carcinoma antigen [11], were used in the early diagnosis of tumors, they all have corresponding limitations and poor popularity in relatively backward areas; therefore rapid and economical laboratory indicators are urgently needed for clinical screening and early diagnosis.

Platelets are known to participate in hemostasis, thrombosis and immunological defense [12], but increasing evidence suggests that platelets also play important roles in tumor growth and metastasis [13–15]. The earliest study on the association between platelets and tumors dates back to 1865 [16]. In previous decades, platelets involved in tumor growth and metastasis were defined as tumor-education platelets [17], and the mechanisms by which platelets promote tumor growth and metastasis were unveiled step by step. The main structural components of platelets and platelet receptors were found to be associated with the malignant progression of cancer, including the following: VEGF- and PDGF-D-induced tumor angiogenesis [18], the complex of Aggrus expressed in cancer cells and platelet receptor CLEC-2-induced tumor metastasis [19], and platelet α6β1-induced cancer cell extravasation and platelet activation [20].

Platelets are accompanied by changes in count and volume while promoting the occurrence and development of tumors. Patients with platelet count (PLT) greater than 400×10^9/l are defined as having thrombocytosis [21]. Previous studies have reported that thrombocytosis exists in 10–57% of patients with malignant tumors [22] and is relevant to adverse prognosis of patients with epithelial ovarian cancer [23], endometrial cancer [24], colorectal cancer [25], rectal cancer [26] and gastric cancer [27]. Mean platelet volume (MPV) is also a potential biomarker

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for the diagnosis and follow-up of cancer, while reduced MPV was relevant to poor prognosis of patients with non-small-cell lung cancer [28], renal cell carcinoma [29] and bladder cancer [30].

However, previous studies rarely included the analysis of benign tumors and rarely conducted a comprehensive and systematic analysis of digestive tumors. The platelet difference in various tumors remains unclear. Therefore the changes in platelet parameters in patients with digestive benign and malignant tumors were explored in the present study. The diagnostic and prognostic role of platelet parameters in patients with digestive tumors was also determined.

Patients & methods

Patients

The data of patients who underwent excision of digestive system tumors were retrospectively analyzed for the first time in the Second Affiliated Hospital of Wenzhou Medical University from electronic medical records between January 2014 and December 2016. People with normal liver and kidney function and without primary or secondary thrombocytopenia and chronic inflammation in the physical examination center from January 2014 to December 2016 served as the control group. Age, sex, anamnesis, location of tumor, size of tumor, pathological type of tumor, distant metastasis, preoperative platelet parameters, white blood cell count (WBC), alanine aminotransferase (ALT), aspartate transaminase (AST) and overall survival (OS) post-operation were collected. All the included patients must have been pathologically diagnosed as having digestive tumors and had normal results of liver and kidney examination. Old people were considered as those aged >60 years [31]. Patients were excluded in accordance with the following exclusion criteria: patients with primary or secondary thrombocytopenia (such as chronic obstructive pulmonary disease or collagen vascular disease); patients with anamnesis of tumor who received neoadjuvant therapy; patients with chronic inflammation (such as connective tissue disease or cirrhosis); and patients with abnormal liver and kidney function. OS was defined as the time from operation to the time of death or last follow-up. Informed consent was obtained from all the patients or their guardians prior to the study.

Laboratory measurement

Laboratory data generated within 2 weeks before surgery were obtained from the hospital information system. Platelet parameters and WBC were measured using the Sysmex XE5000 hematology analyzer (Sysmex, Kobe, Japan). ALT and AST were measured using Cobas 6000 c501 (Roche Diagnostics, Rotkreuz, Switzerland).

Statistical analysis

SPSS (v. 23.0, IBM, Inc., NY, USA) was used for all statistical analyses. Receiver operating characteristic (ROC) and OS curves were constructed on GraphPad Prism 7 (GraphPad Software, Inc., CA, USA). The indices of non-normal distribution were described in median and interquartile ranges. The Kruskal–Wallis *H*-test and Mann–Whitney *U*-test were used to analyze the difference between groups. The ROC curves were used to select optimal cut-off values, area under the curve (AUC), sensitivity and specificity in predicting tumor occurrence; $p < 0.05$ was considered statistically significant.

Results

General characteristics of patients

A total of 974 people were analyzed, including 323 patients with digestive malignant tumors, 234 patients with digestive benign tumors and 417 healthy individuals. The median age of patients with digestive malignant tumors was 67 years (range: 26–96); the lesions were mainly concentrated in stomach, colon and rectum and the pathological type was mainly adenocarcinoma. The median age of patients with digestive benign tumors was 54 years (range: 20–83); the main sites were colon and rectum and the main pathological type was adenoma. The median age of the control group was 58 years (range: 31–90). The proportions of patients with PLT $\geq 400 \times 10^9$/l in the digestive malignant tumor group, digestive benign tumor group and control group were 6, 1 and 0%, respectively (Table 1).

Differences of platelet parameters in groups, tumor locations & pathological types

As shown in Table 2, the PLT and plateletcrit (PCT) in the malignant group were higher than those in the benign group and control group (244 [202–303] vs 216 [186–256] and 225 [197–255]; 0.26 [0.22–0.31] vs 0.23 [0.20–0.26] and 0.23 [0.21–0.26]). The MPV in the malignant group was lower than those in the benign group and control group (10.35 [9.70–11.10] vs 11.30 [10.30–27.30] and 11.40 [9.90–12.00]). The platelet-large cell rates (P-LCR) in the malignant group and benign group were lower than that in the control group, with statistically

Table 1. Clinical characteristics.

Characteristics	Malignant group n (%)	Benign group n (%)	Control group n (%)
Patients (n)	323	234	417
Age (years)			
– <60	89 (28)	152 (65)	225 (82.8)
– ≥60	233 (72)	82 (35)	
Gender			
– Male	218 (67)	151 (64)	192 (17.2)
– Female	104 (32)	83 (36)	
Tumor location			
– Esophagus	41 (13)	10 (4)	202 (48)
– Stomach	121 (37)	31 (13)	215 (52)
– Colon	74 (23)	132 (57)	
– Rectum	83 (26)	50 (21)	
– Others	4 (1)	11 (5)	
Pathological type			
– SCC	19 (6)		
– Adenocarcinoma	297 (92)		
– Mesenchymoma		22 (9)	
– Leiomyoma		14 (6)	
– Adenoma		183 (78)	
– Others	7 (2)	15 (6)	
Distant metastasis			
– Yes	136 (42)		
– No	186 (58)		
PLT ($\times 10^9$/l)			
– <300	240 (74)	219 (93)	386 (93)
– ≥300	82 (25)	15 (6)	31 (7)
– ≥400	19 (6)	2 (1)	0
PCT			
– <0.28	197 (61)	186 (79)	335 (80)
– ≥0.28	126 (39)	48 (21)	82 (20)
MPV (fl)			
– <12.00	297 (92)	157 (67)	386 (93)
– ≥12.00	26 (8)	77 (33)	31 (7)
PDW (%)			
– <17	304 (94)	227 (97)	401 (96)
– ≥17	19 (6)	7 (3)	16 (4)

MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; PLT: Platelet count; SCC: Squamous cell carcinoma.

Table 2. Differences of parameters in malignant, benign and control groups.

Parameter	Malignant group (n = 323)	Benign group (n = 234)	Control group (n = 417)	p-value
WBC	6.34 (5.16–7.64)	6.62 (5.30–7.64)	6.35 (5.13–7.70)	0.872
ALT	15 (11–20)	16 (11–23)	15 (11–21)	0.113
AST	18 (15–22)	18 (15–22)	19 (15–23)	0.463
PLT	244 (202–303)	216 (186–256)	225 (197–255)	<0.001
PCT	0.26 (0.22–0.31)	0.23 (0.20–0.26)	0.23 (0.21–0.26)	<0.001
MPV	10.35 (9.70–11.10)	11.30 (10.30–27.30)	11.40 (9.90–12.00)	<0.001
P-LCR	26.10 (21.80–33.90)	25.20 (13.90–31.60)	28.60 (23.85–33.57)	<0.001
PDW	11.90 (10.70–13.40)	11.70 (10.80–12.90)	12.30 (11.10–13.60)	0.463

ALT: Alanine aminotransferase; AST: Aspartate transaminase; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell rate; PLT: Platelet count; WBC: White blood cell count.

significant differences (p < 0.001). No statistically significant differences were identified in WBC, ALT, AST and platelet distribution width (PDW) (p > 0.05).

In addition, no significant differences were found in ALT, AST, PLT, PCT, MPV, P-LCR and PDW between disparate digestive malignant tumor locations, while WBC was adverse (p = 0.026). For digestive benign tumors, no significant differences were observed in WBC, ALT, AST, PLT, MPV and PDW between disparate locations, while PCT and P-LCR were adverse (p = 0.032 and 0.019, respectively; Tables 3 & 4).

Table 3. Difference of parameters in different locations of malignant tumors.

Parameter	Esophagus (n = 41)	Stomach (n = 121)	Colon (n = 74)	Rectum (n = 83)	p-value
WBC	6.44 (4.76–7.91)	5.95 (4.63–7.64)	7.06 (5.72–8.45)	6.10 (5.24–6.98)	0.026
ALT	13 (10–19)	15 (10–21)	15 (11–20)	15 (12–22)	0.930
AST	18 (16–20)	19 (15–23)	18 (15–22)	18 (15–22)	0.560
PLT	249 (189–282)	246 (207–318)	269 (223–316)	238 (192–268)	0.060
PCT	0.26 (0.20–0.29)	0.26 (0.22–0.32)	0.27 (0.24–0.34)	0.24 (0.21–0.28)	0.079
MPV	10.35 (9.77–11.00)	10.25 (9.60–10.90)	10.50 (9.62–11.10)	10.40 (9.80–11.30)	0.697
P-LCR	27.25 (22.55–33.17)	26.30 (21.05–31.90)	27.95 (21.90–34.72)	27.40 (21.95–35.05)	0.460
PDW	11.95 (10.75–13.30)	11.70 (10.55–13.00)	12.25 (10.82–13.57)	12.00 (10.65–13.75)	0.066

ALT: Alanine aminotransferase; AST: Aspartate transaminase; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell rate; PLT: Platelet count; WBC: White blood cell count.

Table 4. Difference of parameters in different locations of benign tumors.

Parameter	Stomach (n = 31)	Colon (n = 132)	Rectum (n = 50)	p-value
WBC	6.74 (5.86–8.62)	6.53 (5.16–7.64)	6.33 (5.16–7.56)	0.247
ALT	15 (11–19)	15 (11–22)	17 (12–25)	0.845
AST	17 (14–23)	19 (15–22)	18 (14–22)	0.865
PLT	245 (201–291)	217 (186–255)	214 (186–233)	0.058
PCT	0.27 (0.21–0.29)	0.23 (0.20–0.27)	0.23 (0.20–0.26)	0.032
MPV	10.55 (10.10–11.55)	11.60 (10.30–28.40)	11.00 (10.27–31.40)	0.288
P-LCR	27.55 (24.47–33.37)	22.40 (12.90–31.50)	25.60 (14.82–29.92)	0.019
PDW	12.05 (11.40–13.67)	11.50 (10.50–12.70)	11.75 (11.10–12.60)	0.203

ALT: Alanine aminotransferase; AST: Aspartate transaminase; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell rate; PLT: Platelet count; WBC: White blood cell count.

Table 5. Difference of parameters between distant metastasis and no distant metastasis.

Parameter	Distant metastasis (n = 136)	No distant metastasis (n = 186)	p-value
WBC	5.91 (4.88–7.52)	6.62 (5.45–7.66)	0.066
ALT	14 (10–18)	15 (12–21)	0.067
AST	19 (15–22)	18 (15–23)	0.172
PLT	254 (210–320)	236 (199–296)	0.052
PCT	0.26 (0.22–0.32)	0.25 (0.22–0.30)	0.019
MPV	10.20 (9.50–10.90)	10.40 (9.80–11.10)	0.024
P-LCR	25.80 (19.55–32.25)	28.30 (22.40–34.10)	0.020
PDW	11.60 (10.30–13.00)	12.10 (10.80–13.60)	0.496

ALT: Alanine aminotransferase; AST: Aspartate transaminase; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell rate; PLT: Platelet count; WBC: White blood cell count.

Distant metastasis versus no distant metastasis of malignant tumor

PCT was higher in patients with distant metastasis than in patients without distant metastasis (0.26 [0.22–0.32] vs 0.25 [0.22–0.30]) but the difference was not clinically significant. The MPV and P-LCR in patients with distant metastasis were lower than those in patients without distant metastasis (10.20 [9.50–10.90] vs 10.40 [9.80–11.10]; 25.80 [19.55–32.25] vs 28.30 [22.40–34.10]). The results showed that lower MPV and P-LCR indicated a more severe tumor burden (Table 5).

Predicting values

Significant differences were shown in PLT, PCT, MPV and P-LCR between the malignant group and the control group; therefore PLT, PCT, MPV and P-LCR could be used to predict the existence of digestive malignant tumors. According to the ROC curves (Figure 1), the best critical values of PLT, PCT, MPV and P-LCR were 275.5 (AUC = 0.609; 95% CI: 0.567–0.651; $p < 0.001$), 0.255 (AUC = 0.605; 95% CI: 0.562–0.647; $p < 0.001$), 10.05 (AUC = 0.557; 95% CI: 0.514–0.599; $p = 0.008$) and 25.25 (AUC = 0.545; 95% CI: 0.501–0.590; $p = 0.042$),
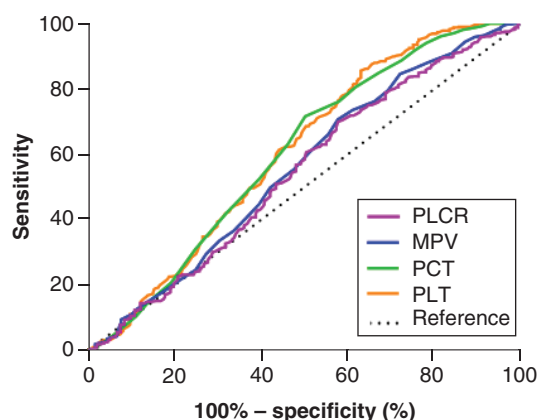
Figure 1.   Receiver operating characteristic curves for platelet count, plateletcrit, mean platelet volume and platelet-large cell rate, showing sensitivity and 100% specificity for differential diagnosis of the digestive malignant group versus control group.
MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet-large cell rate; PLT: Platelet count.

Table 6. Area under the curve, 95% CI, p-value, cut-off value, sensitivity and specificity calculated according to the pathological results.

Parameter	AUC	95% CI	p-value	Cut-off value	Sensitivity	Specificity
PLT	0.609	0.567–0.651	<0.001	275.5	85.61	36.96
PCT	0.605	0.562–0.647	<0.001	0.255	71.63	49.84
MPV	0.557	0.514–0.599	0.008	10.05	70.67	42.32
P-LCR	0.545	0.501–0.59	0.042	25.25	69.95	42.33

AUC: Area under the curve; MPV: Mean platelet volume; PCT: Plateletcrit; P-LCR: Platelet-large cell rate; PLT: Platelet count.

respectively. The critical sensitivities were 85.61, 71.63, 70.67 and 69.95%, respectively, while the critical specificity was slightly lower (Table 6).

The benign group and the control group did not show any significant difference in terms of platelet parameters. PCT and P-LCR did not significantly differ among the locations of benign tumors. Thus platelet parameters may not be good at predicting the existence of digestive benign tumors.

Survival analysis

Survival analysis (median follow-up time: 42.5 [1–64] months) showed that the patients with digestive tumors with increased PLT ($\geq$275.5 $\times$ 10^9/l) and PCT ($\geq$0.255) showed poorer OS than those with decreased PLT (<275.5 $\times$ 10^9/l) and PCT (<0.255) (hazard ratio [HR]: 3.07; 95% CI: 2.21–4.29; p < 0.0001 and HR: 2.02; 95% CI: 1.50–2.73; p < 0.0001, respectively). As shown in Figure 2, the OS of patients with digestive malignant tumors with increased MPV ($\geq$10.05 fl) and P-LCR ($\geq$25.25%) was better than those with reduced MPV (<10.05 fl) and P-LCR (<25.25%) (HR: 1.91; 95% CI: 1.42–2.56; p = 0.0045 and HR: 1.97; 95% CI: 1.47–2.64; p = 0.0044, respectively).

Discussion

In recent years, several studies have shown that PLT and MPV could be used as predictors and prognostic markers for patients with digestive malignant tumors. For example, increased PLT could be used as a predictor of liver metastasis in rectal cancer [32] and it was related to poor prognosis of gastric cancer [33] and colon cancer [34]. Increased MPV was significantly correlated with favorable prognosis of esophageal cancer [35], while decreased MPV was related to poor prognosis of non-small-cell lung cancer [28] and bladder cancer [30]. However, the digestive system is a complete physiological unit which lacks a comprehensive study between it and platelet parameters. In addition, the role of platelets in digestive benign tumors is still unclear. Therefore the present study aimed to explore whether platelet parameters could be used as biomarkers of digestive tumors.

In this study, 6% of digestive malignant tumors were associated with thrombocytosis, consistent with the 7.5% incidence of concomitant thrombocytosis found by Li *et al.* [36]. The PLT in the malignant group was significantly higher than those in the benign group and control group. Thus the increased PLT in patients with digestive malignant tumors was considered to be caused by tumor-induced platelet activation. According to existing studies, platelet production is affected by primary tumors through the direct paracrine activity of megakaryocytes and their
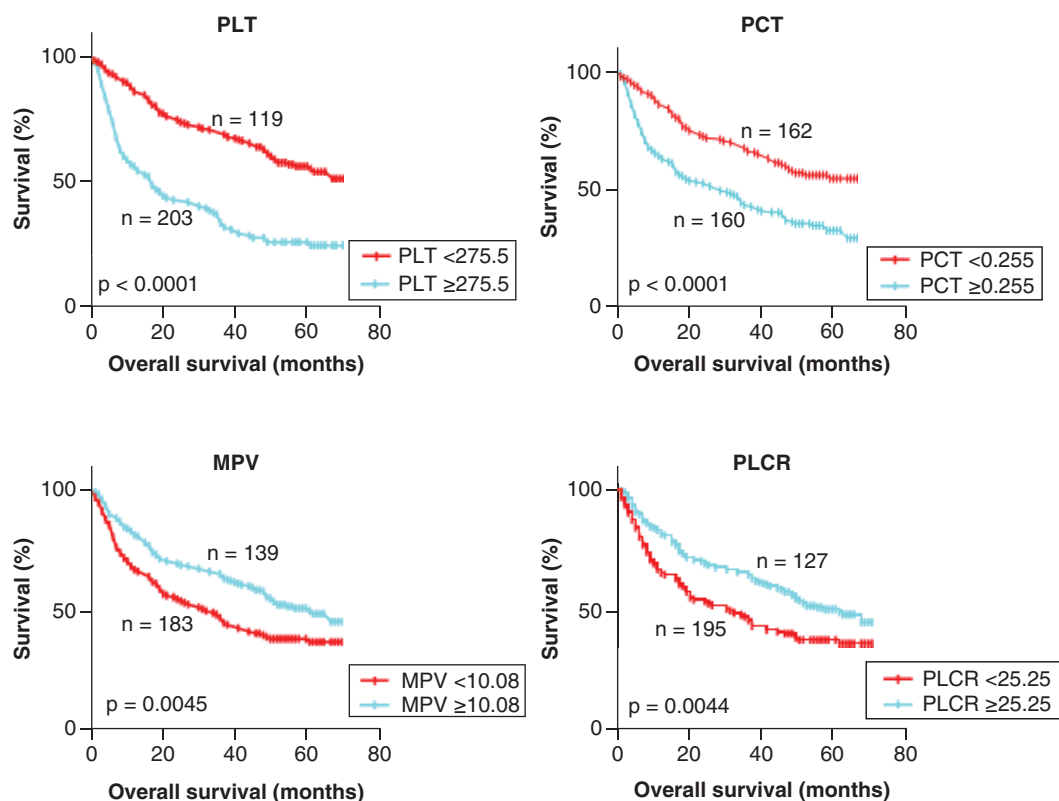
Figure 2.   The effect of platelet count, plateletcrit, mean platelet volume and platelet-large cell rate on the overall survival rate analyzed by Kaplan–Meier analysis. (A) Overall survival stratified based on low or high PLT. **(B)** Overall survival stratified based on low or high PCT. **(C)** OS stratified based on low or high MPV. **(D)** Overall survival stratified based on low or high P-LCR.
MPV: Mean platelet volume; PCT: Platelet crit; P-LCR: Platelet- large cell ratio; PLT: Platelet count.

ability to activate platelets [37]. Cancer cells could activate platelets by indirectly releasing a large number of factors, such as adenosine diphosphate [38], thromboxane A2 [39] and thrombin [40]. The release of thrombopoietin from the liver, kidney and skeletal muscle is promoted by activated platelets, thus stimulating megakaryocyte proliferation and maturation and platelet production. Platelets and cancer cells constitute a positive feedback cascade; they stimulate each other and enhance their effect [41]. However, in the present study, the incidence of thrombocytosis was 1% in the benign group, similar to the normal group. This finding suggests that the above effect does not exist in digestive benign tumors or that platelets play a minimal role in the growth of digestive benign tumors. In addition, PCT was higher in patients with digestive malignant tumors than in those with benign tumors and the control group. This result was considered to be due to the increased PLT.

MPV was significantly lower in patients with digestive malignant tumors than in those with digestive benign tumors and the control group. MPV, a parameter used to evaluate the average size of circulating platelets, is related to the content of α granules, and is an important marker of platelet activation [42]. MPV has been identified as a biomarker for the early diagnosis of gastric and colorectal cancer [43,44]. The present study suggested that MPV could be used as a biomarker of digestive malignant tumors, which is consistent with the results of the above studies. In addition, the decreased MPV in patients with digestive malignant tumors may be caused by the increased consumption of large platelets in the state of tumorous inflammation [45]. The results of the present study showed that the P-LCR of patients in the malignant group was significantly lower than that of patients in the benign group and the control group, which could support the theory on the decrease in MPV.

In addition, no significant difference was found among the gastric cancer group, colon cancer group and rectal cancer group, thereby proving that the change in platelet parameters was not affected by the anatomical site. Platelets were considered to have similar changes in gastrointestinal tumors with different biological properties and behavior. PLT, PCT, MPV and P-LCR could be used as biomarkers for the diagnosis of digestive malignant tumors.

Moreover, best critical value, sensitivity and specificity were obtained in accordance with the ROC curve. PLT, PCT, MPV and P-LCR exhibited good sensitivity in predicting digestive malignant tumors.

This study showed that patients with malignant tumors who had increased PLT, increased PCT, decreased MPV or decreased P-LCR showed low overall survival (Figure 2), the mechanism for which is complex.

Analysis of the OS of patients with malignant tumors indicated that increased PLT and PCT were associated with poor prognosis; this finding was consistent with the result of a meta-analysis of 3413 patients with colorectal cancer [34]. Masataka *et al.* also confirmed that elevated PLT was associated with poor prognosis of gastric cancer [33]. Increased activated platelets release various effector factors, such as VEGF, EGF, TGF-β, PDGF and IL-6, to accelerate vascular maturation in the tumor microenvironment and mediate the invasion of cancer cells [15]. Circulating cancer cells combined with platelets could form metastatic emboli and promote the implantation of cancer cells [46]. From the above statement, increased PLT and PCT promoted the tumors' progression and metastasis, thus explaining the association between increased PLT or PCT and poor prognosis.

In addition, the present study showed that decreased MPV and P-LCR were associated with poor prognosis in patients with digestive malignant tumors, although the mechanisms were not entirely clear. The relationship between MPV and OS was not consistent among different studies. Some studies have supported an association between elevated MPV and poor prognosis of patients with colorectal cancer [47] and gastric cancer [48]. Their explanation was that elevated platelets with MPV exacerbate inflammation because larger platelets contain more particles and release more prethrombotic substances. However, other studies have found that decreased MPV was associated with poor prognosis of patients with esophageal cancer [49] and colorectal cancer [50]. The underlying mechanism may be that more large platelets are involved in neoplastic infections and consumed [45], thereby speeding up the progression of the tumor. The present study supported the latter finding, and the reduced P-LCR provided proof; decreased MPV and P-LCR indicated more active platelets were involved in tumor growth and metastasis, ultimately leading to cancer progression and poor prognosis.

Conclusion

Platelets may play a minimal role in the growth of digestive benign tumors. PLT, PCT, MPV and P-LCR were proven to be diagnostic biomarkers for patients with digestive malignant tumors. Elevated PLT and PCT or decreased MPV and P-LCR indicated poor OS.

Future perspective

This research has several limitations. Firstly, it was a single-center retrospective study and more districts are needed to confirm the results. Secondly, information on progression-free survival was not included in the study because of the retrospective follow-up. Thirdly, the sample size was limited because only the electronic information of patients admitted to the hospital after 2014 could be obtained. Fourthly, the study of microsatellite instability is considerably important for tumor diagnosis, prognosis and treatment choice. However, almost no patient with microsatellite instability data was found in this hospital in the past and so the above information could not be reflected in the study.

Summary points

- A cheap and easily detectable biomarker is needed to systematically predict the diagnosis and prognosis of patients with digestive tumors.
- Digestive malignant tumors are accompanied by an increase in circulating platelet count and a decrease in volume.
- No significant difference was found in the platelet parameters between the digestive benign tumor group and the control group, indicating platelets may play a small role in the growth of digestive benign tumors.
- Receiver operating characteristic analysis was performed for platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV) and platelet-large cell rate (P-LCR) ability. The area under the curve was the highest in PLT, followed by PCT, MPV and P-LCR.
- Preoperative PLT, PCT, MPV and P-LCR could predict the prognosis of patients with digestive malignant tumors. Elevated PLT and PCT or decreased MPV and P-LCR indicated poor overall survival.

Author contributions

M Jiang, Y Chen and W Yang focused on study conception and design. W Yang, L Ye, S Lin, X Ai and Y Yao were involved in the acquisition of data. M Jiang, Y Chen, W Yang and K Shu performed data analysis and interpretation. M Jiang, W Yang and X Yang contributed in statistical analysis. Y Chen, W Yang and X Yang collaborated in preparing the draft manuscript. Y Chen, L Ye, S Lin, K Shu, X Ai, Y Yao and M Jiang revised the scientific contents of the final manuscript.

Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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