Prognostic value of mean platelet volume/platelet count ratio in patients with resectable esophageal squamous cell carcinoma: a retrospective study

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Background. Mean platelet volume (MPV) to platelet count (PC) ratio (MPV/PC) is a useful indicator in several cancers. However, the role for MPV/PC ratio in esophageal squamous cell carcinoma (ESCC) is still controversial.

Methods. A retrospective study was conducted including 277 resectable ESCC patients. The optimal cut-off values were calculated by the X-tile program. The receiver operator characteristic (ROC) curves were also created to show the candidate cut-off points. The comparisons between the X-tile plot and ROC curve were performed. The Kaplan-Meier method was utilized to analyze the cancer-specific survival (CSS). Prognostic factors for CSS were calculated with Cox regression univariate and multivariate analyses.

Results. According to the X-tile program, the cut-off values for MPV, PC and MPV/PC ratio were 8.5 (fl), 200 (giga/l) and 0.04, respectively. However, the cut-off values for MPV, PC and MPV/PC ratio by the ROC curves were 8.25 (fl), 243.5 (giga/l) and 0.0410, respectively. The cut-off values were similar between the X-tile and ROC curve. A low MPV/PC ratio level (≤ 0.04) was associated with poor CSS (22.4% vs. 43.1%, P <0.001). In multivariate analyses, we found that MPV/PC ratio was an independent predictor for CSS (P <0.001). When we set the cut-off point using ROC curve, the MPV/PC ratio was still an independent predictor for CSS (P <0.001).

Conclusion. The MPV/PC ratio is a useful ~~predictive~~ indicator in patients with ESCC.

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Abstract

Background. Mean platelet volume (MPV) to platelet count (PC) ratio (MPV/PC) is a useful indicator in several cancers. However, the role for MPV/PC ratio in esophageal squamous cell carcinoma (ESCC) is still controversial.

Methods. A retrospective study was conducted including 277 resectable ESCC patients. The optimal cut-off values were calculated by the X-tile program. The receiver operator characteristic (ROC) curves were also created to show the candidate cut-off points. The comparisons between the X-tile plot and ROC curve were performed. The Kaplan-Meier method was utilized to analyze the cancer-specific survival (CSS). Prognostic factors for CSS were calculated with Cox regression univariate and multivariate analyses.

Results. According to the X-tile program, the cut-off values for MPV, PC and MPV/PC ratio were 8.5 (fl), 200 (giga/l) and 0.04, respectively. However, the cut-off values for MPV, PC and MPV/PC ratio by the ROC curves were 8.25 (fl), 243.5 (giga/l) and 0.0410, respectively. The cut-off values were similar between the X-tile and ROC curve. A low MPV/PC ratio level ($\leq$0.04) was associated with poor CSS (22.4% vs. 43.1%, P <0.001). In multivariate analyses, we found that MPV/PC ratio was an independent predictor for CSS (P <0.001). When we set the cut-off point using ROC curve, the MPV/PC ratio was still an independent predictor for CSS (P <0.001).

Conclusion. The MPV/PC ratio is a useful ~~predictive~~ indicator in patients with ESCC.

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60 **Introduction**

61 Esophageal cancer (EC) is the 8th most common cancer worldwide and the 6th most common

62 cause of death from cancer (*Ferlay et al., 2010*). The incidences vary widely in different

63 countries and regions. To date, approximately 53.8% and 51.9% of all ECs occurred and died in

64 China (*Siegel et al., 2015*; *Ferlay et al., 2010*). Esophageal adenocarcinoma is the most common

65 malignancy in the West. In China, however, esophageal squamous cell carcinoma (ESCC) is the

66 predominant subtype (*Napier et al., 2014*). Radical esophagectomy remains the most effective

67 therapy for patients with EC. However, the prognosis for EC remains poor (*Bedenne et al., 2007*;

68 *Domper et al., 2015*). Therefore, it is very important to find more and more useful and effective

69 prognostic indicators for patients with EC.

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71 Over the past few decades, a number of prognostic factors for EC have been identified, including

72 tumor length, vessel invasion, lymph node status (N stage), depth of invasion (T stage), TNM

73 stage and other serum biomarkers, such as squamus cell carcinoma antigen (SCCA) and

74 carcinoembryonic antigen (CEA) (*Peyre et al., 2008*; *Wijnhoven et al., 2007*; *Feng et al., 2013*).

75 Inflammation plays an important role in cancer progression and prognosis (*Balkwill et al., 2001*;

76 *Mantovani et al., 2008*). C-reactive protein (CRP), as a most sensitive inflammatory biomarker,

77 has been confirmed in a series of cancers to predict the prognosis, including patients with EC

78 (*Shimada et al., 2003; Nozoe et al., 2001; Platt et al., 2012*). In addition, there are other

79   parameters like neutrophil and lymphocyte that are easy-to-measure inflammatory markers

80   (*Dutta et al., 2011*).

81

82   Mean platelet volume (MPV) is recognized as a hallmark for platelet count (PC) activation

83   (*Kamath et al., 2001*). Several studies showed that MPV and PC are associated with mortality in

84   cardiovascular disease, such as ischemic cardiovascular disease and acute myocardial infarction

85   (*Guenancia et al., 2017; Azab et al., 2011*). Moreover, recent studies have shown that the ratio

86   for MPV to PC (MPV/PC) is associated with prognosis in some malignancies, such as

87   hepatocellular carcinoma and lung cancer (*Cho et al., 2013; Inagaki et al., 2014; Omar et al.,*

88   *2018*). However, the role for MPV/PC ratio in ESCC is still controversial. Furthermore,

89   controversy exists concerning the optimal cut-off points for MPV/PC to predict the prognosis of

90   ESCC. Therefore, the purpose of our study here was to explore the prognostic role of MPV/PC

91   ratio in patients with ESCC.

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93   **Patients and Methods**

94   From January 2007 to December 2010 at the Department of Thoracic Surgery, Zhejiang Cancer

95   Hospital, a retrospective study was conducted including 277 resectable ESCC patients. The

96   exclusion criteria were as follows: 1). patients who received preoperative treatment, such as

97   chemotherapy and/or radiotherapy; 2). patients who had any form of acute or chronic

98   inflammatory diseases or infections; 3). patients who had systemic diseases, and 4) those

99   diagnosed with distant metastases. Written informed consent for the collection of specimen and

100 other medical information were obtained from all patients before surgery. The current study was

101 approved by the Ethics Committees of Zhejiang Cancer Hospital (IRB Approval No. IRB-2018-

102 130).

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104 The main clinical characteristics, such as age, gender, tumor location (upper, middle and lower),

105 tumor length, vessel invasion, differentiation (well, moderate and poor) and tumor stage (T stage,

106 N stage and TNM stage), were retrospectively reviewed and collected. The tumor length was

107 defined as the long diameter for pathological specimens. Blood samples were obtained within

108 one week prior to surgery to measure the neutrophil (Neu), MPV, PC, CRP and CEA levels.

109 MPV/PC was defined as MPV to PC ratio. Neu/PC was defined as Neu to PC ratio. The levels of

110 Neu, MPV and PC were measured by automated blood cell counter (Sysmex XE-2100, Kobe,

111 Japan). Serum levels of CRP were determined by latex-enhanced homogeneous immunoassay

112 (Hitachi 917; Skill, Munich, Germany). Serum levels of CEA were measured using enzyme

113 immunoassay kits (Abbott, Chicago, USA). The AJCC/UICC TNM staging system (the 7th

114 edition) was utilized to classify the stage for this study (*Rice et al., 2010*).

115

116 All the above patients were followed-up postoperatively (regularly evaluated every 3-6 months).

117 The assessment included physical examination, blood tumor markers and computed tomography

118 scan. In this study, we conducted a cancer-specific survival (CSS) to analyze the prognosis of

119 patients with ESCC. The mean follow-up for patients was 45 months.

120

121 **Statistical analyses**

122 In the current study, the optimal cut-off values for Neu, MPV, PC, MPV/PC ratio, and Neu/PC

123 ratio were calculated by the X-tile program (*Camp et al., 2004*). The receiver operator

124 characteristic (ROC) curves were also created to show the candidate cut-off points. The

125 comparisons between the X-tile plot and ROC curve were performed. The areas under the curve

126 (AUC) for Neu, MPV, PC, MPV/PC and Neu/PC were calculated and compared by the ROC

127 curve. The chi-squared tests were used to compare the MPV/PC ratio, MPV and PC. The CSS

128 curves were generated by the Kaplan-Meier method. Univariate analyses were performed with

129 log-rank test. Multivariate analyses with cox proportional hazards regression model were utilized

130 to analyze prognostic factors for CSS. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was utilized to

131 perform the statistical analyses. R 3.2.3 software (Institute for Statistics and Mathematics,

132 Vienna, Austria) was also utilized to conduct the nomogram model by Harrell's concordance

133 index (c-index) (*Iasonos et al., 2008*).

134

135 **Results**

136 There were 37 (13.4%) women and 240 (86.6%) men in all 277 patients with the mean age of

137 59.2 ± 7.8 years (36-80 years). In the current study, the mean values for Neu, MPV, PC,

138 MPV/PC and Neu/PC were 4.2 ± 1.5 (giga/l) (range 1.5-9.5 giga/l), 9.3 ± 1.3 (fl) (range 6.7-12.9

139 fl), 232 ± 72 (giga/l) (range 60-473 giga/l), 0.04 ± 0.02 (range 0.02-0.14), and 0.020 ± 0.010

140 (range 0.0053-0.0667), respectively. The histograms of the preoperative MPV/PC ratio, MPV

141 and PC are shown in Figure 1.

142

143 According to the X-tile program, the optimum cut-off points for MPV, PC, MPV/PC, Neu and

144 Neu/PC ratio were 8.5 (fl), 200 (giga/l), 0.04, 4.2 (giga/l) and 0.02, respectively (Fig. 2).

145 According to the optimum cut-off points of the above values, patients then were divided into 2

146 groups (MPV ≤8.5 fl and >8.5 fl; PC ≤200 giga/l and >200 giga/l; MPV/PC ratio ≤0.04 and

147 >0.04). Clinicopathologic characters for the above values (MPV/PC ratio, MPV and PC) were

148 shown in Table 1. The levels of MPV/PC ratio were significantly correlated with the CRP levels

149 (P =0.029).

150

151 Kaplan-Meier analyses showed that a low MPV/PC ratio level (≤0.04) was associated with poor

152 CSS (P <0.001). The 5-year CSS was 43.1% in patients with MPV/PC ratio >0.04, and 22.4% in

153 patients with MPV/PC ratio ≤0.04 (Fig. 3A). There were also significantly different for MPV

154 (42.4% vs. 27.0%, P =0.010) and PC (41.0% vs. 26.7%, P =0.009) (Fig. 3B-C). In multivariate

155 analyses, we found that MPV/PC ratio was an independent predictor for CSS (P <0.001) (Table

156 2). In addition, TNM stage (P <0.001), CEA (P =0.019), Neu (P =0.007) and CRP (P <0.001)

157 were other significant prognostic variables by multivariate analyses (Table 2).

158

159 We also created ROC curves to show the candidate cut-off points. The cut-off values for Neu,

160   MPV, PC, MPV/PC, and Neu/PC ratio by the ROC curves were 4.25 (giga/l), 8.25(fl), 243.5

161   (giga/l), 0.0410, and 0.0213, respectively (Fig. 4). The candidate cut-off points and the area

162   under ROC curve (AUC) are shown in Table 3. When we set the cut-off points using ROC curve,

163   the MPV/PC ratio (42.7% vs. 23.5%, *P* <0.001), MPV (51.7% vs. 26.7%, *P* =0.001), and PC

164   (41.8% vs. 19.3%, *P* <0.001) were also associated with CSS (D-F) (Fig. 3D-F). In multivariate

165   analyses, MPV/PC ratio was still an independent predictor for CSS (*P* <0.001) (Table 4).

166

167   Moreover, we wanted to predict the survival risk (CSS) for patients with ESCC, a nomogram

168   model was conducted including age, gender, TNM, CEA, Neu, MPV/PC ratio and CRP for CSS

169   (Fig. 5). From this model, the probability of survival for ESCC patients could be predicted (c-

170   index=0.72).

171

172   **Discussion**

173   Our study demonstrated some important findings: (1) MPV/PC ratio was a strong predictor of

174   CSS; (2) MPV/PC ratio, but not MPV or PC, was a useful predictive indicator. This study used

175   X-tile program and ROC curves as candidate cut-off points. The comparisons between the X-tile

176   plot and ROC curve were performed. The cut-off values were similar between the X-tile and

177   ROC curve. Moreover, our study is also the first attempt to predict the survival risk by a

178   nomogram model based on MPV/PC ratio.

179

180   Platelet activation has been demonstrated as a common phenomenon in some cardiovascular

181   diseases (*Guenancia et al., 2017; Azab et al., 2011*). To assess the platelet activation status,

182   MPV and PC are two main aspects. Moreover, studies have shown that MPV/PC ratio is

183   associated with prognosis in some malignancies, such as hepatocellular carcinoma and lung

184   cancer (*Cho et al., 2013; Inagaki et al., 2014; Omar et al., 2018*). Cho et al. (*Cho et al., 2013*)

185   have shown that the ratio of MPV/PC levels in hepatocellular carcinoma were higher than the

186   control group. Inagaki et al. (*Inagaki et al., 2014*) have revealed that MPV/PC ratio was

187   significantly different on survival in lung cancer. However, Omar et al. (*Omar et al., 2018*)

188   showed that increased MPV and increased PC were significant higher than the control group. In

189   their study, however, MPV/PC was not an independent predictor in lung cancer.

190

191   MPV is an indicator of platelet activation. Shen et al. *(Shen et al., 2018)* demonstrated that

192   reduced MPV is associated with worse survival outcome in EC. The role for MPV/PC ratio in

193   ESCC patients has not yet been well evaluated. A study reported by Sun et al. showed that the

194   levels of MPV/PC ratio in ESCC were significantly lower than the healthy group, and which

195   were significantly correlated with the tumor length (*Sun et al., 2018*). In our study, however, the

196   MPV/PC ratio was not significantly correlated with the tumor length (*P* =0.087). In addition,

197   they revealed that decreased MPV and MPV/PC ratio were significantly associated with locally

198   advanced ESCC. In our study, MPV was not a significant prognostic factor by multivariate

199   analyses. Recently, Zhang et al. (*Zhang et al., 2016*) initial conducted a COP-MPV (combination

200   of MPV and PC) model to predict the prognosis in ESCC. They revealed that COP-MPV was a

201   useful independent predictor, but not for MPV or PC. As everyone knows, MPV and PC may be

202   influenced by a variety of other non-cancer related conditions, the potential basis could be

203   decreased by the MPV to PC ratio (MPV/PC). Therefore, the role of the MPV/PC ratio would be

204   more reliable than the effect of either MPV or PC. In the current study, a low MPV/PC ratio

205   level (≤0.04) was associated with poor CSS (*P* <0.001) and was confirmed by multivariate

206   analyses (*P* <0.001).

207

208   In previous studies, controversy exists about the optimum cut-off point for MPV/PC ratio to

209   predict prognosis. Cho et al. (*Cho et al., 2013*) demonstrated that 0.0491 might be the optimum

210   cut-off point for MPV/PC ratio in hepatocellular carcinoma according to the ROC curve. Inagaki

211   et al. (*Inagaki et al., 2014*) and Omar et al. (*Omar et al., 2018*) also conducted the ROC curve

212   analyses to calculate the optimum cut-off point for MPV/PC in lung cancer. They concluded that

213   the optimum cut-off points for MPV/PC ratio were 0.40873 and 0.47424, respectively. Recently,

214   Camp et al. (*Camp et al., 2004*) initial conducted a program to explore the optimum cut-off point

215   (X-tile plot). In our study, according to their method, 0.04 was the optimum cut-off point for

216   MPV/PC ratio. We also created ROC curves to show the candidate cut-off points. When we set

217   the cut-off point using ROC curve, the MPV/PC ratio was also associated with CSS. In

218   multivariate analyses, MPV/PC ratio was still an independent predictor for CSS.

219

220   The mechanism between MPV/PC ratio and cancer remains unknown. Inflammation and cancer

221   are closely related (*Balkwill et al., 2001; Mantovani et al., 2008*). As everyone knows, platelets

222   can release a variety of cytokines, such as platelet-derived growth factor (PDGF) and vascular

223   endothelial growth factor (VEGF), which have an important role in regulating angiogenesis

224   (*Blair et al., 2009; Borsig et al., 2008*; *Dineen et al., 2009*). The inflammation will be inevitably

225   caused by chemotherapy and/or radiation. Therefore, we analyze the role of MPV/PC ratio in

226   ESCC patients without neoadjuvant chemotherapy and/or radiation.

227

228   Limitations should be acknowledged in this study. The major limitations of this study are small

229   samples and its retrospective character. Moreover, patients who received preoperative

230   chemotherapy and/or radiotherapy were excluded, which might have influenced the result in the

231   current study. On the one hand, neoadjuvant treatment will have a side effect on MPV and PC.

232   On the other hand, neoadjuvant treatment can improve cancer survival for locally advanced EC,

233   but not for early stage EC (*Rawat et al., 2013; Mariette et al., 2014*). In addition, we did not set

234   up a validation group to verify the conclusion. Thus, the results of our study are expected more

235   large-sample trials to confirm in future.

236

237   **Conclusion**

238   In summary, we found that the ratio of MPV/PC is a potential prognostic biomarkers in patients

239   with ESCC.

240

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Table 1(on next page)

Comparison of baseline clinical characteristics in ESCC

Comparison of baseline clinical characteristics in ESCC

1   **Table 1 Comparison of baseline clinical characteristics in ESCC**

	Total	MPV (fl)		P value	PC (giga/l)		P value	MPV/PC		P value
		≤8.5	>8.5		≤200	>200		≤0.04	>0.04	
Age (years)				0.704			0.221			0.488
≤ 60	158	51	107		55	103		81	77	
> 60	119	41	78		50	69		66	53	
Gender				0.521			0.271			0.629
Female	37	14	23		11	26		21	16	
Male	240	78	162		94	146		126	114	
Tumor length (cm)				0.246			0.020			0.087
≤ 3.0	78	30	48		38	40		35	43	
> 3.0	199	62	137		67	132		112	87	
CRP (mg/l)				0.031			0.152			0.029
≤ 10.0	200	74	126		81	119		98	102	
> 10.0	77	18	59		24	53		49	28	
Tumor location				0.242			0.096			0.057
Upper	16	7	9		10	6		4	12	
Middle	127	36	91		44	83		72	55	
Lower	134	49	85		51	83		71	63	
Vessel invasion				0.744			0.097			0.111
Negative	232	78	154		83	149		128	104	
Positive	45	14	31		22	23		19	26	
Differentiation				0.927			0.826			0.454
Well	43	15	28		16	27		25	18	
Moderate	179	58	121		70	109		90	89	
Poor	55	19	36		19	36		32	23	
T stage				0.106			0.313			0.425
T1	50	22	28		18	32		28	22	
T2	49	20	29		24	25		21	28	
T3	154	44	110		56	98		86	68	
T4	24	6	18		7	17		12	12	
N stage				0.054			0.720			0.899
N0	150	60	90		61	89		78	72	
N1	74	21	53		27	47		39	35	
N2	32	7	25		10	22		19	13	
N3	21	4	17		7	14		11	10	
TNM stage				0.003			0.357			0.546
I	69	31	38		31	38		33	36	
II	92	35	57		34	58		52	40	
III	116	26	90		40	76		62	54	
CEA (ng/ml)				0.818			0.566			0.954

≤ 5.0	239	80	159		89	50		127	112	
> 5.0	38	12	26		16	22		20	18	
Neu (giga/l)				0.249			0.681			0.186
≤ 4.2	146	53	93		57	89		72	74	
> 4.2	131	39	92		48	83		75	56	
Neu/PC				0.090			<0.001			<0.001
≤ 0.02	170	50	120		35	135		114	56	
> 0.02	107	42	65		70	37		33	74	

2   ESCC: esophageal squamous cell carcinoma; CRP: c-reactive protein; MPV: mean platelet volume; PC:

3   platelet count; TNM: tumor node metastasis; CEA: carcinoembryonic antigen; Neu: neutrophil.

Table 2(on next page)

Univariate and multivariate analyses for cancer-specific survival

Univariate and multivariate analyses for cancer-specific survival

1 **Table 2 Univariate and multivariate analyses for cancer-specific survival**

	CSS (%)	P value	Univariate analysis HR (95% CI)	P value	Multivariate analysis HR (95% CI)	P value
Age (years)		0.412		0.417	-	-
≤ 60	33.5		1.000			
> 60	30.3		1.127 (0.845-1.502)			
Gender		0.114		0.120	-	-
Female	45.9		1.000			
Male	30.0		1.445 (0.909-2.298)			
Tumor length		0.003		0.004	-	-
≤ 3 cm	42.3		1.000			
> 3 cm	28.1		1.642 (1.173-2.297)			
Tumor location		0.336		0.342	-	-
Upper/Middle	35.7		1.000			
Lower	28.4		1.149 (0.863-1.530)			
Vessel invasion		0.003		0.003	-	-
Negative	35.3		1.000			
Positive	15.6		1.710 (1.197-2.444)			
Differentiation		0.054		0.058	-	-
Well/Moderate	33.8		1.000			
Poor	25.5		1.398 (0.989-1.978)			
T stage		<0.001		<0.001	-	-
T1-2	45.5		1.000			
T3-4	24.7		1.898 (1.382-2.606)			
N stage		<0.001		<0.001	-	-
N0	49.3		1.000			
N1-3	11.8		2.852 (2.120-3.836)			
TNM stage		<0.001		<0.001		<0.001
I	58.0		1.000		1.000	
II	38.9		1.966 (1.259-3.067)	0.003	1.825 (1.164-2.861)	0.009
III	13.8		3.799 (2.490-5.736)	<0.001	3.624 (2.362-5.560)	<0.001
Adjuvant therapy		0.085		0.090	-	-
No	35.6		1.000			
Yes	24.4		1.297 (0.960-1.753)			
CRP (mg/l)		<0.001		<0.001		<0.001
≤ 10.0	39.5		1.000		1.000	
> 10.0	13.0		2.066 (1.526-2.798)		1.994 (1.461-2.722)	
MPV (fl)		0.019		0.021	-	-
≤ 8.5	41.3		1.000			
> 8.5	27.6		1.451 (1.057-1.992)			
PC (giga/l)		0.009		0.011	-	-

≤ 200	41.0		1.000			
> 200	26.7		1.488 (1.097-2.019)			
MPV/PC		<0.001		<0.001		<0.001
> 0.04	43.1		1.000		1.000	
≤ 0.04	22.4		1.861 (1.386-2.498)		1.823 (1.347-2.469)	
CEA (ng/ml)		0.027		0.031		0.019
≤ 5.0	33.5		1.000		1.000	
> 5.0	23.7		1.549 (1.042-2.302)		1.613 (1.082-2.407)	
Neu (giga/l)		<0.001		<0.001		0.007
≤ 4.2	43.8		1.000		1.000	
> 4.2	19.1		1.945 (1.455-2.600)		1.512 (1.120-2.040)	
Neu/PC		0.223		0.229	-	-
≤ 0.02	35.3		1.000			
> 0.02	27.1		1.195 (0.894-1.597)			

2   ESCC: esophageal squamous cell carcinoma; CRP: c-reactive protein; MPV: mean platelet volume; PC:

3   platelet count; TNM: tumor node metastasis; CEA: carcinoembryonic antigen; Neu: neutrophil; CI: confidence

4   interval; HR: hazard ratio.

Table 3(on next page)

Comparison of AUC areas for the prognostic factors in ESCC

Comparison of AUC areas for the prognostic factors in ESCC

1 **Table 3 Comparison of AUC areas for the prognostic factors in ESCC**

	Cut-off	Sensibility	Specificity	AUC	95% CI	P-value
MPV/PC	0.0410	62.9	61.7	0.608	0.548-0.666	Reference
MPV	8.25	84.6	34.8	0.609	0.549-0.667	0.9834
PC	243.5	50.0	74.2	0.648	0.588-0.704	0.0181
Neu	4.25	53.7	76.4	0.689	0.630-0.743	0.1123
Neu/PC	0.0213	38.3	74.2	0.543	0.482-0.603	0.3269

2 ESCC: esophageal squamous cell carcinoma; AUC: area under the curve; MPV: mean platelet volume; PC:

3 platelet count; Neu: neutrophil.

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Table 4(on next page)

Multivariate analyses with the cut-off values by ROC curve

Multivariate analyses in ESCC with the cut-off values by ROC curve

1   **Table 4 Multivariate analyses in ESCC with the cut-off values by ROC curve**

	HR (95% CI)	P-value
CRP (mg/l) (> 10.0 vs. ≤ 10.0)	2.060 (1.511-2.807)	<0.001
TNM stage		
II vs. I	1.816 (1.160-2.844)	0.009
III vs. I	3.529 (2.298-5.417)	<0.001
MPV/PC (≤ 0.0410 vs. > 0.0410)	1.728 (1.275-2.342)	<0.001
CEA (ng/ml) (> 5.0 vs. ≤ 5.0)	1.636 (1.097-2.438)	0.016
Neu (giga/l) (> 4.25 vs. ≤ 4.25)	1.553 (1.150-2.096)	0.004

2   ESCC: esophageal squamous cell carcinoma; CSS: cancer-specific survival; CRP: c-reactive protein; MPV:

3   mean platelet volume; PC: platelet count; TNM: tumor node metastasis; CEA: carcinoembryonic antigen; Neu:

4   neutrophil; CI: confidence interval; HR: hazard ratio.

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Figure 1

The histograms of the MPV (A), PC (B) and MPV/PC ratio (C)

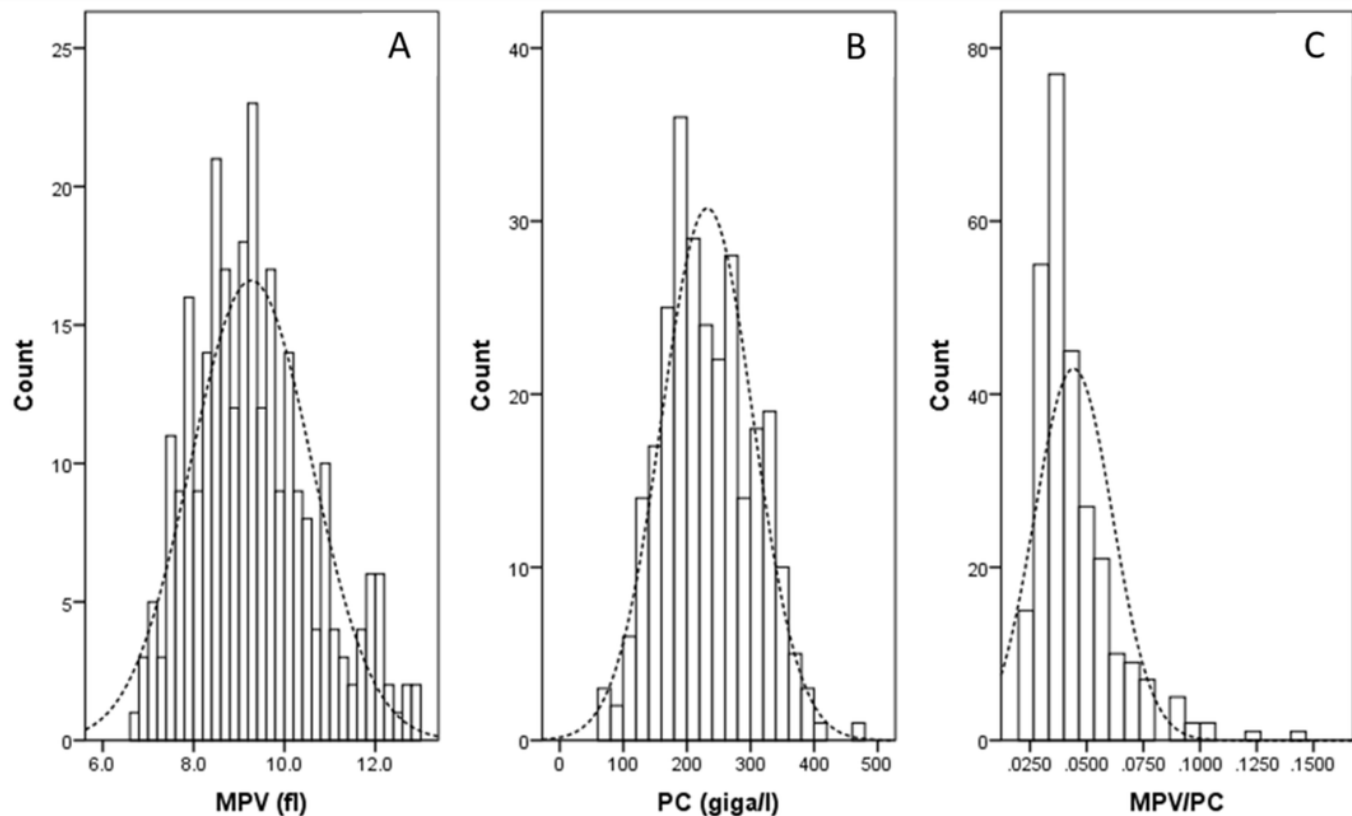The histograms of the MPV (A), PC (B) and MPV/PC ratio (C)

Figure 2

X-tile analyses.

X-tile plots of the training sets are shown in the left panels, with plots of matched validation sets shown in the smaller inset. The optimal cut-off points highlighted by the black circle in Fig. A, D, G, J, M are shown on the histograms of the entire cohort (Fig. B, E, H, K, N) and Kaplan-Meier plots (Fig. C, F, I, L, O). According to the X-tile program, the optimum cut-off points for MPV (A-C), PC (D-F), MPV/PC (G-I), Neu (J-L) and Neu/PC ratio (M-O) were 8.5 (fl), 200 (giga/l), 0.04, 4.2 (giga/l) and 0.02, respectively.
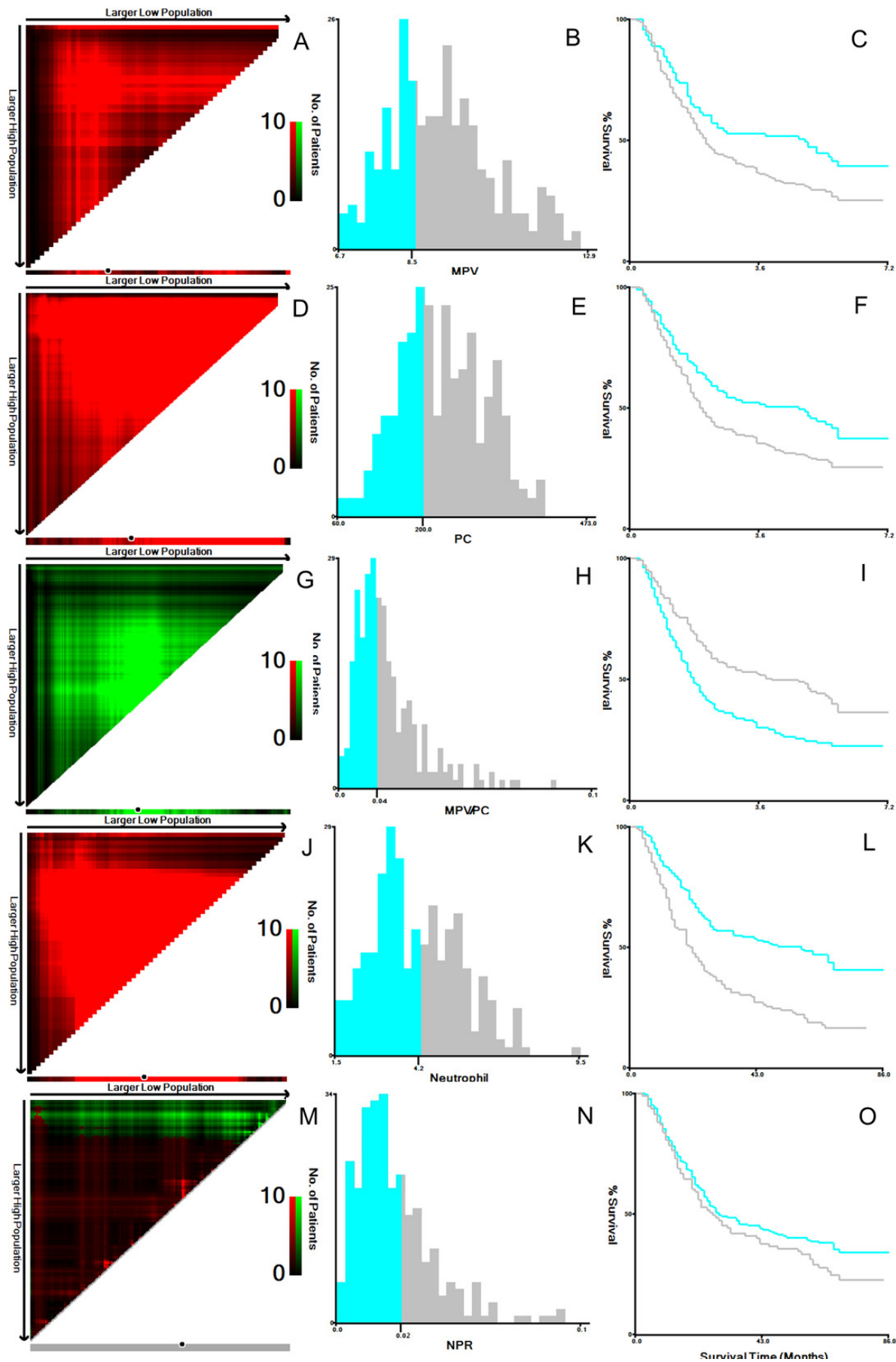
Figure 3

Kaplan-Meier CSS curves.

Patients with MPV/PC ratio >0.04 had a significantly better 5-year CSS than patients with MPV/PC ratio ≤0.04 (43.1% vs. 22.4%, P <0.001; A). The 5-year CSS were also significantly different for MPV (42.4% vs. 27.0%, P =0.010; B) and PC (41.0% vs. 26.7%, P =0.009; C). When we set the cut-off points using ROC curve, the MPV/PC ratio (42.7% vs. 23.5%, P <0.001; D), MPV (51.7% vs. 26.7%, P =0.001; E), and PC (41.8% vs. 19.3%, P <0.001; F) were also associated with CSS.
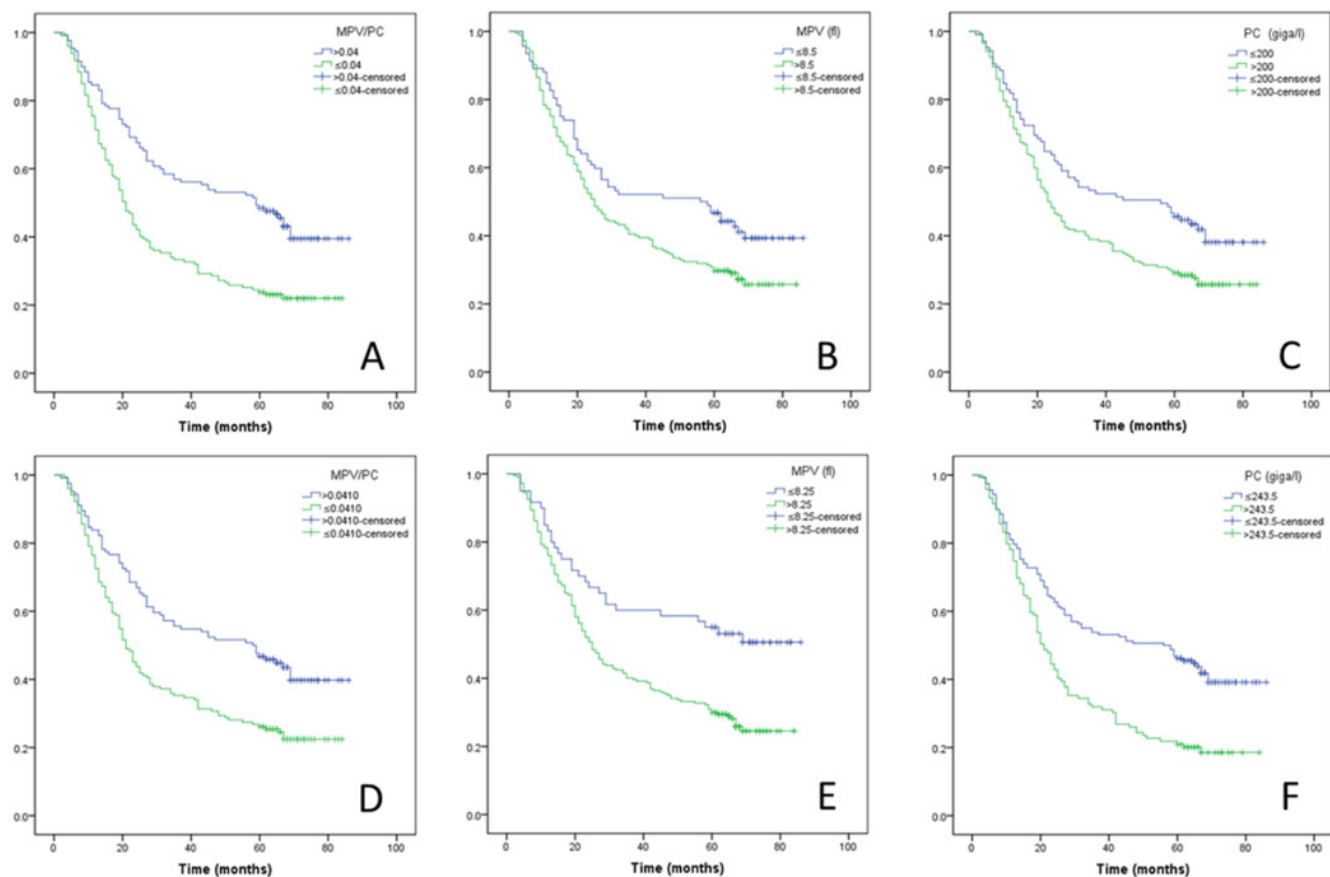
Figure 4

ROC curve analysis.

The cut-off values for Neu, MPV, PC, MPV/PC, and Neu/PC ratio by the ROC curves were 4.25 (giga/l), 8.25(fl), 243.5 (giga/l), 0.0410, and 0.0213, respectively.
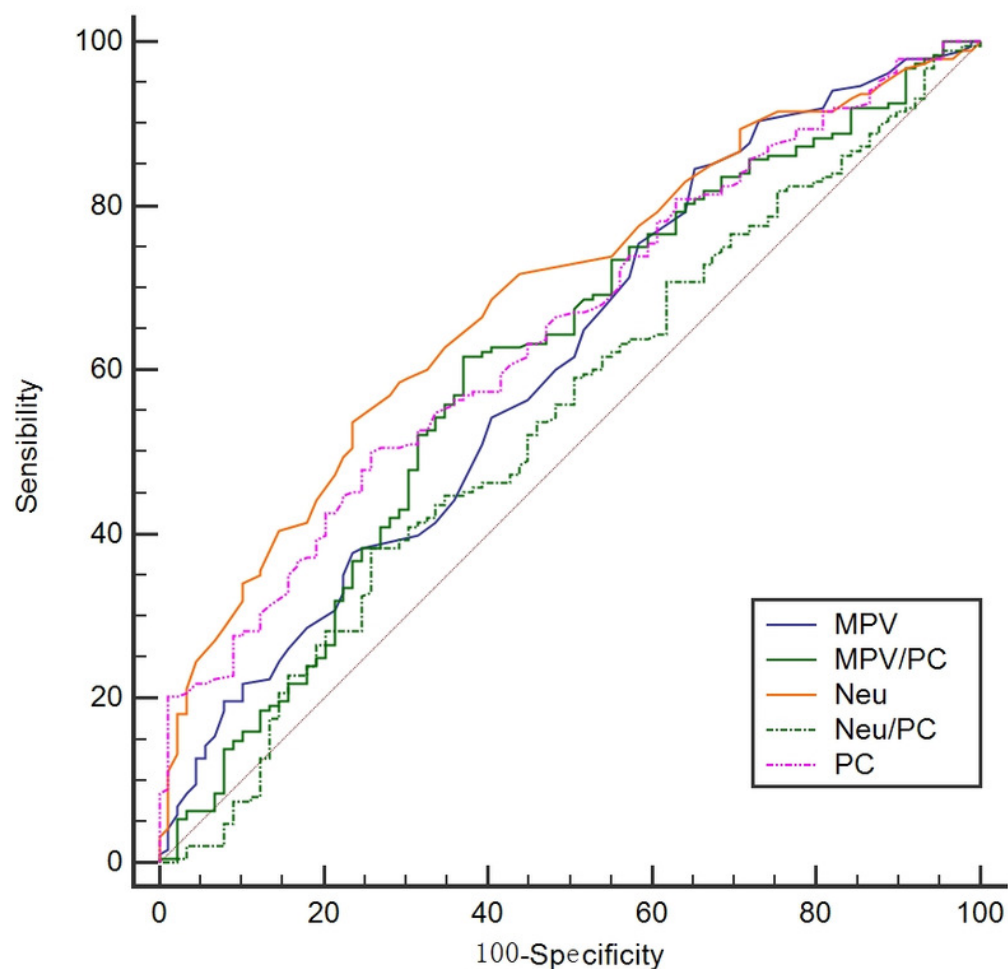
Figure 5

Nomogram model for prediction

The Harrell's c-index for CSS prediction was 0.72. A nomogram predicts survival prediction based on MPV/PC and other prognostic factors in patients with ESCC. The nomogram is used by totalling the points identified at the top of the scale for each independent factor. This total point score is then identified on the total points scale to determine the probability of risk prediction (A) and survival prediction (B).