Prognostic Role of Preoperative D-Dimer, Fibrinogen and Platelet Levels in Patients with Oral Squamous Cell Carcinoma

Yu-jie Liang
Sun Yat-Sen University Guanghua School of Stomatology
Xue-ying Mei
Sun Yat-Sen University Guanghua School of Stomatology
Bin Zeng
Sun Yat-Sen University Guanghua School of Stomatology
Si-en Zhang
Sun Yat-Sen University Guanghua School of Stomatology
Le Yang
Sun Yat-Sen University Guanghua School of Stomatology
Xiao-mei Lao (laoxm3@mail.sysu.edu.cn)
Sun Yat-Sen University Guanghua School of Stomatology https://orcid.org/0000-0001-5767-1823
Gui-qing Liao
Sun Yat-Sen University Guanghua School of Stomatology

Research article

Keywords: D-dimer, fibrinogen, platelet, oral squamous cell carcinoma, prognosis

Posted Date: July 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-39808/v1

Version of Record: A version of this preprint was published on February 5th, 2021. See the published version at https://doi.org/10.1186/s12885-021-07841-5.

Abstract

Background: The relationship between cancer and coagulation have been intensively studied in recent years, however, the effects of coagulation factors on oral squamous cell carcinoma (OSCC) had not been reported. This study aimed to investigate the relationship between preoperative D-dimer (DD), fibrinogen (FIB), platelet (PLT) and OSCC, as well as the prognostic value of them.

Methods: We retrospectively investigate a total of 202 OSCC patients treated in Guanghua Hospital of Stomatology, Sun Yat-sen University. Baseline demographic and clinicopathological information as well as both preoperative and postoperative DD, FIB and PLT results were collected from each patient if available, all patients were follow-up to disease progression, death or end of study. The correlations between preoperative DD, FIB, PLT and other clinical features, therapeutic effect and PFS were analyzed statistically, postoperative DD and surgical parameters were also analyzed.

Results: Preoperative DD were found significantly correlated with T stage, N stage, Clinical stage and relapse of OSCC (*P*=0.000, 0.001, 0.000 and 0.000, respectively). Univariate and multivariate Cox regression analysis showed that, high preoperative DD independently predict poor prognosis in patients with OSCC (r=2.1, *P*=0.033). While FIB and PLT showed no prognostic values. Postoperative DD were found significantly correlated with preoperative DD and surgical type, but not the time consuming of surgery (*P*=0.005, 0.001 and 0.244, respectively).

Conclusion: In this study, for the first time, we reported that, preoperative plasma DD was an independent predictor for OSCC stage and patient survival.

Background

Oral squamous cell carcinoma (OSCC) is one of the most commonly seen malignancy in head and neck region, tumor cell proliferation and metastasis was in high rate even at the very first stage of primary tumor. Approximately one-half of patients were already in advanced stages of diseases when diagnosis (1). And despite remarkable advances in diagnostic techniques and therapeutic methods, long-term survival rates of oral squamous cell carcinoma remain poor.

Correlation between cancer and hypercoagulation has been noticed since 19th century, as global hemostasis is more frequently activated in patients with cancer, and much attention has been devoted into this research field. D-dimer (DD) is a degradation product of the cross-linked fibrin polymer, sensitive for both coagulation and fibrinolysis activation (2). Fibrinogen (FIB) and platelet (PLT) can also partly review the coagulation state of the patient. Previous studies have reported that pretreatment plasma DD, FIB and PLT level can predict prognosis in serval types of malignancies including ovarian (3), breast (4, 5), lung (6, 7), colorectal (8), gastric (9), and pancreatic cancers (10). However, few studies have reported the use of preoperative DD level to predict the prognosis of oral cancer. To our best knowledge, this is the first study to address the prognostic significance of perioperative DD, FIB and PLT levels and their relationship with clinicopathologic parameters in OSCC patients.

Methods

Patients

This study was carried out at Guanghua Hospital of Stomatology, Sun Yat-sen University, all procedures involving human participants were approved by the hospital Ethics Committee, and written informed consent have been obtained. We retrospectively review cases from January 2015 to December 2018, patients included in the study were pathologically confirmed oral squamous cell carcinoma cases, without distant metastasis, and both primary and recurrent cases were analyzed. Patients with either following criteria were excluded: 1) with any other malignancy; 2) venous thromboembolic diseases; 3) unstable angina; 4) severe infection; 5) history of anticoagulant drug use within two weeks before surgery. Finally, a total of 202 cases were included, TNM classification was established according to the Union for International Cancer Control (UICC) 2015 guidelines. Preoperative plasma DD, FIB and PLT level (measured within 1week before surgery), and postoperative DD, FIB and PLT level (measured 24 hours, 48 hours and 96 hours after surgery) were collected. Other demographic and clinical information collected included: age, sex, tumor location, TNM staging, treatment type, surgical duration, as well as postoperative adverse effects.

Treatment and follow-up

Patients were prescribed to different treatment schedule according to NCCN guidelines for head and neck cancer, 2015 version. Patient follow-up was conducted at three-month intervals for the first 3 years after surgery, and then every 6 months later, until April 2019, disease progression, death, or lost to follow-up. And was carried out either by patient follow-up visit or telephone follow-up at each scheduled time.

Progression free survival (PFS) was chosen as the study endpoint, and was defined as the interval from surgery to local or distant relapse and/or metastasis, whichever happened first. Survival time was considered as censored if the patients died, were lost to follow-up, or were progression-free at the end of the study.

Statistical analysis

Quantitative data are described by mean (range), and qualitative data are described as counts and percentages. The χ^2 test was used to evaluate the association between clinicopathologic parameters and preoperative plasma DD, FIB and PLT levels. The PFS was estimated by the Kaplan-Meier method, and differences in various prognostic factors were analyzed by Cox regression analysis. Univariate analysis was used to identify significant prognostic predictors for PFS, and factors with *P* values of ≤0.1 were subjected to multivariate analysis for PFS by Cox proportional hazard analysis. *P* values ≤0.05 were regarded statistically significant. All confidence intervals were set as 95% confidence level. All statistical calculations were conducted by SPSS version 20.0.

Results

Patient characteristics

We collected a total of 202 cases in this retrospective study, including 148 male and 54 female, with a mean age of 56.3 (median 56, range 25-89) years old. Of the 202 patients, 155 showed up in our department with primary OSCC, and the remaining 47 had recurrent lesions after surgical treatment in other medical institutions. The mean follow-up period was 13.62 (median 10, range 1 to 56) months. The clinical parameters of all 202 patients are shown in table 1.

Relationship between preoperative plasma DD, FIB, PLT level and clinicopathologic parameters

Of the 202 patients, preoperative FIB and PLT levels were closely related with each other (r=0.376, *P*=0.000), however, preoperative DD level and preoperative FIB and PLT levels were not significantly related (*P*=0.053 and 0.636, respectively).

Preoperative plasma DD, FIB、PLT level and clinicopathologic parameters including age, sex, tumor location, TNM staging, surgical treatment and duration are summarized in table 2. The mean preoperative DD level was 499.45μg/L, and refer to the manufacturer's recommendation, plasma DD level of 500μg/L was set as cutoff value for normal and high DD values. The mean preoperative FIB and PLT level was 3.33 g/L and 259.5*10^9/L, and were set as cutoff value for low and high value of FIB and PLT respectively. In this study, we found that preoperative DD level in different sex or age group patients was not statistically different (*P*=0.187 and 0.062 respectively), however, in different site of tumor, different T stage, N stage, and clinical stage patients, preoperative DD level was significantly different (*P*=0.040, 0.000, 0.001 and 0000 respectively). However, when concerning preoperative FIB and PLT levels, we found different results, preoperative FIB level was different in sex and N stage category only (*P*=0.025 and 0.002 respectively), and preoperative PLT level was different in tumor site and clinical stage category only (*P*=0.048 and 0.040 respectively).

The means of DD, FIB and PLT in primary oral cancer patients were 424.96μg/L, 3.49 g/L and 249.11*10^9/L respectively, and in patients with recurrent tumor were 752.07μg/L, 3.82 g/L and 283.72*10^9/L respectively. The difference of DD and FIB level between primary and recurrent cancer was of statistical significance (*P*=0.018 and 0.038 respectively) (Figure 1).

Relationship between postoperative DD change and treatment related parameters

We retrospectively observed postoperative DD level in the first 3 days after surgery, and 96 patients with postoperative DD results. Postoperative DD level was found elevated in all the 96 patients in the very first day after surgery, and slowly goes down with time. The elevated level was correlated with preoperative DD level (r=0.284, *P*=0.005) as well as the surgical type (r=0.344, *P*=0.001), but not the time consuming of surgery (*P*=0.244) (Table 3).

Survival analysis of primary OSCC patients

According to NCCN guideline and patient desire, the 155 primary OSCC patients were prescribed to different surgical plant, including 1) excision of primary lesion (19.4%), 2) excision of primary lesion and neck dissection (25%), 3) excision of primary lesion and vascularized free flap transplantation (0.9%), 4) excision of primary lesion, neck dissection and vascularized free flap transplantation (51.9%), and 5) un-operated (2.8%). Of the 155 primary oral cancer patients, recurrence was diagnosed in 33 patients after surgical treatment in our department, rated 21.29%，and 26 of them died in follow-up time. The time from surgery to disease progression ranged from 1 to 34 months. Univariate analyses revealed that N stage (P=0.003) and preoperative DD level (P=0.033) were predictors of PFS. And in multivariate analysis, we demonstrated that pre-surgery plasma DD level was an independent prognostic factor in patients with primary OSCC (P=0.042) (Table 4, figure 2).

In our study, PFS was 78.7%. Patients with normal preoperative DD (＜500μg/L) had a significant better PFS than patients with high preoperative DD (≥500μg/L) (81.7% vs.74.2%, P=0.027) .

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Discussion

In this study, we evaluate the relationship between preoperative DD, FIB, PLT level and the clinicopathological characters of OSCC, as well as the prognostic effect of preoperative DD, FIB and PLT. To our best knowledge, this is the first study to address such issue. We found that, preoperative DD was significantly different in OSCCs with different primary site or clinical stage, and DD could serve as an independent prognostic factor for OSCC patients.

However, preoperative FIB and PLT did not show such strong predictive effects. Previous studies had reported that preoperative DD, FIB and PLT had certain prognostic value in several types of cancer (11), including small cell lung cancer (7), hepatocellular carcinoma (6), pancreatic adenocarcinoma (10), gastric cancer (12), and melanoma (13). PLT was found contributed to cancer progression through both thrombin-dependent and thrombin-independent mechanisms (14). FIB is important in blood clotting, fibrinolysis as well as cellular and matrix interactions (15). Zheng S et al. found that, FIB can enhance PLT adhesion to tumor cells, and PLT in turn can release thrombin and facilitate FIB aggregation (16). But not as most studies of DD, which set the cut-off value in 500 ng/L, there was no consistent cut-off value of FIB and PLT in most of the studies. Hou C et al. (7) set the cut-off value of FIB and PLT as 2.75 g/L and 215*10^9/L, respectively, and they found marginally significant relationship between elevated PLT and unfavorable PFS (P = 0.05), and no prognostic role for FIB. In study by Liu Z and Liu P (6, 10), they use 4.0 g/L as cut-off value for FIB, and 300*10^9/L for PLT, both found significantly correlated with overall survival (P＜0.001, and P = 0.010, respectively). In our study, the cut-off values of FIB and PLT were set as the mean value, and found no significant predictive value for PFS. We supposed that, the inconsistent result between our study and previous studies might be tumor type specific or it can partly be attributed to the different sensitivity and different cut-off values of FIB and PLT in different articles.

It is well known that surgical trauma is associated with coagulation, and Friedrich found that DD increased at the end of surgery and remained increased 24 hours after surgery (17). To further reveal the trauma caused by surgical treatment on OSCC patients, we evaluate the postoperative DD levels and found that postoperative DD was remarkably elevated within 24 hours, and then went down slowly with time, if there were no adverse effects like local or general infection or venous thrombosis happened. Moreover, the rising DD significantly correlated with surgical types, but not the duration of surgery. In particularly, patients who underwent the most extensive surgery had the highest elevation of postoperative DD level, suggesting that surgical trauma is correlated with the extent of surgery, but not the time consuming of surgery. Relationship of elevated DD and local or general infection and deep vein thrombosis (DVT) was not found in our study, as there were limited cases developed infection (6/202) and DVT (1/202) after surgery. We also investigated the postoperative DD level with PFS, and found it was of no prediction effect of PFS.

Conclusions

DD is an easily measured and reproducible molecular marker. Plasma DD can be routinely measured prior to operations various hospitals. In this study, we found that preoperative DD was significantly correlated with T stage and N stage, and predicts poor PFS of OSCC patients. Thus, we suggest that preoperative DD can be useful in predicting tumor stage and postoperative survival in patients with OSCC. In addition, postoperative DD can partly reflect surgical trauma and postoperative adverse effects like infection or venous thrombosis. Therefore, we suggest that preoperative and postoperative DD can be obtained as part of routine care for OSCC patients.

List Of Abbreviations

abbreviation	Full name
DD	D-dimer
FIB	Fibrinogen
PLT	Platelet
OSCC	Oral squamous cell carcinoma
PFS	Progression free survival
UICC	Union for International Cancer Control
NCCN	National Comprehensive Cancer Network

Declarations

Conflict of interest statement: The authors declare no potential conflicts of interest.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guanghua Hospital of Stomatology, Sun Yat-sen University, with the approval number signed as 2011-02.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study is supported by grant from 5010 clinical medical research project of Sun Yat-sen University, grant number: 2010018.

Authors' contributions

Yujie Liang, Xiaomei Lao and Guiqing Liao conceived and designed the experiments. Yujie Liang and Xueying Mei contributed in acquisition of data, performed the experiments. Sien Zhang contributed in patient followed-up. Bin Zeng and Le Yang analyzed and interpretation of the data. Yu-jie Liang wrote the paper. Xiaomei Lao and Guiqing Liao revised the manuscript and gave final approval of the version to be published. And all authors read and approved the final manuscript.

Acknowledgment

This study is supported by grant from 5010 clinical medical research project of Sun Yat-sen University, grant number: 2010018.We thank Xiao Dongtao from clinical laboratory, Guanghua Hospital of Stomatology, Sun Yat-sen University, for providing results of DD, FIB, and PLT testing.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43–66.
2. Adam SS, Key NS, Greenberg CS. D-dimer antigen: Current concepts and future prospects. Blood. 2009;113:2878–87.

3. Man Y, Wang Y, Hao J, Liu X, Liu C, Zhu C, et al. Pretreatment plasma D-dimer, fibrinogen, and platelet levels significantly impact prognosis in patients with epithelial ovarian cancer independently of venous thromboembolism. Int J Gynecol Cancer. 2015;25:24–32.
4. Batschauer AP, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LM, Fernandes AP, et al. D-dimer as a possible prognostic marker of operable hormone receptor negative breast cancer. Ann Oncol. 2010;21:1267–72.
5. Ghadhban BR. Plasma d-dimer level correlated with advanced breast carcinoma in female patients. Ann medic surg. 2018;36:75–8.
6. Liu Z, Guo H, Gao F, Shan Q, Li J, Xie H, et al. Fibrinogen and D-dimer levels elevate in advanced hepatocellular carcinoma: High pretreatment fibrinogen levels predict poor outcomes. Hepatol Res. 2017;47:1108–17.
7. Hou C, Jiang F, Ma H, Zhu Q, Wang Z, Zhao B, et al. Prognostic role of preoperative platelet, fibrinogen, and D-dimer levels in patients with non-small cell lung cancer: A multicenter prospective study. Thorac cancer. 2019;10:304–11.
8. Yamamoto M, Yoshinaga K, Matsuyama A, Iwasa T, Osoegawa A, Tsujita E, et al. Plasma D-dimer level as a mortality predictor in patients with advanced or recurrent colorectal cancer. Oncology. 2012;83:10–5.
9. Go SI, Lee MJ, Lee WS, Choi HJ, Lee US, Kim RB, et al. D-dimer can serve as a prognostic and predictive biomarker for metastatic gastric cancer treated by chemotherapy. Med (Baltim). 2015;94:e951.
10. Liu P, Zhu Y, Liu L. Elevated pretreatment plasma D-dimer levels and platelet counts predict poor prognosis in pancreatic adenocarcinoma. Onco Targets Ther. 2015;8:1335–40.
11. Li W, Tang Y, Song Y, Chen S, Sisliyan N, Ni M, et al. Prognostic role of pretreatment plasma D-dimer in patients with solid tumors: a systematic review and Meta-analysis. Cell Physiol Biochem. 2018;45:1663–76.
12. Kanda M, Tanaka C, Kobayashi D, Mizuno A, Tanaka Y, Takami H, et al. Proposal of the Coagulation Score as a Predictor for Short-Term and Long-Term Outcomes of Patients with Resectable Gastric Cancer. Ann Surg Oncol. 2017;24(2):502–9.
13. Anna D, Christoffer G, Jochen U, Stefan WS. D-dimers in malignant melanoma: Association with prognosis and dynamic variation in disease progress. Int J Cancer. 2017;140:914–21.
14. Camerer E, Qazi AA, Duong DN, Cornelissen I, Advincula R, Coughlin SR. Platelets, protease-activated receptors, and fibrinogen in hematogenous metastasis. Blood. 2004;104:397–401.
15. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost. 2005;3(8):1894–904.
16. Zheng S, Shen J, Jiao Y, Liu Y, Zhang C, Wei M, et al. Platelets and fibrinogen facilitate each other in protecting tumor cells from natural killer cytotoxicity. Cancer Sci. 2009;100:859–65.
17. Friedrich MJ, Schmolders J, Rommelspacher Y, Strauss A, Ruhl H, Mayer G, et al. Activity pattern analysis indicates increased but balanced systemic coagulation activity in response to surgical

trauma. TH Open. 2018;2(4):e350-6.

Tables

Table 1
Demographic and clinical characteristics of the patients.

Clinical characteristic	Category	N(%)
Sex		
	Male	148(73.3)
	Female	54(26.7)
Age(years)		
	60	130(64.4)
	≥ 61	72(35.6)
Tumor site		
	Tongue	93 (46.0)
	Buccal mucosa	33 (16.3)
	Gingiva	40 (19.8)
	Floor of mouth	18 (8.9)
	Palate	8 (4.0)
	Lip	4 (2.0)
	Lymph node in the neck	6 (3.0)
T stage		
	T1(primary)	29(14.36)
	T2(primary)	53(26.24)
	T3(primary)	26(12.87)
	T4(primary)	47(23.27)
	Relapse & metastasis	47(23.27)
N stage		
	N0(primary + relapse)	95 + 28(60.89)
	N+(primary + relapse)	60 + 19(39.11)
Clinical stage		
		25(12.38)
		40(19.80)
		25(12.38)

Clinical characteristic	Category	N(%)
	□	65(32.18)
	Relapse	47(23.27)
Primary or relapse		
	Primary	155(76.73)
	Relapse	47(23.27)
Preoperative D-dimer		
(μg/L)	Median	358.47
	First and third quality	184.36, 581.74
Preoperative FIB		
(g/L)	Median	3.56
	First and third quality	2.88, 4.08
Preoperative PLT		
(10^9/L)	Median	246.5
	First and third quality	210.00, 305.00

Table 2
Correlation between plasma DD, FIB, PLT levels and patient/tumor characteristics in OSCC cases.

Variables	Preoperative DD (μg/L)			Preoperative FIB (g/L)			Preoperative PLT (10^9/L)		
	□500	≥ 500	*P*	□3.33	≥ 3.33	*P*	□259.5	≥ 259.5	*P*
Sex			0.187			0.025			0.114
Male	105	43		51	97		78	63	
Female	34	20		28	26		40	21	
Age			0.062			0.070			0.415
□60	92	33		55	70		70	53	
≥60	47	30		24	53		47	32	
Tumor site			0.040			0.387			0.048
Tongue	74	19		42	51		58	28	
Buccal mucosa	18	15		12	21		18	11	
Gingiva	23	17		13	27		22	25	
Floor of mouth	14	4		8	10		11	9	
Palate	4	4		1	7		1	7	
Lip	2	2		2	2		1	1	
Neck (LN)	4	2		1	5		6	4	
T stage			0.000			0.129			0.194
T1(primary)	26	3		14	15		15	9	
T2(primary)	39	14		21	32		36	16	
T3(primary)	23	3		11	15		14	7	
T4(primary)	30	17		22	25		30	28	
Relapse	21	26		11	36		23	24	
N stage			0.001			0.002			0.167
N0(Primary)	75	20		34	61		56	28	
N+(Primary)	43	17		34	26		39	32	
N0(Relapse)	12	16		9	19		15	13	

Variables	Preoperative DD (μg/L)			Preoperative FIB (g/L)			Preoperative PLT (10^9/L)		
	<500	≥ 500	*P*	<3.33	≥ 3.33	*P*	<259.5	≥ 259.5	*P*
N+(Relapse)	9	10		2	17		8	11	
Clinical stage			0.000			0.094			0.040
Ⅰ	22	3		11	14		14	3	
Ⅱ	30	10		15	25		27	10	
Ⅲ	21	4		10	15		13	12	
Ⅳ	45	20		32	33		41	35	
Relapse	21	26		11	36		23	24	
Primary/Relapse			0.000			0.012			0.113
Primary	118	37		68	87		96	59	
Relapse	21	26		11	36		23	24	

Table 3
Correlation between postoperative DD change and treatment related characters.

	Preoperative DD		Surgery type		Time consuming of surgery	
	r	*P*	r	*P*	r	*P*
Postoperative DD	0.284	0.005	0.344	0.001	0.132	0.244

Table 4
Univariate and multivariate analysis for disease-free survival of patients with primary OSCC.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex		0.466		
Male	1.00			
Female	0.73(0.32–1.69)			
Age(years)		0.834		
60	1.00			
≥60	1.08(0.52–2.23)			
T stage		0.884		
T1 ~ T2	1.00			
T3 ~ T4	1.05(0.53–2.08)			
N stage		0.003		0.007
N0	1.00		1.00	
N1	0.68(0.20–2.38)	0.548	0.723(0.21–2.55)	0.619
N2	2.20(1.05–4.57)	0.036	2.46(1.16–5.23)	0.019
N3	33.94(3.65–315.9)	0.002	19.34(2.00-186.96)	0.010
Clinical stage		0.499		
~	1.00			
~	1.29(0.62–2.72)			
Pre. D-dimer		0.033		0.040
500 μg/L	1.00		1.00	
≥500 μg/L	2.10(1.06–4.16)		1.98(0.98–3.97)	
Pre. FIB		0.097		0.100
3.33 g/L	1.00		1.00	
≥3.33 g/L	1.88(0.89–3.95)		1.94(0.88–4.26)	
Pre. PLT		0.699		
259.5*10^9/L	1.00			

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
≥ 259.5*10^9/L	0.86(0.40–1.84)			
Surgical type		0.732		
1	1.00			
2	1.40(0.57–3.44)	0.461		
3	1.53(0.70–3.34)	0.284		
4	0.00(0.00-)	0.983		
Post.DD change		0.791		
1000 μg/L	1.00			
≥ 1000 μg/L	1.16(0.39–3.46)			
Post. PLT change		0.622		
60*10^9/L	1.00			
≥ 60*10^9/L	1.22(0.55–2.74)			

Figures

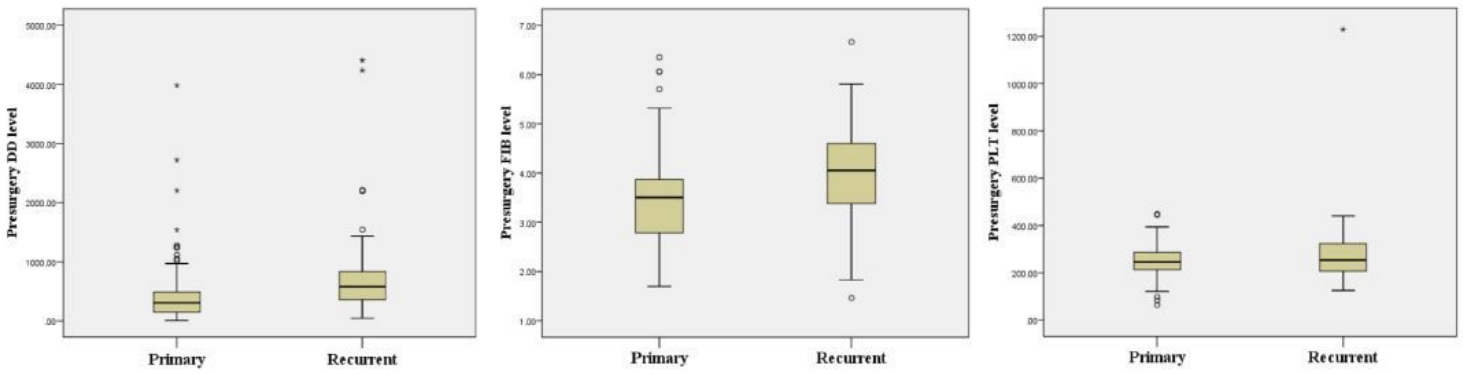

Figure 1

The difference of DD, FIB and PLT levels between primary and recurrent OSCC. P=0.018, 0.038 and 0.062, respectively.

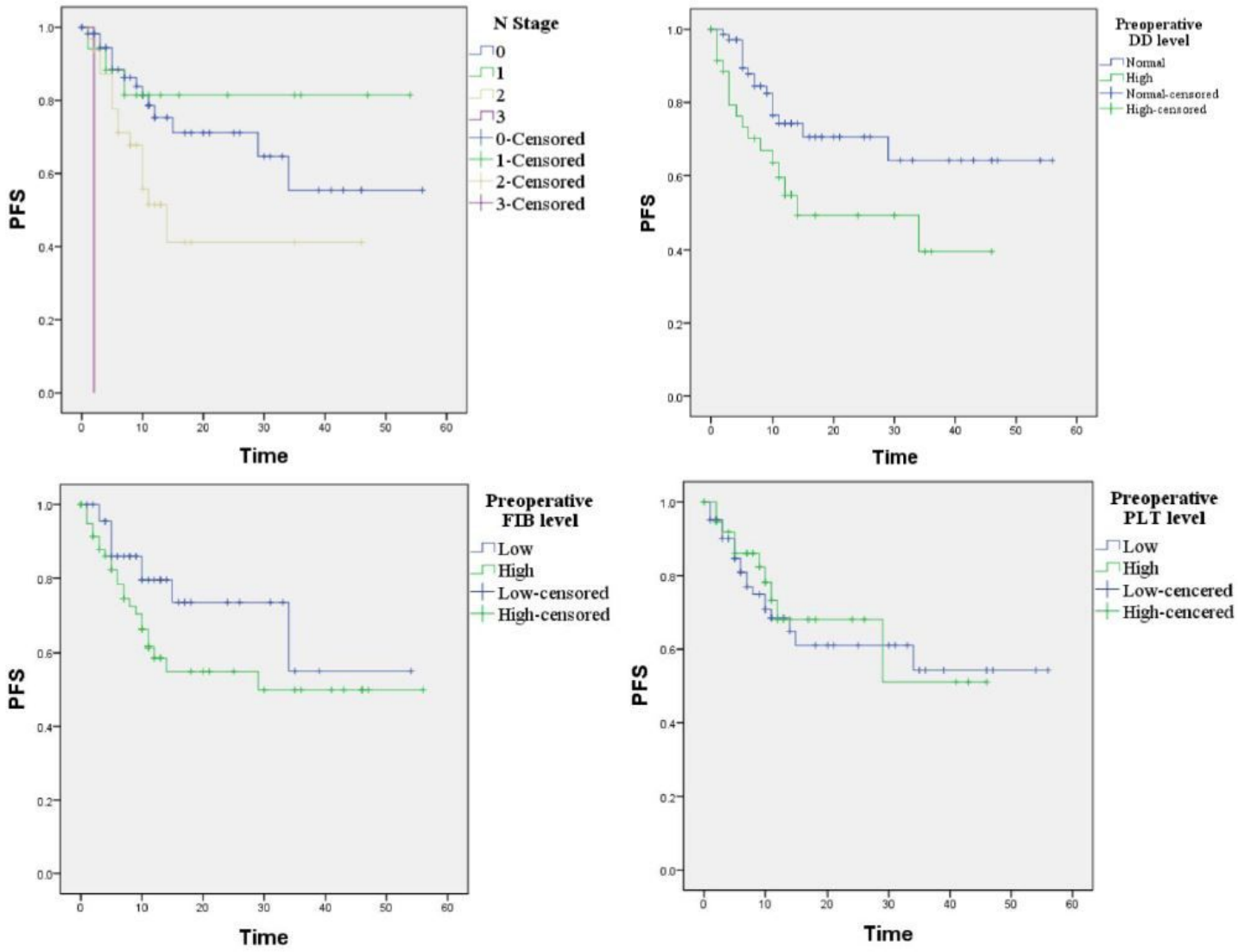

Figure 2

Survival analysis of primary OSCC patients. P=0.003、0.033、0.097 and 0.699, respectively.