Journal of Research in Clinical Medicine

J Res Clin Med, 2021, 9: 39
doi: 10.34172/jrcm.2021.039
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

The association between preoperative plasma D-dimer levels and early postoperative outcomes in patients with esophageal cancer

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Article info

Article History:
Received: 27 Nov. 2020
Accepted: 1 Jan. 2021
e-Published: 25 Dec. 2021

Keywords:
- Esophageal cancer
- D-dimer
- Clinical outcomes
- Complications
- Mortality
- Morbidity

Abstract

Introduction: The present study aimed to evaluate the efficacy of plasma D-dimer levels as predicting early morbidity and mortality in patients with esophageal cancer.

Methods: For this purpose, 60 patients who had surgery for middle- (n=35) and lower-thoracic esophageal cancer (n=25) were recruited. Then, preoperative plasma D-dimer levels were measured in a quantitative and qualitative manner and their relation with postoperative outcomes in each type of cancer was assessed for six months.

Results: With regard to the middle-thoracic esophageal cancer, complications were observed in 14 cases and six deaths were reported. Considering the lower type, morbidity was found in 11 cases and mortality was seen in five patients. In both types of cancer, plasma D-dimer levels were significantly higher in patients with complications or deaths compared to those without complications and survivors. Sensitivity, specificity, as well as positive, and negative predictive value (P/NPV) of plasma D-dimer levels were 90.91%, 78.57%, 76.92%, and 91.67% for diagnosing morbidity of the lower-thoracic esophageal cancer and 80%, 85%, 57.14%, and 94.44% for predicting mortality in this type of cancer. Moreover, the given values were equal to 71.43%, 76.19%, 66.67%, and 80% for diagnosing complications of the middle-thoracic esophageal cancer and 83.3%, 72.41%, 38.46%, and 95.45% in predicting deaths induced by this type of cancer.

Conclusion: It was concluded that elevated plasma D-dimer levels could be accompanied by adverse events and early poor postoperative outcomes for esophageal cancer.

Introduction

Esophageal cancer (EC) is known as the eighth most common cancer worldwide and even the sixth leading cause of deaths due to cancer in the Iranian population.[1] This type of cancer needs surgery in 74.6% of cases; however, it is accompanied by morbidity and mortality.[2] Besides, EC, as reported in the related literature, is associated with high postoperative recurrence and five-year survival rates up to 49.4% even with surgical resection.[3]

Generally, various factors may form short- and long-term outcomes in EC patients.[4,5] It has been correspondingly reported that numerous coagulation factors may contribute to cancer growth, progression, and metastasis.[6] Generalized activation of blood coagulation along with procoagulant changes have been additionally associated with angiogenesis, tumor cell invasion and progression, as well as metastasis.[7] In this regard, plasma D-dimer, as an end-degradation product of fibrin, shows hemostasis activation and hypercoagulable state. In previous studies, elevated plasma D-dimer levels had been observed in acute venous thromboembolism, surgeries, infectious diseases, pregnancies, and various types of cancer. Likewise, high plasma D-dimer levels had been seen in patients affected with various malignant tumors including breast, lung, colorectal, and ovarian cancers.[8-11]

Similarly, some studies had demonstrated that higher plasma D-dimer levels were related to adverse outcomes in EC.[12] Therefore, D-dimer levels may provide significant information on lesion development and consequently predict surgical outcomes.

The present study was done to evaluate the prognostic value of plasma D dimer levels for predicting outcomes in patients with middle- and lower-thoracic EC undergoing transhiatal esophagectomy.

Methods

A total number of 60 patients (viz. 35 cases with middle- and 25 cases with lower-thoracic EC), undergoing surgery from August 2013 to February 2015, were recruited in this retrospective study. The inclusion criteria were patients aged 18-75 with pathologic diagnosis of EC, those with no history of neoadjuvant therapy, and cases with

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normal cardiopulmonary function. On the other hand, patients with simultaneous gastric pathology, deep vein thrombosis or anticoagulation therapy, as well as those with limitations for general anesthesia to perform surgery were excluded. For all patients, chest and abdomen computed tomography (CT) with contrast in association with endoscopic ultrasound was routinely performed.

The baseline demographic information such as age, gender, tumor location, size, smoking status, and the TNM Classification stage were recorded for all patients. Venous blood samples were taken one to three days before hospitalization. Plasma D-dimer assays were subsequently conducted by using immunometric flow analysis through sandwich enzyme-linked immunosorbent assay (ELISA) (Nycocard Reader), with the reference value < 500 ng/mL. All measurements were fulfilled in one laboratory. Afterwards, the patients received 5000 IU/mL unfractionated heparin subcutaneously until they were fully ambulant and wore compression stocking prior to surgery. Besides, transhiatal esophagectomy along with lymphadenectomy was further performed for the EC patients. Mortality was also defined as patient death during hospitalization or six months later during the follow-up period.

Statistical methods

All the data were analyzed using the SPSS Statistics software (version 17.0). The baseline data were additionally reported as mean standard deviation (SD) (namely, continuous data) or percentage (i.e., categorical data). The independent samples t-test was also utilized for quantitative data and Chi-square test or Fisher's exact test, as appropriate, were employed for between-group comparisons. Receiver operating characteristic (ROC) curve was additionally illustrated and area under the ROC curve (AUC) was calculated to define the cut-off point for the plasma D-dimer levels in predicting morbidity/mortality in EC. Using the cut-off point, sensitivity, specificity, and positive/negative predictive value (P/NPV) were computed. The P value < 0.05 was also considered significant.

Results

The baseline demographic information for the EC patients is presented in Table 1. The median age was 60. As well, 15 patients were smokers over the past year. By considering patients' age, gender, cigarette smoking history, and TNM staging, no significant difference was observed between two groups in this study.

The study showed that the plasma D-dimer levels were abnormal in 68.6% of cases who were affected with the middle-thoracic EC and 76% of those who suffered from the lower type.

Furthermore, postoperative complications were observed in 14 (40%) patients with the middle-thoracic EC including six cases with arrhythmias, four cases with pulmonary complications, two cases with anastomotic leak, and one patient with chylothorax. However, out of 11 (44%) patients with lower-thoracic EC, four cases had arrhythmias, three individuals had cervical anastomotic fistula, five cases had pulmonary thromboembolism, and one patient had acute respiratory distress syndrome. Mortality was also reported in six patients (17.4%) with the middle-thoracic EC and five individuals (20%) with the lower type. The leading causes of death were arrhythmias or pulmonary thromboembolism and even unknown ones (Table 2).

In patients with lower-thoracic EC who had complications, the mean plasma D-dimer levels were significantly higher than those who did not have any complication (1898.63 ± 1103.00 vs. 454.35 ± 172.09 ng/mL, $P < 0.001$). As well, the plasma D-dimer levels were significantly higher in individuals with mortality compared with alive patients (2605.20 ± 1334.55 vs. 711.00 ± 454.48 ng/mL, $P < 0.001$) (Table 2).

Moreover, the plasma D-dimer levels were significantly higher in middle-thoracic EC patients with morbidity compared with those without postoperative complications (2022.07 ± 640.67 vs. 570.47 ± 367.50 ng/mL, P value = 0.01) and in individuals with mortality compared with patients who were alive (3220.16 ± 1385.87 vs. 723.03 ± 481.26 ng/mL, $P < 0.001$).

Figure 1 demonstrates the ROC for the plasma D-dimer levels in predicting morbidity/mortality in patients with lower-thoracic EC. As well, the AUC of the plasma D-dimer levels for complications and deaths were equal to 0.922 ($P < 0.001$) and 0.965 ($P < 0.001$) with cut-off points of 614.5 and 1398.5 ng/mL, respectively. In lower-thoracic EC, sensitivity, specificity, and P/NPV of the plasma D-dimer levels in predicting complications were 90.91%, 78.57%, and 76.92%/91.67%, respectively. They were correspondingly equal to 80%, 85%, and 57.14%/94.44% in predicting mortality. The ROC for the plasma D-dimer levels in predicting morbidity and deaths in patients with middle-thoracic EC are shown in Figure 2. The AUC for complications and mortality were thus 0.878 ($P < 0.001$) and 0.920 (P value = 0.001), respectively. Moreover, the calculated cut-off points were 597.5 and 920 ng/mL, respectively. With regard to middle-thoracic EC patients, sensitivity, specificity, and P/NPV of the plasma D-dimer levels in predicting morbidity were 71.43%, 76.19%, and 66.67%/80%, respectively, and such values were separately equal to 83.3%, 72.41%, and 38.46%/95.45% in predicting mortality.

Discussion

Both of clinical manifestations and laboratory findings have demonstrated a well-documented relation between cancer and hemostasis.[13] It has been accordingly established that activation of coagulation and fibrinolytic systems are associated with tumor growth and its spread, regulation of inflammatory cell responses, as well as tumor

Table 1. Baseline, laboratory findings and outcomes

Variables		Middle thoracic EC (n=35)	Lower thoracic EC (n=25)	*P* value
Age (y)		62.63+6.28	67.82+3.28	0.182
Gender	Male	24 (40%)	17 (28.4%)	0.59
	Female	11 (18.3%)	8 (13.3%)	
Pathology	SCC	26 (74.3%)	2 (8%)	<0.0001
	Adenocarcinoma	9 (25.7%)	23 (92%)	
Postoperative complications	Arrhythmia	6 (17.1%)	4 (16%)	0.103
	ARDS	3 (8.5%)	2 (8%)	
	PTE	1 (2.8%)	3 (12%)	
	Anastomotic leak	2 (5.7%)	2 (8%)	
	Chylothorax	1 (2.8%)	0	
	RLN injury	1 (2.8%)	0	
Total mortality (n)		6 (17.1%)	5 (20%)	
Hospital mortality (n)		3 (8.55%)	3 (12%)	
	Stage			
	I	0	1	
	II	1	1	
	III	2	1	
180- day mortality (n)		3 (8.55%)	2 (8%)	0.197
	Stage			
	I	1	0	
	II	0	1	
	III	2	1	
	ARDS	1 (2.8%)	2 (8%)	
	PTE	2 (5.7%)	1 (4%)	
	Arrhythmia	2 (5.7%)	1 (4%)	
	MI	1 (2.8%)	0	
	Unknown	0	1 (4%)	
Stage	I	7 (20%)	3 (12%)	0.086
	II	18 (51.4%)	12 (48%)	
	III	10 (28.5%)	10 (40%)	
	IV	0	0	

Table 2. Comparison of mean plasma d-dimer levels and postoperative outcomes

	Tumor location	Variables	Mean ± SE		*P* value
			Non-present	Present	
Plasma D-dimer	Lower thoracic EC	Complications	454.35±172.09	1898.63±1103	<0.0001
		Mortality	711+454.48	1334.56±260.5	<0.0001
	Middle thoracic EC	Complications	570.47±367.5	2022.07±640.67	<0.0001
		Mortality	723±481.26	1385.87±322.16	<0.0001

SE: standard error; EC: esophageal carcinoma.

angiogenesis in cancer patients.[14] In this regard, D-dimer has been defined as the smallest particle produced from fibrin degradation in the coagulation activation system, which is considered as a sensitive marker of fibrinolytic activation.[15]

Previous studies have so far reported that the hemostatic system activation, especially plasma D-dimer levels, plays a significant role in tumor progression, as well as its dispersion and metastasis.[15-17] However, there is little research reflecting on the efficacy of D-dimer in EC outcomes.

In this study, the surgical outcomes for EC along with the role of plasma D-dimer levels in predicting short-term morbidity/mortality were evaluated. In view of this, postoperative complications and deaths had occurred in 14 and six cases with the lower-thoracic EC and in 11 and

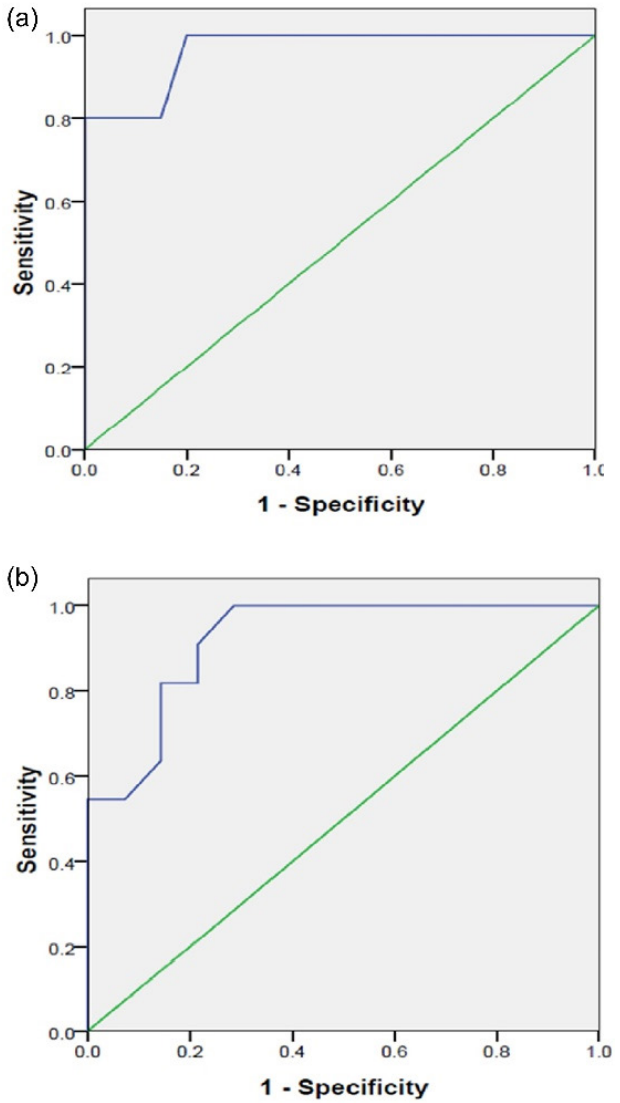

Figure 1. (a) ROC curve analysis of D-dimer levels in predicting complication in lower thoracic EC surgery. (b)ROC curve analysis of D-dimer levels in predicting mortality in lower thoracic EC surgery.

five individuals with the middle type, respectively. In both types of cancer, the plasma D-dimer levels were also higher in cases with complications and mortality compared with those who had normal outcomes. Similarly, Liu et al observed that the mean plasma D-dimer levels in patients with mortality were significantly higher than alive cases in their last follow-up.[17] Ay et al also reported that the overall survival rates of cancer patients had dropped as the plasma D-dimer levels had elevated.[7] Moreover, Oya et al established that the higher plasma D-dimer levels prior to surgery could be associated with lower overall survival rates.[10] Previous studies had further recommended measuring plasma D-dimer levels in preoperative work-up in EC patients.[18-20] Measurement of D-dimer levels had correspondingly shown acceptable but different sensitivity and specificity in predicting disease outcomes, responses to treatments, and overall survival rates after surgery in different types of cancer. The results in the present study were accordingly consistent with those in previous research, implying that D-dimer and albumin could be deemed as prognostic factors for EC. However, the findings were in contrast with the results reported by Zhang et al, suggesting that D-dimer was not a prognostic factor.[21,22] In the study by Diao et al, sensitivity and specificity of the plasma D-dimer levels in diagnosing metastases had been by 61.9% and 86.6%, respectively.[18] Besides, Tomimaru et al observed sensitivity and specificity values of 62.9% and 88.2% for the D-dimer levels >4 μg/mL in predicting the involvement of the lymph nodes in EC.[19] In one other research, Tomimaru et al obtained sensitivity and specificity values of 68% and 73% for the D-dimer levels in predicting responses to chemotherapy in EC.[13]

The present study established that the plasma D-dimer levels had acceptable sensitivity, specificity, and P/NPV in predicting morbidity/mortality in EC. Unlike the discrepancies in previous studies including sample size and type of cancer, all these investigations had indicated an increasing trend in complications and adverse events

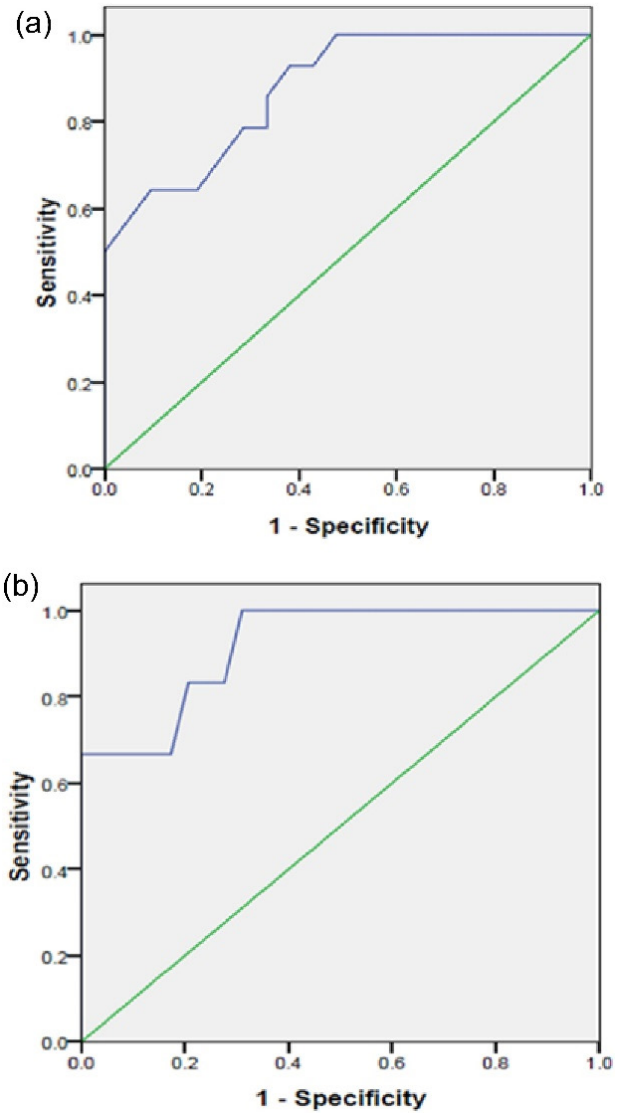

Figure 2. (a) ROC curve analysis of D-dimer levels in predicting complications in middle thoracic EC surgery. (b) ROC curve analysis of D-dimer levels in predicting mortality in middle thoracic EC surgery

in cancer patients along with a growth in plasma D-dimer levels. Accordingly, D-dimer measurement could be utilized as a marker for diagnosing outcomes in these patients. The results of a recent study in China had also revealed that the preoperative D-dimer levels were associated with survival rates and they could serve as an independent prognostic indicator in EC patients treated with transthoracic esophagectomy.[21]

The exact mechanism between plasma D-dimer levels and cancer thus remains unclear. Previous studies had further reported that plasma D-dimer, as a stable fibrin end-degradation product, was closely correlated with cancer progression.[10] The results of another study had correspondingly revealed that the plasma D-dimer levels could indicate micrometastases or circular tumor cells, possibly responsible for cancer recurrence.[23]

Moreover, Yu et al showed that the plasma D-dimer levels were not gender-dependent but they could be determined by age, tumor primary site, and tumor stage.[24] In addition, monitoring changes in the plasma D-dimer levels was critical for all perioperative cancer patients. They had additionally revealed that thrombosis prevention was necessary if the D-dimer had not decreased to the tumor-specific baseline one week after surgery.[24]

There were some limitations in the present study. First, the sample size was small, which might have avoided reaching a much stronger conclusion on the efficacy of the preoperative plasma D-dimer levels for predicting postoperative morbidity/mortality in EC patients as surgical candidates. Furthermore the study failed to detect sufficient thrombotic events after therapy. Second, the follow up period spanned 6 months and we were unable to follow up on patients for 5-year survival. Thus, the influence of thrombotic events on prognosis could not be assessed. Accordingly, it is necessary to conduct a study with larger cohort of patients to substantiate these conclusions. However, this study can be an important step towards further evaluations including complete assessment of symptomatic/asymptomatic arrhythmias, deep vein thrombosis, and pulmonary embolism in patients with high preoperative D-dimer levels.

Conclusion

It was concluded that the elevated plasma D-dimer levels were accompanied by adverse postoperative events for EC and they had acceptable sensitivity and specificity for diagnosing these complications. Thus preoperative measurement of plasma D-dimer levels can be regarded as a useful marker for mortality. However, further clinical research on a much larger cohort of patients will be required to verify these findings.

Study Highlights

What is current knowledge?

- In the literature, systemic activation of homeostasis is often observed in cancer patients. Elevated D-dimer levels indicate global activation of homeostasis and fibrinolysis

What is new here?

- Increased plasma D-dimer levels had acceptable sensitivity and specificity for diagnosing postoperative complications in esophageal cancer.
- Elevated plasma D-dimer levels could be accompanied by adverse events and early poor postoperative outcomes for esophageal cancer.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethical Approval

All study procedures were performed in accordance with the ethical standards of the institutional and national research committee and followed 1964 Helsinki declaration and its later amendments. This study was approved by the Regional Ethics Committee headed by the Vice-Chancellor of Research and Development at Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.REC.5/4/10438) and the informed written consent was obtained from all the participants.

Authors' contribution

SZR designed the study and carried out coordination and contributed in manuscript editing. SR and SH contribution in literature search, data collection and analysis and manuscript writing. All authors have read and approved the manuscript.

Acknowledgments

We would like to thank all nurses and staffs of thoracic surgery ward at Imam Reza hospital for their kind full cares of all patients.

Funding

None.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917. doi: 10.1002/ijc.25516.
2. Bafandeh Y, Hashemzadeh S, Sokouti M, Esmaili H. Clinicopathologic characteristics of esophageal cancer patients in northwest Iran--very low incidence of adenocarcinomas. Asian Pac J Cancer Prev. 2006;7(3):480-2.
3. Liu J, Xie X, Zhou C, Peng S, Rao D, Fu J. Which factors are associated with actual 5-year survival of oesophageal squamous cell carcinoma? Eur J Cardiothorac Surg. 2012;41(3):e7-11. doi: 10.1093/ejcts/ezr240.
4. Mir MR, Vand Rajabpour M, Maleki Delarestaghi M, Hadji M, Harirchi I, Mir P, et al. Short- and long-term survival of esophageal cancer patients treated at the Cancer Institute of Iran. Dig Surg. 2013;30(4-6):331-6. doi: 10.1159/000354854.
5. Mariette C, Taillier G, Van Seuningen I, Triboulet JP. Factors affecting postoperative course and survival after en bloc resection for esophageal carcinoma. Ann Thorac Surg. 2004;78(4):1177-83. doi: 10.1016/j.athoracsur.2004.02.068.
6. Murray JC. Coagulation and cancer. Br J Cancer. 1991;64(3):422-4. doi: 10.1038/bjc.1991.325.
7. Ay C, Dunkler D, Pirker R, Thaler J, Quehenberger P, Wagner O, et al. High D-dimer levels are associated with poor prognosis in cancer patients. Haematologica. 2012;97(8):1158-64. doi: 10.3324/haematol.2011.054718.

8. Komurcuoglu B, Ulusoy S, Gayaf M, Guler A, Ozden E. Prognostic value of plasma D-dimer levels in lung carcinoma. Tumori. 2011;97(6):743-8. doi: 10.1700/1018.11091.
9. Diao D, Zhu K, Wang Z, Cheng Y, Li K, Pei L, et al. Prognostic value of the D-dimer test in oesophageal cancer during the perioperative period. J Surg Oncol. 2013;108(1):34-41. doi: 10.1002/jso.23339.
10. Oya M, Akiyama Y, Okuyama T, Ishikawa H. High preoperative plasma D-dimer level is associated with advanced tumor stage and short survival after curative resection in patients with colorectal cancer. Jpn J Clin Oncol. 2001; 31(8):388-94. doi. org/10.1093/jjco/hye075
11. Blackwell K, Haroon Z, Broadwater G, Berry D, Harris L, Iglehart JD, et al. Plasma D-dimer levels in operable breast cancer patients correlate with clinical stage and axillary lymph node status. J Clin Oncol. 2000;18(3):600-8. doi: 10.1200/jco.2000.18.3.600.
12. Moriyama H, Hirata S, Kubo Y. [Alteration of serum levels of endotoxin, polymorphonuclear leukocyte elastase, and the molecular markers of the coagulation and fibrinolytic system in the patients with esophageal cancer and lung cancer before and following operation]. Rinsho Byori. 1995;43(3):233-7. [Japanese].
13. Tomimaru Y, Yano M, Takachi K, Kishi K, Miyashiro I, Ohue M, et al. Correlation between pretherapeutic D-dimer levels and response to neoadjuvant chemotherapy in patients with advanced esophageal cancer. Dis Esophagus. 2008;21(4):281-7. doi: 10.1111/j.1442-2050.2007.00758.x.
14. Bick RL. Coagulation abnormalities in malignancy: a review. Semin Thromb Hemost. 1992;18(4):353-72. doi: 10.1055/s-2007-1002575.
15. Buccheri G, Torchio P, Ferrigno D. Plasma levels of D-dimer in lung carcinoma: clinical and prognostic significance. Cancer. 2003;97(12):3044-52. doi: 10.1002/cncr.11432.
16. Suega K, Bakta IM. Correlation between clinical stage of solid tumor and D-dimer as a marker of coagulation activation. Acta Med Indones. 2011;43(3):162-7.
17. Liu L, Zhang X, Yan B, Gu Q, Zhang X, Jiao J, et al. Elevated plasma D-dimer levels correlate with long term survival of gastric cancer patients. PLoS One. 2014;9(3):e90547. doi: 10.1371/journal.pone.0090547.
18. Diao D, Wang Z, Cheng Y, Zhang H, Guo Q, Song Y, et al. D-dimer: not just an indicator of venous thrombosis but a predictor of asymptomatic hematogenous metastasis in gastric cancer patients. PLoS One. 2014;9(7):e101125. doi: 10.1371/journal.pone.0101125.
19. Tomimaru Y, Yano M, Takachi K, Kishi K, Miyashiro I, Ohue M, et al. Plasma D-dimer levels show correlation with number of lymph node metastases in patients with esophageal cancer. J Am Coll Surg. 2006;202(1):139-45. doi: 10.1016/j.jamcollsurg.2005.08.008.
20. Li J, Zheng Z, Fang M. Impact of pretreatment plasma D-dimer levels and its perioperative change on prognosis in operable esophageal squamous cell carcinoma. Oncotarget. 2017;8(45):79537-45. doi: 10.18632/oncotarget.18552.
21. Liu DQ, Li FF, Jia WH. Cumulative scores based on plasma D-dimer and serum albumin levels predict survival in esophageal squamous cell carcinoma patients treated with transthoracic esophagectomy. Chin J Cancer. 2016;35:11. doi: 10.1186/s40880-015-0062-2.
22. Zhang F, Chen Z, Wang P, Hu X, Gao Y, He J. Combination of platelet count and mean platelet volume (COP-MPV) predicts postoperative prognosis in both resectable early and advanced stage esophageal squamous cell cancer patients. Tumour Biol. 2016;37(7):9323-31. doi: 10.1007/s13277-015-4774-3.
23. Fukumoto K, Taniguchi T, Usami N, Kawaguchi K, Fukui T, Ishiguro F, et al. Preoperative plasma D-dimer level is an independent prognostic factor in patients with completely resected non-small cell lung cancer. Surg Today. 2015;45(1):63-7. doi: 10.1007/s00595-014-0894-4.
24. Yu J, Li D, Lei D, Yuan F, Pei F, Zhang H, et al. Tumor-specific D-dimer concentration ranges and influencing factors: a cross-sectional study. PLoS One. 2016;11(11):e0165390. doi: 10.1371/journal.pone.0165390.