RESEARCH ARTICLE

The D-dimer level predicts the postoperative prognosis in patients with non-small cell lung cancer

Yuki Shiina[ORCID]**, Takahiro Nakajima*, Takayoshi Yamamoto, Kazuhisa Tanaka, Yuichi Sakairi, Hironobu Wada, Hidemi Suzuki, Ichiro Yoshino**

Department of General Thoracic Surgery, Chiba University Graduate School of Medicine, Chiba Japan

* takahiro_nakajima@med.miyazaki-u.ac.jp

Abstract

Background

Carcinoma cells often modulate coagulation and fibrinolysis among cancer patients. Plasma dimerized plasmin fragment D (D-dimer) has been reported as a prognostic marker of various types of malignancies, including non-small cell lung cancer (NSCLC). However, the associations between the plasma D-dimer level and peripheral small NSCLC remain unclear.

Methods

Three hundred and sixty-two patients with NSCLC who underwent radical surgery were retrospectively reviewed. Patients who received anticoagulation therapy before surgery or who lacked preoperative D-dimer data were excluded. The other 235 patients were divided into a high D-dimer (over 1.0 μg/mL) group (HDD group, n = 47) and a normal D-dimer group (NDD group, n = 188) and investigated for their clinical characteristics, computed tomography (CT) findings, pathological findings, and clinical outcomes.

Results

The mean D-dimer levels was 2.49±2.58 μg/ml in the HDD group and 0.42±0.23 μg/ml in the NDD group. The HDD group was characterized by a predominance of male gender, older age, pure solid appearance on chest CT, vascular invasion in pathology, and a large solid part of the tumor. The HDD group showed a worse overall survival, disease-free survival, and disease-specific survival than the NDD group (p<0.001, <0.001, <0.001, respectively). These survival features were also observed in p-Stage IA disease. There was no marked survival difference when tumors showed ground-glass opacity on CT.

Conclusion

In NSCLC patients with a solid tumor appearance on CT, high D-dimer levels predict a poor survival and early recurrence.

Introduction

Carcinoma cells often affect coagulation and fibrinolysis in cancer patients due to their inducing cytokines and coagulation factors. Plasma dimerized plasmin fragment D (D-dimer) has been reported as a prognostic marker of various types of malignancies. Man et al. showed that pretreatment plasma D-dimer, fibrinogen, and platelet levels reflected the prognosis in patients with epithelial ovarian cancer [1]. Several previous studies have reported that, in operable non-small cell lung cancer (NSCLC) patients, the D-dimer levels predict the risk of postoperative early recurrence and a poor prognosis [2, 3]. Little information has been obtained regarding the relationship between the plasma D-dimer level and the detailed clinicopathologic features of NSCLC patients, although multiple overlapping and interacting mechanisms that can explain the increased incidence of thrombosis in patients with malignancies are reported [4–5].

Recently, improvements in and the spread of computed tomography (CT) have increased the chance of detecting small-size peripheral lung cancers. Hattori et al. showed that patients with tumors showing a ground-glass appearance on CT had a better prognosis than those with tumors with a pure solid appearance [6]. Such a radiologic feature is very important when considering surgical management for peripheral small NSCLC, i.e. whether to perform limited resection or conventional lobectomy.

Therefore, in the present study, we investigated the associations between the plasma D-dimer levels and clinicopathologic factors, including the tumor appearances on chest CT.

Materials and methods

Patients

A total of 362 patients with NSCLC who underwent radical surgery at Chiba University Hospital between April 2015 and March 2017 were retrospectively reviewed using a prospectively registered database. Patients who had received anticoagulation therapy that affected the D-dimer level before surgery were excluded. In 235 patients, the plasma D-dimer level was measured within 2 months before surgery for a routine checkup of deep vein thrombosis (n = 78) or for an observational study to monitor postoperative thrombus of pulmonary venous stump (UMIN000017528) (n = 157). We divided the patients into 2 groups: a high D-dimer (over 1.0 μg/mL) group (HDD group, n = 47) and a normal D-dimer (less than 1.0 μg/mL) group (NDD group, n = 188) (Fig 1). The cut off value of D-dimer was decided based on the Japanese guidelines, "Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis" [7]. The 235 subjects of this study and the 119 patients excluded due to a lack of available D-dimer data showed a similar clinicopathologic profile except for age (S1 Table), and their survival curves were almost perfectly superimposed (S1 Fig).

All patients had undergone thin slice CT (1 mm every 1 mm) prior to surgery, and the CT findings were reviewed by all thoracic surgeons and a board-certified radiologist (AN) at the clinical conference. The two groups were compared for their clinical characteristics, tumor appearance on chest CT, histology and histological subtypes and clinical outcomes. In this study, clinical staging was determined based on preoperative findings for CT, fluorodeoxyglucose-positron emission tomography (PET) and magnetic resonance imaging of the head. Lymph nodes greater than 1.0 cm in the short axis by CT or with a standardized uptake value (SUV) of > 2.5 by Pere considered positive and subjected to a biopsy for precise nodal staging. TNM staging was coded according to the International Association for the Study of Lung
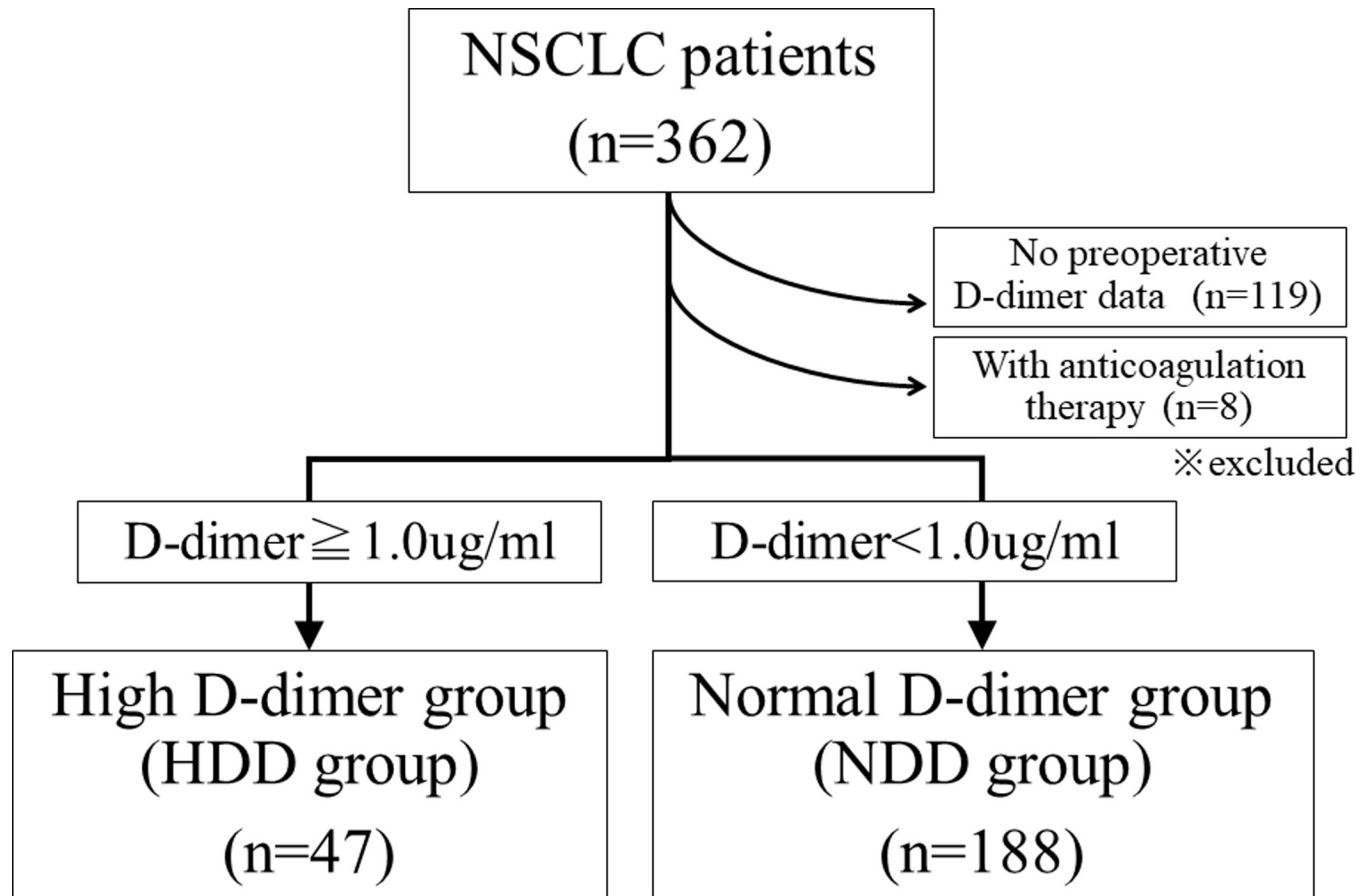
Fig 1. The flow chart of the patients in this study. The patients were divided into 2 groups: a high D-dimer (over 1.0 μg/mL) group (HDD group, n = 47) and a normal D-dimer group (NDD group, n = 188).

Cancer (IASLC) staging system (the 8th edition). In uni/multiple analyses, not pathological TNM staging but clinical staging is used so as to search for predict survival factors prior to surgery. All patients had 0 or 1 ECOG performance status.

This study was approved by the ethics committee of Chiba University, Graduate School of Medicine (No.3093). All patients' data were fully anonymized before we accessed them and the ethics committee of Chiba University waived the requirement for informed consent.

Statistical analyses

Statistical analyses were performed using the JMP pro software program, ver. 13 (SAS Institute Inc, Tokyo, Japan). Survival curves were estimated using the Kaplan-Meier method. The log-rank statistic was used for the comparison of the overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) distributions. Cox proportional hazards models were used to estimate the hazard ratios for the OS. We considered results to be significant at $p < 0.05$.

Results

Patients' characteristics by D-dimer level

The mean D-dimer level was 2.49±2.58 μg/ml in the HDD group and 0.42±0.23 μg/ml in the NDD group. The HDD group was characterized by a predominance of male gender, older age, pure solid appearance on chest CT, a large solid part of the tumor, advanced c-T factor, advanced c-N factor and advanced c-staging compared with the NDD group (Table 1). Regarding pathology and treatment, the HDD group was also characterized by a predominance of advanced p-staging, pathological upstaging, vessel involvement (v+), and undergoing induction therapy than NDD group (Table 2). There were no significant differences in histologic subtypes of adenocarcinomas, surgical procedure, and adjuvant therapy between the two groups.

Clinical outcomes

During postoperative follow-up, recurrence was observed in 14 (29.8%) and 28 (13.7%) patients in the HDD and NDD groups, respectively ($p = 0.015$). The HDD group had more distant recurrences than did the NDD group ($p = 0.045$) (Table 3). In contrast, there was no significant difference in the local recurrence between the 2 groups ($p = 0.218$). The HDD group showed a worse OS ($p<0.001$), DFS, ($p<0.001$) and DSS ($p<0.001$) than the NDD

Table 1. Clinical characteristics of both groups.

		HDD group	NDD group	P value
		n = 47	**n = 188**	
D-dimer	, μg/ml	2.5±2.6	0.4±0.2	-
Age	, years	71.4±7.5	67.0±9.3	**0.001**
Gender	(%)			**0.028**
	Male	36 (77)	110 (59)	
	Female	11 (23)	78 (41)	
Size of the solid part of the tumor (mm)		33.3±25.8	21.9±15.7	**0.003**
CT appearance				**0.020**
	Pure solid	40 (85)	123 (65)	
	Part solid GGN	7 (15)	52 (28)	
	Pure GGN	0 (0)	13 (7)	
cT				**<0.001**
	T1	24(51)	138(73)	
	T2	11(23)	42(22)	
	T3	5(11)	3(2)	
	T4	7(15)	5(3)	
cN				**0.012**
	N0	39(83)	177(94)	
	N1-3	8(17)	11(6)	
cStage				**0.009**
	I	163(87)	32(68)	
	II	15(8)	8(17)	
	III	10(5)	7(15)	

D-dimer: plasma dimerized plasmin fragment D, HDD: patients with a high D-dimer level, NDD: patients with a normal D-dimer level, GGN: ground-glass attenuation-dominant nodule, CT: computed tomography

https://doi.org/10.1371/journal.pone.0222050.t001

Table 2. Pathological and treatment parameters of both groups.

		HDD group	NDD group	P value
		n = 47	n = 188	
p-Stage				0.398
	I	27 (57)	146 (78)	
	II	10 (21)	25 (13)	
	III	10 (21)	17 (9)	
Pathologic upstaging		19(40)	41(20)	**0.004**
Histology				0.185
	Adenocarcinoma	31 (66)	155 (82)	
	Squamous cell carcinoma	14 (30)	41 (22)	
	LCNEC	0 (0)	2 (1)	
	Large cell carcinoma	1 (2)	1 (1)	
	Pleomorphic carcinoma	0 (0)	2 (1)	
	Carcinoid	0 (0)	2 (1)	
Micropapillary pattern				0.746
	(+)	2 (4)	14 (30)	
	(-)	45 (96)	174 (93)	
pleural invasion				0.416
	(-)	40 (85)	144 (77)	
	(+)	7 (15)	44 (23)	
Nodule count				0.700
	Single nodule	46 (98)	184 (98)	
	Separate nodule in the same lobe	0 (0)	1 (1)	
	Separate nodule in a different ipsilateral lobe	1 (2)	1 (1)	
Lymphatic invasion				0.066
	(-)	38 (81)	168 (89)	
	(+)	9 (19)	18 (10)	
Vascular invasion				**0.014**
	(-)	28 (60)	148 (79)	
	(+)	19 (40)	40 (21)	
Surgical procedure				0.433
	Lobectomy or more	12(26)	38(20)	
	Sublobar resection	35(75)	150(80)	
Induction therapy		6(13)	4(2)	**<0.001**
	Chemotherapy	2(4)	2(1)	
	Chemo-radiation therapy	4(8)	2(1)	
Adjuvant therapy		9(19)	38(19)	0.984
	Chemotherapy	6(13)	36(18)	
	Radiation therapy	1(2)	1(0)	
	Chemo-radiation therapy	2(4)	1(0)	

HDD: patients with a high D-dimer level, NDD: patients with a normal D-dimer level, LCNEC: large cell neuroendocrine carcinoma.

group (Fig 2). Even in p-Stage IA patients, the HDD group showed a worse OS (p<0.001), DFS, (p<0.001) and DSS (p<0.001) than the NDD group (Fig 3).

In a multivariate analysis, a high D-dimer level (hazard ratio [HR] 5.75; 95% confidence interval [CI], 2.12–15.56; p<0.001) and c-T (HR: 4.60, 95% CI, 1.42–14.92; p = 0.011) were independent prognostic factors (Table 4). The HR of CT findings could not be calculated due

Table 3. Types of recurrence of both groups.

		HDD group n = 47	NDD group n = 188	P value
Recurrence				
	Local	6(13)	14(7)	0.218
	Distant	8(17)	14(7)	**0.045**

HDD: patients with a high D-dimer level, NDD: patients with a normal D-dimer level.

to no events occurring in patients with ground-glass attenuation-dominant nodules. In an analysis of patients with a pure solid appearance, a high D-dimer level (HR: 5.50; 95% CI, 1.67–11.56; p = 0.003) and c-T (HR: 4.30, 95% CI, 1.54–18.09; p = 0.011) were also found to be independent prognostic factors according to a multivariate analysis (S2 Table). Regarding the patients with ground-glass attenuation-dominant nodules (n = 72), only 1 patient in the NDD group showed recurrence of disease. There was no significant difference in the OS, DFS or DSS between the HDD and NDD groups. In patients with a pure solid appearance on CT (n = 163), the HDD group showed a worse OS (p < 0.001), DFS (p = 0.008) and DSS (p = 0.002) than the NDD group (Fig 4).
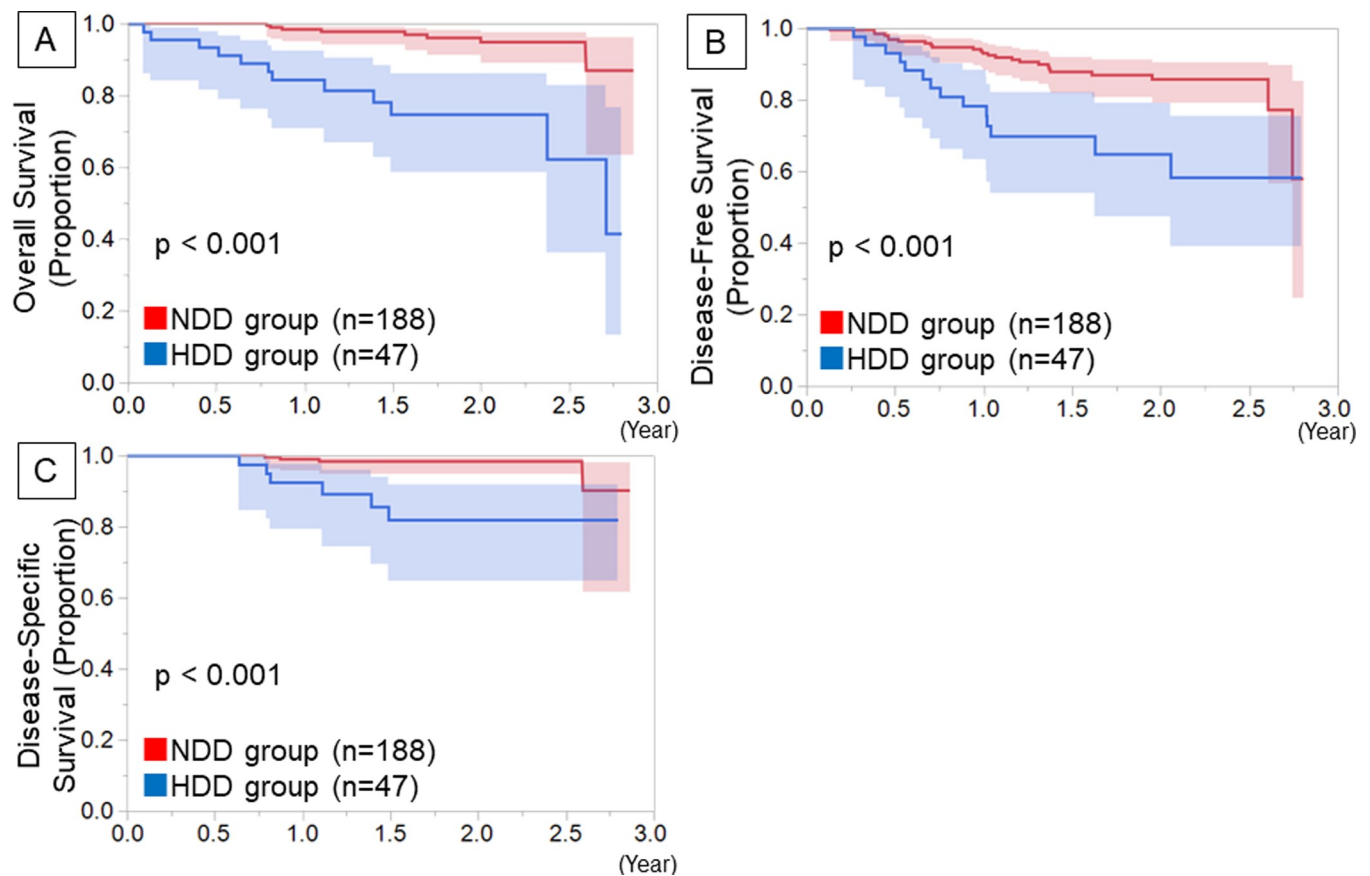

Fig 2. Kaplan-Meier survival curves among the total patients. Kaplan-Meier survival curves of the postoperative overall survival (A), disease-free survival (B) and disease-specific survival (C) by preoperative D-dimer level among the total patients in this study.
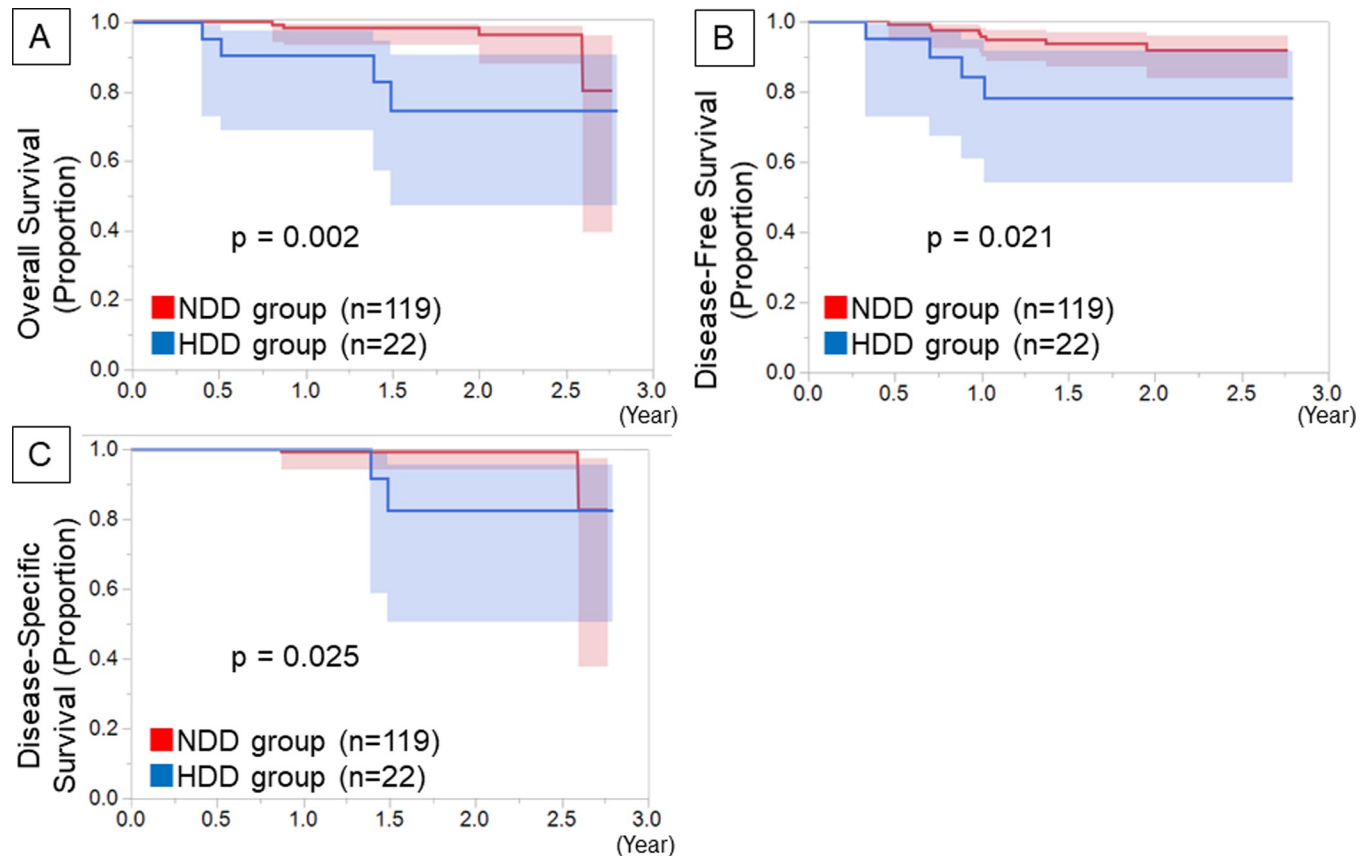
Fig 3. Kaplan-Meier survival curves among patients with p-Stage IA disease. Kaplan-Meier survival curves of the postoperative overall survival (A), disease-free survival (B) and disease-specific survival (C) by preoperative D-dimer level among patients with p-Stage IA disease.

https://doi.org/10.1371/journal.pone.0222050.g003

Discussion

Peripheral small-size lung cancer is basically treated by lobectomy if possible, with the role of segmentectomy for such tumors still controversial [8–10]. Even among peripheral early-stage lung cancers, micropapillary- or solid predominant-type adenocarcinoma has been reported to have a poor prognosis [11, 12], and anatomical lobectomy is recommended over segmentectomy because of the increased frequency of local recurrence [13]. NSCLC with ground-glass opacity on CT has shown favor clinical outcomes; however, the preoperative projection of the prognosis is difficult in NSCLC with a pure solid appearance.

We focused on the serum D-dimer level and CT findings to identify new predictors of postoperative outcomes in peripheral small NSCLC. While no correlation was noted between the histology or histological subtypes and the D-dimer level, surgical pathology revealed a relationship between the D-dimer level and vessel involvement of tumors. However, we also found that the patients with ground-glass opacity had favor prognoses despite their serum level of D-dimer. Hattori et al. recently showed that the presence of a ground-glass nodule component is a significant prognostic factor in early-stage NSCLC and that patients with ground-grass opacity tumors had an excellent prognosis (≥90%) irrespective of clinical T factors [6, 14]. Given the results of this study, the preoperative serum D-dimer level did not affect in NSCLC patients with ground-glass opacity tumor.

Previous studies have reported the utility of several coagulation parameters, such as D-dimer, fibrinogen or platelet count, as prognostic markers in patients with several types of

Table 4. Uni- and multivariate analyses for the OS.

		Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
Age (years)					
	<70	-			
	≥70	1.34 (0.54–3.38)	0.522		
Gender					
	Male	2.34 (0.85–8.21)	0.105		
	Female	-			
cN					
	0	-		-	
	1	1.39 (0.08–6.84)	0.760	1.35 (0.07–7.59)	0.788
	2	3.60 (0.57–12.71)	0.147	2.03 (0.30–8.22)	0.412
	3	-		-	
cT					
	1	-		-	
	2	0.89 (0.20–2.91)	0.857	0.69 (0.17–2.86)	0.604
	3	5.48 (0.84–20.91)	0.070	3.00 (0.63–14.36)	0.169
	4	9.29 (2.88–26.29)	**< 0.001**	4.60 (1.42–14.92)	**0.011**
CT appearance					
	Pure solid		- *		- *
	With GGN				
D-dimer (μg/mL)					
	≥1	7.54(3.12–19.26)	**< 0.001**	5.75(2.12–15.56)	**< 0.001**
	< 1	-		-	

GGN: ground-glass attenuation-dominant nodule, CI: confidence interval, CT: computed tomography, OS: overall survival

*The hazard ratio of computed tomography findings could not be calculated because no events occurred in patients with ground-glass attenuation-dominant nodules.

https://doi.org/10.1371/journal.pone.0222050.t004

malignancies, including lung cancer. Ma et al. showed that high serum D-dimer levels were associated with a poor prognosis in lung cancer patients in a meta-analysis of 11 studies [15]. Zhu et al. showed that D-dimer and fibrinogen could be used to predict the chemotherapy efficacy and prognosis in patients with small cell lung cancer [16]. Inal et al. showed that the D-dimer levels were decreased in chemotherapy responders but increased in non-responders among lung cancer patients [17]. Several recent studies have described the association of a poor prognosis with high D-dimer levels in operable NSCLC patients [2–3]. Gao et al. revealed that the D-dimer level is useful for predicting lymph node metastasis [18]. Several prospective studies of other organs have shown that the association of high coagulation parameters with a poor prognosis was independent of venous thromboembolism [19–20]. The D-dimer level might thus affect the prognosis solely through an important role in tumorigenesis separately from the venous thromboembolism pathway.

Several reports have shown that tumor-mediated coagulation activation is associated with tumor growth, angiogenesis promotion and metastasis [21]. Platelets are reported to increase the metastatic success via multiple mechanisms, including direct shielding of tumor cells and protection of tumor cells from cytokines [22–23]. The fibrinolytic system has been reported to promote tumor growth through several different mechanisms, including angiogenesis, suppressing apoptosis, proliferation of tumor cells and degradation of the extracellular matrix [24]. These previous findings may explain why the HDD group had more distant metastasis in
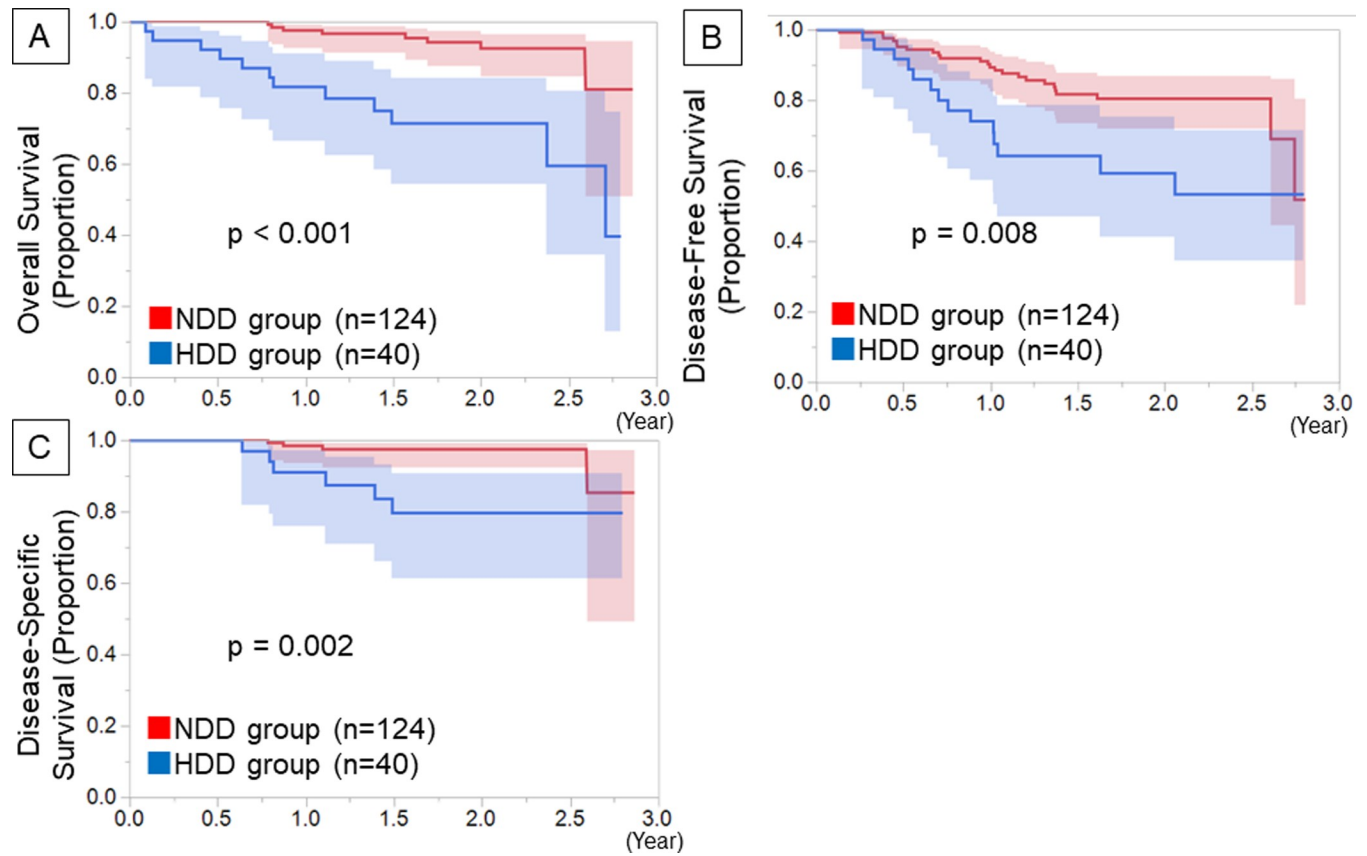
Fig 4. Kaplan-Meier survival curves among patients with solid CT appearance. Kaplan-Meier survival curves of postoperative overall survival (A), disease free survival (B), and disease specific survival (C) by preoperative D-dimer level, among patients with solid CT appearance.

https://doi.org/10.1371/journal.pone.0222050.g004

the present study than NDD group did. However, the mechanism underlying the association between the serum D-dimer level and the aggressiveness of NSCLC remains unclear. Regarding the pathology in the present study, tumors in the HDD group frequently invaded vessels. Some studies have found that thrombin increased the invasiveness of cancer [25–26], although no report has mentioned the coagulation system and vessel invasion. Although increased D-dimer levels might be a result of vessel injury due to tumor invasion, the association between the D-dimer levels and vessel invasion is unclear and more detailed studies are required.

One limitation of this study was the retrospective nature of the analysis and its performance at a single center. Most of the patients in this study were subjects of an observational study to monitor pulmonary venous thrombosis, as described in the Materials and Methods section; however, there were no marked differences in the clinicopathologic profiles and survival outcomes between the 235 subjects of this study and the 119 patients who were excluded due to a lack of available D-dimer data. A prospective study will be needed to confirm the existence of a relationship between the D-dimer level and tumor aggressiveness as well as the clinical outcome in NSCLC, especially in peripheral small disease. Another limitation was that no aberrant driver genes were assessed in the study. A certain proportion of patients with adenocarcinoma have driver gene alterations. For example, the existence of epidermal growth factor receptor (EGFR) gene mutations and the use of EGFR tyrosine kinase inhibitors contributes to a better survival.

Conclusions

In NSCLC patients with a solid tumor appearance on CT, high D-dimer levels predict a poor survival and early recurrence. The type of surgery as well as careful post-operative follow-up should be considered in this population.

Supporting information

S1 Fig. Survival curves of the subject of this study and excluded patients. For the 235 subjects of this study and 119 excluded patients due to no available D-dimer data, Kaplan-Meier curves of postoperative overall survival (A), disease free survival (B) and disease specific survival (C) were compared.
(TIF)

S1 Table. Clinicopathologic profiles of the subjects of this study and patients excluded from the study.
(DOCX)

S2 Table. Uni- and multivariate analyses for the OS in patients with a pure solid appearance.
(DOCX)

S1 Dataset. The data of patients used in this study.
(XLS)

Author Contributions

Conceptualization: Takahiro Nakajima.

Data curation: Yuki Shiina, Takayoshi Yamamoto, Kazuhisa Tanaka, Yuichi Sakairi, Hironobu Wada, Hidemi Suzuki.

Formal analysis: Yuki Shiina.

Funding acquisition: Takahiro Nakajima.

Investigation: Takahiro Nakajima.

Project administration: Ichiro Yoshino.

Supervision: Ichiro Yoshino.

Validation: Takayoshi Yamamoto, Kazuhisa Tanaka, Yuichi Sakairi, Hironobu Wada, Hidemi Suzuki.

Writing – original draft: Yuki Shiina.

Writing – review & editing: Takahiro Nakajima, Ichiro Yoshino.

References

1. Man YN, Wang YN, 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(1):24–32. Epub 2014/10/28. https://doi.org/10.1097/IGC.0000000000000303 PMID: 25347092

2. 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. Epub 2014/05/02. https://doi.org/10.1007/s00595-014-0894-4 PMID: 24781600

3. Wang Z, Fu J, Diao D, Dang C. [Pre-operative plasma D-dimer level may predict the poor prognosis within one year after the surgery for non-small cell lung cancer]. Zhongguo Fei Ai Za Zhi. 2011; 14 (6):534–7. Epub 2011/06/08. https://doi.org/10.3779/j.issn.1009-3419.2011.06.10 PMID: 21645459

4. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. Blood. 2007; 110 (6):1723–9. Epub 2007/05/15. https://doi.org/10.1182/blood-2006-10-053736 PMID: 17496204; PubMed Central PMCID: PMC1976377.

5. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer—a cohort study using linked United Kingdom databases. Eur J Cancer. 2013; 49(6):1404–13. Epub 2012/11/14. https://doi.org/10.1016/j.ejca.2012.10.021 PMID: 23146958

6. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Importance of Ground Glass Opacity Component in Clinical Stage IA Radiologic Invasive Lung Cancer. Ann Thorac Surg. 2017; 104(1):313–20. Epub 2017/04/24. https://doi.org/10.1016/j.athoracsur.2017.01.076 PMID: 28433219

7. Ando M FI, Ito M, Kobayashi T, Masuda M, Miyahara Y, Nakanishi N, Niwa A, Ohgi S, Tajima H, Ishibashi H, Kanaoka Y, Nakamura M, Sakuma M, Satoh T, Tanabe N, Yamada N, Yamashita M, Kuriyama T, Matsubara J, Nakano T, Ozaki Y, Sakata R. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). Circ J. 2011; 75(5):1258–81. Epub 2011/03/29. https://doi.org/10.1253/circj.cj-88-0010 PMID: 21441695

8. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995; 60(3):615–22; discussion 22–3. Epub 1995/09/01. https://doi.org/10.1016/0003-4975(95)00537-u PMID: 7677489

9. Okada M, Mimae T, Tsutani Y, Nakayama H, Okumura S, Yoshimura M, et al. Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma. Annals of cardiothoracic surgery. 2014; 3(2):153–9. Epub 2014/05/03. https://doi.org/10.3978/j.issn.2225-319X.2014.02.10 PMID: 24790838; PubMed Central PMCID: PMC3988306.

10. Bao F, Ye P, Yang Y, Wang L, Zhang C, Lv X, et al. Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis. Eur J Cardiothorac Surg. 2014; 46(1):1–7. Epub 2013/12/11. https://doi.org/10.1093/ejcts/ezt554 PMID: 24321996

11. Kamiya K, Hayashi Y, Douguchi J, Hashiguchi A, Yamada T, Izumi Y, et al. Histopathological features and prognostic significance of the micropapillary pattern in lung adenocarcinoma. Mod Pathol. 2008; 21 (8):992–1001. Epub 2008/06/03. https://doi.org/10.1038/modpathol.2008.79 PMID: 18516041

12. Morimoto J, Nakajima T, Suzuki H, Nagato K, Iwata T, Yoshida S, et al. Impact of free tumor clusters on prognosis after resection of pulmonary adenocarcinoma. J Thorac Cardiovasc Surg. 2016; 152(1):64-72.e1. Epub 2016/06/28. https://doi.org/10.1016/j.jtcvs.2016.03.088 PMID: 27343907

13. Ujiie H, Kadota K, Chaft JE, Buitrago D, Sima CS, Lee MC, et al. Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival. J Clin Oncol. 2015; 33(26):2877–84. Epub 2015/08/12. https://doi.org/10.1200/JCO.2015.60.9818 PMID: 26261257; PubMed Central PMCID: PMC4554749.

14. Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Prognostic impact of a ground glass opacity component in the clinical T classification of non-small cell lung cancer. J Thorac Cardiovasc Surg. 2017; 154(6):2102-10.e1. Epub 2017/09/28. https://doi.org/10.1016/j.jtcvs.2017.08.037 PMID: 28947198

15. Ma X, Li Y, Zhang J, Huang J, Liu L. Prognostic role of D-dimer in patients with lung cancer: a meta-analysis. Tumour Biol. 2014; 35(3):2103–9. Epub 2013/10/12. https://doi.org/10.1007/s13277-013-1279-9 PMID: 24114016

16. Zhu LR, Li J, Chen P, Jiang Q, Tang XP. Clinical significance of plasma fibrinogen and D-dimer in predicting the chemotherapy efficacy and prognosis for small cell lung cancer patients. Clin Transl Oncol. 2016; 18(2):178–88. Epub 2015/07/18. https://doi.org/10.1007/s12094-015-1350-7 PMID: 26184726

17. Inal T, Anar C, Polat G, Unsal I, Halilcolar H. The prognostic value of D-dimer in lung cancer. Clin Respir J. 2015; 9(3):305–13. Epub 2014/04/12. https://doi.org/10.1111/crj.12144 PMID: 24720709

18. Gao XL, Wang SS, Cao DB, Liu W. The role of plasma D-dimer levels for predicting lymph node and mediastinal lymph node involvement in non-small cell lung cancer. Clin Respir J. 2018. Epub 2018/03/03. https://doi.org/10.1111/crj.12786 PMID: 29498801

19. Stender MT, Larsen TB, Sorensen HT, Thorlacius-Ussing O. Preoperative plasma D-dimer predicts 1-year survival in colorectal cancer patients with absence of venous thromboembolism (VTE): a prospective clinical cohort study. J Thromb Haemost. 2012; 10(10):2027–31. Epub 2012/08/21. https://doi.org/10.1111/j.1538-7836.2012.04887.x PMID: 22900573

20. Stender MT, Larsen AC, Sall M, Thorlacius-Ussing O. D-Dimer predicts prognosis and non-resectability in patients with pancreatic cancer: a prospective cohort study. Blood Coagul Fibrinolysis. 2016; 27 (5):597–601. Epub 2016/05/18. https://doi.org/10.1097/MBC.0000000000000559 PMID: 27182687

21. Lal I, Dittus K, Holmes CE. Platelets, coagulation and fibrinolysis in breast cancer progression. Breast Cancer Res. 2013; 15(4):207. Epub 2013/08/03. https://doi.org/10.1186/bcr3425 PMID: 23905544; PubMed Central PMCID: PMC3979075.

22. Bambace NM, Holmes CE. The platelet contribution to cancer progression. J Thromb Haemost. 2011; 9 (2):237–49. Epub 2010/11/03. https://doi.org/10.1111/j.1538-7836.2010.04131.x PMID: 21040448

23. Kopp HG, Placke T, Salih HR. Platelet-derived transforming growth factor-beta down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer Res. 2009; 69(19):7775–83. Epub 2009/09/10. https://doi.org/10.1158/0008-5472.CAN-09-2123 PMID: 19738039

24. Han B, Nakamura M, Mori I, Nakamura Y, Kakudo K. Urokinase-type plasminogen activator system and breast cancer (Review). Oncol Rep. 2005; 14(1):105–12. Epub 2005/06/10. PMID: 15944776

25. Even-Ram S, Uziely B, Cohen P, Grisaru-Granovsky S, Maoz M, Ginzburg Y, et al. Thrombin receptor overexpression in malignant and physiological invasion processes. Nat Med. 1998; 4(8):909–14. Epub 1998/08/13. https://doi.org/10.1038/nm0898-909 PMID: 9701242

26. Hu L, Lee M, Campbell W, Perez-Soler R, Karpatkin S. Role of endogenous thrombin in tumor implantation, seeding, and spontaneous metastasis. Blood. 2004; 104(9):2746–51. Epub 2004/07/22. https://doi.org/10.1182/blood-2004-03-1047 PMID: 15265791