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ORIGINAL COMMUNICATION

Impact of D-dimer levels for short-term or long-term outcomes in cryptogenic stroke patients

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Abstract

Background D-dimer levels are used in several clinical settings, such as in predicting venous thrombosis, cardioembolic stroke and cancer status. In the present study, we investigated the associations between plasma D-dimer levels at admission, clinical characteristics and mortality at discharge in cryptogenic stroke patients. We also investigated whether D-dimer levels can predict long-term outcomes in those patients, including those with and without right-to-left shunt (RLS).

Methods Acute cryptogenic stroke patients ($n = 295$, 72 ± 13 years old) were consecutively enrolled and retrospectively analyzed. We defined the cryptogenic stroke as an undetermined etiology according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Plasma D-dimer levels at admission were evaluated. Assessments for RLS were performed using saline contrast-transcranial Doppler ultrasonography or contrast-transesophageal echography. Survivors (at discharge) underwent follow-up for up to 3 years after stroke onset.

Results Of the total enrolled cohort, 17 patients died at discharge. D-dimer levels correlated with initial National Institutes of Health Stroke Scale (NIHSS) score ($r = 0.391$, $P < 0.001$) and were associated with mortality at discharge [odds ratio 1.04; 95% confidence interval (CI) 1.00–1.08, $P = 0.049$] after adjusting for age, sex and initial NIHSS score. Of the 278 survivors at discharge, 266 patients were evaluated to assess RLS during hospitalization, and 62 patients (23.3%) exhibited RLS. According to the median plasma D-dimer levels at admission (0.7 μg/ml), the patients were divided into a low D-dimer group ($n = 136$, < median) and a high D-dimer group ($n = 130$, ≥ median). Patients in the high D-dimer group were older, more frequently female, had a lower BMI, had a higher prevalence of cancer and had greater initial neurological severity compared to the patients in the low D-dimer group. During the follow-up period (median, 1093 days), 31 patients developed recurrent stroke and 33 patients died. High D-dimer levels at admission were independently associated with recurrent stroke and all-cause mortality [hazard ratio (HR) 3.76; 95% CI 1.21–14.1, $P = 0.021$) in patients with RLS, but not in those without RLS (HR 1.35; 95% CI 0.74–2.50, $P = 0.335$).

Conclusions Increased D-dimer levels at admission were associated with mortality at discharge in cryptogenic stroke patients. In addition, high D-dimer levels were also associated with long-term outcomes in cryptogenic stroke patients with RLS.

Keywords D-dimer · Outcome · Cryptogenic stroke

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Introduction

Plasma D-dimer, which is a byproduct of fibrin degradation, provides useful information in clinical settings for acute and chronic stroke patients. Several studies have shown that plasma D-dimer levels in patients experiencing cardioembolic stroke are higher than those in other stoke subtypes [2, 18, 22]. In addition, increased D-dimer levels have been associated with infarction volume and short-term functional outcome in ischemic stroke patients with atrial fibrillation (AF) [21]. In the general population, high D-dimer concentration is also a risk marker for ischemic stroke, especially cardioembolic stroke [5].

Cryptogenic stroke, defined as stroke with undetermined etiology, accounts for 20–40% of all ischemic strokes [7, 20]. Paroxysmal AF is thought to be the most frequent potential mechanism in patients with cryptogenic stroke. Some of these patients are also thought to have experienced paradoxical embolism. Paradoxical embolism refers to the embolic entry of a venous thrombus into the systemic circulation through a right-to-left shunt (RLS) [19]. In addition, cancer-related stroke (including occult cancer) was also one possible cause of cryptogenic stroke. We hypothesized that D-dimer levels might be useful for predicting the degrees of clinical conditions that indicate the presence of AF, venous thrombus and cancer in patients experiencing cryptogenic stroke. There is little evidence regarding whether D-dimer levels at admission can predict the short-term and long-term clinical outcomes of these patients; hence, we investigated the associations between plasma D-dimer levels at admission, clinical characteristics and mortality at discharge in this patient population. We also investigated whether D-dimer levels can predict long-term outcomes in patients with cryptogenic stroke, including those with and without RLS.

Methods

Subjects

This was a retrospective, observational study. This study complied with the Declaration of Helsinki for investigations involving humans, and the study protocol was approved by the Ethics Committee of the Kawasaki Medical School Hospital. We enrolled consecutive, acute ischemic stroke patients who were admitted to the Kawasaki Medical School Hospital within 7 days of stroke onset between April 2008 and March 2012. A total of 1338 acute ischemic stroke patients were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [1]. Among these patients, we excluded patients with small vessel occlusion ($n = 221$), large artery atherosclerosis ($n = 137$) and cardioembolism ($n = 412$). Of the remaining 568 patients, we diagnosed 122 patients with stroke due to other determined etiologies and 446 patients with stroke due to undetermined etiologies. Among the 446 patients with undetermined etiologies, we excluded 151 patients with more than one possible cause. Finally, 295 patients with cryptogenic stroke were analyzed in the present study (Fig. 1).

Clinical information during hospitalization

Patient data, including age, sex, body mass index, known vascular risk factors (e.g., hypertension, diabetes mellitus and dyslipidemia) and past disease history (e.g., ischemic stroke, intracerebral hemorrhage, coronary artery disease and cancer), were collected by attending physicians. Physicians also assessed neurological deficits and scored patients according to the National Institutes of Health Stroke Scale (NIHSS) upon admission and the modified Rankin Scale (mRS) prior to discharge. Plasma D-dimer levels were assessed for all patients upon admission and measured using

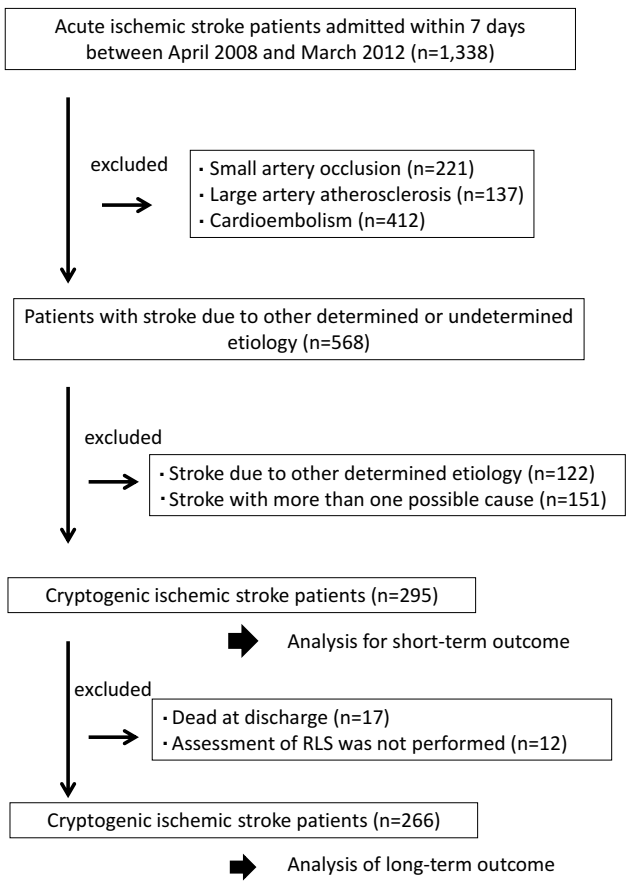

Fig. 1 Patient selection

the same technique during the study period. Secondary prevention methods (e.g., antiplatelet use, anticoagulant use or none) were comprehensively determined by the attending physicians.

Assessments for RLS were performed using saline contrast-transcranial Doppler ultrasonography (c-TCD) and/or contrast-transesophageal echography (TEE). RLS was diagnosed if more than 1 microembolic signal was detected in any of the four c-TCD tests (one test without and three tests with the Valsalva method). In c-TEE analyses, RLS was diagnosed if microbubbles were visualized in transition from the right atrium to the left atrium after performing the Valsalva method. These methods were performed as previously described [10, 11, 27]. The occurrence of RLS was determined by the attending physicians following an examination of the c-TCD and/or c-TEE results. We collected information from medical records to assess RLS among the patients.

Follow-up and long-term outcomes

Patient follow-up was performed at 3, 6, 12 months, 2 and 3 years after stroke onset. Trained research assistants were blinded to the detailed clinical data and used standardized questionnaires to contact the patients or their caregivers by telephone or postal mail. The following endpoints were considered: "recurrent stroke", "all-cause mortality" and the combination of "recurrent stroke and all-cause mortality". Recurrent stroke was defined as brain infarction (including transient ischemic attack) or intracranial hemorrhage that was diagnosed at the hospital. Additionally, detailed information for stroke type (i.e., ischemic stroke subtype) and causes of mortality were assessed using multiple approaches, including reviewing hospital and outpatient medical records and contacting patients or their caregivers.

Statistical analysis

Statistical analyses were performed using JMP 10.0 statistical software (SAS Institute Inc., USA). For continuous variables, data are expressed either as the means ± standard deviations (SD) or medians (25th and 75th percentiles). Discrete variables are expressed as frequencies and percentages. The statistical significance of inter-group differences was assessed by χ^2, unpaired t and Mann–Whitney U tests, as appropriate. The relationship between initial NIHSS score and plasma D-dimer levels was examined using Spearman's correlation. Multiple logistic regression analysis was performed to estimate the risk of mortality at discharge using several factors, including age, sex, initial NIHSS score and D-dimer levels. Next, survivors at discharge in whom RLS could be assessed were analyzed as follows. The patients were divided into two categories (high D-dimer group vs. low D-dimer group) according to their median plasma D-dimer levels at admission. Event-free survival analysis was performed using Kaplan–Meier plots and the log-rank test to compare patients with high D-dimer levels to those with low D-dimer levels. The Cox proportional-hazards model was used to estimate the association between long-term outcomes and high D-dimer levels compared to low D-dimer levels after adjustments for age and sex. Statistical significance was established at $P < 0.05$.

Results

Associations between D-dimer levels and stroke mortality at discharge

A total of 295 patients with cryptogenic stroke (143 women, 72 ± 13 years old) were enrolled. Of these patients, 17 (5.8%) died at discharge: eight from stroke, four from pneumonia, three from disseminated intravascular coagulation due to various causes and two from cancer. Old age, initial neurological severity (high NIHSS score) and high D-dimer levels were associated with mortality at discharge (Table 1). Increased D-dimer levels correlated with initial NIHSS score ($r = 0.391$, $P < 0.001$). Multivariate logistic analysis revealed that both increased NIHSS (per 1 points) and increased D-dimer levels (per 1 μg/ml) were associated with stroke mortality at discharge [odds ratio (OR), 1.16; 95% confidence interval (CI) 1.09–1.25, $P < 0.001$ and OR 1.04; 95% CI 1.00–1.08, $P = 0.049$, respectively].

Associations between D-dimer levels and long-term stroke outcomes

Among the survivors at discharge ($n = 278$), 266 patients (95.7%) were assessed for RLS (Fig. 1). Of these patients, 62 (23.3%) exhibited RLS. According to the median plasma D-dimer levels at admission (0.7 μg/ml), the patients were divided into a low D-dimer group ($n = 136$, < median) and a high D-dimer group ($n = 130$, ≥ median). Patients in the high D-dimer group were older, more frequently female, had a lower BMI, had a higher prevalence of cancer and had greater initial neurological severity (NIHSS score at admission) compared to the patients in the low D-dimer group (Table 2).

During the follow-up period [median (interquartile range) 1093 (374–1106) days], 31 patients (11.7%) had recurrent stroke and 33 patients (12.4%) died. Among the 31 patients with recurrent stroke, 18 were affected by ischemic stroke (12 patients were cryptogenic, 3 patients had large artery atherosclerosis, 1 patient had cardioembolism, and 2 patients had transient ischemic attack), 7 developed intracerebral hemorrhage, and 6 patients had an unknown stroke subtype. Among the 33 patients who died, 4 died from cancer,

Table 1 Baseline characteristics of patients with and without mortality at discharge

	Survivor ($n = 278$)	Mortality ($n = 17$)	P
Age (years)	71.8 ± 12.9	79.6 ± 14.6	0.016
Male	145 (52.2)	7 (41.2)	0.379
Body mass index (kg/m^2)	22.2 ± 3.8	21.2 ± 5.4	0.289
Past smoking	121 (43.5)	7 (41.2)	0.850
Hypertension	195 (70.1)	11 (64.7)	0.635
Diabetes mellitus	71 (25.5)	1 (5.9)	0.067
Dyslipidemia	77 (27.7)	4 (23.5)	0.709
History of ischemic stroke	49 (17.6)	2 (11.8)	0.535
History of intracranial hemorrhage	16 (5.8)	0 (0.0)	0.309
History of coronary artery disease	9 (3.2)	0 (0.0)	0.451
History of cancer	40 (14.4)	1 (5.9)	0.325
NIHSS score at admission	4 (1–9)	21 (10.5–28.5)	<0.001
D-dimer at admission (μg/ml)	0.7 (0.5–1.9)	4.1 (1.9–24.7)	<0.001

The data are presented as the means ± SD for age and body mass index, as medians (interquartile ranges) for the National Institutes of Health Stroke Scale (NIHSS) score at admission and D-dimer levels, and as the number (%) of patients for the remaining characteristics

Table 2 Baseline characteristics of patients in the low D-dimer group and the high D-dimer group

	Low D-dimer group (< 0.7 μg/ml, $n = 136$)	High D-dimer group (≥ 0.7 μg/ml, $n = 130$)	P
Age (years)	67.4 ± 13.1	75.7 ± 11.4	<0.001
Male	85 (62.5)	53 (40.8)	<0.001
Body mass index (kg/m^2)	22.7 ± 3.6	21.8 ± 3.9	0.047
Past smoking	68 (50.0)	47 (36.2)	0.023
Hypertension	95 (69.9)	93 (71.5)	0.763
Diabetes mellitus	34 (25.0)	34 (26.2)	0.829
Dyslipidemia	38 (27.9)	35 (26.9)	0.852
History of ischemic stroke	25 (18.4)	22 (16.9)	0.755
History of intracranial hemorrhage	11 (8.1)	5 (3.9)	0.146
History of coronary artery disease	6 (4.4)	3 (2.3)	0.343
History of cancer	12 (8.8)	23 (17.7)	0.032
NIHSS score at admission	3 (1-5)	5 (1-13.3)	0.001
Right-to-left shunt	33 (24.3)	29 (22.3)	0.706
Stroke outcomes at discharge			
mRS score	2 (1–4)	3 (1–5)	<0.001
Independence (mRS 0–2)	82 (60.3)	47 (36.2)	<0.001
Secondary prevention at discharge			0.008
Antiplatelet use ($n = 205$)	115 (84.6)	90 (69.2)	
Anticoagulant use ($n = 19$)	5 (3.7)	14 (10.8)	
None ($n = 42$)	16 (11.8)	26 (20.0)	

The data are presented as the means ± SD for age and body mass index, as medians (interquartile ranges) for the National Institutes of Health Stroke Scale (NIHSS) score at admission and modified Rankin Scale (mRS) score, and as the number (%) of patients for the remaining characteristics

5 from pneumonia, 2 from stroke, 5 from heart disease, 2 from liver failure, and 15 from unknown causes (including sudden death or aging).

Figure 2 shows the Kaplan–Meier curves for each endpoint. Kaplan–Meier curve analysis showed that the patients in the high D-dimer group had a higher risk for the combined endpoint (recurrent stoke and all-cause mortality) and all-cause mortality than the patients in the low D-dimer group (log-rank test, $P = 0.012$ or $P < 0.001$, respectively; Fig. 2a, c), although there was no significant difference for the association between D-dimer levels and recurrent stroke (log-rank test, $P = 0.858$, Fig. 2b). The multivariate Cox

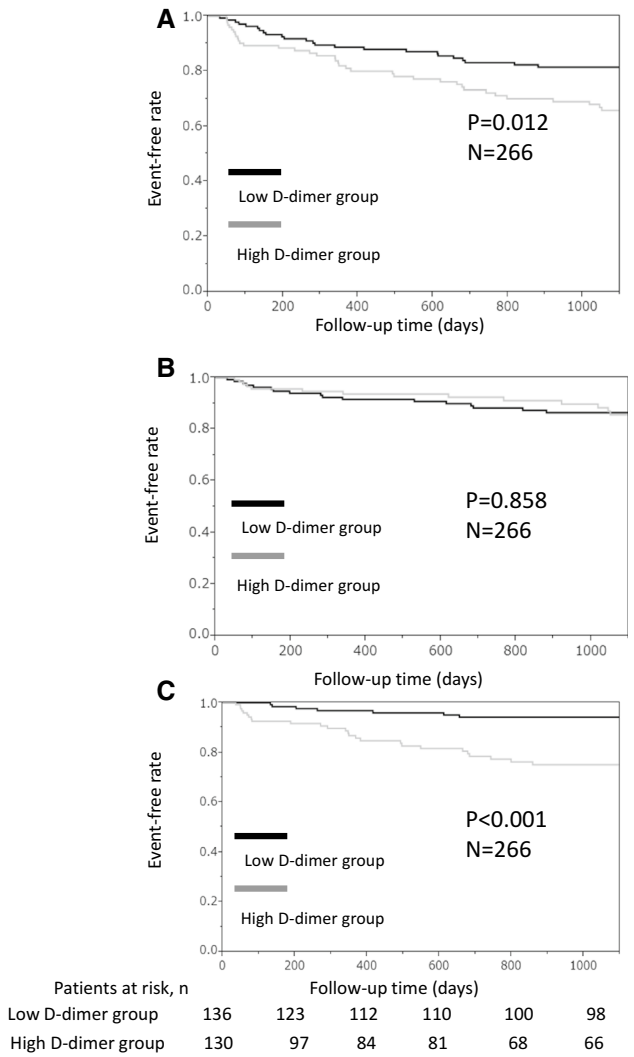

Fig. 2 Kaplan-Meier curves of the cumulative risk for the combined outcome (recurrent stroke and all-cause mortality) (**a**), recurrent stroke (**b**) and all-cause mortality (**c**), stratified by D-dimer levels. *P* values were obtained from the log-rank test

proportional-hazards model showed that high D-dimer levels were independently associated with all-cause mortality [hazard ratio (HR) 3.34; 95% CI 1.49–8.53, $P = 0.003$] after adjusting for age and sex (Fig. 3).

Of the 266 patients assessed for RLS, 224 used antithrombotics for secondary prevention (205 patients used antiplatelet drugs and 19 patients used anticoagulants). The 42 patients (15.8%) who did not use antithrombotic agents frequently exhibited diabetes mellitus, had higher D-dimer levels, and had lower rates of independence at discharge than those who used antithrombotic agents (Supplemental Table I). Independence at discharge (mRS 0–2) was also significantly different between patients with low D-dimer levels and those with high D-dimer levels. After adjusting for age, sex, use of antithrombotic agents and independence at discharge, high D-dimer levels were also independently associated with all-cause mortality (HR 3.19; 95% CI 1.44–8.06, $P = 0.003$).

Association between D-dimer levels and long-term stroke outcomes for patients with or without right-to-left shunt

There was no significant difference in baseline characteristics between the patients with RLS and those without (Supplemental Table II). High D-dimer levels in patients without RLS ($n = 204$) were associated with all-cause mortality (log-rank test, $P < 0.001$), however, no significant associations with the combined endpoint or stroke recurrence were noted (Fig. 4). High D-dimer levels were also independently associated with all-cause mortality after adjusting for age and sex (HR 3.49; 95% CI 1.35–10.9, $P = 0.009$) among patients without RLS (Fig. 3).

Among the patients with RLS ($n = 62$), Kaplan–Meier curve analysis revealed that patients with high D-dimer levels had a higher risk of the combined endpoint and of stroke recurrence than patients with low D-dimer levels (log-rank test, $P = 0.013$ or $P = 0.044$), although there was no significant difference in all-cause mortality (log-rank test, $P = 0.071$) (Fig. 5). High D-dimer levels were independently associated with the combined endpoint [hazard ratio (HR) 3.76; 95% CI 1.21–14.1, $P = 0.021$] in patients with RLS after adjusting for age and sex. In addition, high D-dimer levels were slightly associated with stroke recurrence in this group (HR 4.37; 95% CI 0.98-30.3, $P = 0.053$) (Fig. 3).

Discussion

In the present study, increased D-dimer levels at admission correlated to initial NIHSS score and were also independently associated with mortality at discharge after adjusting for stroke severity in patients with cryptogenic stroke. For long-term stroke outcomes, we found an independent association between high D-dimer levels and the combined endpoint (stroke recurrence and all-cause mortality) in patients with cryptogenic stroke with RLS.

Several studies have shown that plasma D-dimer levels in patients with cardioembolic stroke are higher than those in patients with other stoke subtypes because D-dimer levels could reflect thrombus formation activity in the left atrium or in the left ventricle [2, 18, 22]. In addition, initial stroke severity and initial infarct volume correlated with D-dimer levels in patients with cardioembolic stroke with AF, which could be a result of increased D-dimer levels produced by a large thrombus. In this study, plasma D-dimer levels at admission correlated with initial NIHSS score in patients with cryptogenic stroke. Most of these patients are likely

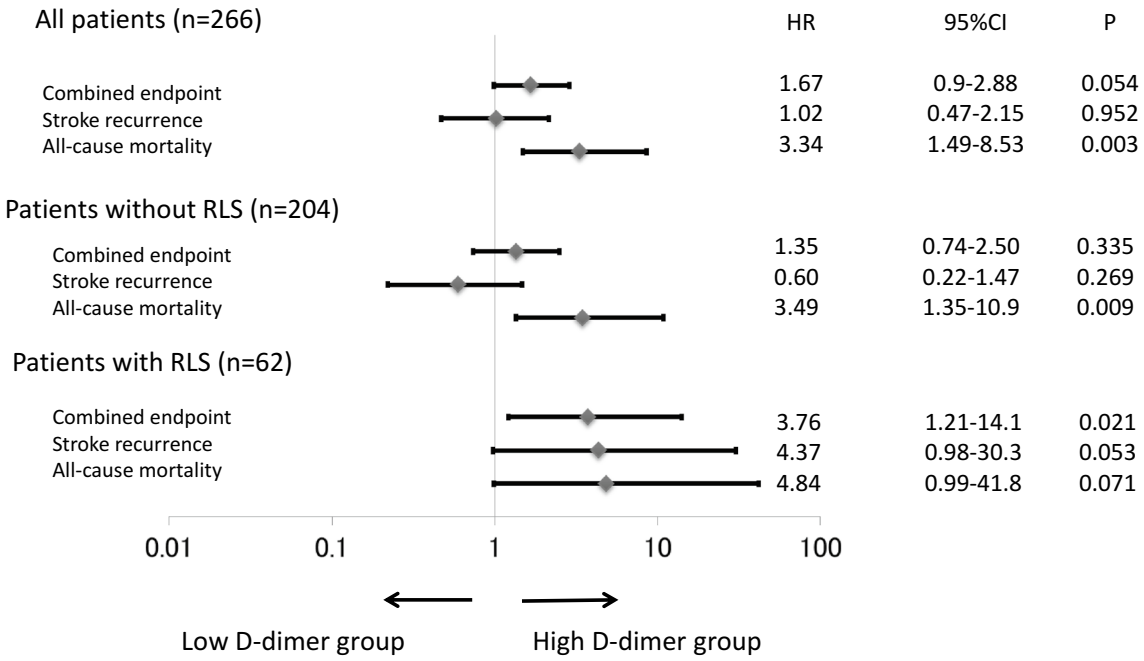

Fig. 3 Age- and sex-adjusted hazard ratio (HR) for the long-term outcomes in all cryptogenic patients, patients with right-to-left shunt (RLS) and those without RLS. *CI* confidence interval

to experience stroke from an embolic mechanism, such as a cardioembolism. Our results indicate that some patients with cryptogenic stroke had occult AF. D-dimer also activates inflammatory cytokines and causes advanced blood coagulation or progression of stroke status [3, 23]. These factors might contribute to the association between high D-dimer levels and short-term mortality independently of initial severity. In addition, increased D-dimer levels have also been associated with advanced cancer [16]. Indeed, in the present study, two patients died of cancer at discharge and were diagnosed with Trousseau syndrome.

Although recent studies have reported an association between D-dimer levels in acute ischemic stroke patients and short-term outcomes [28, 30], whether D-dimer levels are associated with long-term outcomes remains unknown [8, 26]. In addition, few studies have evaluated the association between D-dimer levels and long-term outcomes in patients with cryptogenic stroke. For these patients, D-dimer levels could provide useful information for several occult statuses, such as venous thrombus, atrial fibrillation and cancer. In the present study, high D-dimer levels were associated with all-cause mortality in all patients with cryptogenic stroke. A prior study also reported that high D-dimer levels serve as an independent predictor of poor survival in cancer patients with cryptogenic stroke [25]. Additionally, high D-dimer levels may be used to predict occult cancer in patients with cryptogenic stroke. Therefore, one explanation for the association between high D-dimer levels and mortality was the presence of known or occult cancer in this study. Among the 33 patients who died during follow-up period, 4 died from cancer. Notably, several studies have shown an association between increased D-dimer levels and all-cause mortality in the general population [4, 17, 29]. Therefore, the associations observed here might not be specific to patients with cryptogenic stroke. Although D-dimer is thought to stimulate inflammatory mediators, D-dimer levels have also been associated with all-cause mortality independent of inflammation in prior studies. D-dimer levels might also reflect the occult AF, as previously mentioned. A meta-analysis demonstrated that new AF was detected in 15.9% of 425 cryptogenic stroke patients [15]. Recently, two randomized trials of prolonged monitoring to detect new paroxysmal AF after ischemic stroke were conducted among patients with cryptogenic stroke [6, 24]. These clinical trials also found that 10–20% of cryptogenic stroke patients have underlying paroxysmal AF. In our study, the work-protocols for the detection of AF were not unified for long-term follow-up periods, and no cryptogenic patients received the implantable cardiac monitoring. Therefore, data regarding the number of cryptogenic stroke patients who experienced news AF during the study period were not available, although one patient had recurrent stroke caused by cardioembolism. Further studies assessing whether D-dimer levels might be useful for the detection of paroxysmal AF in cryptogenic stroke patients over long-term periods are needed.

Notably, our results showed that the association between D-dimer levels and stroke recurrence differed between cryptogenic patients with RLS and those without. These

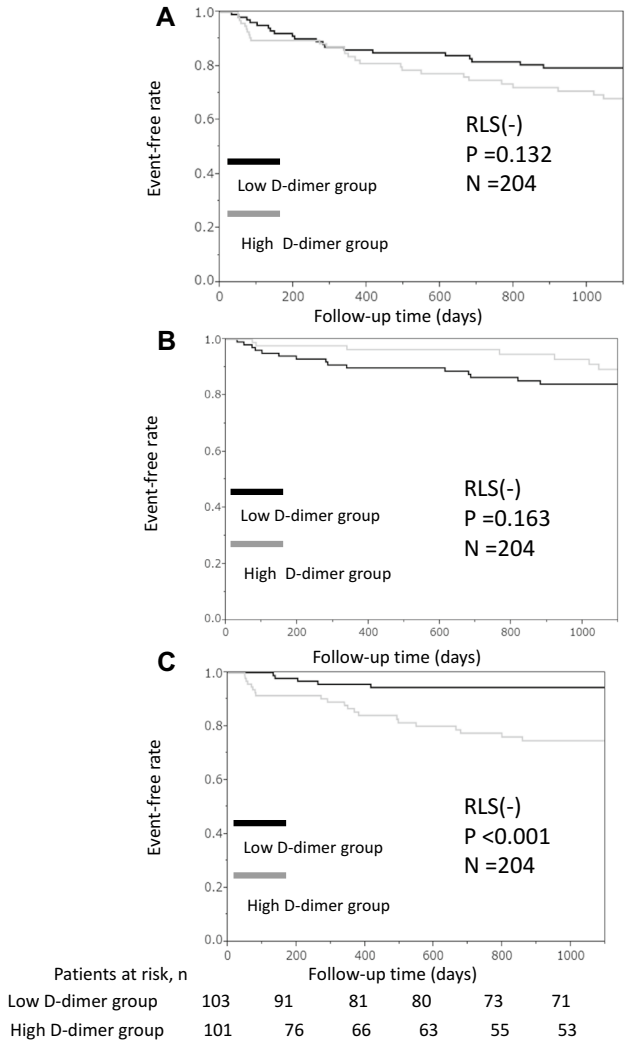

Fig. 4 Kaplan-Meier curves of the cumulative risk for the combined outcome (recurrent stroke and all-cause mortality) (**a**), recurrent stroke (**b**) and all-cause mortality (**c**), stratified by D-dimer levels for patients without right-left-shunt (RLS). *P* values were obtained from the log-rank test

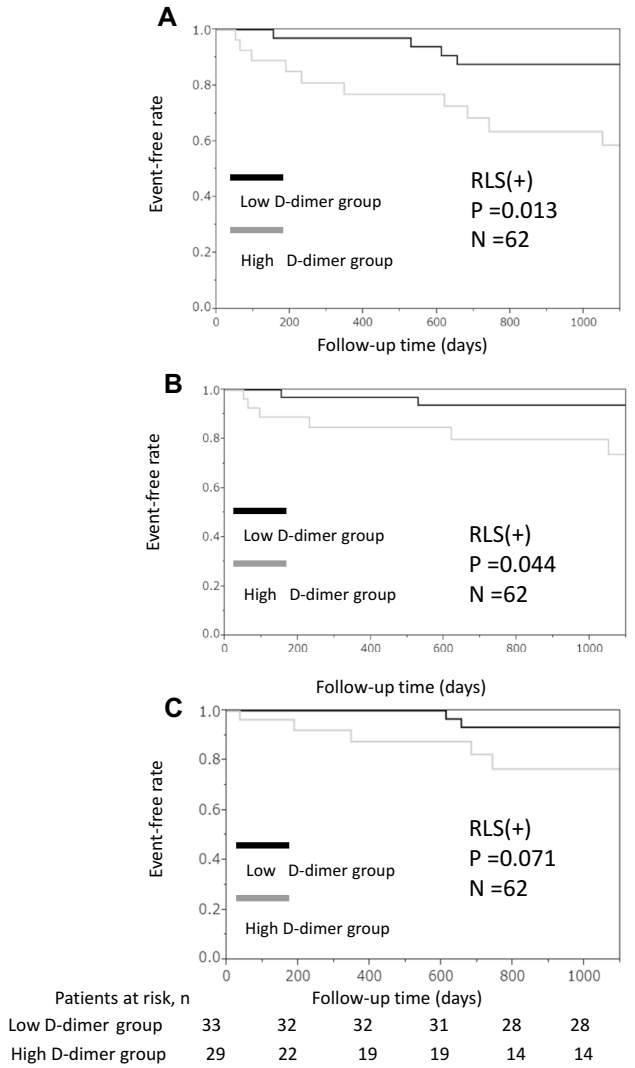

Fig. 5 Kaplan-Meier curves of the cumulative risk for the combined outcome (recurrent stroke or all-cause mortality) (**a**), recurrent stroke (**b**) and all-cause mortality (**c**), stratified by D-dimer levels for patients with right-left-shunt (RLS). *P* values were obtained from the log-rank test

differences in stoke recurrence might be explained by the etiology of paradoxical embolism. Of the 62 patients with RLS, 59 (95.2%) were evaluated for deep venous thrombosis (DVT) by ultrasonography or angiography, and none were found to have DVT. However, the timing of the DVT evaluations was different among individuals. A previous report investigated whether D-dimer levels can predict long-term stroke outcomes in patients with cryptogenic stroke with patent foramen ovale (PFO) [14]. Our results provide additional evidence for the usefulness of D-dimer levels in predicting recurrent stroke in patients with cryptogenic stroke with RLS. There are insufficient data to establish that anticoagulation is equivalent or superior to antiplatelet therapy in patients with PFO, hence, antiplatelet therapy is generally recommended in these patients if there are no findings of DVT [12]. D-dimer levels might be useful for predicting recurrent stroke events, especially those assumed to result from paradoxical embolism, in this patient population. Anticoagulation therapy might be useful for patients with RLS and high D-dimer levels, even with no evidence of DVT.

The current study has several limitations. First, the retrospective study design limited our analyses, and the single-center study design led to potential selection bias. Second, RLS data were collected from medical records; therefore, RLS diagnoses were determined by attending physicians. The present study showed that 62 (23.3%) of 266 patients with cryptogenic stroke exhibited RLS. This prevalence is lower than that reported in previous cryptogenic stroke studies (43 and 61%) [9, 13]. We were also unable to evaluate the

detailed causes of RLS, such as PFO. Third, we could not evaluate the presence of DVT in all patients. Indeed, patients with an incomplete negative investigation based on TOAST criteria were included in this study. However, D-dimer levels provided useful information regarding these patients even when there was insufficient work-up to detect the embolic source of a stroke.

In conclusion, increased D-dimer levels at admission were associated with mortality at discharge in patients with cryptogenic stroke. Additionally, high D-dimer levels were associated with long-term stroke outcomes in these patients, especially those with RLS. Large, prospective studies are needed to determine whether anticoagulation therapy could be useful for ameliorating recurrent stroke in patients with cryptogenic stroke with RLS and high D-dimer levels.

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Author contributions Study concept and design by Nezu and Yagita; acquisition of data by Nezu, Kitano, Kubo, Uemura, Yamashita, Iwanaga, Inoue; analysis and interpretation of data by Nezu and Yagita; manuscript drafting by Nezu; critical revision of the manuscript for important intellectual content by all the coauthors; study supervision by Kimura and Yagita.

Compliance with ethical standards

Conflicts of interest Naohisa Hosomi reports an honorarium from Mochida Pharmaceutical Co., Ltd which is outside the submitted work. Hirofumi Maruyama reports grants from Daiichi Sankyo Co., Ltd which is outside the submitted work. Masayasu Matsumoto reports grants from Takeda Pharmaceutical Co., LTD., Sanofi K.K., Mochida Pharmaceutical Co., LTD., Otsuka Pharmaceutical, and Daiichi Sankyo Co., LTD. and honoraria from Sanofi K.K., Bayer Health Care, and Daiichi Sankyo Co., LTD, which is outside the submitted work. Yoshiki Yagita reports an honorarium from Daiichi Sankyo Co., Ltd which is outside the submitted work. Other authors declare that there is no conflict of interest.

Ethical standards This study complied with the Declaration of Helsinki for investigations involving humans, and the study protocol was approved by the Ethics Committee of the Kawasaki Medical School Hospital (#2334).

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