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A score using left ventricular diastolic dysfunction to predict 90-day mortality in acute ischemic stroke: The DONE score

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ABSTRACT

Purpose: The aim of this study was to identify whether diastolic dysfunction predicts death at 90 days after acute ischemic stroke.

Methods: We retrospectively analyzed patients with ischemic stroke. All patients underwent transthoracic echocardiography to evaluate systolic function and diastolic function by means of assessing ejection fraction and septal E/e'. We evaluated the initial National Institute of Health Stroke Scale (NIHSS) score, arterial occlusion, and laboratory data. We used multivariate regression models to identify independent predictors of 90-day mortality.

Results: Among 1208 patients, the overall 90-day mortality rate was 8%. In multivariate logistic regression analysis, a higher initial NIHSS score, plasma D-dimer level and E/e', and occlusion of internal carotid artery or basilar artery were independent predictors of 90-day mortality. The DONE score derived from these valuables showed good discrimination with area under the curve (AUC) value of 0.82 (95% confidence interval [CI], 0.78–0.87) to predict 90-day mortality. The DONE score also predicted poor outcome (modified Rankin scale score, 4–6) at 90 days (AUC, 0.82; 95% CI 0.80–0.85).

Conclusions: Higher E/e', indicating diastolic dysfunction, may be associated with 90-day mortality in patients with acute ischemic stroke. The DONE score could readily predict poor outcome after acute ischemic stroke.

1. Introduction

Ischemic stroke is one of the main causes of death worldwide [1]. Identifying a patient at risk of death on admission could enable early and more intensive clinical care by providing valuable prognostic information to patients and their family members. Several prediction models for mortality after acute ischemic stroke have been developed [2–4]. However, few of those scores have been widely used in clinical practice. Clinical predictive scores are likely to be accepted in clinical practice if they are not cumbersome and easy to memorize. Several factors related to cardiac dysfunction may contribute to short-term and long-term mortality after acute ischemic stroke, such as a high serum brain natriuretic peptide (BNP) value and the coexistence of atrial fibrillation or heart failure [5–7].

Left ventricular diastolic dysfunction could be used to predict long-term mortality in patients with heart failure with preserved systolic function [8]. It has been reported that elevated left ventricular filling pressure estimated by an increased Doppler E velocity to tissue Doppler e' velocity ratio (E/e') was independently associated with the presence of stroke or transient ischemic attack in patients with paroxysmal atrial fibrillation [9]. In patients with ischemic stroke, higher E/e' was associated with poor outcome at 90 days compared with lower E/e' [10,11]. However, the relationship is not yet clearly defined in acute ischemic stroke. The purpose of this study was to determine whether elevated E/e' is associated with 90-day mortality in patients with acute ischemic stroke, and to develop a score that can be assessed on admission to predict the outcome.

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2. Methods

2.1. Patients

We retrospectively analyzed a prospectively collected cohort from a single center. Between April 2012 and March 2017, we studied patients with acute ischemic stroke who were admitted to our hospital within 7 days of symptom onset. We excluded patients with prior mitral valve surgery ($n = 10$) and terminal cancer ($n = 19$). Patients with a modified Rankin scale (mRS) score > 2 were defined as having preadmission dependence. Stroke neurologists made the diagnosis of acute ischemic stroke. Brain magnetic resonance imaging (MRI) was routinely performed on arrival at the emergency department, except in patients with a contraindication to MRI. The arterial occlusion sites were diagnosed based on computed tomography (CT) angiography or magnetic resonance angiography. Electrocardiography (ECG), continuous ECG monitoring, and 24-hour Holter ECG were used to document atrial fibrillation. We also performed carotid duplex ultrasonography, transcranial Doppler, transthoracic echocardiography, and transesophageal echocardiography to identify the mechanism of stroke. All the patients were followed for 90 days or until death. We divided patients into two groups: the deceased group and survival group. The study was approved by the institutional review board of Nagasaki University Hospital (Nagasaki, Japan).

The following patient characteristics were recorded: age, sex, previous ischemic heart disease and ischemic stroke, and vascular risk factors (hypertension, diabetes, dyslipidemia, and smoking). The National Institutes of Health Stroke Scale (NIHSS) score was used to assess stroke severity. All patients underwent blood tests on admission. The main variables were BNP, glucose, and D-dimer levels.

2.2. Echocardiographic methods

All patients underwent transthoracic echocardiography within 24 h of hospital arrival, and the findings were examined by an experienced sonographer (AT) who was blinded to the patient's clinical background. Patients were imaged in the left decubitus position with a commercially available system (iE33, Philips Ultrasound, Bothell, WA, USA; and Vivid 7; GE Healthcare, Milwaukee, WI). Diastolic function was assessed by diastolic left ventricular filling pressure, which was estimated as the ratio of early transmitral flow velocity (E) to mitral annular velocity (e') at the septal mitral annulus (E/e') on transthoracic echocardiography [12]. We calculated E/e' based on an average value of both E and e' during three cardiac cycles. We also measured the left ventricular ejection fraction. To determine repeatability of measurements, a second transthoracic echocardiography was performed within 24 h among 453 patients (37%).

2.3. Statistical analysis

Clinical and imaging baseline parameters were compared between the deceased group and survival group, using the Mann-Whitney *U* test to analyze numerical variables, and the Fisher exact test was used to analyze categorical variables. The data are presented as a median (interquartile range [IQR]) or frequency (%). All variables with a *p*-value $< .1$ in univariate analyses were entered into the multivariate model. A prediction score for the 90-day mortality was derived from the regression coefficients. The model parsimony was checked via the Akaike information criterion. The logistic regression model was fitted to the data of 90-day mortality. With taking account for the distribution of the measurement, laboratory variables and E/e' were converted to decadic logarithm. The coefficients were calibrated by the bootstrap method [13]. We did not put the data of intravenous recombinant tissue plasminogen activator and endovascular therapy into the multivariate logistic regression analysis because we would explore potential independent predictors at presentation. Accuracy was assessed by the area under the receiver operating characteristic curve (AUC). Results were considered significant when the *p*-value was < 0.05. Repeatability for the E/e' was assessed by the limit of agreement (LOA) [14]. All analyses were performed using JMP software, version 13 (SAS Institute Inc., Cary, NC, USA) or R version 3.5.0 (R foundation for statistical computing, Vienna, Austria).

3. Results

Of 1208 enrolled patients, 718 were men (59%), with a median age of 76 years (IQR, 67–83 years) and median NIHSS score of 5 (IQR, 2–15). Seventy patients (6%) underwent CT to evaluate for presence of acute ischemic lesion because of pacemaker implantation or insufficient evaluation time for acute recanalization treatment. The intervals of time from presentation to transthoracic echocardiography were 89 min (IQR, 58–240 min). Death was documented in 91 (8%) patients at 90 days. Causes of death at 90 days after acute ischemic stroke were as follows: stroke ($n = 34$, 37%), heart failure ($n = 15$, 16%), pneumonia ($n = 10$, 11%), multiple organ failure ($n = 6$, 6%), renal failure ($n = 4$, 4%), respiratory failure ($n = 4$, 4%), cancer ($n = 3$, 3%. These patients were unexpectedly deceased earlier due to pleural effusion, rupture of hepatocellular carcinoma and bleeding from esophageal varices), gastrointestinal bleeding ($n = 2$, 2%), myocardial infarction ($n = 1$, 1%), rupture of aortic aneurysm ($n = 1$, 1%), sepsis ($n = 1$, 1%), perforative peritonitis ($n = 1$, 1%), and unknown ($n = 9$, 10%).

The results of univariate analysis are shown in Table 1. Patients in the deceased group were significantly older (median, 81 versus 76; $p < .001$) and had a higher prevalence of atrial fibrillation (73 versus 37%; $p < .001$) than those in the survival group. The number of patients with preadmission dependence in the deceased group was larger than that in the survival group (30 versus 11%; $p < .001$). Dyslipidemia and smoking history were more common in patients in the survival group (23 versus 37%, $p = .006$ and 9 versus 20%, $p = .008$, respectively). On admission, the NIHSS scores were significantly higher in patients in the deceased group than in those in the survival group (median, 21 versus 4; $p < .001$). In terms of laboratory and imaging findings, patients in the deceased group had a higher BNP level (median, 301 versus 90; $p < .001$), D-dimer level (median, 3.6 versus 1.1; $p < .001$), glucose level (median, 143 versus 124; $p = .001$), E/e' (median, 19 versus 12; $p < .001$), and higher prevalence of acute internal carotid artery and basilar artery occlusion (35 versus 9% and 22 versus 4%; $p < .001$) than those in the survival group. The repeatability for the E/e' was excellent with the mean difference of 0.02 (95% LOA, −0.19 to 0.23; 95% CI of the lower LOA, −0.20 to −0.18; 95% CI of the upper LOA, 0.22–0.24).

Age, preadmission dependence, previous ischemic heart disease, history of dyslipidemia and smoking, the initial NIHSS score, atrial fibrillation, log10 BNP level, log10 D-dimer level, log10 glucose, internal carotid artery or basilar artery occlusion, and log10 E/e' were chosen as possible predictors of 90-day mortality. We dropped the data of medication before admission and stroke subtypes from the multivariate logistic regression analysis because taking an anticoagulant agent and cardioembolic stroke had significant relationship with atrial fibrillation. Multivariate logistic regression analysis demonstrated that the initial NIHSS score (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.05–1.12; $p < .001$), log10 D-dimer level (OR, 3.60; 95% CI, 2.05–6.31; $p < .001$), occlusion of internal carotid artery or basilar artery (OR, 2.25; 95% CI, 1.22–4.13; $p = .009$) and log10 E/e' (OR, 11.73; 95% CI, 2.16–63.76; $p = .004$) were independent predictors of 90-day mortality (Table 2). The DONE score was defined as consisting of D-dimer, occlusion of internal carotid artery or basilar artery, initial NIHSS score and E/e'. Aiming of the usability of the score in a clinical setting, each component in the score was precalculated as product values of the calibrated coefficients and the average of quartile interval. (Table 3) To predict 90-day mortality, the DONE score showed better discrimination with AUC value of 0.82 (95% CI, 0.78–0.87) as

Table 1
Baseline characteristics of the study population.

		Deceased group		Survival group		*p* value
		n = 91		*n* = 1117		
Age, year	Median (IQR)	81	(74–88)	76	(66–83)	< 0.001[a]
Sex	Male/female	49/42		669/448		0.268[b]
Past medical history	n (%)					
Ischemic stroke		26	(29)	234	(21)	0.110[b]
Ischemic heart disease		18	(20)	130	(12)	0.029[b]
Renal dialysis		5	(6)	38	(3)	0.247[b]
Vascular risk factors	n (%)					
Hypertension		72	(79)	869	(78)	0.896[b]
Diabetes mellitus		18	(20)	228	(21)	1.000[b]
Dyslipidemia		21	(23)	416	(37)	0.006[b]
Atrial fibrillation		66	(73)	409	(37)	< 0.001[b]
Smoking		8	(9)	221	(20)	0.008[b]
Medication before admission	n (%)					
Antiplatelet agent		32	(35)	317	(28)	0.187[b]
Anticoagulant agent		22	(24)	149	(13)	0.007[b]
Dependence before admission		27	(30)	118	(11)	< 0.001[b]
Initial NIHSS score	Median (IQR)	21	(14–26)	4	(2 − 12)	< 0.001[a]
Laboratory findings	Median (IQR)					
BNP, pg/mL		301	(161–522)	90	(29–237)	< 0.001[a]
D-dimer, μg/mL		3.6	(2.2–10.5)	1.1	(0.7–2.1)	< 0.001[a]
Glucose, mg/dL		143	(115–170)	124	(106–154)	0.001[a]
Location of vessel occlusion	n (%)					< 0.001[b]
ICA occlusion		28/79	(35)	85/938	(9)	
MCA M1 occlusion		14/79	(18)	106/938	(11)	
MCA M2 occlusion		9/79	(11)	106/938	(11)	
BA occlusion		17/79	(22)	39/938	(4)	
No occlusion		11/79	(14)	602/938	(64)	
Transthoracic echocardiography						
Ejection fraction < 40%	n (%)	7	(8)	33	(3)	0.018[b]
E/e'	Median (IQR)	19	(14–24)	12	(10–16)	< 0.001[a]
Stroke subtype	n (%)					< 0.001[b]
Cardioembolism		70	(77)	419	(38)	
Large artery atherosclerosis		5	(6)	220	(20)	
Small vessel occlusion		1	(1)	183	(16)	
Other etiology		4	(4)	60	(5)	
Undetermined etiology		11	(12)	233	(21)	
Acute stroke treatment	n (%)					
IV tPA		17	(19)	199	(18)	0.887[b]
Endovascular therapy		27	(30)	109	(10)	< 0.001[b]

IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; BNP, brain natriuretic peptide; ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; E, peak early transmitral filling velocities during early diastole; e', peak velocities of septal mitral annuli on the tissue Doppler image; IV tPA, intravenous tissue plasminogen activator.

[a] Mann-Whitney *U* test.

[b] Fisher exact test.

Table 2
Multivariate logistic regression model for 90-day mortality.

		Odds ratio	95% confidence interval	p value
Age	Per year	1.00	0.97–1.03	0.971
Dependence before admission		1.81	0.95–3.46	0.073
Atrial fibrillation		1.40	0.68–2.89	0.357
Dyslipidemia		0.67	0.34–1.30	0.233
Previous ischemic heart disease		2.06	0.96–4.40	0.063
Smoking		0.74	0.27–2.03	0.558
Initial NIHSS score	Per score	1.08	1.05–1.12	< 0.001
log10 D-dimer		3.60	2.05–6.31	< 0.001
log10 glucose		5.19	0.53–50.91	0.158
log10 BNP		1.62	0.80–3.28	0.182
ICA or BA occlusion		2.25	1.22–4.13	0.009
Ejection fraction < 40%		1.98	0.57–6.85	0.283
log10 E/e'		11.73	2.16–63.76	0.004

NIHSS, National Institute of Health Stroke Scale; BNP, brain natriuretic peptide; ICA, internal carotid artery; BA, basilar artery; E, peak early transmitral filling velocities during early diastole; and e', peak velocities of septal mitral annuli on the tissue Doppler image.

compared to the initial NIHSS score with AUC value of 0.77 (95% CI, 0.72–0.82). When the DONE score was adapted to poor functional outcome (mRS score 4 to 6), the AUC was 0.82 (95% CI 0.80–0.85). Table 4 shows the sensitivity, specificity and positive likelihood ratio for different cutoff values of the DONE score for mortality and poor functional outcome at 90 days. The distribution of 90-day mortality per increasing point of the DONE score is shown in Fig. 1.

This new score was well adapted to predict 90-day mortality in patients with cardioembolism (median, 73.0 vs. 51.6; $p < .001$). In patients with large artery atherosclerosis, five patients died with the median score of 53.5 (vs. 37.2; $p = .006$). One deceased patient with small vessel occlusion had the score of 43.0. In four deceased patients of other etiology, the median score was 73.0 (vs. 33.0; $p = .001$). In undetermined etiology, the median score of deceased patients was higher than that of survival patients (median, 56.0 vs. 39.5; $p < .001$). (Fig. 2) When adjusted for age, sex, initial NIHSS score and internal carotid artery or basilar artery occlusion, elevated E/e' and D-dimer level in patients with cardioembolic stroke were associated with 90-day mortality (OR, 1.04 95% CI, 1.01–1.07; $p = .005$ and OR, 1.03 95% CI, 1.00–1.06; $p = .006$, respectively).

Table 3
The DONE score (21.5 - 83): predicting 90-day mortality after acute ischemic stroke.

	No. of points	
Variable	90-day mortality score	
D-dimer		
< 0.6	−	6
0.6–1.1	−	0.8
1.2–2.2	+	3
≥2.3	+	12
Occlusion of arteries		
ICA or BA occlusion	+	10
NIHSS score on admission		
< 2	+	0.5
2–4	+	3
5–13	+	8
≥14	+	20
E/e'		
< 10.9	+	27
11.0–12.9	+	32
13.0–16.9	+	35
≥17.0	+	41

ICA, internal carotid artery; BA, basilar artery; NIHSS, National Institute of Health Stroke Scale; E, peak early transmitral filling velocities during early diastole; and e', peak velocities of septal mitral annuli on the tissue Doppler image.

4. Discussion

In this study, left ventricular diastolic dysfunction was an independent predictor of 90-day mortality after acute ischemic stroke. The DONE score, consisting of D-dimer level, occlusion of internal carotid artery or basilar artery, initial NIHSS score and E/e' could be used to predict a poor prognosis at 90 days.

In this study, multiple logistic regression analysis showed that left ventricular diastolic dysfunction could predict 90-day mortality of all types of ischemic stroke, not just that of cardioembolic stroke. A previous study reported that diastolic dysfunction was a key factor of poor outcome in patients with acute ischemic stroke [11]. Left ventricular diastolic dysfunction is believed to be associated with congestive heart failure with preserved left ventricular ejection fraction [15]. In a large single-center cohort study, which included 36,261 patients with normal ejection fraction, moderate and severe diastolic dysfunction were independent predictors of mortality [8]. All patients underwent transthoracic echocardiography within 24 h after admission in this study. Patients with elevated E/e' could be in the state of subclinical heart failure. Therefore, high E/e' in patients with acute ischemic stroke may be associated with a high mortality rate at 90 days. Diastolic dysfunction has been considered as a predictive marker of all-cause mortality [16,17]. Although the underlying mechanism of the association between diastolic dysfunction and all-cause mortality remains unclear, diastolic dysfunction may directly contribute to the worse outcome by leading to the progression of heart failure due to malnutrition and

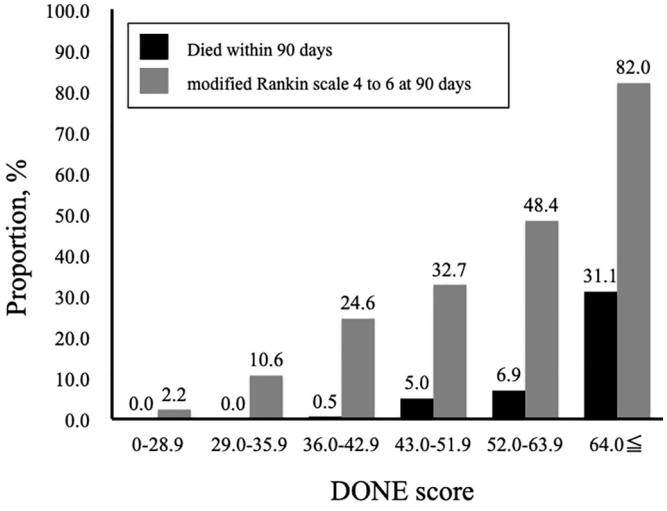

Fig. 1. Proportion of patients who had died within 90 days of admission and poor outcome (modified Rankin scale 4 to 6) at 90-day by the DONE (D-dimer, Occlusion of internal carotid artery or basilar artery, initial NIHSS score and E/e') score.

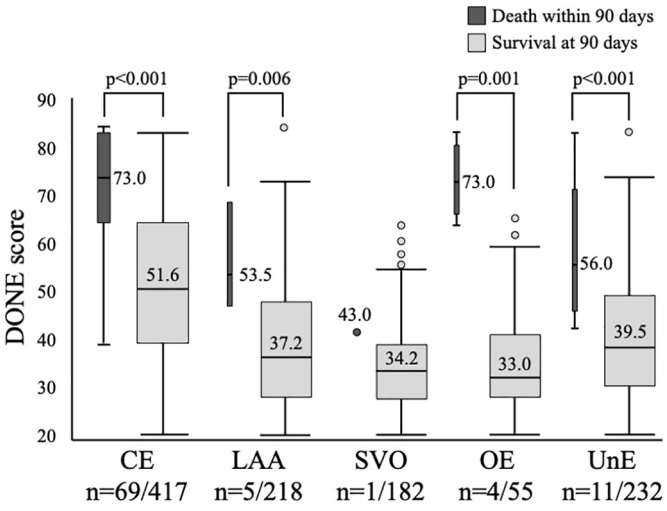

Fig. 2. Box and whisker plots comparing DONE scores between patients with death within 90 days and survival at 90 days in each stroke subtype. The horizontal line in the middle of each box indicates the median, while top and bottom of the box mark the 75th and 25th percentiles, respectively. The whiskers above and below the box mark the 90th and 10th percentiles. The points beyond the whiskers are outliers beyond the 90th percentile. One patient with SVO died within 90 days. The score was 43.0. CE, cardioembolism; LAA, large artery atherosclerosis; SVO, small vessel occlusion; OE, other etiology; UnE, undetermined etiology.

Table 4
Sensitivity, specificity and positive likelihood ratio for different cutoff values of the DONE score for mortality and poor functional outcome.

DONE score	90-day mortality			Poor outcome (mRS score, 4–6)		
	Sensitivity	Specificity	Positive LR	Sensitivity	Specificity	Positive LR
0–28.9	0.0	87.4	0.0	0.7	82.7	0.1
29.0–35.9	0.0	76.2	0.0	7.0	70.1	0.2
36.0–42.9	1.1	82.5	0.1	11.7	81.4	0.6
43.0–51.9	11.1	82.9	0.7	15.9	83.0	0.9
52.0–63.9	14.4	84.2	0.9	22.3	87.7	1.8
≥64.0	73.3	86.8	5.6	42.5	95.2	8.8

LR, likelihood ratio.

frailty [17,18]. The leading cause of mortality in our study was stroke. Patients with internal carotid artery occlusions were more likely to have larger ischemic lesions and those with basilar artery occlusion could induce brain stem ischemia. Therefore, they may have a high mortality [19,20]. In this study, patients with internal carotid artery or basilar artery occlusion had higher E/e' than those without (median, 16.0 vs. 12.4; $p < .001$). Left ventricular diastolic dysfunction with atrial fibrillation could contribute to development of left atrial appendage thrombus, which tends to occlude intracranial large arteries [21]. Therefore, we believe that left ventricular diastolic dysfunction may play an important role in stroke death.

We demonstrated the DONE score, which consisted of initial NIHSS score, internal carotid artery or basilar artery occlusion, E/e', and D-dimer level. Some scores have been designed to predict functional outcome after acute stroke. Especially, the iScore and PLAN score initially focused on mortality in patients with acute ischemic stroke [2,3]. Congestive heart failure, which could involve both systolic and diastolic dysfunction, was included in those scores. In this study, diastolic dysfunction was associated with 90-day mortality, whereas systolic dysfunction could not predict the outcome. Evaluating diastolic dysfunction in patients with acute ischemic stroke may be valuable for predicting mortality rather than measuring ejection fraction. An elevated plasma D-dimer level was an independent predictor of 90-day functional outcome and mortality after acute ischemic stroke [22]. Elevation of the plasma D-dimer level may reflect that thrombi have resistance to the induced fibrinolytic system and thrombolytic therapy [23]. It is generally accepted that older age and preadmission dependence are associated with an increased risk of mortality after acute ischemic stroke [2,3,24]. However, they were not independent predictors of 90-day mortality in this study. We could not clearly understand the reason. The significant relationship between older age and mortality might disappear by including E/e' in multiple regression analysis. Pre-stroke dependent patients had higher initial NIHSS score ($p < .001$), E/e' ($p < .001$) and D-dimer ($p < .001$) level as compared with pre-stroke independent patients, however the number of internal carotid artery or basilar artery occlusion was comparable between pre-stroke dependent and independent patients ($p = 1.000$). They might have small ischemic lesions. Dyslipidemia and smoking history were associated with survival at 90 days after acute ischemic stroke in univariate analysis. These are important risk factors for coronary artery disease and stroke due to the development of atherosclerosis. However, previous studies have shown that they seem to be associated with lower mortality after coronary artery disease or acute ischemic stroke [25,26]. Mechanisms of these paradoxes remain unclear.

Our study has some limitations including its single center design and retrospective nature. In addition, we were unable to divide the cohort into a derivation and validation sets because the number of deaths was small. Instead, an internal validation was performed with the bootstrap method to assess the optimism of the prediction model. Moreover, we did not include the initial lesion volume from diffusion-weighted imaging, which is a predictive biomarker of poor prognosis, [27] as a variable for 90-day mortality. Alternatively, we adopted occluded arteries as an imaging factor for predicting prognosis after acute ischemic stroke. In this study, a large number of patients underwent MRI for the evaluation of ischemic and vascular lesions. Recently, stroke physicians prefer to perform CT angiography and perfusion to identify an eligible patient for endovascular recanalization therapy rather than to perform MRI because of the shorter examination time and evidence from multicenter, randomised trials [28]. Therefore, we assessed only occlusion of the cerebral artery, which can be evaluated by CT angiography, without considering the size of the ischemic lesion by MRI. Finally, The value of E/e' could be affected by acute myocardial infarction and hydration states. There was no patient with acute myocardial infarction. To avoid the effect of hydration status as much as possible, we performed transthoracic echocardiography within 24 h from presentation.

5. Conclusions

Left ventricular diastolic dysfunction indicated by higher E/e' on admission may be associated with 90-day mortality in patients with acute ischemic stroke. The DONE score consisted of D-dimer level, occlusion of internal carotid artery or basilar artery, the initial NIHSS score and E/e' was a simple score for predicting poor outcome after acute ischemic stroke. Future study is warranted to elucidate the efficacy of the score in an external validation cohort.

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