Serum resolvin D1 potentially predicts neurofunctional recovery, the risk of recurrence and death in patients with acute ischemic stroke

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Abstract. Resolvin D1 (RvD1) represses inflammation, oxidative damage and neural injury related to acute ischemic stroke (AIS) progression. The present study aimed to explore the association of serum RvD1 with disease features, neurological recovery and prognosis in patients with AIS. A total of 212 patients with newly diagnosed AIS, whose serum RvD1 was quantified at admission and at discharge using an ELISA were enrolled in the current study. The modified Rankin scale (mRS) score was noted at 3 months after patient enrolment (M3), and patients were followed up for a median duration of 11.4 (range, 1.1-21.0) months. The median RvD1 in patients with AIS at admission was 1.07 (range, 0.11-9.29) ng/ml and it was negatively correlated with the neutrophil/lymphocyte ratio (r=-0.160; P=0.009) and C-reactive protein level (r=-0.272; P<0.001), but it was not correlated with comorbidities or other biochemical indexes. RvD1 at admission was lower in patients with mRS >2 at M3 (P=0.001), recurrence (P=0.001) or death (P=0.032) compared with that in patients without the aforementioned characteristics, which had a general ability to estimate mRS >2 at M3 [area under curve (AUC), 0.633], as well as lower risk of recurrence (AUC, 0.745) and death (AUC, 0.757) according to receiver operator characteristic (ROC) curve analyses. The median RvD1 was raised to 1.70 (range, 0.30-16.62) ng/ml at discharge. RvD1 at discharge was able to forecast mRS >2 at M3 (AUC, 0.678) and was able to predict the risk of recurrence (AUC, 0.796) and death (AUC, 0.826) in the ROC curve analyses. Increased serum RvD1 was associated with an attenuated inflammation status, and predicted improved neurological recovery, and lower risk of recurrence and death in patients with AIS. More specifically, its level at discharge exhibits a better prognostic utility than that at admission.

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Introduction

Acute ischemic stroke (AIS) is the most common type of stroke, which may lead to severe brain injury and further induce a considerable disease burden, such as disability and even death (1). In China, it is reported that ~90% of strokes are categorized as AIS and 15.5 million AIS incidents were recorded in 2020, which was reported to be a leading cause of disability and death between 2018 and 2020 (2,3). The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio and C-reactive protein (CRP) are recognized as the common hallmark of inflammation, whose level is aberrant in diseases characterized by inflammation. Specifically, the NLR is found abnormal in inflammatory bowel disease, diabetes mellitus, gastrointestinal conditions, cardiac conditions, thyroiditis and severe acute respiratory virus coronavirus (Covid) 2 infection (4-8); CRP is increased in diabetes mellitus, thyroiditis, diabetic neuropathy, hepatitis and Covid 2019 (Covid-19) infection (9-13); the platelet-to-lymphocyte ratio also reflects inflammatory burden in thyroid conditions, gastrointestinal diseases, thyroiditis, cancer, diabetes mellitus, irritable bowel disease and Covid-19 infection (14-19). During the progression of AIS, the inflammation reflected by the NLR, platelet-to-lymphocyte ratio and CRP has a crucial role in promoting ischemic injury, endothelial cell dysregulation and neural death (20-24). Once these ischemic damages occur, they may cause aggravated neuroinflammation by inducing the release of reactive oxygen species and pro-inflammatory cytokines (25,26).

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids that serve as protective factors in cerebral diseases; the optimal concentration of EPA and DHA is nearly 8-11% and a lower level correlates with reduced brain volume, aggravated brain damage and elevated risk for total mortality and ischemic stroke (27,28). The resolvin family is a group of anti-inflammatory mediators originating from EPA and DHA, which was reported to improve the prognosis

of stroke (29). Resolvin D1 (RvD1), the main derivative, is a mediator during the metabolic process of DHA, which is closely engaged in inhibiting vascular chronic inflammation, neuroinflammation, and neuronal injury (30-34). For instance, a previous study reported that RvD1 inhibits the production of inflammatory cytokines from macrophages and peripheral blood mononuclear cells (30). In another study, RvD1 was shown to repress the microglial pro-inflammatory response, neuronal oxidative damage and apoptosis through several potential pathways such as the MAPK pathway (31). Even though a small number of current studies have preliminarily explored the dysregulation of RvD1 in patients with stroke and its association with short-term functional outcomes, these are limited by small sample size, lack of an extended follow-up and single time assessment; therefore, a definite exploration of the clinical value of RvD1 measurement in assessing AIS prognosis is still warranted (35,36).

In the current study, the serum RvD1 levels of patients with AIS on admission and at discharge were detected, aiming to evaluate the relationship of RvD1 at different time-points with inflammation, neurological function recovery and risk of recurrence and death in patients with AIS.

Materials and methods

Patients. A total of 261 patients with newly diagnosed AIS were recruited between July 2021 and May 2023. The inclusion criteria were as follows: i) Patients with newly diagnosed AIS following the American Stroke Association Guidelines (37); ii) patients aged ≥18 years; iii) patients who were admitted within 24 h since AIS symptoms occurred; iv) either the patients or their guardians consented to the patients undergoing serum collection and follow-up. The exclusion criteria involved: i) Patients with intracranial hemorrhage; ii) patients with other cancers or hematological malignant diseases; iii) patients with severe infections. Besides, a total of 30 healthy people who were age-, gender- and body mass index (BMI)-matched with the AIS group were enrolled as healthy controls (HCs). The eligibility criteria were: i) No abnormalities in recent physical examination; ii) no history of alcohol and drug abuse; iii) consent to participate in the study. The present study was approved by the Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China; approval no. 2020-082-01). Informed consent was obtained from the patients or their guardians and HCs.

Data documentation. The clinical characteristics of the patients with AIS enrolled in the current study were collected on admission and included demographics, comorbidities, National Institutes of Health Stroke Scale (NIHSS) score (38), timeframe since first AIS symptom to admission, fasting plasma glucose (FBG), serum creatinine (Scr), serum lipid indexes, NLR, CRP and treatment information.

Serum RvD1 detection. Serum was collected within 24 h of admission and on the day of discharge from the patients with AIS and within 24 h after enrollment from the HCs. Serum RvD1 was detected using an ELISA kit (cat. no. EK11723; SAB Biotherapeutics, Inc.). The experimental procedure was briefly as follows: First, a microplate pre-coated with an antibody specific to RvD1 was prepared, then the standards or samples were pipetted into the wells and RvD1 was bound through the immobilized antibody. After washing, a biotin-conjugated antibody specific for RvD1 and streptavidin-conjugated horseradish peroxidase were added. Finally, a substrate solution was added for color rendering and the optical intensity was detected at 450 nm using a microplate photometer (Multiskan FC; Thermo Fisher Scientific, Inc.). The test was conducted following the manufacturers' instructions and each serum sample was tested in triplicate.

Assessments. Patients with AIS were regularly followed up until July 2023. During the follow-up, recurrence and death were recorded. The modified Rankin scale (mRS) score was assessed at 3 months after enrollment (M3) (39). mRS≤2 indicated favorable prognosis, while mRS>2 indicated poor prognosis (40).

Statistical analysis. SPSS (version 26.0; IBM, Corp.) was used for data analysis. The normality distribution analysis was performed via the Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± standard deviation or median (interquartile range) and count data as n (%). Correlation analyses were performed using Spearman's correlation. Comparison between groups and among multiple groups was performed by the Wilcoxon rank-sum test and the Kruskal-Wallis test, respectively. The effect size '*Z*' was calculated by the Wilcoxon rank-sum test and the effect size '*H*' was calculated by the Kruskal-Wallis test. Comparison of RvD1 levels at admission and discharge was performed using the Wilcoxon signed-rank test. The distinguishing ability of RvD1 was determined by receiver operator characteristic (ROC) curve analyses. $P<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics of patients with AIS and HCs. A total of 261 patients with AIS were included in the present study with a mean age of 67.3±8.8 years, consisting of 170 males (65.1%) and 91 females (34.9%) (Table SI). The mean NIHSS score was 8.9±4.5. Furthermore, the NLR and CRP levels were 4.0 (2.9-6.0) and 4.5 (2.9-7.0) mg/l, respectively, in the patients with AIS. Other detailed information is provided in Table I. In addition, the mean age of the HCs was 66.6±6.9 years and the group comprised 10 (33.3%) females and 20 (66.7%) males. The mean BMI of the HCs was 24.7±3.0 kg/m^2. Of note, no difference was seen in age (P=0.661), gender (P=0.867) or BMI (P=0.189) between patients with AIS and HCs (Table SI).

Comparison of serum RvD1 between patients with AIS and HCs. The distribution of serum RvD1 in patients with AIS at admission is presented in Fig. 1 [median: 1.07 (range: 0.11-9.29) ng/ml]; specifically, serum RvD1 at admission was insufficient in most patients with AIS and only a minority of patients had serum RvD1 at admission >4.00 ng/ml. Besides, RvD1 was declined in patients with AIS compared to HCs [median: 1.07 (range: 0.51-1.86) vs. 5.65 (range: 2.19-9.43) ng/ml, P<0.001; Table SI].

Association of serum RvD1 with comorbidities and common biochemical indexes in patients with AIS. Serum RvD1 at admission was not significantly associated with any

Table I. Clinical characteristics of patients with AIS (n=261).

Characteristic	Value
Age, years	67.3±8.8
Gender	
Female	91 (34.9)
Male	170 (65.1)
BMI, kg/m^2	25.4±2.7
Current or former smoker	105 (40.2)
Hypertension	213 (81.6)
Hyperlipidemia	121 (46.4)
Diabetes	74 (28.4)
Cardiovascular disease	111 (42.5)
Time since stroke symptom to admission, h	5.0 (3.0-7.0)
NIHSS score	8.9±4.5
FBG, mmol/l	5.7 (4.9-6.8)
Scr, μmol/l	84.5 (75.2-98.0)
TG, mmol/l	1.8 (1.1-2.5)
TC, mmol/l	4.8 (4.1-5.5)
LDL-C, mmol/l	3.3 (2.7-4.2)
HDL-C, mmol/l	1.0 (0.8-1.2)
NLR	4.0 (2.9-6.0)
CRP, mg/l	4.5 (2.9-7.0)
Treatment	
IVT with rtPA	44 (16.9)
IVT with rtPA bridging to MT	98 (37.5)
IVT with UK	17 (6.5)
IVT with UK bridging to MT	35 (13.4)
MT	67 (25.7)
Median follow-up time, months	11.4
Follow-up range, months	1.1-21.0
Recurrence	17 (6.5)
Death	6 (2.3)

Values are expressed as the mean ± standard deviation, median (interquartile range) or n (%). AIS, acute ischemic stroke; BMI, body mass index; NIHSS, National Institute of Health Stroke Scale; FBG, fasting plasma glucose; Scr, serum creatinine; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; IVT, intravenous thrombolysis; rtPA, recombinant tissue plasminogen activator; MT, mechanical thrombectomy; UK, urokinase.

comorbidities, including hypertension, hyperlipidemia, diabetes and cardiovascular disease. Furthermore, it was not correlated with any common biochemical indexes, including FBG, Scr, triglyceride, total cholesterol, low- and high-density lipoprotein cholesterol (all P>0.05; Table II).

Association of serum RvD1 at admission with inflammation in patients with AIS. Serum RvD1 at admission was negatively correlated with the neurofunctional status reflected by the NIHSS score (r=-0.202; P=0.001; Fig. 2A). Of note, serum RvD1 at admission was negatively correlated with the

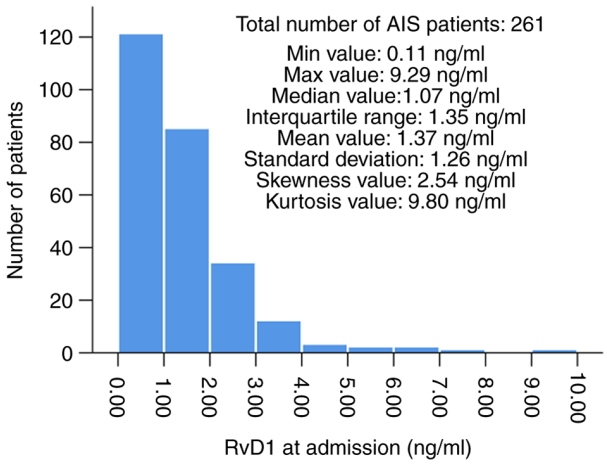


Figure 1. Detailed information on the serum RvD1 level at admission in patients with AIS. RvD1, resolvin D1; AIS, acute ischemic stroke.

NLR index (r=-0.160; P=0.009; Fig. 2B) and the CRP level (r=-0.272; P<0.001; Fig. 2C).

Relationship of serum RvD1 at admission with neurofunctional rehabilitation, recurrence and death in patients with AIS. During a median follow-up of 11.4 months (range, 1.1-21.0), there were 17 recurrence cases (6.5%) and six deaths (2.3%) in the cohort of patients with AIS (Table I). Serum RvD1 at admission was lower in patients with AIS and mRS score >2 compared with that in patients with mRS score ≤2 at M3 (P=0.001; Fig. 3A). Furthermore, it was shown that serum RvD1 at admission was also lower in patients who experienced recurrence of AIS (P=0.001; Fig. 3B) or death (P=0.032; Fig. 3C) during follow-up compared with those who did not.

Subsequent ROC curve analysis indicated that serum RvD1 at admission may be used to estimate neurofunctional recovery reflected by the mRS score at M3 [area under curve (AUC), 0.633; 95% CI, 0.558-0.709; Fig. 3D]. Serum RvD1 at admission also revealed acceptable values in predicting risk of recurrence (AUC, 0.745; 95% CI, 0.633-0.857; Fig. 3E) and death (AUC, 0.757; 95% CI, 0.555-0.985; Fig. 3F).

Change of serum RvD1 from admission to discharge in patients with AIS. The median level of serum RvD1 was 1.07 (0.51-1.86) ng/ml at admission, while it was 1.70 (0.96-2.66) ng/ml at discharge. It was shown that the serum RvD1 was increased from admission to discharge (P<0.001; Fig. 4). The median hospital stay of patients with AIS was 15 days, ranging from 8 to 29 days. Besides, serum RvD1 at admission (r=-0.086; P=0.165; Fig. S1A) and RvD1 at discharge (r=-0.097; P=0.131; Fig. S1B) were not associated with hospital stay in patients with AIS.

Relationship of serum RvD1 at discharge with neurofunctional rehabilitation, recurrence and death in patients with AIS. Serum RvD1 at discharge was decreased in patients with AIS and an mRS score >2 compared with that in patients with an mRS score ≤2 at M3 (P<0.001; Fig. 5A). It was also shown that serum RvD1 at discharge was decreased in patients with AIS who experienced either recurrence (P<0.001; Fig. 5B) or

Table II. Comparison of RvD1 at admission in patients with different characteristics.

A, Categorical variables

Item	RvD1 at admission, ng/ml	Z	P-value
Hypertension		-0.859	0.390
No	1.14 (0.58-2.11)		
Yes	1.05 (0.51-1.81)		
Hyperlipidemia		-1.378	0.168
No	1.09 (0.56-1.87)		
Yes	1.01 (0.45-1.82)		
Diabetes		-1.285	0.199
No	1.09 (0.56-1.87)		
Yes	0.91 (0.45-1.78)		
Cardiovascular disease		-1.218	0.223
No	1.08 (0.57-1.94)		
Yes	1.05 (0.46-1.62)		

B, Continuous variables

Item	RvD1 at admission, ng/ml	r	P-value
FBG	1.07 (0.51-1.86)	-0.073	0.240
Scr	1.07 (0.51-1.86)	-0.031	0.618
TG	1.07 (0.51-1.86)	-0.108	0.083
TC	1.07 (0.51-1.86)	-0.073	0.241
LDL-C	1.07 (0.51-1.86)	-0.044	0.480
HDL-C	1.07 (0.51-1.86)	-0.059	0.340

Values are expressed as the median (interquartile range). The effect size 'Z' was used for categorical variables, while the correlation coefficient 'r' was used for continuous variables. RvD1, resolvin D1; FBG, fasting plasma glucose; Scr, serum creatinine; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

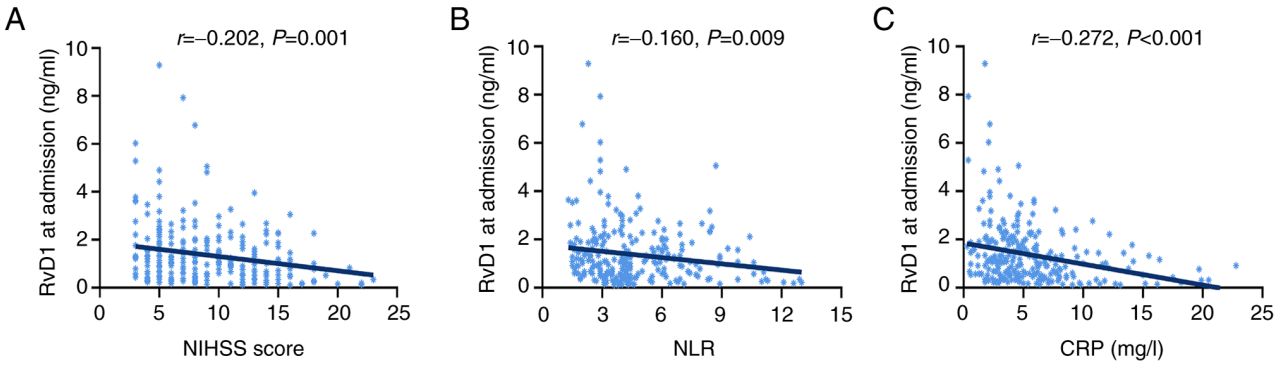


Figure 2. Serum RvD1 levels of patients with AIS were negatively correlated with the NIHSS score, NLR and CRP. Correlation of serum RvD1 at admission with the (A) NIHSS score, (B) NLR and (C) CRP in patients with AIS. RvD1, resolvin D1; AIS, acute ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil/lymphocyte ratio; CRP, C-reactive protein.

death (P=0.006; Fig. 5C) compared with that in those patients with AIS who did not.

ROC analysis indicated that the ability of serum RvD1 at discharge to predict neurofunctional recovery reflected by the mRS score at M3 was fair (AUC, 0.678; 95% CI, 0.603-0.753; Fig. 5D). Of note, serum RvD1 at discharge had a potential utility in predicting risk of recurrence (AUC, 0.796; 95% CI, 0.724-0.867; Fig. 5E) and death (AUC, 0.826; 95% CI, 0.742-0.910; Fig. 5F). Referring to the AUC values, it was shown that compared with the serum RvD1 level at admission, serum RvD1 at discharge may be used for making predictions regarding the prognosis of patients with AIS.

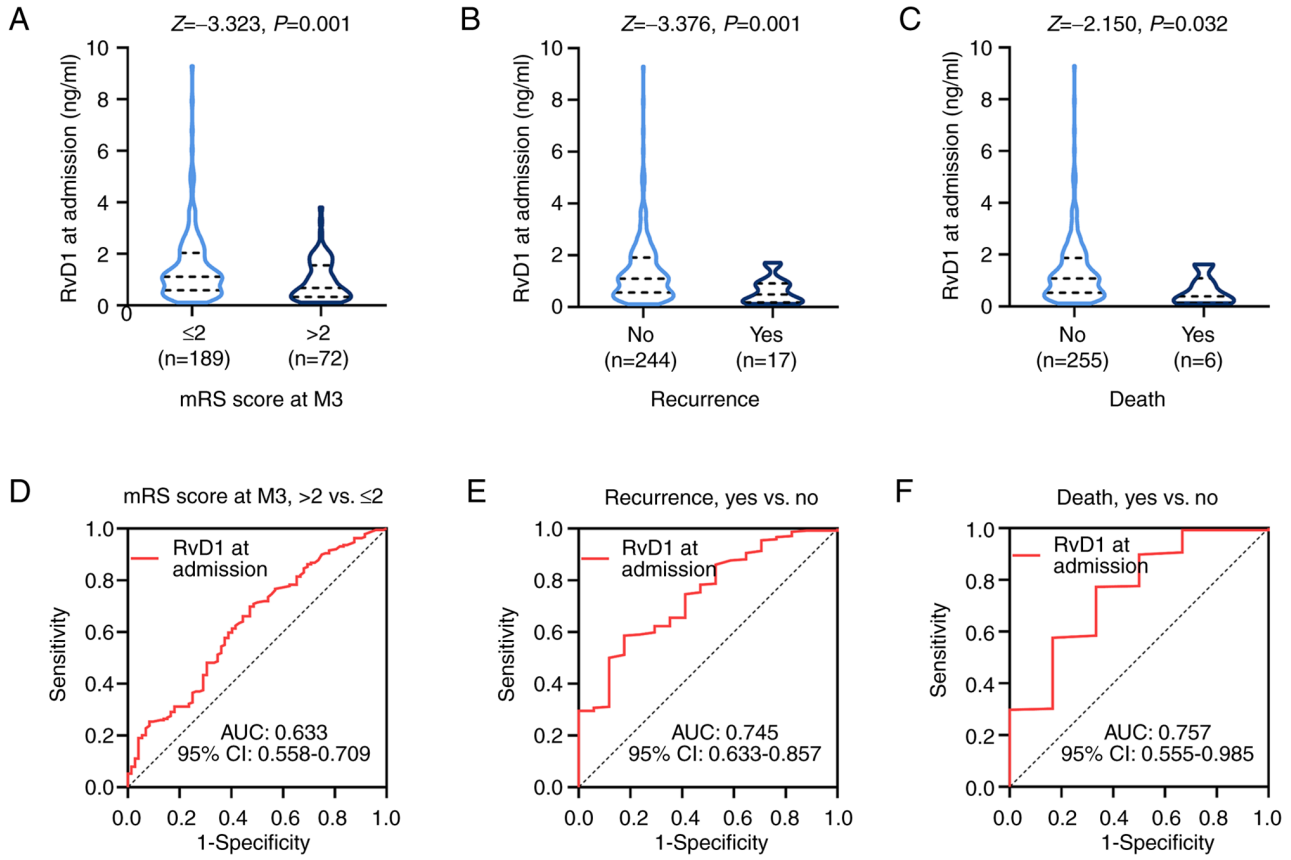


Figure 3. Serum RvD1 levels in patients with AIS at admission reflected neurofunction and the risk of recurrence and death. Comparison of serum RvD1 at admission with (A) the mRS score at M3, (B) recurrence and (C) death in patients with AIS. ROC curves for the value of serum RvD1 at admission used to predict (D) neurofunction, (E) risk of recurrence and (F) death of patients with AIS. RvD1, resolvin D1; AIS, acute ischemic stroke; mRS, modified Rankin scale; M3, 3 months after patient enrolment; ROC, receiver operating characteristic; AUC, area under the ROC curve.

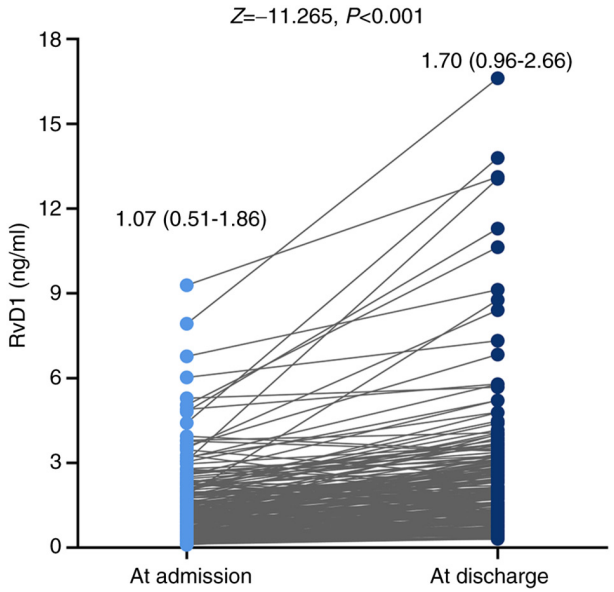


Figure 4. Serum RvD1 was increased from admission to discharge of patients with acute ischemic stroke. RvD1, resolvin D1.

Comparison of serum RvD1 at admission and discharge among patients with AIS receiving different treatments. Serum RvD1 at admission did not differ among patients with AIS receiving different regimens (P=0.063; Fig. 6A). However, subsequent muti-comparison indicated that serum RvD1 at admission was higher in patients with AIS receiving intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) compared with that in patients receiving mechanical thrombectomy (MT) monotherapy (P=0.023). In addition, serum RvD1 at admission was higher in patients with AIS receiving IVT with rtPA bridging to MT compared with that in patients receiving MT alone (P=0.006).

Serum RvD1 at discharge also differed among patients with AIS receiving different regimens (P=0.025; Fig. 6B). Further muti-group comparison indicated that serum RvD1 at discharge in patients with AIS receiving IVT with rtPA was higher than that in patients receiving MT monotherapy (P=0.025). Serum RvD1 was also higher in those patients receiving IVT with rtPA bridging to MT compared with that in patients receiving MT alone (P=0.001).

Discussion

RvD1 is a well-recognized endogenous anti-inflammatory lipid mediator involved in acute inflammation, chronic inflammation and neuroinflammation (33,41-44). A previous study showed that RvD1 supports the resolution of acute inflammation in mice with post-myocardial infarction (41). Another study indicated that RvD1 limits vascular chronic inflammation, thereby serving as a potential strategy for atherosclerotic inflammation (33). Furthermore, a previous

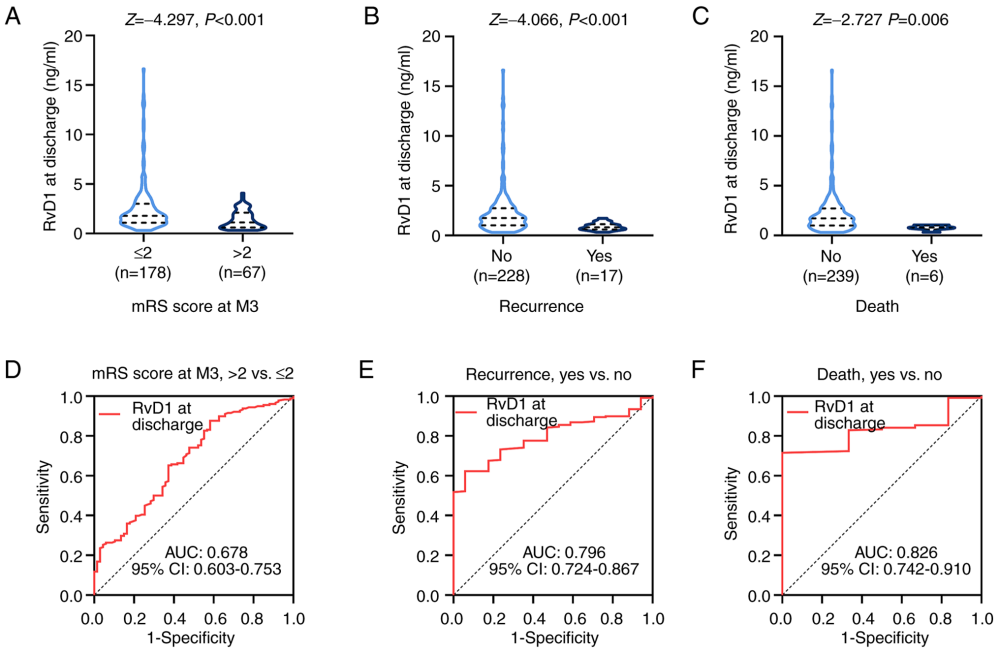
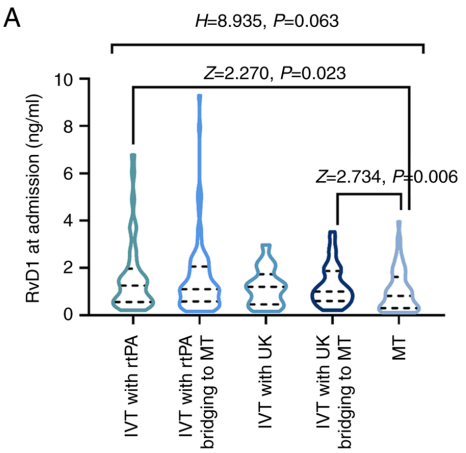
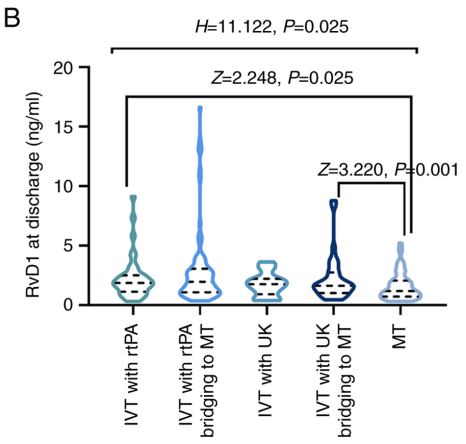


Figure 5. Serum RvD1 at discharge may reflect neurofunction, and risk of recurrence and death of patients with AIS. Comparison of serum RvD1 at discharge with (A) the mRS score at M3, and risk of (B) recurrence and (C) death in patients with AIS. ROC curves for the value of serum RvD1 at discharge in predicting (D) neurofunction, and risk of (E) recurrence and (F) death of patients with AIS. RvD1, resolvin D1; AIS, acute ischemic stroke; ROC, receiver operating characteristic; AUC, area under the ROC curve; M3, 3 months after patient enrolment; mRS, modified Rankin scale.



P value of multi-comparison	
IVT with rtPA vs. IVT with rtPA bridging to MT	0.944
IVT with rtPA vs. IVT with UK	0.450
IVT with rtPA vs. IVT with UK bridging to MT	0.678
IVT with rtPA vs. MT	0.023
IVT with rtPA bridging to MT vs. IVT with UK	0.560
IVT with rtPA bridging to MT vs. IVT with UK bridging to MT	0.688
IVT with rtPA bridging to MT vs. MT	0.006
IVT with UK vs. IVT with UK bridging to MT	0.961
IVT with UK vs. MT	0.268
IVT with UK bridging to MT vs. MT	0.082



P value of multi-comparison	
IVT with rtPA vs. IVT with rtPA bridging to MT	0.684
IVT with rtPA vs. IVT with UK	0.560
IVT with rtPA vs. IVT with UK bridging to MT	0.736
IVT with rtPA vs. MT	0.025
IVT with rtPA bridging to MT vs. IVT with UK	0.365
IVT with rtPA bridging to MT vs. IVT with UK bridging to MT	0.438
IVT with rtPA bridging to MT vs. MT	0.001
IVT with UK vs. IVT with UK bridging to MT	0.750
IVT with UK vs. MT	0.340
IVT with UK bridging to MT vs. MT	0.077

Figure 6. Serum RvD1 was elevated in patients with AIS undergoing IVT with rtPA or IVT with rtPA bridging to MT compared with that in patients treated with MT alone. Comparison of serum RvD1 at (A) admission and (B) discharge among patients with AIS with different treatment regimens and further multi-comparisons. RvD1, resolvin D1; AIS, acute ischemic stroke; IVT, intravenous thrombolysis; rtPA, recombinant tissue plasminogen activator; MT, mechanical thrombectomy; UK, urokinase.

study indicated that RvD1 was responsible for inflammation resolution in early neuroinflammatory changes (42). However, the available clinical evidence that supports the association of RvD1 with inflammation in patients with AIS is currently insufficient. The present study revealed that serum RvD1 was negatively correlated with CRP and NLR in patients with AIS. The possible reasons behind this finding include the following: i) RvD1 represses leukocyte recruitment and infiltration in the ischemic core (32); and ii) RvD1 enhances the chemotaxis of anti-inflammatory macrophages (M2-polarized macrophages) for them to exert their anti-inflammatory properties (45,46). Elevated serum RvD1 was associated with reduced CRP and NLR in patients with AIS.

Sustained neuroinflammation and microglia activation was observed to lead to neuronal damage and degeneration (47). Given that RvD1 ameliorates neuroinflammation and inactivates inflammatory signaling in microglial cells, its engagement in cerebral neurological dysfunction has been revealed in several studies (36,48-50). A previous study suggested that RvD1 triggers functional recovery and neuroprotection after focal brain injury (49). Another study showed that RvD1 serves as a beneficial factor for cognitive impairment following traumatic brain injury by protecting astrocytic mitochondria (50). The present study revealed that elevated serum RvD1 was associated with a reduced NIHSS score and an mRS score ≤2 at M3 in patients with AIS. A likely explanation could be that RvD1 suppressed microglia activation, inhibited neuronal cell death and restrained neuroinflammation in remote regions to improve neurological function (49,51). As a result, increased serum RvD1 was related to improved neurological rehabilitation in patients with AIS.

The present study also revealed elevation of serum RvD1 from admission to discharge in patients with AIS, likely due to the level of inflammation in patients with AIS being correspondingly ameliorated by in-hospital treatment (52,53). In addition, serum RvD1 is a widely endorsed anti-inflammatory factor, the elevation of which represents resolution of acute inflammation (54). Thus, serum RvD1 in patients with AIS was increased at discharge compared with that at admission. Furthermore, the present study also showed that serum RvD1 was elevated in patients undergoing IVT with rtPA compared with that in patients treated with MT alone. Also, RvD1 was increased in patients receiving IVT with rtPA bridging to MT compared with that in patients treated with MT alone. A relevant explanation may be that the selection of either IVT or MT was mainly based on the time window as well as assessment of the infarct core and salvageable penumbra; therefore, patients with AIS who were ineligible for IVT tended to experience a higher level of AIS severity, manifested by an elevated inflammatory level (55). Combined with the finding that serum RvD1 was negatively associated with inflammation as mentioned above, patients with AIS receiving MT therefore had reduced serum RvD1 compared with that in patients who received IVT with rtPA or IVT with rtPA bridging to MT.

The value of RvD1 for estimating clinical outcomes of certain cardiovascular and cerebrovascular events has been previously reported (35,56,57). According to a recent study, RvD1 has prognostic potency for its association with left ventricular ejection fraction in patients with ST-segment elevation myocardial infarction (56). In addition, another study indicated that RvD1 may be used to predict early neurological deterioration and worse outcomes in patients with acute supratentorial intracerebral hemorrhage (57). The current study showed that high serum RvD1 was associated with lower risks of recurrence and death in patients with AIS. The likely reasons for this finding include the following: i) RvD1 restrained atherosclerotic plaque rupture and necrosis by modulating macrophage-mediated clearance of necrotic cells; meanwhile, the enhanced stability of atherosclerosis resulted in a reduced risk of recurrence in patients with AIS (33,58); and ii) RvD1 suppressed pro-fibrotic genes and collagen deposition to protect against fibrosis, which alleviated central nervous system injury and improved survival in patients with AIS (39,59). Combining the aforementioned aspects, high serum RvD1 may reflect a reduced risk of recurrence and death in patients with AIS. In addition, it is noteworthy that the ability of serum RvD1 to estimate the risks of recurrence and death was increased at discharge compared with that at admission, which may be explained by the fact that after treatment, the difference in every patient with AIS was enhanced. Consequently, the clinical value of serum RvD1 at discharge was greater than that of RvD1 at admission in patients with AIS; however, further validation is necessary.

Some inevitable limitations should be mentioned: i) In the current study, the mRS score was only analyzed within 3 months of patient enrolment, while the predictive role of RvD1 for more extended neurological rehabilitation in patients with AIS requires further exploration; ii) serum RvD1 was only determined at admission and at discharge, and its longitudinal change in patients with AIS remains elusive; iii) this study only enrolled patients with AIS, but lacked a control group, which may cause confounders; and iv) RvD1 levels were not determined in the cerebrospinal fluid of patients with AIS, which requires further investigation.

Collectively, the present study indicated that elevated serum RvD1 reflects improved inflammation status and is a predictor of better neurological recovery and lower risks of recurrence and death in patients with AIS. More specifically, compared with the level of RvD1 on admission, the level of RvD1 at discharge exhibits a higher predictive value in estimating prognosis of AIS. The findings of the present study suggest that patients with AIS with abnormally reduced RvD1 levels tend to have inferior outcomes and require more intensive and specific treatment in clinical practice.

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Availability of data and materials

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

Authors' contributions

EC was responsible for study conception and design. EC and DZ interpreted the data and drafted the manuscript. DZ and RD helped with the data analysis and edited the manuscript. All authors have read and approved the final version of the manuscript. EC and DZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study gained the approval of the Ethics Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China; approval no. 2020-082-01). Informed consent was obtained from the patients or their guardians and the HCs.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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