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ORIGINAL RESEARCH

Emerging Implications of Serum Resolvin D2 as a Biochemical Marker for Severity Assessment and Prognosis Prediction Following Moderate-Severe Traumatic Brain Injury: A Prospective Cohort Study

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Background: Resolvin D2 (RvD2), which exhibits anti-inflammatory properties, is neuroprotective. This study aimed to ascertain the potential of serum RvD2 level as a prognostic predictor of moderate-to-severe traumatic brain injury (msTBI).

Methods: In this prospective cohort study, serum RvD2 levels were measured in 136 patients with msTBI and 100 healthy controls. The severity scoring systems encompassed the Rotterdam computed tomography classification and Glasgow Coma Scale (GCS). Post-trauma six-month Glasgow outcome scale (GOS) was deemed an outcome indicator, with GOS scores below 4 indicating poor prognosis. Sequential univariate and multivariate analyses were used to determine the correlative factors of changeable serum RvD2 levels and the predictors of adverse prognosis.

Results: Patients displayed a marked decline in serum RvD2 levels compared to controls (median, 95.2 versus 252.8 pg/mL; P<0.001). Serum RvD2 levels were independently correlated with GCS scores (beta, 8.989; 95% confidence interval (CI), 3.678–14.280; P=0.001) and Rotterdam scores (beta, −14.676; 95% CI, −25.885–3.468; P=0.011), and were independently associated with continuous GOS scores (beta, 0.004; 95% CI, 0.002–0.007; P=0.003), ordinal GOS scores (odds ratio, 1.008; 95% CI, 1.002–1.015; P=0.015), and poor prognosis (odds ratio, 0.991; 95% CI, 0.983–0.999; P=0.037) at the six-month mark. A linear correlation was observed between serum RvD2 levels and the likelihood of poor prognosis (P for nonlinear = 0.090). Serum RvD2 levels exhibited strong discrimination efficiency for the probability of poor prognosis (P<0.001), with similar ability as Rotterdam scores (P=0.337) and GCS scores (P=0.300). The integrative model encompassing serum RvD2, Rotterdam scores and GCS scores performed well using a series of statistical methods.

Conclusion: A significant decrease in serum RvD2 levels after msTBI may accurately indicate trauma severity and efficiently distinguish the possibility of poor neurological outcomes in msTBI, signifying that serum RvD2 may be of clinical significance in the prognostic prediction of TBI.

Keywords: resolvin 2, traumatic brain injury, prognosis, severity, biomarkers

Introduction

Moderate-severe traumatic brain injury (msTBI), one of the most severe forms of trauma marked by high fatality, is among the main causes of disability burden globally.[1] Primary brain injury is associated with secondary brain injury, leading to a more intricate interplay of numerous pathophysiological processes, and a complex array of inflammatory, oxidative, and apoptotic pathways composing a singular mechanistic entity after TBI.[2] Among various factors confirmed as prognostic predictors of TBI, clinical severity scoring popularly using the Glasgow Coma Scale (GCS) and radiological severity scaling frequently using Rotterdam computed tomography (CT) classification are firmly linked to

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the likelihood of posttraumatic adverse outcomes.[3,4] Serological markers, such as xanthine oxidase, ST2 and translocator protein, which may enable early and quick prognostic prediction after TBI, have garnered significant attention in the neuroscience field over the past decades.[5–7]

Resolvin D2 (RvD2) is a member of the resolvin family and is derived from ω–3 polyunsaturated fatty acids.[8] RvD2, similar to other members, harbors the interesting potential to modulate inflammatory courses.[9,10] There is an obvious reduction in endogenous RvD2 expression in rat brain tissues injured by middle cerebral artery occlusion and reperfusion.[11] Additionally, in rats with acute ischemic stroke or acute subarachnoid hemorrhage, exogenous supplementation with RvD2 substantially diminished cerebral lesion size, reduced inflammatory and oxidative reactions, attenuated cerebral edema, and subsequently improved neurological deficits.[11,12] Also, RvD2 levels in peripheral blood were markedly reduced shortly after traumatic brain injury or acute ischemic stroke.[13] Hypothetically, RvD2, which acts as a protective factor, may be a biomarker of acute brain injury. Here, serum RvD2 quantification was conducted to further explore whether serum RvD2 levels are related to severity and poor prognosis following msTBI.

Materials and Methods

Study Design and Ethical Requirements

The study was conducted at Changzhi People's Hospital from April 2020 to May 2023. A single-site observational analytical study was designed and then performed in the form of two sub-studies. One part constituted a cross-sectional study of controls and patients with msTBI, in which the posttraumatic alteration in serum RvD2 levels was disclosed. The second segment entailed a prospective cohort study of patients sustaining msTBI, with the objective of discovering the prognostic potential of serum RvD2 in msTBI. This study adhered to the guidelines formulated in the Declaration of Helsinki and its subsequent updates. The study protocol was approved by the Ethics Committee of Changzhi People's Hospital (approval number: 2024K086). Informed consent forms were signed by the legal guardians and controls themselves.

Participant Enrollments

Consecutive collections of patients with TBI were performed. TBI was diagnosed based on a within the initial 12 h following trauma. The exclusion criteria were as follows: (1) traumatic history and head computed tomography (CT) readings. The recruitment criteria were as follows: (1) age ≥ 18 years, (2) blunt trauma, (3) GCS score from 3 to 12, (4) abbreviated injury scale score of 2 or below in any non-cranial location, and (5) hospital admission previous attack of other neurological diseases, such as ischemic cerebral stroke, intracranial neoplasms, and infections in the central nervous system; (2) serious illnesses affecting other organs, such as malignancies and cardiac, hepatic, pulmonary, and renal dysfunctions; and (3) certain special conditions, including pregnancies, loss of individuals to follow-up, deficient materials, reluctance to participate, and samples unfitting the required criteria. The controls did not experience severe illnesses or certain common chronic disorders, including hypertension, diabetes mellitus, and hyperuricemia. Using conventional diagnostic tests, the blood cell counts, blood glucose levels, and blood electrolyte levels were within the normal ranges.

Data Collection, Follow-up and Outcome Evaluation

Upon entry into the emergency room, information on age, sex, tobacco smoking, alcohol consumption, diabetes, and hypertension was obtained. In addition, the duration from trauma to arrival at the hospital and interval between trauma and blood sampling were recorded. Traumatic causes were categorized as traffic accidents or others. Systolic and diastolic blood pressures were measured using noninvasive methods. The GCS score was used to estimate the clinical severity. Rotterdam CT scores were calculated based on the positive appearance on the head CT scans. By applying the Glasgow outcome scale (GOS), posttraumatic six-month GOS scores from 1 to 3 indicated poor neurological function status.[14]

Sample Collection and Processing, and Immune Analysis

In compliance with voluntary compliance principles, venous blood of patients and controls was drawn at admission to the hospital and recruitment into our study, respectively. Five milliliters of blood was extracted via venipuncture in the antecubital area from each participant and then promptly deposited into a biochemistry tube pre-filled with gel. Once

coagulation was observed, the blood samples were centrifuged at 2000 × g for 10 min. Finally, the supernatants were transferred into Eppendorf tubes for further preservation at −80 °C until later measurements. A batch method was used to measure serum RvD2 levels to prevent protein decomposition. Specifically, all serum samples collected within the last quarter were thawed for quantification of serum levels using a commercially available Enzyme-Linked Immunosorbent Assay (Item No. 501120; Cayman Chemical Co., Ann Arbor, MI, United States). The kit's detection range spanned from 1.6–1000 pg/mL, with intra- and inter-assay variabilities below 10%, respectively. The same skilled technician, who was unavailable for clinical details, performed all the measurements in duplicate. Dual-measurement data were calculated to yield the mean values for further statistical assessments.

Statistical Analysis

The softwares for statistical analyses and plotting figures in current application encompassed the SPSS 23.0 (SPSS Inc., Chicago, IL, USA), MedCalc 20 (MedCalc Software, Ltd, Ostend, Belgium), GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, California, USA) and R 3.5.1 (https://www.r-project.org). Categorical variables are reported as frequencies (percentages), and comparisons between two groups or among multiple groups were performed using the chi-square test or Fisher's exact test, as applicable. The Kolmogorov–Smirnov test was utilized for the initial analyses of quantitative variables to determine normality of their distribution, and therefore the variables were summarized as either mean with standard deviation (SD) or median with lower-upper quartiles in accordance with patterns of data distribution; as well as using the independent-sample Student's *t*-test, Mann–Whitney *U*-test or Kruskal–Wallis *H*-test as suitable, data distinctions were compared between two groups or among multiple groups. Bivariate correlations were assessed using Spearman's test. Four multivariate models were constructed to determine whether serum RvD2 levels were related to severity and clinical outcomes after msTBI. First, two separate multivariate linear regression models were formulated in which continuous serum RvD2 levels and GOS scores were identified as dependent variables. Second, a binary multivariable logistic regression model was built, in which a dichotomous GOS score (scores 1–3 versus 4–5) was regarded as the dependent variable. Finally, an ordinal multivariate logistic regression model was established in which the ordinal GOS score was selected as the dependent variable. To investigate discrimination efficiency, a receiver operating characteristic (ROC) curve was constructed. To explore the additive effect of serum RvD2 levels on other independent predictors of poor prognosis (GOS scores 1–3), a restricted cubic spline, nomogram, decision curve, calibration curve, and ROC curve were built. Differences were deemed statistically significant when the two-sided P value was < 0.05.

Results

Participant Selection and Characteristics

As outlined in Figure 1, a total of 178 patients with msTBI were enrolled according to the initially formulated requirements, 42 cases were excluded based on the predefined exclusion criteria, and 136 eligible patients with msTBI were retained for a serial epidemiological investigation. The basic characteristics of the patients are listed in Table 1. Additionally, a collective of 100 controls were chosen, who were aged from 19 to 79 years (mean, 43.8 years; SD, 19.1 years), with 62 males, 21 tobacco smokers, 19 alcohol users, 19 hypertensive suffers, 8 diabetic subjects and 17 hyperlipidemic individuals. Statistically, the above seven baseline variables were not significantly different between controls and patients (all P>0.05).

Serum RvD2 Levels Following Trauma and Its Relevance to Trauma Severity

A notable decline in RvD2 levels was observed in the serum of patients with msTBI compared with controls (P<0.001; Figure 2). Serum RvD2 levels were profoundly lowest in patients with a GCS score of 3, exhibited a gradually incremental status with increasing scores from 4 to 11, and were highest in those with a score of 12 (P<0.001; Supplemental Figure 1). In addition, patients with GCS scores of 3–5, 6–8 and 9–12 displayed markedly lower, medium, and highest serum RvD2 levels, respectively (P<0.001; Supplemental Figure 2). Also, serum RvD2 levels were positively correlated with GCS scores (P<0.001; Supplemental Figure 3). Moreover, serum RvD2 levels were significantly reduced in the order of Rotterdam CT scores from 2 to 6 (P<0.001; Supplemental Figure 4) and had a strong reverse relation to the CT scores (P<0.001; Supplemental Figure 5). Furthermore, a multivariate linear regression model was formulated in

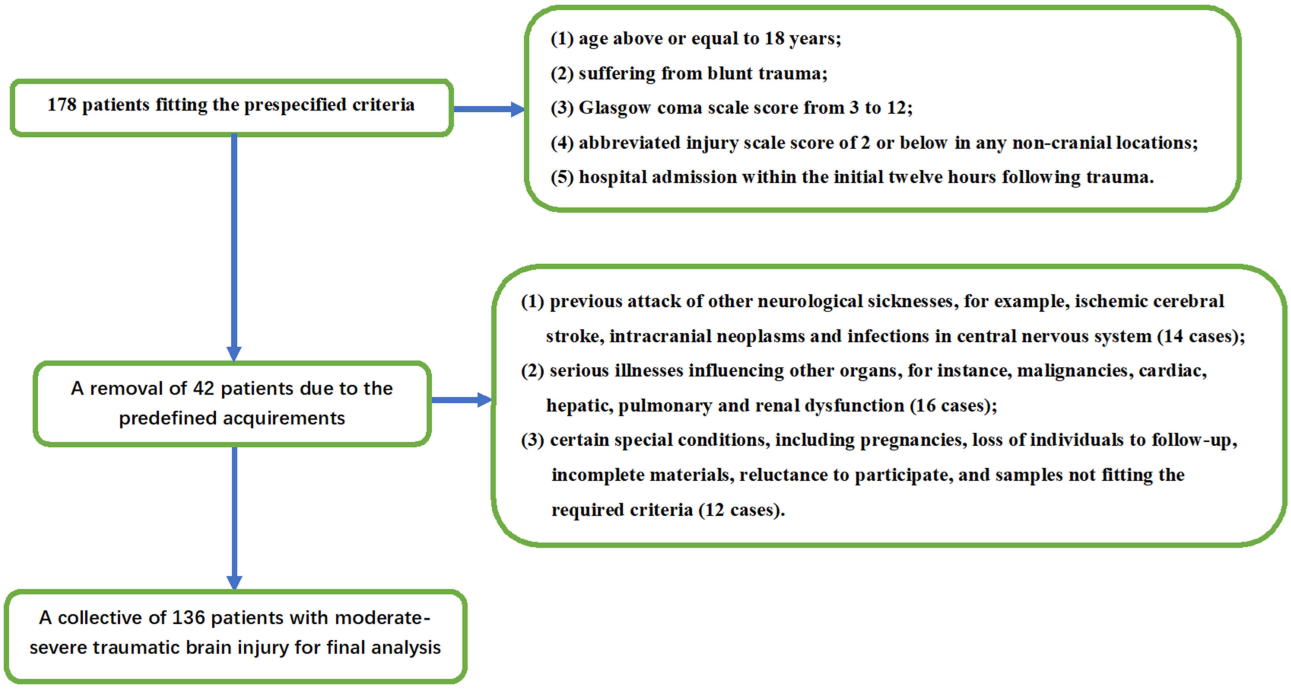

Figure 1 Enrollment process of eligible patients with moderate-severe traumatic brain injury. A group of consecutively recruited 178 patients with moderate-to-severe traumatic brain injury underwent an initial assessment, and a final cohort of 136 patients was selected for further clinical investigation.

which the significant variables on univariate correlation analysis in Table 1, including blood glucose levels (P<0.05), along with Rotterdam CT scores (P<0.001) and GCS scores (P<0.001), were entered. Two components of the Rotterdam CT classification, namely, midline shift and abnormal cisterns, were not included in the multivariate model. Accordingly, the factors of independent correlation with serum RvD2 levels were GCS scores (beta, 8.989; 95% confidence interval (CI), 3.678–14.280; variance inflation factor (VIF), 2.351; P=0.001) and Rotterdam CT scores (beta, −14.676; 95% CI, −25.885–3.468; VIF, 2.166; P=0.011).

Table 1 Baseline Features of Patients with Severe Traumatic Brain Injury and Their Correlations with Serum Resolvin D2 Levels

	The Total Patients	Correlations with Serum Resolvin D2 Levels	
		ρ	P value
Male	81 (59.6%)	0.023	0.793
Age (years)	44.0±16.9	0.068	0.431
Cigarette smoking	31 (22.8%)	−0.067	0.440
Alcohol consumption	30 (22.1%)	−0.041	0.635
Hypertension	21 (15.4%)	−0.053	0.543
Diabetes mellitus	12 (8.8%)	0.026	0.760
Hyperlipidemia	24 (17.7%)	−0.037	0.666
Admission time (h)	5.7 (3.5–8.6)	0.097	0.263
Blood-collection time (h)	6.7 (4.4–9.4)	0.096	0.268
Glasgow coma scale scores	9 (6–10)	0.550	<0.001
Traumatic causes (traffic accidents)	65 (47.8%)	−0.157	0.068
Systolic arterial blood pressure (mmHg)	121.9±29.7	0.010	0.904
Diastolic arterial blood pressure (mmHg)	76.5±20.4	−0.030	0.732
Rotterdam CT classification	4 (3–4)	−0.543	<0.001
Abnormal cisterns	94 (69.1%)	−0.272	0.001

(*Continued*)

Table 1 (Continued).

	The Total Patients	Correlations with Serum Resolvin D2 Levels	
		ρ	P value
Midline shift > 5 mm	78 (57.4%)	−0.250	0.003
Epidural hematoma	65 (47.8%)	−0.152	0.078
Subdural hematoma	82 (60.3%)	−0.144	0.094
Subarachnoid hemorrhage	99 (72.8%)	−0.102	0.235
Intraventricular hemorrhage	14 (10.3%)	−0.122	0.157
Intracerebral hematoma	61 (44.9%)	−0.063	0.466
Brain contusion	75 (55.2%)	−0.100	0.245
Pneumocephalus	45 (33.1%)	−0.057	0.512
Skull-cap fracture	83 (61.0%)	−0.062	0.476
Skull-base fracture	66 (48.5%)	−0.002	0.983
Blood glucose levels (mmol/l)	11.2 (6.5–13.0)	−0.211	0.014
Blood leucocyte count ($\times 10^9$)	7.0 (5.4–9.2)	−0.074	0.393

Notes: Data were presented as mean ± standard deviation, median (25th-75th percentiles) or count (percentage) as applicable. Bivariate correlative analyses were implemented using Spearman's rank correlation coefficient. CT signifies computed tomography.

Serum RvD2 Levels and Poor Neurological Function Outcome

As shown in Supplemental Figure 6, serum RvD2 levels were slowly increased with increasing GOS score from 1 to 5 (P<0.001). As outlined in Table 2, age, GCS score, Rotterdam CT score, abnormal cisterns, midline shift, blood glucose levels, and serum RvD2 levels differed notably among the five groups with GOS scores from 1 to 5 (all P<0.05). Apart from abnormal cisterns and midline shift, the remaining five variables were incorporated into the ordinal logistic regression model. Serum RvD2 levels (odds ratio (OR), 1.008; 95% CI, 1.002–1.015; VIF, 1.531; P=0.015), GCS scores (OR, 1.547; 95% CI, 1.252–1.910; VIF, 2.552; P=0.001), and Rotterdam CT scores (OR, 0.649; 95% CI, 0.425–0.990; VIF, 2.276; P=0.045) were independently associated with the GOS scores.

Serum RvD2 levels were significantly positively correlated with the GOS scores (P<0.001; Supplemental Figure 7). Eight variables, as listed in Table 3 (age, presence of hypertension history, GCS scores, Rotterdam CT scores, serum

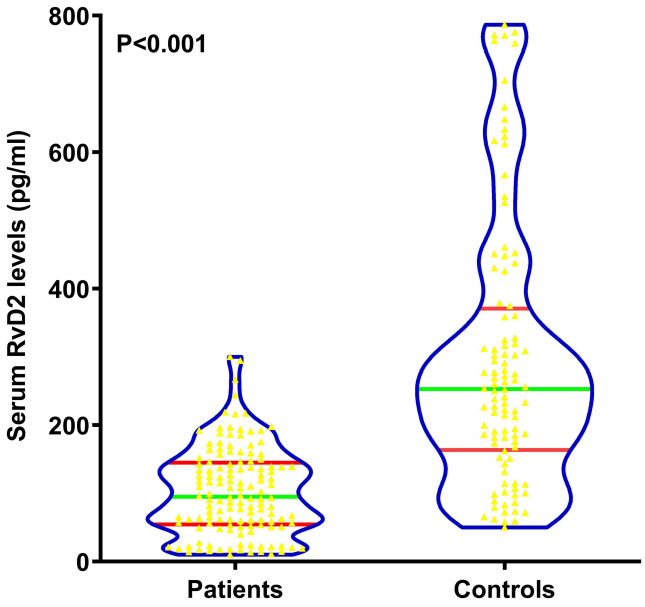

Figure 2 Serum resolvin D2 levels subsequent to moderate-severe traumatic brain injury. Patients with moderate-to-severe traumatic brain injury exhibited significantly reduced serum resolvin D2 levels relative to controls (P<0.001).
Abbreviation: RvD2, resolvin D2.

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Table 2 Differences of Baseline Parameters Among Five Subgroups Based on Glasgow Outcome Scale Scores at Six Months Following Severe Traumatic Brain Injury

	GOS 1	GOS 2	GOS 3	GOS 4	GOS 5	P value
Male	6 (42.9%)	13 (56.5%)	12 (57.1%)	35 (63.6%)	15 (65.2%)	0.654
Age (years)	61 (50–67)	46 (34–57)	45 (29–53)	36 (25–51)	43 (26–65)	0.034
Cigarette smoking	2 (14.3%)	9 (39.1%)	4 (19.1%)	12 (21.8%)	4 (17.4%)	0.469
Alcohol consumption	3 (21.4%)	5 (21.7%)	4 (19.1%)	12 (21.8%)	6 (26.1%)	0.987
Hypertension	2 (14.3%)	5 (21.7%)	7 (33.3%)	7 (12.7%)	0 (0%)	0.063
Diabetes mellitus	1 (7.1%)	3 (13.0%)	2 (9.5%)	4 (7.3%)	2 (8.7%)	0.731
Hyperlipidemia	2 (14.3%)	4 (17.4%)	6 (28.6%)	8 (14.6%)	4 (17.4%)	0.734
Admission time (h)	2.9 (2.6–9.9)	6.7 (3.6–10.3)	5.7 (3.0–7.5)	5.5 (3.5–8.3)	5.8 (4.0–8.5)	0.470
Blood-collection time (h)	3.7 (3.1–10.4)	7.2 (4.4–11.1)	6.8 (4.0–8.2)	6.5 (4.7–9.0)	7.0 (5.1–9.3)	0.508
GCS scores	4 (3–6)	5 (4–7)	9 (8–9)	9 (8–10)	11 (10–12)	<0.001
Traffic accidents	8 (57.1%)	13 (56.5%)	11 (52.4%)	26 (47.3%)	7 (30.4%)	0.386
Systolic AP (mmHg)	99 (77–126)	125 (112–158)	123 (101–154)	127 (108–143)	116 (87–130)	0.068
Diastolic AP (mmHg)	60 (47–81)	78 (69–103)	73 (60–103)	76 (65–96)	71 (50–89)	0.112
Rotterdam CT classification	5 (4–5)	5 (4–5)	4 (3–4)	3 (3–4)	2 (2–3)	<0.001
Abnormal cisterns	14 (100.0%)	21 (91.3%)	18 (85.7%)	31 (56.4%)	10 (43.5%)	<0.001
Midline shift > 5 mm	10 (71.4%)	20 (87.0%)	13 (61.9%)	30 (54.6%)	5 (21.7%)	<0.001
Epidural hematoma	7 (50.0%)	16 (69.6%)	10 (47.6%)	23 (41.8%)	9 (39.1%)	0.209
Subdural hematoma	8 (57.1%)	16 (69.6%)	9 (42.9%)	34 (61.8%)	15 (65.2%)	0.428
Subarachnoid hemorrhage	11 (78.6%)	19 (82.6%)	13 (61.9%)	39 (70.9%)	17 (73.9%)	0.494
Intraventricular hemorrhage	4 (28.6%)	1 (4.4%)	3 (14.3%)	4 (7.3%)	2 (8.7%)	0.162
Intracerebral hematoma	5 (35.7%)	11 (47.8%)	8 (38.1%)	29 (52.7%)	8 (34.8%)	0.515
Brain contusion	9 (64.3%)	13 (56.5%)	10 (47.6%)	33 (60.0%)	10 (43.5%)	0.599
Pneumocephalus	8 (57.1%)	7 (30.4%)	8 (38.1%)	14 (25.5%)	8 (34.8%)	0.161
Skull-cap fracture	7 (50.0%)	15 (65.2%)	14 (66.7%)	31 (56.4%)	16 (69.6%)	0.667
Skull-base fracture	6 (42.9%)	13 (65.5%)	9 (42.9%)	26 (47.3%)	12 (52.2%)	0.879
Blood glucose levels (mmol/l)	13.5 (10.9–14.7)	12.4 (10.9–13.8)	11.7 (6.5–12.9)	10.1 (5.3–12.1)	9.0 (5.7–12.5)	0.009
Blood leucocyte count ($\times 10^9$)	6.3 (5.1–8.3)	7.4 (5.6–11.6)	7.3 (5.7–8.9)	6.3 (5.2–7.9)	8.8 (5.9–10.6)	0.100
Serum RvD2 levels (pg/mL)	21.3 (16.8–50.4)	53.9 (22.8–65.8)	110.1 (79.9–165.3)	124.6 (85.1–146.6)	142.8 (87.6–174.6)	<0.001

Notes: All continuous data were non-normally distributed and therefore were presented as median (25th-75th percentiles). Categorical variables were reported in form of count (percentage). The Kruskal-Wallis test was done for multiple-group comparison of quantitative data and the Chi-Square test for qualitative variable.
Abbreviations: CT, computed tomography; GCS, Glasgow coma scale; CRP, C-reactive protein; RvD2, resolvin D2; AP, arterial blood pressure; GOS, Glasgow outcome scale.

Table 3 Basic Parameters Related to Glasgow Outcome Scale Scores and Poor Prognosis at Six Months Following Severe Traumatic Brain Injury

	Bivariate Correlations		Bivariate Comparisons		
	ρ	P value	GOS 1–3	GOS 4–5	P value
Male	0.118	0.173	31 (53.5%)	50 (64.1%)	0.211
Age (years)	−0.180	0.036	47.9±16.1	41.0±17.1	0.018
Cigarette smoking	−0.070	0.418	15 (25.9%)	16 (20.5%)	0.462
Alcohol consumption	0.034	0.697	12 (20.7%)	18 (23.1%)	0.740
Hypertension	−0.192	0.025	14 (24.1%)	7 (9.0%)	0.016
Diabetes mellitus	−0.032	0.711	6 (10.3%)	6 (7.7%)	0.590
Hyperlipidemia	−0.025	0.772	12 (20.7%)	12 (15.4%)	0.422
Admission time (h)	0.059	0.492	5.7 (2.9–9.9)	5.8 (3.7–8.3)	0.710
Blood-collection time (h)	0.065	0.450	6.8 (3.8–10.4)	6.6 (4.7–9.1)	0.635
GCS scores	0.646	<0.001	7 (4–9)	9 (8–11)	<0.001
Traumatic causes (traffic accidents)	−0.162	0.059	32 (55.2%)	33 (42.3%)	0.137
Systolic AP (mmHg)	−0.015	0.858	122.6±32.8	121.5±27.3	0.829

(*Continued*)

Table 3 (Continued).

	Bivariate Correlations		Bivariate Comparisons		
	ρ	P value	GOS 1–3	GOS 4–5	P value
Diastolic AP (mmHg)	−0.029	0.739	76.3±21.3	76.3±19.8	0.926
Rotterdam CT classification	−0.614	<0.001	4 (4–5)	3 (2–4)	<0.001
Abnormal cisterns	−0.426	<0.001	53 (91.4%)	41 (52.6%)	<0.001
Midline shift > 5 mm	−0.363	<0.001	43 (74.1%)	35 (44.9%)	0.001
Epidural hematoma	−0.157	0.068	33 (56.9%)	32 (41.0%)	0.067
Subdural hematoma	0.036	0.678	33 (56.9%)	49 (62.8%)	0.485
Subarachnoid hemorrhage	−0.045	0.605	43 (74.1%)	56 (71.8%)	0.761
Intraventricular hemorrhage	−0.106	0.219	8 (13.8%)	6 (7.7%)	0.247
Intracerebral hematoma	0.009	0.917	24 (41.4%)	37 (47.4%)	0.482
Brain contusion	−0.064	0.456	32 (55.2%)	43 (55.1%)	0.996
Pneumocephalus	−0.105	0.225	23 (39.7%)	22 (28.2%)	0.160
Skull-cap fracture	0.038	0.660	36 (62.1%)	47 (60.3%)	0.830
Skull-base fracture	0.012	0.892	28 (48.3%)	38 (48.7%)	0.959
Blood glucose levels (mmol/l)	−0.271	0.001	12.4 (9.6–14.1)	10.0 (5.3–12.1)	0.002
Blood leucocyte count ($\times 10^9$)	0.001	0.991	7.3 (5.6–9.2)	6.4 (5.2–8.8)	0.306
Serum RvD2 levels (pg/mL)	0.530	<0.001	61.1 (21.9–99.3)	126.9 (84.4–158.6)	<0.001

Notes: Data were presented as mean ± standard deviation, median (25th-75th percentiles) or count (percentage) as applicable. Bivariate correlative analyses were implemented using Spearman's rank correlation coefficient. Intergroup comparisons of various data were done using the Student's *t*-test, Mann–Whitney *U*-test, Pearson chi-square test or Fisher's exact test as appropriate.
Abbreviations: CT signifies computed tomography; GCS, Glasgow coma scale; CRP, C-reactive protein; RvD2, resolvin D2; AP, arterial blood pressure; GOS, Glasgow outcome scale.

RvD2 levels, blood glucose levels, presence of abnormal cisterns, and existence of midline shift > 5 mm), were significantly related to GOS scores (all P<0.05). Similarly, abnormal cisterns and midline shift of > 5 mm were excluded from the multivariate linear regression model. The other six surplus parameters were incorporated into the multivariate model, and serum RvD2 levels (beta, 0.004; 95% CI, 0.002–0.007; VIF, 1.651; P=0.003), GCS scores (beta, 0.190; 95% CI, 0.099–0.282; VIF, 2.598; P=0.001), and Rotterdam CT scores (beta, −0.194; 95% CI, −0.385–0.002; VIF, 2.330; P=0.047) were significantly correlated with GOS scores, independent of other confounding factors.

Serum RvD2 levels were markedly lower in patients with poor prognosis (GOS score 1–3) than in those without poor prognosis (GOS score 4–5) (P<0.001; Supplemental Figure 8). By employing the ROC curve, serum RvD2 levels were shown to have high discrimination efficiency for patients at risk of poor prognosis (Figure 3). Moreover, using the Youden method, an optimal value for RvD2 levels was identified, which yielded medium-to-high sensitivity and specificity values (Figure 3). Within the framework of the restricted cubic spline, serum RvD2 levels were linearly correlated with the likelihood of a poor prognosis (P for nonlinear >0.05; Figure 4). As shown in Table 3, significant differences were observed in terms of age, presence of a history of hypertension, GCS scores, Rotterdam CT scores, serum RvD2 levels, blood glucose levels, presence of abnormal cisterns, and existence of midline shift > 5 mm (all P<0.05). Likewise, the integration of abnormal cisterns and midline shift of > 5 mm into the multivariate linear regression model was not implemented. The entry of the remaining six parameters into the multivariate model revealed that serum RvD2 levels (OR, 0.991; 95% CI, 0.983–0.999; VIF, 1.531; P=0.037), GCS scores (OR, 0.753; 95% CI, 0.588–0.964; VIF, 2.352; P=0.024), and Rotterdam CT scores (OR, 1.839; 95% CI, 1.066–3.173; VIF, 2.258; P=0.029) were independently associated with poor prognosis. The three independent predictors of poor prognosis were merged to establish a model that was visually described by a nomogram (Figure 5). As shown in Figure 6, there were negligible differences in the area under the ROC curve between serum RvD2 levels and GCS scores as well as between serum RvD2 levels and Rotterdam CT scores (all P>0.05). Moreover, the prognostic predictive ability of the combination model significantly surpassed that of serum RvD2 levels, Rotterdam CT scores, and GCS scores alone as well as that of Rotterdam CT scores combined with GCS scores (all P<0.05; Figure 6). In the context of calibration curve analysis (Figure 7), the model exhibited high stability. Its clinical value was satisfactory based on decision curve analysis (Figure 8).

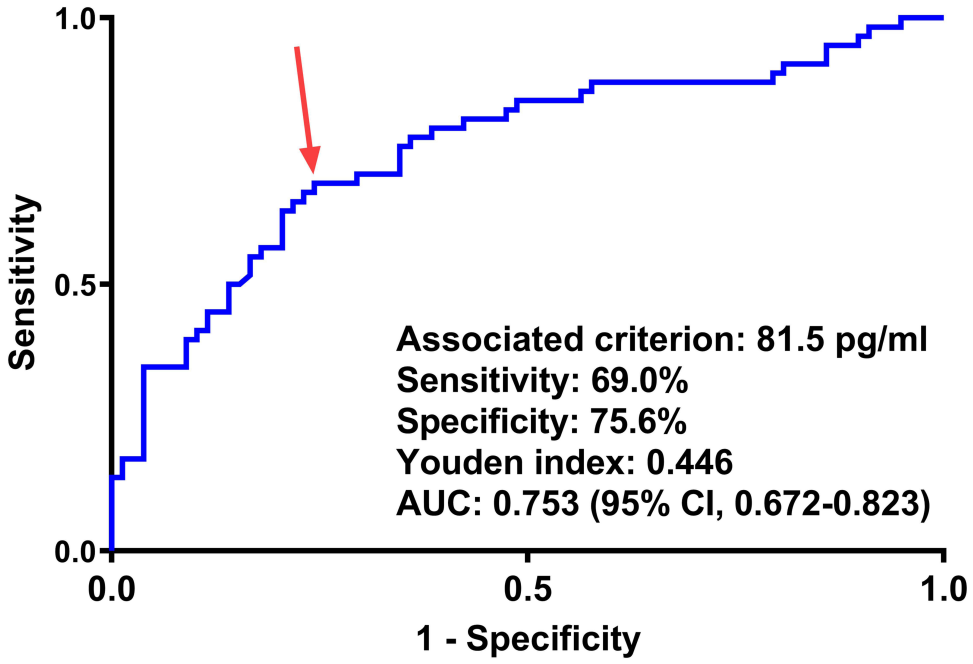

Figure 3 Receiver operating characteristic curve showing discriminatory ability of serum resolvin D2 levels for risk of poor prognosis after moderate-severe traumatic brain injury. Poor prognosis after head trauma was predicted using serum resolvin D2 levels, and a suitable threshold value was selected using the Youden approach. Red arrow points to associated criterion of serum resolvin D2 levels.
Abbreviations: AUC, area under curve; 95% CI, 95% confidence interval.

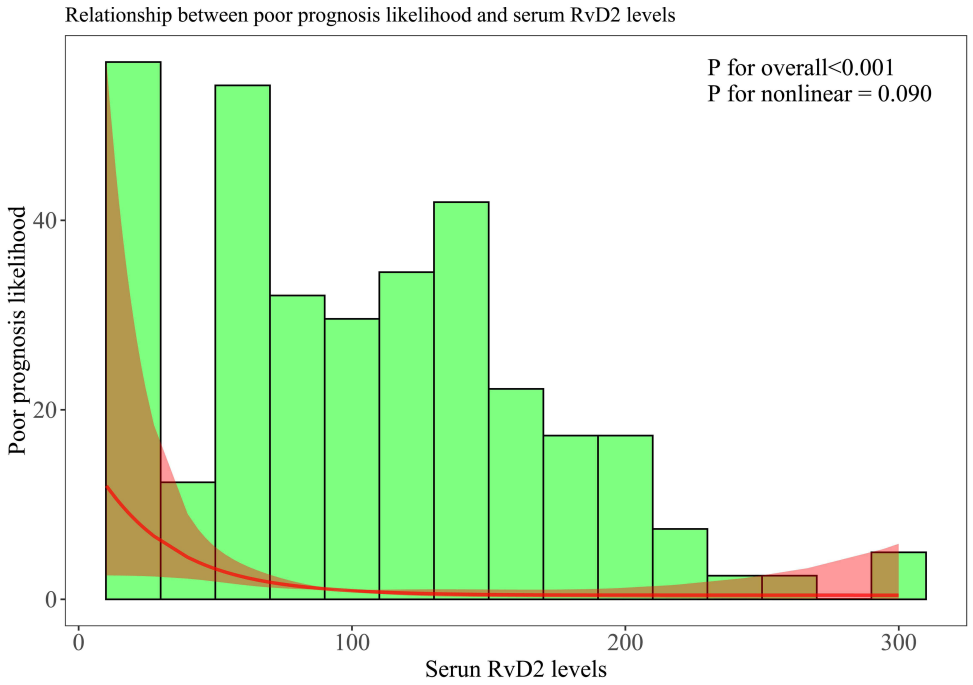

Figure 4 Restricted cubic spline describing linearity between serum resolvin D2 levels and probability of poor prognosis after moderate-severe traumatic brain injury. Serum resolvin D2 levels had a linear relationship with the possibility of poor prognosis six months after head trauma (P for nonlinear >0.05).
Abbreviation: RvD2, resolvin D2.

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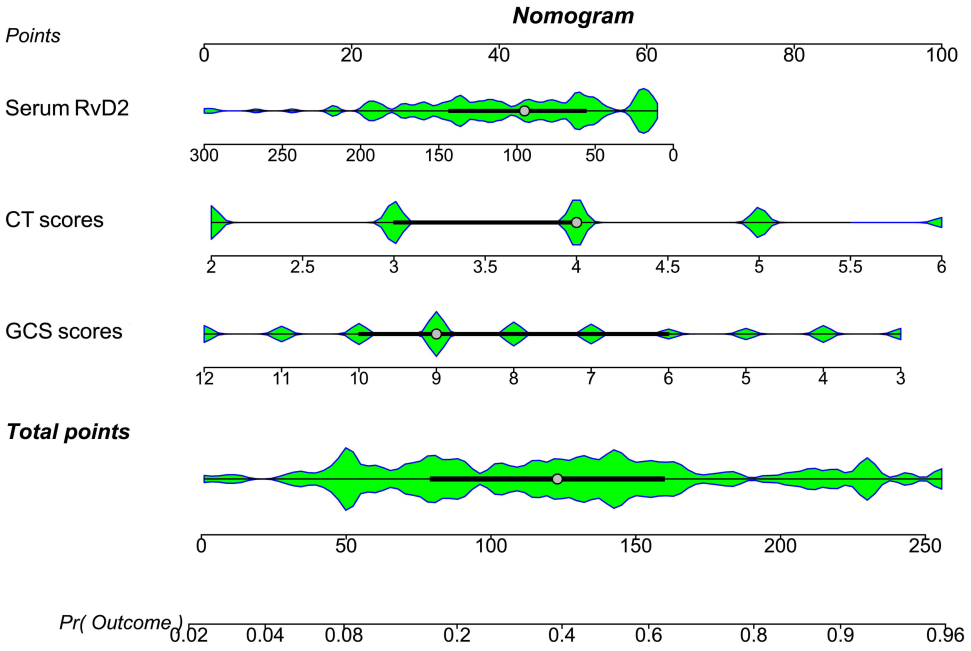

Figure 5 Nomogram evaluating the predictive model for poor prognosis in individuals with moderate-severe traumatic brain injury. Serum resolvin D2, Glasgow coma scale scores, and Rotterdam computerized tomography scores were integrated to distinguish the likelihood of an adverse outcome six months after moderate to severe traumatic brain injury.
Abbreviations: RvD2, resolvin D2; CT, computed tomography; GCS, Glasgow Coma Scale.

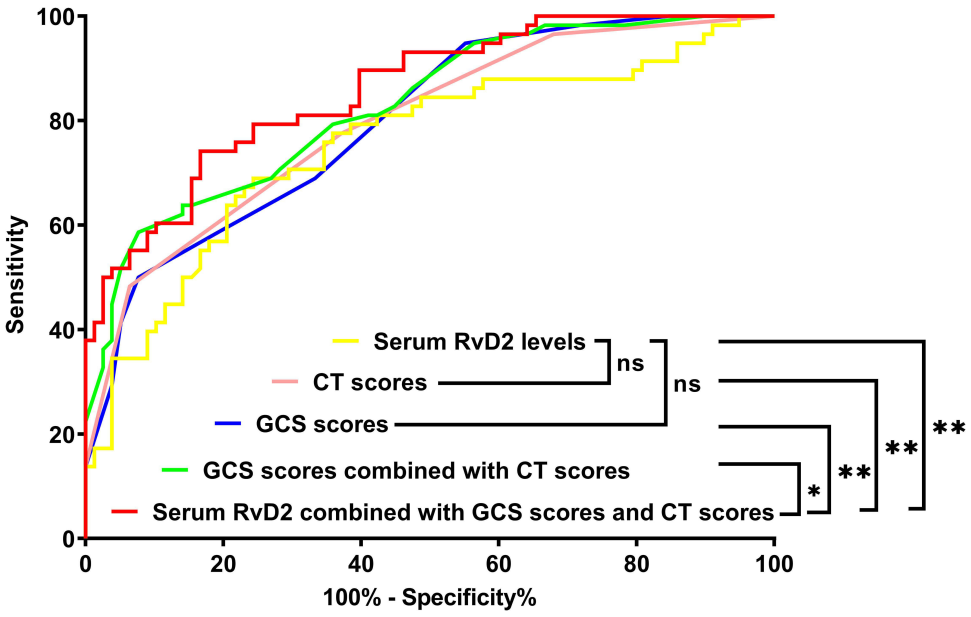

Figure 6 Predictive performance for poor prognosis of the combination model following moderate-severe traumatic brain injury under receiver operating characteristic curve. Serum resolvin D2 had a similar predictive ability, in contrast to the Glasgow coma scale scores and Rotterdam computerized tomography scores (all P>0.05). Serum resolvin D2, Glasgow coma scale scores, and Rotterdam computerized tomography scores were integrated to form a model to distinguish the likelihood of an adverse outcome six months after moderate to severe traumatic brain injury. Compared to any metric in the figures, the model displayed a substantially stronger predictive ability for prognosis (all P<0.05). *P<0.05; **P<0.01.
Abbreviations: RvD2, resolvin D2; CT, computed tomography; GCS, Glasgow Coma Scale; ns, non-significant.

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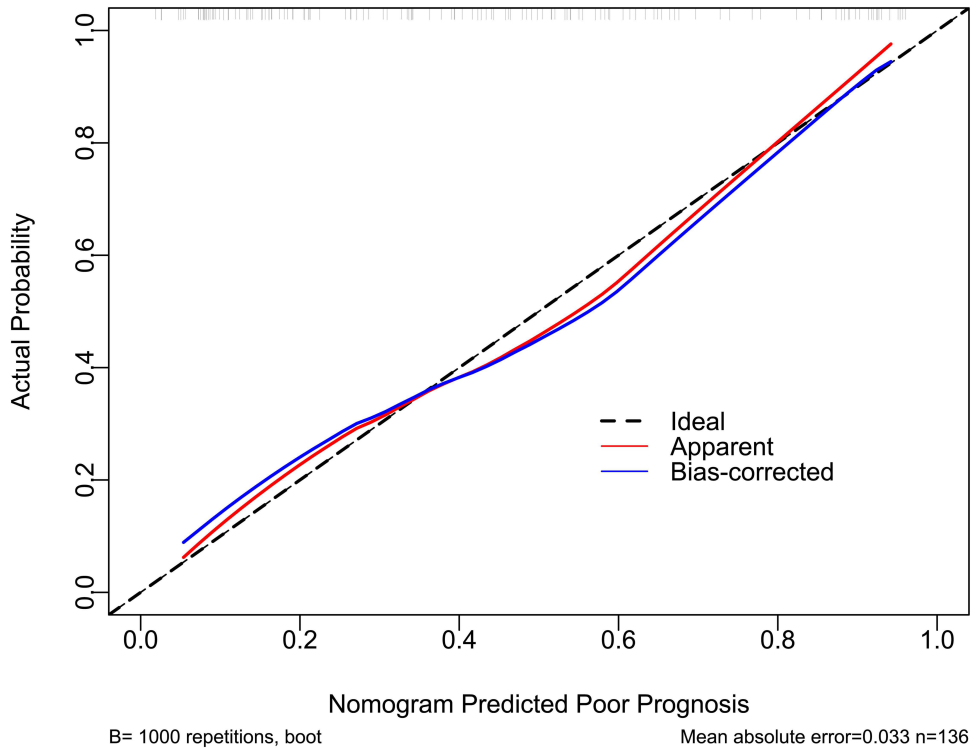

Figure 7 Calibration plot evaluating the reliability of the nomogram for predicting risk of worse prognosis six months after stroke. The built framework remained consistent in prognosticating poor outcomes at six-month mark after moderate to severe traumatic brain injury.

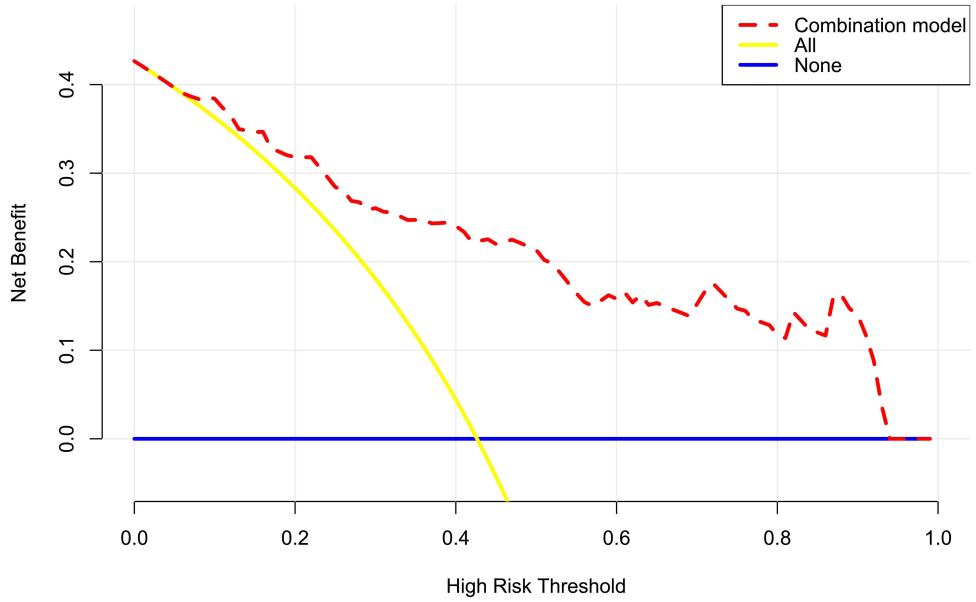

Figure 8 The decision curve analyzing the clinical applicability of the prediction model for discriminating the possibility of an adverse outcome at six months after head trauma. The serum resolvin D2, Glasgow coma scale, and Rotterdam computerized tomography scores were merged to form the model. The constructed model was clinically useful in forecasting adverse outcomes six months after moderate-to-severe traumatic brain injury.

Discussion

To the best of our knowledge, it remains undetermined whether there is an alteration in serum RvD2 levels following msTBI, and whether these levels are relevant to trauma severity and clinical outcomes of patients at six-month mark after

head trauma. Several notable observational findings were identified within our study framework. First, in contrast to controls, serum RvD2 levels dramatically decreased upon admission. Second, serum RvD2 levels were independently correlated with GCS and Rotterdam CT scores. Third, serum RvD2 levels were linearly correlated with the probability of poor prognosis six months after trauma. Fourth, serum RvD2 levels were independently associated with poor prognosis at six months post-trauma. Fifth, serum RvD2 levels displayed substantial prognosis prediction performance. Finally, the model with integration of serum RvD2, GCS, and Rotterdam CT scaling demonstrated satisfactory effectiveness in predicting worse prognosis at six-month interval. These results may offer sufficient evidence to support the assumption that serum RvD2 may represent a promising indicator for severity evaluation and outcome prognostication in msTBI.

RvD2 may act as a protective factor because it possesses potent counter-regulatory activities under pro-inflammatory conditions.[9,10] RvD2 is expressed in the central nervous system and its levels are significantly decreased in the brain ischemic foci of rats subjected to cerebral ischemia.[11] In the context of acute brain injury, RvD2 may have neuroprotective functions. Specifically, intraperitoneal administration of RvD2 effectively reduced infarct size, inflammatory reactions, and cerebral edema, thereby improving neurological deficits in rats with cerebral ischemia/reperfusion injury.[11] In another experimental study of subarachnoid hemorrhage, intranasal supply of RvD2 efficaciously diminished oxidative stress and neuronal apoptosis, strongly modulated blood-brain barrier permeability, reduced brain edema, and recovered neurological impairments.[12] Therefore, RvD2 expression may be depleted in response to brain injury. Thus, RvD2 supplementation may be a potential therapeutic tool for acute brain injury.

Systemic inflammatory response syndrome (SIRS) is a phenomenon frequently observed during acute brain injury (TBI,[15] intracerebral hemorrhage,[16] cerebral ischemia[17] and subarachnoid hemorrhage.[18] SIRS is one of the main causes of poor prognosis in patients,[19,20] thus, SIRS represents systemic injury secondary to acute brain injury. Blood RvD2 levels are dramatically reduced in rats with head trauma or brain ischemia.[13] In our study, serum RvD2 levels at admission were markedly reduced in patients with msTBI compared with controls. Considering the protective properties of RvD2, lowered blood RvD2 levels may be a result of RvD2 depletion to resist systemic injury following an acute brain injury.

Severity correlation analysis is an important aspect of biomarker assessment. GCS and Rotterdam CT classifications are two conventional indicators for mirroring trauma severity and prognosticating patient outcomes.[3,4] In this study, these two parameters were regarded as categorical or continuous variables. Univariate analysis showed that serum RvD2 levels were closely correlated with one of the two indicators, which were considered quantitative or qualitative variables. Moreover, a thorough investigation using multivariate analysis showed that serum RvD2 levels were strongly related to GCS and Rotterdam CT scores, independent of other possible confounding factors. More scientifically, collinearity was estimated by calculating the VIF values in our study. Weak collinearity in the current study indicated a high stability in the model, which effectively strengthened the feasibility of serum RvD2 as an indicator for reflecting trauma of msTBI severity.

The GOS has been widely acknowledged as a prognostic assessment system.[21,22] Statistically, it can generally be recognized as a categorical or continuous variable. In addition, GOS can be transformed into another kind of qualitative variable when dichotomized. In the current study, three types of multivariate models, binary logistic regression, linear regression, and ordinal regression models, were built separately to determine the relationship between serum RvD2 levels and GOS. Accumulating statistical results indicate that serum RvD2 levels may be independently associated with the neurological outcomes of msTBI. The preceding data strongly suggest that serum RvD2 may be a good prognosticator for predicting the clinical outcome of patients with msTBI.

In the framework of restricted cubic spline analysis, serum RvD2 levels manifested a linear relationship with the likelihood of poor prognosis at the six-month mark after msTBI. The severity metrics, namely GCS and Rotterdam CT scaling, have been repeatedly validated as two poor prognostic determinants of head trauma. These two variables, coupled with serum RvD2, were verified as independent predictors of poor prognosis in this cohort of patients with msTBI. These were consolidated to form a prognosis prediction model that was visually represented by a nomogram. The model operated steadily under the calibration curve and demonstrated high clinical validity by employing the decision curve approach. In the context of the ROC curve assessment, the model displayed an exceptionally high predictive capability for six-month poor prognosis after msTBI. Taken together, serum RvD2 appears to be a promising indicator for facilitating the promotion of prognostic prediction ability in the medical management of msTBI.

Conclusions

In contrast to the controls, a decline in serum RvD2 levels was significant in patients with msTBI. There were independent correlations between serum RvD2 levels, GCS scores, and Rotterdam CT scores. Serum Rvd2 levels were linearly related to and independently associated with the possibility of worse prognosis at the 6-month follow-up. Serum RvD2 levels have an effective discrimination efficiency for poor prognosis under the ROC curve, and the model incorporating serum RvD2, GCS, and Rotterdam CT scores is effective for predicting poor prognosis. Taken together, serum RvD2 may emerge as a valuable prognostic biomarker and could assist in risk stratification and prognostication of the outcomes of msTBI.

Data Sharing Statement

The study data were not stored in publicly accessible repository. However, interested parties may request access to the data from the corresponding author upon inquiry.

Acknowledgments

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Disclosure

The authors stated that they have no conflicts of interest to disclose for this work.

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