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ORIGINAL ARTICLE

Predictors of the therapeutic effect of corticosteroids on radiation-induced optic neuropathy following nasopharyngeal carcinoma

Bowen Zheng[1] · Jinpeng Lin[2] · Yi Li[2] · Xiaohuang Zhuo[2] · Xiaolong Huang[2] · Qingyu Shen[1,2] · Yamie Tang[2,3,4]

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Abstract

Radiation-induced optic neuropathy (RION) is a severe visual complication resulting from radiotherapy of the head and neck, which mostly occurs in patients with nasopharyngeal carcinoma (NPC) in the southern part of China. The mechanism of RION is unclear. Therefore, identifying risk factors for RION is an important step towards enhancing our understanding. In the current study, we retrospectively reviewed patients with NPC who were admitted to Sun Yat-Sen Memorial Hospital for visual loss between 2006 and 2017. The study included 38 participants (68 eyes) in the corticosteroid-effective group and 35 participants (64 eyes) in the corticosteroids-ineffective group. We analyzed potential risk factors for RION and developed a prediction model for the therapeutic effect of corticosteroid effect based on a random forests method. The prediction model showed a high accuracy with an area under the receiver operating characteristic curve of 0.932 (95% confidence interval = 0.889–0.975). Our results revealed that blood urea nitrogen (BUN) was significantly associated with RION and that RION patients with higher BUN levels responded better to corticosteroid treatment. Altogether, these results suggest that a prediction model, based on clinical factors, could be applied to estimate the therapeutic effect of corticosteroids on RION. Further investigation, however, is needed to confirm the study conclusion.

Keywords Radiation-induced optic neuropathy · Corticosteroids · Random forests · Therapeutic effect

Abbreviations

RION	Radiation-induced optic neuropathy
NPC	Nasopharyngeal carcinoma
VEP	Visual evoked potential
ALT	Alanine transaminase (U/L)
AST	Aspartate transaminase (U/L)
Na	Serum sodium (mmol/L)
BUN	Blood urea nitrogen (mmol/L)
Crea	Creatinine (μmol/L)
UA	Uric Acid (μmol/L)
FBG	Fasting blood glucose (mmol/L)
TC	Total cholesterol (mmol/L)
TG	Triglyceride (mmol/L)
HDL-C	High-density lipoprotein cholesterol (mmol/L)
LDL-C	Low-density lipoprotein cholesterol (mmol/L)
ApoA1	Apolipoprotein A-1 (g/L)
ApoB	Apolipoprotein B (g/L)
ALB	Albumin (g/L)
CK	Creatine phosphate kinase (U/dL)
hs-CRP	High sensitive C-reactive protein (mg/L)
Gy	gray unit.

Bowen Zheng and Jinpeng Lin contributed equally to this work.

✉ Yamie Tang
yameitang@hotmail.com; tangym@mail.sysu.edu.cn

[1] Department of Neurology, Zengcheng People's Hospital, Guangzhou, China

[2] Department of Neurology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

[3] Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

[4] Guangdong Province Key Laboratory of Brain Function and Disease, Zhongshan School of Medicine, Sun Yat-Sen University, 74 Zhongshan 2nd Road, Guangzhou, China

Introduction

Tens of thousands of new cases of nasopharyngeal carcinoma (NPC) are reported annually worldwide [1]. Southeastern

Asia, particularly the Guangdong province of China, reports the highest number of NPC cases [2]. Radiotherapy, the classic treatment for NPC, has been widely adopted due to its effectiveness [3]. However, radiotherapy also results in complications, the most common of which is radiation-induced optic neuropathy (RION), a complication commonly seen among NPC patients who have received radiotherapy.

RION is observed following the exposure of the anterior visual pathway to radiation. RION often presents as acute or subacute, progressive, and painless vision loss in one or both eyes, and the severity can vary from minor to complete blindness, often reaching a peak at 3–4 years after radiotherapy [3, 4]. The consequences of RION can be both disruptive and destructive to an individual's life; therefore, preventing resulting progressive visual loss is important.

The assumed mechanism of RION involves progression from early exudative vasculopathy [5] to late microvascular insufficiency and chronic hypoxia [6], while other researchers believe that RION results from radiation-induced microangiopathy and associated endothelial cell loss and demyelination [4]. However, desired therapeutic effects are not achieved using treatments aimed at the aforementioned mechanisms [2, 6], which reflects inadequacies in the current understanding of RION. Because the mechanism of RION is still controversial, and novel therapy development has stagnated, finding ways to utilize traditional therapies, such as corticosteroid therapy, which is economical and widely-used [6], to treat RION may be a more practical way to mitigate the consequences of RION.

Most studies investigating risk factors for RION concentrate on identifying therapy-associated risk factors, such as radiotherapy dosage, fraction size, and use of chemotherapy [4, 7–9], while clinical features have been largely ignored. In this retrospective, case-controlled study, we analyzed the relationship between the therapeutic effect of corticosteroids and clinical markers in patients with RION. Furthermore, we developed a prediction model of the therapeutic effect of corticosteroids.

Materials and methods

Patients

This study reviewed the cases of patients with NPC who had been admitted to Sun Yat-Sen Memorial Hospital (Sun Yat-Sen University, Guangzhou, Guangdong, China) for visual loss between January 2006 and July 2017. All patients were diagnosed with NPC by nasal-endoscopy and biopsy and were treated with radiotherapy. Following radiotherapy, all patients were readmitted to the hospital for further visual loss and diagnosed with RION. The patients were treated with corticosteroids and other standard therapies like nerve-nurturing. Methylprednisolone, the prescribed corticosteroids, was administered intravenously at 120 mg/day for the first 4 days, 80 mg/day for the next 4 days, followed by 40 mg/day for another 4 days (12 days in total). Oral methylprednisolone (Medrol, 24 mg/day for the first 7 days and 4 mg-less every other 7 days) was prescribed after an intravenous course of corticosteroids. Patients receiving hyperbaric oxygen, anticoagulants, angiotensin-converting enzyme inhibitors, or bevacizumab therapy were excluded.

Diagnostic criteria for RION

The diagnostic criteria of RION were as follow [3, 7]: 1. history of radiotherapy, 2. painless progressive visual loss, 3. abnormal visual evoked potential (VEP) and/or ophthalmoscopic evidence of the blurring of the optic disc margins, dilation of retinal veins, hemorrhages, exudates, and neovascularization. The excluding criteria for a RION diagnosis were as follows: 1. other diseases that may cause visual loss, such as multiple sclerosis, stroke, cataract, glaucoma, or vasculopathy due to diabetes or hypertension; 2. recurrence or metastases of NPC; 3. eyes that cannot be evaluated by VEP or ophthalmoscopy due to lack of patient cooperation or exposure keratitis.

Data collection and group setting

Demographic and clinical data were collected before corticosteroid therapy. We also recorded laboratory data, including levels of alanine transaminase, aspartate transaminase, serum sodium, blood urea nitrogen (BUN), creatinine, uric acid, fasting blood glucose, total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A-1, apolipoprotein B, albumin, creatine phosphate kinase, and high sensitive C-reactive protein. We separately analyzed the left and right eye of each patient because treatment may differentially affect the left and right eye [10]. Patients' eyes were split into two groups according to the exhibited therapeutic effect: the effective group refers to eyes that regained any vision, while the ineffective group represents eyes that regained no vision or exhibited worse vision. The degree of visual change was determined by a qualified ophthalmologist, or two independent senior neurologists, based on at least two visual examinations during hospitalization. Neurologists determined visual change by the following criteria: 1. no sense of light; 2. can see light but cannot tell whether there are examiner's fingers or not; 3. can tell whether there are examiner's fingers or not in certain distance (record the distance, usually describe as *x* centimeter), but cannot tell how many fingers; 4. can tell how many fingers showed by examiner in certain distance (record the distance, usually describe as *x* centimeter or *x* meter).

Statistical analyses

Statistical Program for Social Sciences statistical software (version 22.0, Chicago, IL, USA) and R (version 3.4.3, Vienna, Austria) were used for statistical analyses. When comparing data between the two groups, we used Student's *t* test for normally distributed variables, the Mann-Whitney *U* test for non-normally distributed data, and chi-squared test for categorical data. Statistical significance was set at $P < 0.05$. The random forests method, an ensemble-learning approach for classification and regression, provides us an efficient way to handle noisy data. In this study, the forestFloor package of R was applied to perform random forests method. We applied the random forests method to identify clinical predictors for the therapeutic effect of corticosteroids, with the similar approaches described previously by Li et al. [11]. Five hundred traditional decision trees were developed to improve the accuracy of classification. Variables with no differences between groups were included in the random forests prediction model. We performed an out-of-bag (OOB) error estimate to evaluate the accuracy of the prediction model. We developed each tree with different bootstrap samples from the original data. We defined the relative variable importance as the mean decrease in the Gini index of diversity related to the variable. We evaluated the predictive performance of the random forests model using the area under the receiver operating characteristic curve (AUC) in the OOB error estimate.

Results

The demographics data and radiotherapy-relevant data of all patients are summarized in Table 1. Details on group comparisons of demographic data, radiotherapy-relevant data, and clinical risk factors are listed in Table 2. This study included a total of 73 patients (132 eyes). The effective group included 68 eyes (38 patients, 8 of them only had one eye regained vision). The ineffective group included 64 eyes (35 patients, 6 of them only had one eye regained no vision). Univariate analysis showed that blood urea nitrogen levels were significantly associated with the therapeutic effect of corticosteroids ($P = 0.005$).

Figure 1 shows the variables in the random forests prediction model of corticosteroid response. Our results show that levels of BUN, creatinine, TG, and LDL-C appear to be the main predictors of the therapeutic effect of corticosteroids on RION. The out-of-bag error was 6.82%, and this unbiased estimate of error indicated that the accuracy of this model was 93.12%. Figure 2 shows that the area under curve was 0.932 (95% confidence interval = 0.889–0.975). The feature contribution of the top six clinical variables is plotted in Fig. 3.

Table 1 Baseline characteristics of 73 RION patients

Characteristic	Value
Demographic and clinical characteristics	
Age (years)	52.0 (9.3)
Sex	
Male	57 (78.1)
Female	16 (21.9)
Comorbidity	
Diabetes mellitus	1 (1.4)
Hypertension	7 (9.6)
NPC-associated characteristic	
Latent period (years)	4.6 (3.3)
Radiation dose of nasopharynx (Gy)	70.7(2.6)
Number of times of radiotherapy	34.9(2.0)
Period of radiotherapy (days)	52.5(6.5)

Data are presented as mean (standard deviation) or number (percentage)

Discussion

By using a random forests approach, we developed a prediction model for the therapeutic effect of corticosteroids in patients who develop RION following radiotherapy for NPC. To our knowledge, this study is the first to apply a random forests method to predict the therapeutic effect of corticosteroids in RION.

To treat NPC, radiotherapy still remains the first choice for most patients. However, late consequences of radiotherapy, including RION, decrease the patients' quality of life. According to Seibel et al. [7], more than half of patients treated with radiotherapy will develop RION within 5 years after treatment. Many studies have investigated optimal radiation or medicine dosage in order to maximize the therapeutic effect of the treatment, but studies aimed at investigating the clinical characteristics of radiotherapy are rather rare or inconclusive [3, 4, 12]. To date, corticosteroids, hyperbaric oxygen, anticoagulants, angiotensin-converting enzyme inhibitors, bevacizumab, and other treatments [13] have been adopted to treat RION. However, the effectiveness of these treatments is insufficient [2, 6, 12].

In this retrospective study, demographic characteristics of RION patients like age, sex, and latent period were matched in an effective group and ineffective group. Data on radiotherapy such as dosage, field, and course were basically evaluated in this study as many such studies already exist [7–9]. The present findings showed that of the patients who received corticosteroids for RION those with higher BUN levels demonstrated greater improvements in vision. Furthermore, the random forests prediction model revealed additional possible predictors of treatment efficacy, which can be applied to screen for patients who may respond well to corticosteroid treatment.

Table 2 Clinical characteristics of the 132 eyes with or without effective response to steroids

Characteristics	Therapeutic effect		
	Effective	Ineffective	*P*
Demographic and clinical characteristics			
Age (years)	53.0 (9.9)	51.7 (8.7)	.821
Male	53 (77.9)	50 (78.1)	1.000
Diabetes mellitus	8 (11.8)	5 (7.8)	.271
Hypertension	0 (0.0)	2 (3.1)	.496
Latent period (years)	4.6 (3.2)	4.4 (2.9)	.993
Radiation dose of nasopharynx (Gy)	70.3(2.5)	71.2(2.6)	.141
Number of times of radiotherapy	34.5(2.3)	35.3(1.7)	.095
Period of radiotherapy (days)	52.2(7.6)	52.7(5.1)	.822
Abnormal VEP	32 (60.4)	29 (72.5)	.226
Optic disc edema	8 (11.8)	9 (14.1)	.894
ALT	23.9 (23.5)	19.5 (6.1)	.998
AST	21.5 (23.9)	19.4 (8.9)	.278
Na^+	140.1 (3.0)	139.8 (2.8)	.908
BUN	4.8 (1.4)	4.1 (1.3)	.002*
Crea	89.0 (20.3)	91.3 (18.8)	.256
UA	325.3(95.9)	322.2(122.3)	.320
FBG	5.6 (1.9)	5.8 (1.9)	.428
TC	5.6 (1.3)	5.9 (1.6)	.263
TG	1.3 (0.6)	1.5 (0.8)	.214
HDL-C	1.5 (0.4)	1.4 (0.4)	.619
LDL-C	3.4 (0.8)	3.7 (1.2)	.147
ApoA1	1.3 (0.3)	1.2 (0.3)	.744
ApoB	1.0 (0.4)	1.0 (0.3)	.251
ALB	39.9 (4.3)	39.3 (3.7)	.584
CK	97.8 (55.0)	94.7 (73.7)	.257
hs-CRP	7.9 (13.4)	12.9 (22.0)	.540

Data are presented as mean (standard deviation) or number (percentage)

*Represented the significant finding

Although careful verification of the accuracy of this predictive model is warranted to confirm its validity, this model presents a method to predict whether a patient would benefit from corticosteroid treatment. Moreover, unnecessarily high doses of corticosteroids could be avoided, which would reduce the risk of steroid-associated adverse effects, such as infection caused by immunosuppression, which could lead to poor prognosis.

The main predictors, based on the random forests prediction model, include BUN, LDL-C, TG, and creatinine. According to a recent study by Malgorzata et al. [14], uremic neurotoxins, such as BUN and creatinine, lead to axonal degeneration, secondary demyelination, and optic neuropathy (one of the most severe consequences). Corticosteroids are thought to alleviate RION by reducing tissue edema and preventing demyelination [6]; Seo et al. [15] reported a case of uremic optic neuropathy who responded to corticosteroids rapidly and substantially. We assume that preventing BUN and creatinine from damaging optic nerves might be a mechanism by which corticosteroids alleviate RION. TG and LDL-C are pro-inflammatory mediators [16]. Kardys et al. [17] reported that thinner retinal nerve fiber layer is associated with higher LDL-C levels in patients with optic neuritis, while corticosteroids might alleviate optic neuritis by its anti-inflammatory effect.

The study has several limitations. First, this is a retrospective study that only included patients from a single center, and the sample size of our study is relatively small. Therefore, multiple-center and large-scale cohort studies should be performed to verify our findings and confirm our conjectures upon mechanisms of how our main predictors damaging the

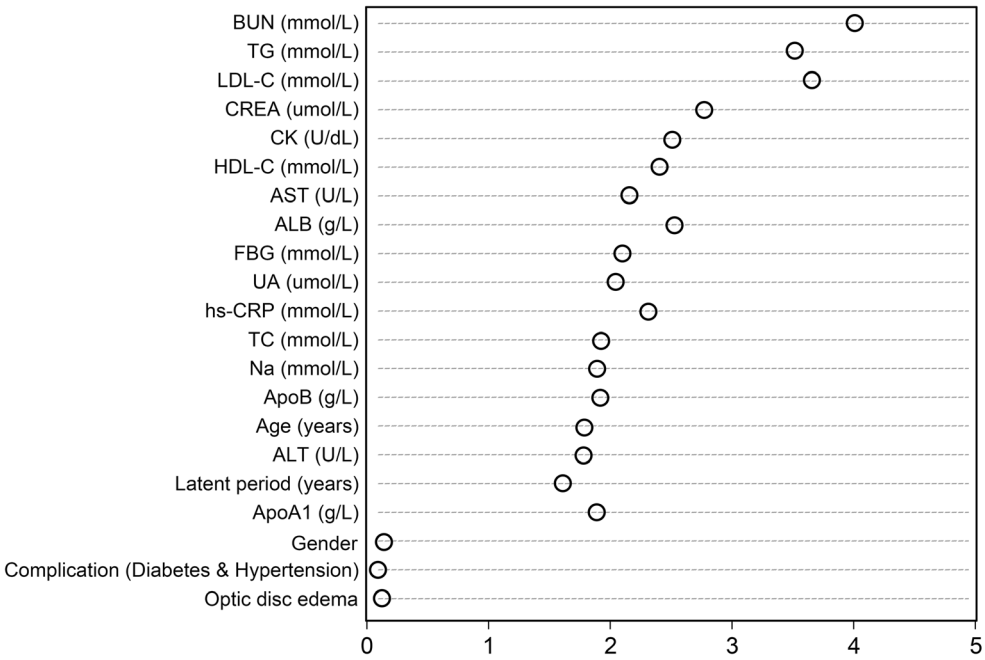

Fig. 1 The relative importance of clinical characteristics. Higher variable values indicate that the variable is relatively more important in predicting the therapeutic effect of corticosteroids. Blood urea nitrogen (BUN) was relatively more important than other variables

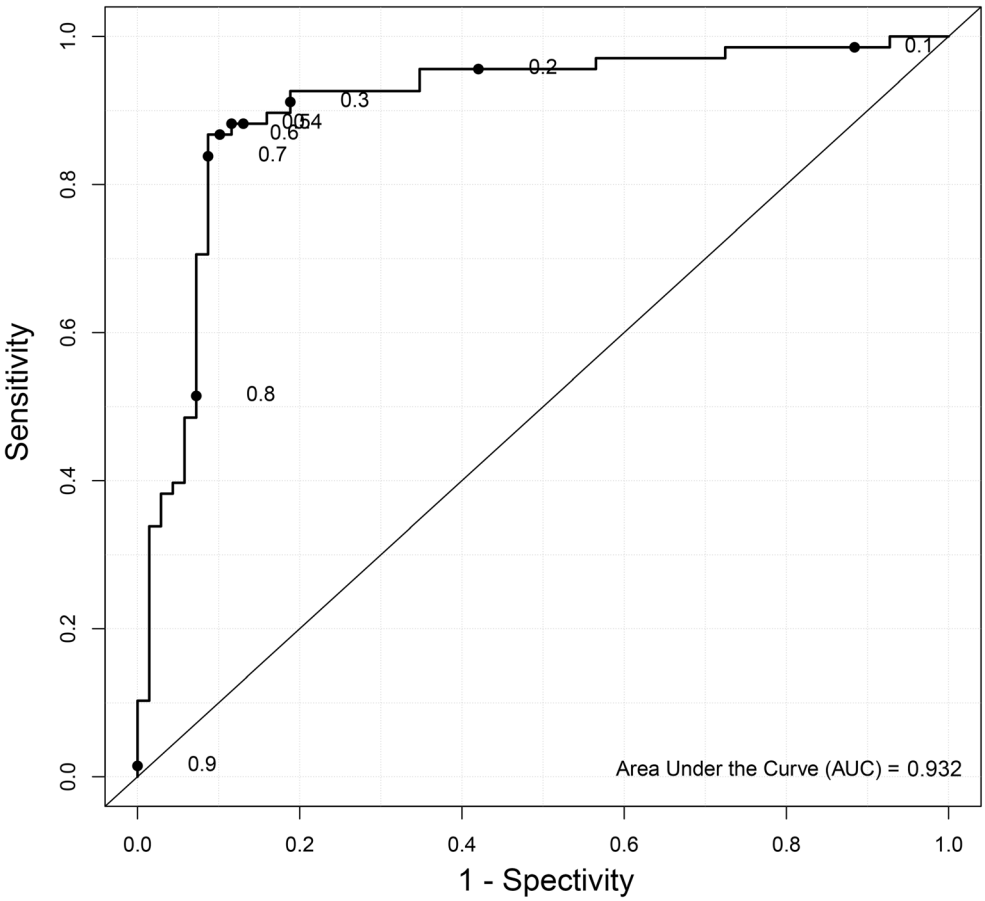

Fig. 2 Receiver operating characteristic curve for out-of-bag estimate. The area under the receiver operating characteristic curve was 0.876 (95% confidence interval = 0.820–0.932)

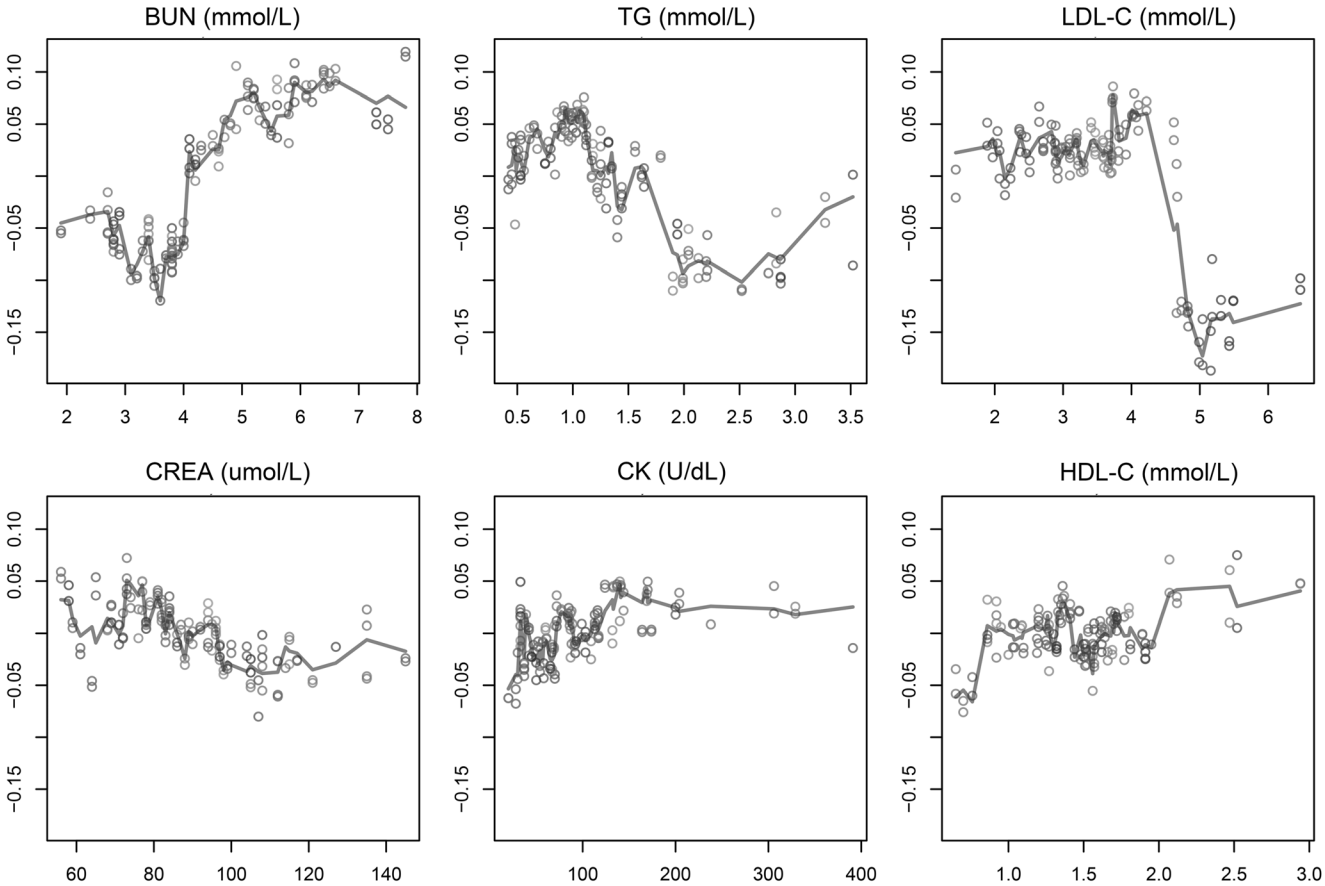

Fig. 3 The forestFloor main effect plots. Feature contribution of the six most important variables was plotted. Variable values were showed in the *x*-axis, and the addictive change of predicted probability was showed in the *y*-axis. Each circle represents one case

optic nerve. Second, the clinical variables we included were determined according to our clinical experience, and some factors, such as erythrocyte sedimentation rate and procalcitonin, were not included concerning the lack of data. Therefore, more clinical factors should be included in future studies to improve upon our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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