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The association and diagnostic value of red blood cell distribution width in colorectal cancer

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Abstract

Red blood cell distribution width (RDW) is associated with several diseases. However, the diagnostic value of RDW and its related factors remain unclear in colorectal cancer (CRC).

This single-center retrospective study evaluated 211 Chinese CRC patients and 103 healthy controls. The association of RDW with the clinical parameters of CRC, as well as its correlations with carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were analyzed. The diagnostic value of RDW alone or combined with CEA and CA19-9 was evaluated using receiver operating characteristic curve analysis. A meta-analysis was also performed to combine our data with previously published data to enhance our findings.

In the CRC patients, RDW was clearly elevated and was significantly associated with CRC tumor location, histological type, T status (but not N or M status), and clinical stage. However, RDW was not significantly correlated with CEA or CA19-9 levels. Using RDW to diagnose CRC provided a sensitivity of 53.1% and specificity of 77.7%. The diagnostic accuracy of RDW was enhanced by combining RDW with CEA and CA19-9 levels. We identified 5 previous studies with 633 CRC patients and 1050 controls, which were combined with our cases and controls. The meta-analysis revealed an overall sensitivity of 69%, specificity of 70%, and an area under the curve of 0.74.

In CRC cases, RDW was associated with tumor location, histological type, T status, and clinical stage. Furthermore, RDW had a moderate value for diagnosing CRC and might be useful in this setting.

Abbreviations: AUC = area under the curve, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, CRC = colorectal cancer, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, RDW = red blood cell distribution width.

Keywords: association, colorectal cancer, diagnosis, red blood cell distribution width

1. Introduction

The emergence of aging populations and unhealthy lifestyles has led to colorectal cancer (CRC) becoming one of the most commonly diagnosed cancers and the leading cause of cancer-related deaths worldwide.[1] Radical resection is the most effective treatment for CRC, although the efficacy of this approach relies on the early diagnosis of CRC.[2] Ongoing research has focused on identifying blood-borne biomarkers that can facilitate the early diagnosis of CRC, although there are no routinely available clinical markers that can be used to diagnose CRC. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are currently thought to be associated with the development of CRC, although the existing studies have revealed varying diagnostic accuracy in this setting.[3,4] Therefore, it would be useful to identify a reliable biomarker that can be used to diagnose CRC.

Red blood cell distribution width (RDW) is a measure of variability in red blood cell volume and is a quantitative measure of anisocytosis.[5,6] Elevated RDW values are associated with several types of anemias, as well as with certain liver disorders and systemic inflammation.[7,8] Recent studies have also indicated that RDW is associated with the development of several cancers, with potential diagnostic and prognostic value for esophageal cancer, multiple myeloma, and hepatocellular carcinoma.[9–11] However, there are scarce and inconsistent data regarding the diagnostic value of RDW in CRC.[12–14] Therefore, the present study aimed to examine the association of RDW with CRC and to explore whether RDW could be used to diagnose CRC using meta-analysis of our data and findings from previous studies.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the data of patients with CRC who were undergoing radical surgery at the People's Hospital of

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Liuzhou between January 2016 and March 2018. The inclusion criteria were

1) CRC was confirmed via historical biopsy,
2) the patient was undergoing radical resection, and
3) blood test data from ≤2 weeks before surgery could be used for the RDW calculation.
4) The exclusion criteria were
5) previous neoadjuvant therapy,
6) presence of infection, and
7) age of >85 years.

As controls, we selected 103 patients with colon polyps, but no evidence of malignant disease, that were diagnosed at our hospital during the same period. The study's retrospective protocol was approval by the Ethics Committee of the People's Hospital of Liuzhou. Written informed consent for data collection had been obtained from each patient.

2.2. Blood testing and data collection

Preoperative data were obtained from routine laboratory blood tests that were performed before surgery. The RDW was directly detected using a Sysmex XN-9000 analyzer (Sysmex Corp., Kobe, Japan). The CEA and CA19-9 levels were measured using a Roche E601 analyzer (Roche Diagnostics, Basel, Switzerland). The patients' medical records were also searched to collect data regarding age, sex, tumor location, tumor differentiation, clinical stage, and TNM stage. The TNM stage had been determined according to the American Joint Committee on Cancer TNM guidelines (7th edition).

2.3. Search strategy for related articles

We searched for articles in any language that described using RDW to diagnose CRC and were published before April 2018. This search included the PubMed, Cochrane Library, Web of Science, Google Scholar, and the Chinese National Knowledge Infrastructure databases. The search terms were "colorectal cancer" or "CRC", "red blood cell distribution width" or "RDW," and "diagnosis". Related reports were only considered relevant if they examined human subjects. For relevant reports, we extracted the first author, year of publication, study location, RDW cut-off, numbers of CRC patients, and controls and reported sensitivity and specificity values for RDW.

2.4. Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using a Mann–Whitney *U* or Student *t* test. The correlations between RDW and CEA or CA19-9 levels were assessed using Spearman correlation analysis. The diagnostic values of RDW, CEA, and/or CA19-9 were estimated using receiver operating characteristic (ROC) curve analysis, based on the area under the curve (AUC) and its 95% confidence interval (CI). The optimal cut-off value for each factor was determined based on the highest Youden index. All basic analyses were performed using R software (version 3.4.3).

The meta-analysis of RDW's diagnostic value was performed using Stata software (version 11.2; Stata Corp., College Station, TX), and the results were reported with 2-tailed *P* values. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with the corresponding 95% CIs were calculated for each study. A summary receiver operating characteristic curve (SROC) was created to determine the maximum combined sensitivity and specificity, as well as its AUC and corresponding 95% CI. Differences were considered statistically significant at *P* values of <.05.

Table 1

Clinical characteristics of the subjects.

	CRC group	Control group	*P* value
Age	60.9±9.7	63.31±10.3	.098
Gender (male/female)	119/92	52/51	
RDW, %	14.3±2.7	12.7±1.1	<.01
CEA, ng/mL	18.7±9.6	2.19±1.2	<.01
CA199, U/mL	24.1±10.3	14.54±6.8	<.01
Tumor location (colon/rectal)	137/74		
Histological type (high/middle/low grade)	17/175/19		
Clinical stage (I/II/III/IV)	33/55/84/39		
T stage (T1/T2/T3/T4)	7/35/16/153		
N stage (N0/N1/M2/N3)	91/72/41/7		
M stage (M0/M1)	175/36		

CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, RDW = red blood cell distribution width.

3. Results

3.1. Subject characteristics

Based on the inclusion and exclusion criteria, we identified 211 CRC patients. Relative to the 103 controls, the CRC patients had significantly elevated values for RDW, CA19-9, and CEA (all $P < .05$). There were no significant inter-group differences in age or sex (both $P > .05$). Table 1 shows the subjects' clinical characteristics.

3.2. Association of RDW with various clinical factors

Figure 1 shows that RDW was significantly associated with CRC tumor location, histological type, T status, and clinical stage (all $P < .05$). However, RDW was not significantly associated with N status or M status. The correlation analyses revealed that RDW was not significantly correlated with CEA or CA19-9 levels in CRC (both $P > .05$).

3.3. Values of RDW, CEA, and CA19-9 for diagnosing CRC

We examined the diagnostic value of RDW using an optimal cut-off value of 13.2, which provided a sensitivity of 53.1% and specificity of 77.7% for diagnosing CRC. The combination of RDW with CEA and CA19-9 provided superior diagnostic performance, relative to any single indicator. Table 2 shows the sensitivity, specificity, AUC, and optimal cut-off values for using RDW, CEA, and/or CA19-9 to diagnose CRC.

3.4. Related studies

Our literature search identified 5 studies that examined the value of RDW for diagnosing CRC.[13,15–18] All studies were retrospective and included a total of 633 CRC patients and 1050 controls. Table 3 shows that there was noticeable

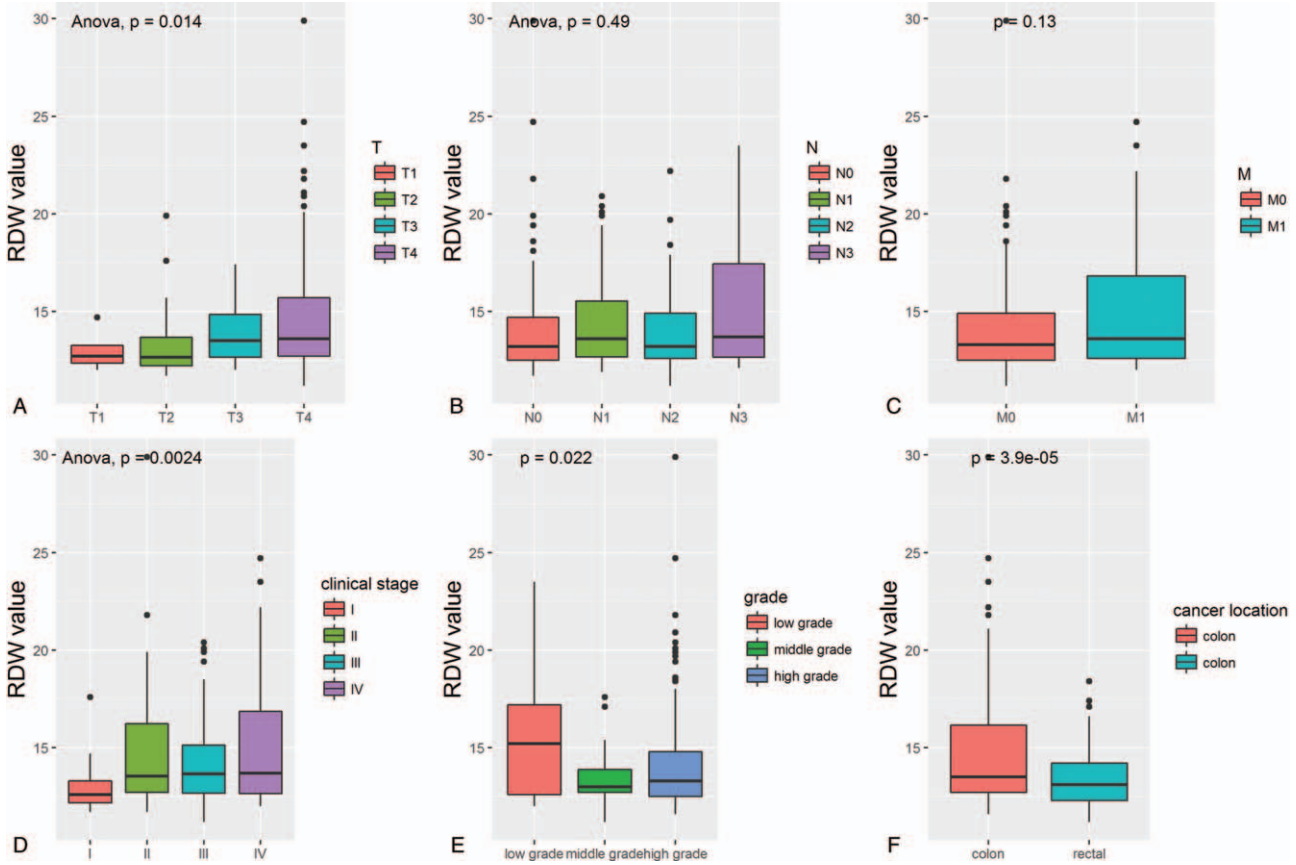

Figure 1. The association of RDW with the clinical parameters of CRC. CRC = colorectal cancer, RDW = red blood cell distribution width.

variability in the studies' sensitivity, specificity, and RDW cut-off values.

3.5. Meta-analysis of using RDW to diagnose CRC

We performed meta-analysis by pooling our data and the previously reported data (Figs. 2 and 3). The results revealed overall sensitivity of 69% (95% CI: 57%–79%), specificity of 70% (95% CI: 48%–86%), a PLR of 2.3 (95% CI: 1.3–4.0), a NLR of 0.44 (95% CI: 0.35–0.57), and a DOR of 5 (95% CI: 3–10). The overall AUC was 0.74 (95% CI: 0.70–0.78).

4. Discussion

The present study revealed that RDW was significantly elevated in CRC patients, relative to the controls, which agrees with the findings of previous studies.[14,19] Thus, the data suggest that RDW is associated with the presence of CRC. We also found that RDW was significantly associated with CRC tumor location, histological type, clinical stage, and T status, which indicates that RDW can be affected by these parameters. However, RDW was not significantly associated with lymphatic or distant metastasis, which suggests that RDW may not be associated with the metastasis of CRC. Furthermore, we found that RDW had moderate diagnostic value in the CRC cases and that combining RDW with CEA and CA19-9 enhanced the diagnostic accuracy. Finally, we performed a meta-analysis of our data and previously published data, which confirmed that RDW may be a useful biomarker for diagnosing CRC.

The efficacy of CRC treatment is largely depending on the stage at the CRC diagnosis. Although many biomarkers have been

Table 2

Diagnostic value of RDW, CEA and CA199 in CRC.

	Cut-off	Sensitivity, %	Specificity, %	AUC (95% CI)
RDW	13.2	53.1	77.7	0.720
CEA	1.83	82.9	50.5	0.802
CA199	11.0	63.0	30.1	0.540
RDW+CEA	–	78.7	100%	0.850
RDW+CEA+CA199	–	76.7	100%	0.851

CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, RDW = red blood cell distribution width.

Table 3

Characteristics of included studies.

Author	Case/ control	Country/ year	Sensitivity/ Specificity, %	Cut-off, %
Spell	225/494	USA/2004	69/88	NA
Ay	30/115	Turkey/2015	91.4/17.5	53.3
Liang	90/90	China/2017	64/82	13.06
Wang	108/100	China/2017	65.7/63.3	13.22
Zhang	180/251	China/2017	62.2/77.7	13.35
Our study	211/103	–	53.1/77.7	13.2

NA = not available.

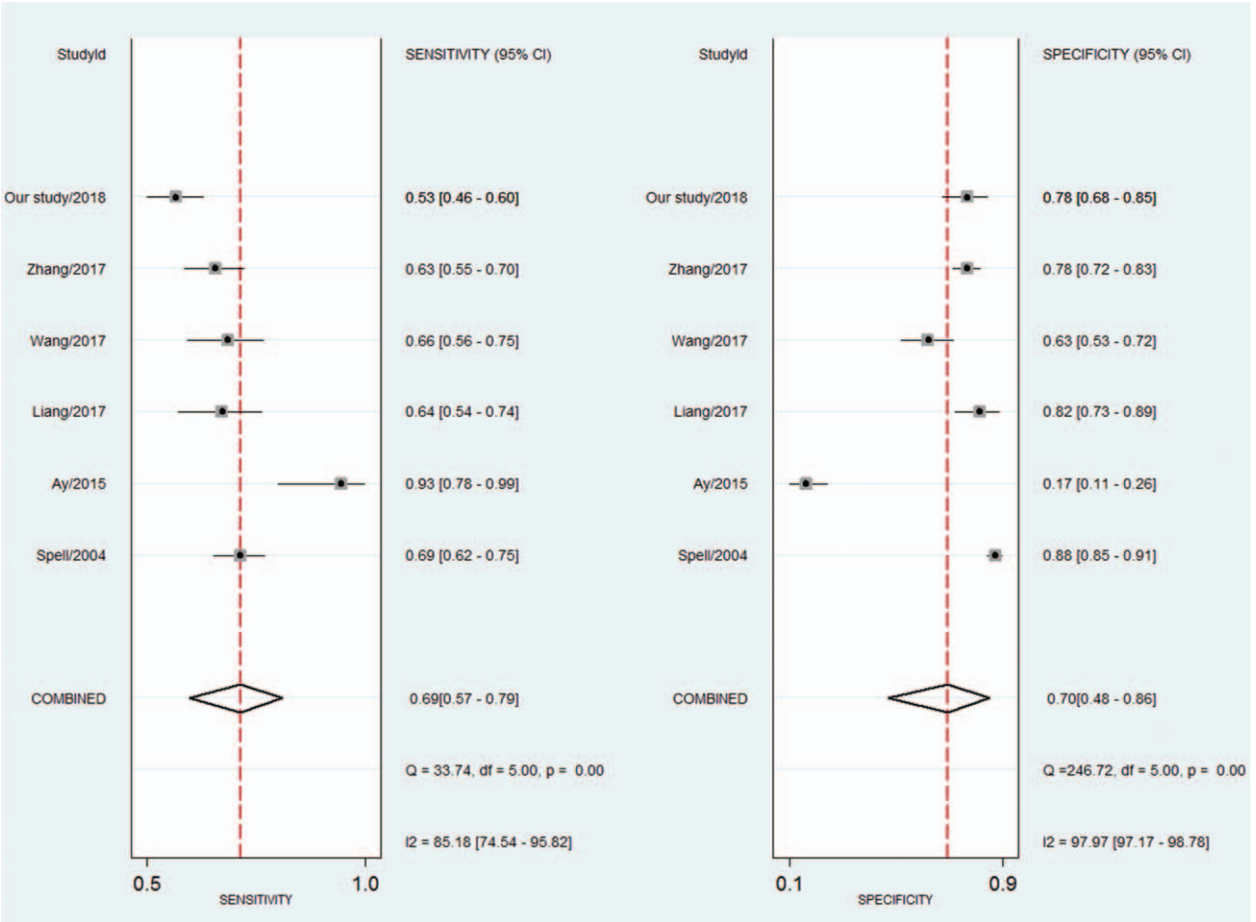

Figure 2. Forest graphs of summary sensitivity, specificity for RDW in diagnosis of CRC. CRC = colorectal cancer, RDW = red blood cell distribution width.

examined for diagnosing CRC, their high cost or other factors have limited their clinical utility.[20,21] Thus, it would be useful to identify a convenient and cost-effective biomarker that would allow clinicians to select appropriate treatment for their patients. In this context, RDW is a hematological parameter that reflects heterogeneity in red blood cell size,[5,6] and is reportedly associated with systemic inflammation.[7,8] Given the readily available nature of RDW, it may be more clinically useful than other markers. Furthermore, RDW has been used to distinguish iron deficiency anemia from thalassemia or other hemoglobinopathies, and recent studies have identified elevated RDW in cases of atherosclerosis, inflammatory diseases, and cancers,[22,23] which highlights the potential utility of RDW in CRC diagnosis and prognostication.

The mechanism underlying the association between RDW and cancer remains unclear. However, inflammation in the tumor microenvironment is a critical factor in the development of cancer, and both inflammation and oxidative stress can also affect RDW.[24] In addition, the pathogenesis is linked to circulating levels of various cytokines (e.g., IL-6, TNF-α, and hepcidin), which are also known to influence RDW.[25] Thus, the association between RDW and cancer might be mediated by inflammation. The associated between RDW and CRC has been revealed in several studies,[13,14,18] with most studies indicating that RDW was elevated in CRC patients relative to the controls. However, there are conflicting data regarding associations between RDW and CRC parameters. For example, Yang et al[14] reported that RDW was significantly associated with clinical stage and TNM stage, although we failed to detect significant associated with lymphatic or distant metastasis. We speculate that this discrepancy may be related to the small number of patients that Yang et al evaluated.

Previous studies have also revealed varying sensitivity and specificity for using RDW to diagnose CRC.[13–15] The present study revealed that RDW had moderate diagnostic accuracy in this setting, which could be improved by combining RDW with CEA and CA19-9. This pattern is consistent with the findings of previous studies. We also combined our data and previously reported data (5 studies with 633 CRC patients and 1050 controls) for a meta-analysis, which confirmed the moderate diagnostic accuracy of RDW, based on sensitivity of 69%, specificity of 70%, and an AUC of 0.74. These results confirm that RDW may be useful in the diagnosis of CRC.

Although our study revealed that RDW was associated with CRC, and had moderate diagnostic value, some limitations should be noted. First, the retrospective design is a known source of selection bias, which might have affected the findings. Second, while our study population was larger than in several previous studies, the overall numbers of patients (n = 211) and controls (n = 103) were relatively small, given the high incidence of CRC.

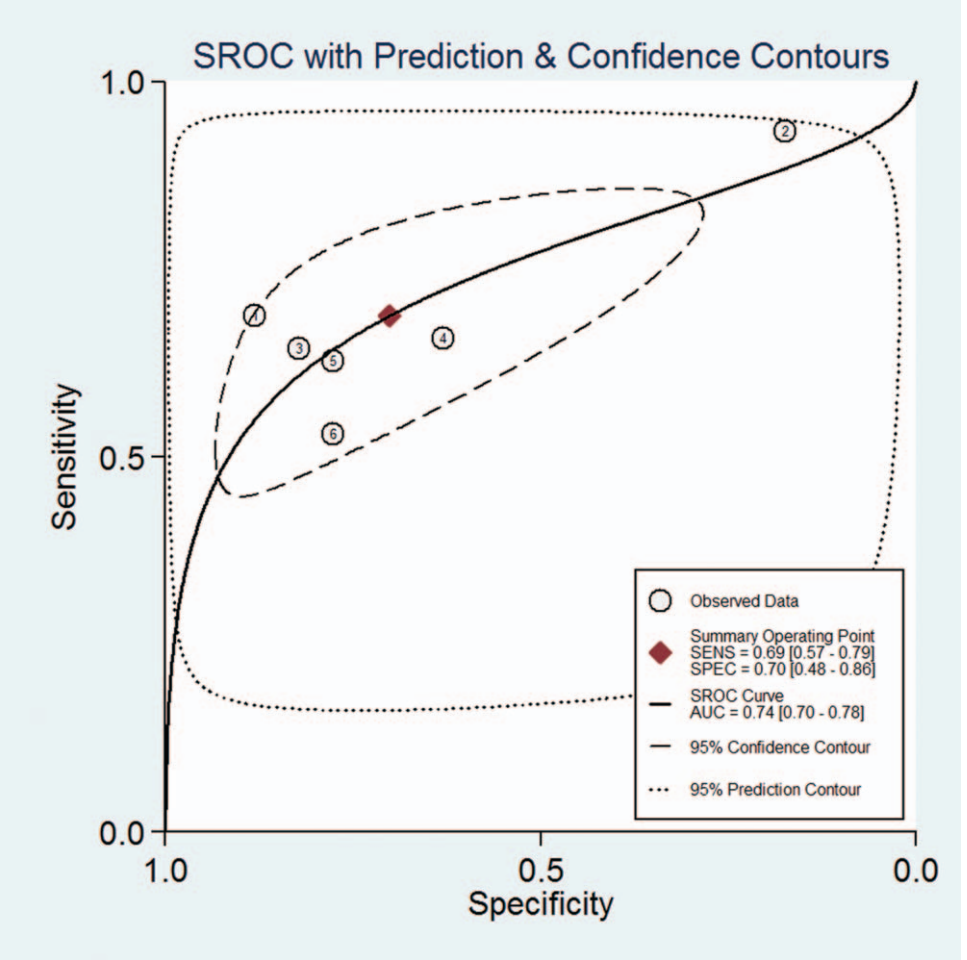

Figure 3. The SROC curve graph for RDW in diagnosis of CRC. CRC = colorectal cancer, RDW = red blood cell distribution width, SROC = summary receiver operating characteristic curve.

Third, the study's design only permitted an analysis of RDW's diagnostic value, and we cannot comment on whether it can be used to predict the prognosis of CRC patients, which is an important factor in selecting appropriate treatment. Therefore, our results should be interpreted with caution, and a large well-designed prospective study is needed to confirm the diagnostic value of RDW and its associated factors in CRC.

5. Conclusion

This study revealed that RDW was associated with the presence of CRC, and was also significantly associated with tumor location, histological type, clinical stage, and T status (but not N status or M status). The results indicate that RDW had moderate diagnostic value and could be useful in the identification and clinical management of CRC patients.

Author contributions

Study concept and design: C Shi and BL Hu; Collection and assembly of data: C Shi, and MZ Xie; Data analysis and interpretation: C Shi and MZ Xie; Manuscript writing and review: All authors

Conceptualization: Bangli Hu.
Data curation: Bangli Hu, Cheng Shi, Mingzhi Xie.
Funding acquisition: Bangli Hu.
Methodology: Cheng Shi, Mingzhi Xie.
Software: Cheng Shi.
Visualization: Mingzhi Xie.
Writing – original draft: Cheng Shi, Mingzhi Xie.
Writing – review & editing: Cheng Shi, Mingzhi Xie, Lihua Li, Kezhi Li.

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