Predictive value of baseline $^{18}$F-FDG PET/CT and interim treatment response for the prognosis of patients with diffuse large B-cell lymphoma receiving R-CHOP chemotherapy

LILI ZHU$^{1,2,*}$, YANKAI MENG$^{3,*}$, LILI GUO$^{2}$, HANQING ZHAO$^{2}$, YUE SHI$^{2}$, SHAODONG LI$^{3}$, ANMING WANG$^{2}$, XIAOJUN ZHANG$^{2}$, JING SHI$^{2}$, JIE ZHU$^{2}$ and KAI XU$^{1,3}$

$^1$The First School of Clinical Medicine, Nanjing Medical University, Nanjing, Jiangsu 210029; $^2$Department of Radiology, Huaihai Hospital Affiliated with Xuzhou Medical University, Xuzhou, Jiangsu 221004; $^3$Department of Radiology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221002, P.R. China

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Abstract. The present study aimed to investigate the prognostic value of baseline $^{18}$F-FDG PET/CT quantitative parameters and interim treatment response, and to assess whether the combination of these could improve the predictive efficacy in patients with diffuse large B-cell lymphoma (DLBCL) receiving R-CHOP chemotherapy. PET/CT images and clinical data of 64 patients with DLBCL who had undergone $^{18}$F-FDG PET/CT scan before and after 3 or 4 cycles of R-CHOP chemotherapy were retrospectively reviewed. The quantitative parameters including standardized uptake value (SUV), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum diameter of the maximum lesion (Dmax) were measured on baseline PET/CT images. Cox proportional hazards model was used to evaluate the influence of baseline PET/CT parameters, clinical indicators and interim treatment response on prognosis. Survival analysis was performed using Kaplan-Meier method. Receiver operating characteristic (ROC) curve analysis was performed to estimate the predictive efficacy of the combination of baseline PET/CT parameters and interim treatment response. Ann Arbor stage, International Prognostic Index (IPI), lactate dehydrogenase (LDH), necrosis, MTVmax, TLGmax, Dmax and interim treatment response showed association with 2-year progression-free survival (PFS, P<0.05). LDH, necrosis, MTVmax, MTVsum, TLGmax, TLGsum, Dmax and interim treatment response showed association with 2-year overall survival (OS, P<0.05). Ann Arbor stage, Dmax and interim treatment response were found to be independent predictors of 2-year PFS (P<0.05), while Dmax and interim treatment response were found to be independent predictors of 2-year OS (P<0.05). The PFS and OS curves of Dmax <5.7 cm group and Dmax ≥5.7 cm group, complete response (CR) group and non-CR group were significantly different, respectively (P<0.05). The baseline $^{18}$F-FDG PET/CT parameters and interim treatment response have important prognostic values in DLBCL patients who received R-CHOP chemotherapy. Combined application of Dmax and interim treatment response improved the predictive efficacy of 2-year PFS. It may be helpful to identify patients who are at high-risk of relapse and to guide early clinical intervention of these patients.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a type of lymphoma with high heterogeneity in regards to immunophenotype, gene expression, morphology, clinical symptoms and prognosis (1). The International Prognostic Index (IPI) is the most commonly used prognostic index for predicting the outcome in clinics for patients with DLBCL. Prognostic evaluation and risk stratification are made by IPI based on 5 aspects, including age, Ann Arbor stage, lactate dehydrogenase (LDH) levels, physical condition score, and the number of extranodal organ involvement. However, DLBCL patients with the same IPI score might still have different outcomes after undergoing similar chemotherapy due to tumor heterogeneity. Furthermore, the prognostic value of an intermediate IPI score still remains to be unclear (2,3). With the introduction of rituximab into the first-line chemotherapy regimens (R-CHOP), the prognostic value of IPI still faced great challenges. Thus, more reliable prognostic indicators or evaluation models are urgently needed to identify patients who are more likely to relapse in clinical practice (4,5). Some scholars have carried out relevant basic research and proposed gene predictors such as cell origin, MYC and BCL2/BCL6 double expression, but their application value still requires further confirmation (6,7).

According to previous studies, baseline $^{18}$F-FDG PET/CT parameters, such as metabolism of tumor volume (MTV)
and total lesion glycolysis (TLG), could provide personalized information on metabolic activity and metabolic volume of the tumor, and have important prognostic value in patients with DLBCL (8,9). However, the results of these studies are not completely consistent, and this may be due to the distribution bias of enrolled cases, different threshold selection methods and standards for measurement of PET/CT parameters. Assessment of interim treatment response based on PET/CT has great prognostic value in DLBCL patients and it has been included in criteria for response assessment (10,11). Interim treatment response has attracted much clinical attention, but some patients with a good interim treatment response and negative interim PET/CT may still have recurrence and progression. Currently, there are relatively few studies that have discussed the prognostic value of the combination of baseline PET/CT quantitative parameters and interim treatment response in DLBCL patients (12,13).

Hence, in the present study, the relationship between baseline PET/CT quantitative parameters, interim treatment response and prognostic survival of 64 patients with DLBCL receiving R-CHOP chemotherapy was analyzed, and the predictive efficacy of the combination of baseline PET/CT parameters and interim treatment response for survival was evaluated with the aim to guide the implementation of appropriate treatment and follow-up strategies for high-risk patients and to improve their long-term survival.

Patients and methods

Patient selection. The inclusion criteria were as follows: i) Patients with pathologically and immunohistochemically confirmed DLBCL after surgery or biopsy, ii) patients who received first-line R-CHOP (rituximab, cyclophosphamide, hydroxydaunomycin, oncovin and prednisone) chemotherapy, iii) patients who underwent 18F-FDG PET/CT scans before and after 3 or 4 cycles of R-CHOP chemotherapy, respectively, iv) patients no less than 18 years of age, and v) patients with complete clinical records. The exclusion criteria were as follows: i) Patients with primary central nervous system lymphoma, ii) patients with a history of malignancy or with other malignancies at present, iii) patients who received chemotherapy, radiotherapy or surgical resection before PET/CT scan prior to the study enrollment, iv) patients who dropped out during the treatment due to any reason, and v) patients with incomplete clinical records. Between July 2014 and December 2018, a total of 358 patients with DLBCL were admitted to our institution, and 294 patients of these were included in criteria for response assessment (10,11). Interim treatment response was evaluated with the aim to guide the implementation of appropriate treatment and follow-up strategies for high-risk patients and to improve their long-term survival.

PET/CT imaging. 18F-FDG PET/CT image acquisition was performed with Discovery PET/CT Elite scanner (GE Healthcare). After fasting for at least 6 h, patients were intravenously injected with 18F-FDG (3.5 to 4.0 MBq/kg). The weight of the patients was obtained and the fasting blood glucose levels were controlled to less than 150 mg/dl before injection. Patients after injection were advised to rest for 1 h before initiating the PET/CT scan. Patients were placed in a supine position with quiet breathing. CT images were acquired from the skull vertex to proximal thigh initially and then the corresponding PET data were collected. CT data were used for attenuation correction and the standard protocol settings were as follows: 120 KV, 180 mA, slice thickness of 3.75 mm. PET scanning images were acquired in 7 to 8 bed positions and the acquisition time was 3 min per bed position. Image fusion was performed after reconstruction by iterative method.

PET/CT parameters. All PET/CT images were reconstructed and reviewed using Volume Viewer software on Workstation AW 4.5 (GE Healthcare) by two experienced radiologists and a nuclear medicine physician who were blinded to the clinical information. Visual assessment and semi-quantitative analysis were used for image analysis. Tumor contours covering the entire lesion volume in axial, coronal and sagittal images were delineated automatically or manually as and when necessary, and then the quantitative parameters such as maximum standardized uptake value (SUVMax), mean standardized uptake value (SUVMean), metabolic tumor volume of the maximum lesion (MTVmax), mean of the metabolic tumor volume (MTVsum), total lesion glycolysis of the maximum lesion (TLGmax), sum of total lesion glycolysis (TLGsum), maximum diameter of the maximum lesion (Dmax) were measured or calculated. MTV was measured with a threshold of 40% SUVMax. TLG was the product of MTV and SUVMean.

Interim treatment response evaluation. Response to 3 or 4 cycles of R-CHOP chemotherapy was assessed according to the Lugano criteria (11) and patients were categorized into four types: Complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) as described here. CR: PET/CT-based response: Score 1, 2, or 3 with or without a residual mass on SPS (1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or no new lesions; X, new areas of uptake unlikely to be related to lymphoma), no new lesions and no evidence of FDG-avid disease in marrow. PR: Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size, no new lesions, residual uptake higher than uptake in normal marrow but reduced compared with baseline. SD: Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment, no new lesions, no change in marrow uptake from baseline. PD: Score 4 or 5 with an increase in intensity of uptake from baseline, new FDG-avid foci consistent with lymphoma rather than another etiology (e.g. infection, inflammation), new or recurrent FDG-avid foci in marrow. In the present study, all patients were divided into patient informed consent was waived due to the retrospective nature of the present study.
two groups including CR group and non-CR group. Patients with CR were included in the CR group and patients with PR, SD or PD were included in the non-CR group.

**Follow-up assessment.** Follow-up was performed by conducting phone interview or reviewing of hospital records. Progression-free survival (PFS) was defined as the time from initial diagnosis until the first occurrence of disease recurrence, progression, death due to any cause or at the end of the follow-up period. Overall survival (OS) was defined as the time from initial diagnosis until death due to any cause or the end of follow-up period.

**Statistical analysis.** Non-normally distributed data are expressed as median (Q1 and Q3). Intraclass correlation coefficient (ICC) was used to assess interobserver consistency of PET/CT parameters. Cox proportional hazard models were used in the univariate and multivariate analyses. Survival curves were constructed using Kaplan-Meier method. Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive efficacy of the indicators. A P-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 21.0) (IBM Corp.).

**Results**

**Patient characteristics.** A total of 64 patients, including 33 men (51.6%) and 31 women (48.4%), were enrolled in this study. The median age at diagnosis was 57 years (range, 25-80 years). The clinical characteristics of the 64 patients with DLBCL are listed in Table I. Of the entire cohort, 39 (60.9%) patients achieved CR and 25 (39.1%) patients had non-CR after 3 or 4 cycles of R-CHOP chemotherapy. Follow-up time ranged from 6 to 62 months, and the median follow-up time was 25 months. Relapse and progression occurred in 23 patients, while 17 patients died within two years. The 2-year PFS rate and 2-year OS rate were 64.1 and 73.4%, respectively.

**Interobserver agreement.** Baseline PET/CT parameters were measured by two observers. Consistency test showed intra-class correlation coefficient (ICC) that ranged between 0.663 and 0.991, showing good agreement. ICC values are shown in Table SI and baseline PET/CT parameters of the patients are listed in Table SII.

**Univariate analysis.** The median SUVmax, SUVmean, MTVmax, MTVsum, TLGmax, TLGsum and Dmax of the entire population were 17.6, 10.6, 63.5 cm$^3$, 132.6 cm$^3$, 628.7 g, 1135.9 g and 5.7 cm, respectively.

Of all the clinical indicators, baseline PET/CT parameters and interim treatment response evaluated, Ann Arbor stage, Dmax and interim treatment response showed association with 2-year PFS (P<0.05). LDH, necrosis, MTVmax, MTVsum, TLGmax, TLGsum, Dmax and interim treatment response showed association with 2-year OS (P<0.05) (Tables II and III).

**Multivariate analysis.** The statistical significant indicators in univariate analysis were included in the multivariate analysis. Due to the close relationship between MTVmax and TLGmax, MTVsum and TLGsum, only TLGmax and TLGsum were included in multivariate analysis.

**Ann Arbor stage, Dmax and interim treatment response were considered as independent prognostic factors for 2-year PFS (P<0.05). Dmax and interim treatment response were shown to be independent prognostic factors for 2-year OS (P<0.05) (Table IV).**

**Survival curves.** Kaplan-Meier survival curves showed that PFS and OS curves of the Dmax ≥5.7 cm group were shown...
to be significantly lower than that of the Dmax <5.7 cm group, respectively. The 2-year PFS rate of the Dmax <5.7 cm group and Dmax ≥5.7 cm group were 88.8 and 49.5%, respectively (P<0.001). The 2-year OS rate of the Dmax <5.7 cm group and Dmax ≥5.7 cm group were 89.5 and 51.1%, respectively (P<0.001) (Figs. 1 and 2).

The PFS and OS curves of the non-CR group were significantly lower than that of CR group, respectively. The 2-year PFS rate of the CR group and non-CR group were 87.6 and 23.7%, respectively (P<0.001). The 2-year OS rate of the CR group and non-CR group were 89.9 and 31.7%, respectively (P<0.001) (Figs. 3 and 4).

Prognostic value of the combination of two factors. The AUC, sensitivity and specificity of the combination of Dmax and interim treatment response for predicting the 2-year PFS were 0.801, 73.9 and 92.7%, respectively. Compared with single index Dmax, the predictive performance of the combination was found to be slightly improved, the specificity was significantly increased, while the sensitivity was lower.

Table II. Univariate analyses of the clinical characteristics for PFS and OS.

| Characteristics          | 2-year PFS | 2-year OS |
|-------------------------|------------|-----------|
|                         | RR         | 95% CI    | P-value | RR         | 95% CI    | P-value |
| Sex                     |            |           |         |            |           |         |
| Male                    | 1          |           |         | 1          |           |         |
| Female                  | 0.418      | 0.170-1.028 | 0.057   | 0.274      | 0.090-0.835 | 0.061   |
| Age (years)             |            |           |         |            |           |         |
| ≤60                     | 1          |           |         | 1          |           |         |
| >60                     | 0.544      | 0.228-1.300 | 0.171   | 0.439      | 0.163-1.180 | 0.103   |
| B symptoms              |            |           |         |            |           |         |
| Yes                     | 1          |           |         | 1          |           |         |
| No                      | 0.513      | 0.214-1.227 | 0.134   | 0.410      | 0.159-1.062 | 0.066   |
| Ann Arbor stage         |            |           |         |            |           |         |
| I+II                    | 1          |           |         | 1          |           |         |
| III+IV                  | 2.754      | 1.013-7.485 | 0.047*  | 1.927      | 0.686-5.414 | 0.213   |
| IPI score               |            |           |         |            |           |         |
| ≤2                      | 1          |           |         | 1          |           |         |
| >2                      | 2.501      | 1.076-5.816 | 0.033*  | 2.381      | 0.943-6.012 | 0.066   |
| LDH level               |            |           |         |            |           |         |
| Normal                  | 1          |           |         | 1          |           |         |
| Abnormal                | 5.926      | 1.986-17.680 | 0.001*  | 4.495      | 1.469-13.758 | 0.008*  |
| β2-MG                   |            |           |         |            |           |         |
| Normal                  | 1          |           |         | 1          |           |         |
| Abnormal                | 1.252      | 0.535-2.930 | 0.605   | 1.469      | 0.579-3.726 | 0.418   |
| Nln                     |            |           |         |            |           |         |
| <2                      | 1          |           |         | 1          |           |         |
| ≥2                      | 2.139      | 0.723-6.327 | 0.170   | 2.381      | 0.686-8.256 | 0.172   |
| Neo                     |            |           |         |            |           |         |
| <2                      | 1          |           |         | 1          |           |         |
| ≥2                      | 2.124      | 0.886-5.092 | 0.091   | 2.202      | 0.850-5.703 | 0.104   |
| BMI                     |            |           |         |            |           |         |
| No                      | 1          |           |         | 1          |           |         |
| Yes                     | 1.307      | 0.442-3.868 | 0.629   | 0.977      | 0.280-3.401 | 0.970   |
| Necrosis                |            |           |         |            |           |         |
| No                      | 1          |           |         | 1          |           |         |
| Yes                     | 3.594      | 1.526-8.465 | 0.003*  | 4.085      | 1.612-10.356 | 0.003*  |

*Statistically significant. PFS, progression-free survival; OS, overall survival; RR, relative risk; CI, confidence interval; IPI, International Prognostic Index; LDH, lactate dehydrogenase; β2-MG, β2 microglobulin; Nln, number of lymph node area involvement; Neo, number of extranodal organ involvement; BMI, bone marrow involvement.
slightly decreased (Fig. 5). The AUC, sensitivity and specificity of the combination of Dmax and interim treatment response for predicting the 2-year OS were found to be 0.689, 76.5 and 76.6%, respectively. Compared with single
index Dmax, the predictive performance of the combination was decreased, the specificity was slightly improved, and the sensitivity was decreased (Fig. 6).

**Discussion**

The prognostic factors associated with diffuse large B-cell lymphoma (DLBCL) patients receiving R-CHOP chemotherapy have been the main research focus of both domestic as well as foreign scholars. It is crucial to identify the patients who are at high-risk of relapse and to select proper treatment strategies for them. The International Prognostic Index (IPI), Revised R-IPI and an Enhanced International Prognostic Index (NCCN-IPI) are currently the internationally recognized prognostic indicators (14,15), and are widely used in risk stratification before treatment, but their prognostic value is challenged to some extent in the rituximab treatment era.

The present study confirmed the correlation between IPI and 2-year progression-free survival (PFS) and overall survival (OS) in DLBCL patients receiving R-CHOP chemotherapy, while multivariate analysis showed that IPI is not an independent predictor. This is similar to the results obtained by Kwon et al (16). Clinical studies have also revealed that although IPI can accurately evaluate the prognosis in most of the patients with DLBCL, a part of patients with similar IPI score still have different rates of long-term survival (3,14). Therefore, individual characteristics and response to chemotherapy of each patient are regarded as the best indicators of prognosis.

Compared with IPI, baseline PET/CT parameters can assist in quantifying the invasion and burden of tumors of individuals, which may in turn be more advantageous in predicting the prognosis and guiding personalized treatment plans. Of all the baseline PET/CT parameters, Dmax was the only independent predictor of 2-year PFS and OS in this study. This result suggests that the tumor burden of the largest lesion acts as a more important prognostic factor than the gross tumor burden. This is similar to the result put forwarded by the previous clinical study by Parvez et al (17). This study further confirmed that patients with large masses usually have a poor prognosis. Compared with other PET/CT parameters such as MTV and TLG, Dmax can be easily obtained, and measurement of the largest lesion might be the simplest and most feasible method for predicting patient prognosis. In the present study, although MTV and TLG were not found to be independent predictors of 2-year PFS and OS, they were shown to be significantly associated with 2-year PFS and
OS. This further confirmed the prognostic value of baseline PET/CT quantitative parameters. Kim et al (18) found TLG to be a better prognostic indicator than IPI in DLBCL patients. A study conducted by Esfahani et al (19) demonstrated that TLG of the baseline PET/CT is the only independent risk factor for PFS. Parvez et al (17) studied 82 patients with invasive B-cell lymphoma and found that MTV with SUV=3 or 6 as the threshold showed an association with OS. Song et al (20) also suggest that MTV is a prognostic factor for DLBCL. Although it is not completely consistent with the results of our study, all the findings discussed above indicate that baseline PET/CT quantitative parameters are valuable for prognostic prediction and can assist clinicians in identifying patients who are at high risk for recurrence before treatment initiation. Yet, a few scholars have come to a negative conclusion (21). Gallicchio et al (22) demonstrated that SUVmax is the most influential factor of event-free survival (EFS) in DLBCL patients, while MTV and TLG are not related with EFS. Adams et al (23) studied 73 DLBCL patients and found that MTV and TLG were not associated with disease prognosis. The main reason for this inconsistency might include distribution bias of the enrolled patients, different methods and standards of threshold selection for measurement and calculation of MTV and TLG, different chemotherapy regimens and different predictive cut-off time of survival. In the present study, relative threshold method of 40% SUVmax was adopted as the threshold to measure MTV. For patients with higher SUVmax, the absolute value of the threshold remained relatively high, which may in turn lead to underestimation of the actual tumor burden. Currently, there is no clear consensus as to which threshold selection method is the most appropriate and there are few literature data available on this (24). In this study, Dmax was found to act as an independent predictor of 2-year PFS and OS, while MTV and TLG did not. We speculated that this might be due to necrosis in the large masses in some patients. In these patients, no uptake of 18F-FDG was observed in necrosis, and MTV and TLG might underestimate the true tumor burden. In addition, there was no significant correlation between SUVmax, SUVmean and PFS, OS in our study, which is consistent with the results obtained by Manohar et al (25). This indicates that the tumor metabolism level is not the key factor that affects prognosis. According to the results of this study, DLBCL patients with high Dmax, MTV and TLG, even if the IPI score was low and might have poor survival prospects, intensive treatment was considered to improve their prognosis.

Previous literature has reported that interim treatment response to first-line chemotherapy acts as an important prognostic factor in DLBCL patients. Patients with poor interim treatment response and positive interim PET are more likely to have recurrence and progression, and the prognosis generally remains worsened (26-29). Poor interim treatment response is an indication for early clinical intervention, including salvage treatment, intensive treatment or autologous stem cell transplantation (30). The present study showed that the risk of recurrence, progression and death within 2 years in the non-CR patients were significantly higher than that in CR patients, and interim treatment response acted as an independent predictor of 2-year PFS and OS. This result is similar to that obtained by previous studies. Huntington et al (31) also believed that patients with interim negative PET/CT or those who reached interim CR had longer PFS and OS. This result is similar to that obtained by previous studies. Huntington et al (31) also believed that patients with interim negative PET/CT or those who reached interim CR had longer PFS and OS. This result is similar to that obtained by previous studies.

Interim treatment response evaluation based on PET/CT is regarded as an important prognostic factor in DLBCL patients. The prognosis of patients who fail to respond to mid-term chemotherapy was found to remain poor, but there is no clear evidence that the prognostic value is better than IPI (33). In clinical practice, even patients with a good interim treatment response and interim negative PET may still have the potential to recur or progress to a later stage. Therefore, it is not sufficient to judge prognosis based solely on interim response to chemotherapy. In the present study, we combined the two risk factors, baseline PET/CT parameters and interim treatment response, in order to identify high-risk patients with
poor prognosis, aiming to provide valuable information for early intervention. At present, there are few scholars who have evaluated the prognosis of DLBCL patients with the combination of baseline PET/CT metabolic parameters and interim treatment response, and relevant reports are rare and the indicators adopted are different (12,13,34). Mikhaeel et al (12) demonstrated improvement in the prognostic value of interim PET and screened out the population with poor prognosis by combining the baseline MTV and interim PET results. Zhang et al combined baseline TLG >1036.61 g and ΔSUVmax <86.02% to predict the recurrence or progression, showing good screening ability (13). Recently, Islam et al (8) found that baseline and interim PET/CT parameters of MTV show important predictive value for PFS, and could be helpful for guiding further treatment strategies in DLBCL patients. In the present study, baseline PET/CT parameter Dmax was screened through univariate and multivariate analyses. Compared with single indicator Dmax, the combination of Dmax and interim treatment response showed improved predictive efficiency for 2-year PFS, but showed no improvement in the predictive efficiency of 2-year OS.

The limitations of this study mainly include four aspects. Firstly, the sample size of this study is relatively small and the results of this study require external verification in the future. Secondly, we directly selected the median PET/CT parameters as the cutoff value for classification of patients in this study. Thus, the correlation of other cutoff points of variables with survival need to be discussed. Thirdly, DLBCL subgroup analysis was not performed in this study. The survival outcomes of DLBCL patients in different molecular subtypes and gene expression warrant further investigation. Finally, the follow-up time of some cases was relatively short. Most of the positive events such as recurrence, progression or death occur within 2 years after diagnosis. Therefore, this study only conducted univariate and multivariate analysis of 2-year PFS and OS. In future, follow-up of these patients will be continued and 3- or 5-year survival analysis will be conducted to further explore the prognostic value of baseline PET/CT parameters.

In conclusion, baseline 18F-FDG PET/CT parameters and interim treatment response have important prognostic value in DLBCL patients receiving R-CHOP chemotherapy. Combined application of Dmax and interim treatment response assists in improving the predictive efficacy of 2-year PFS. It may be helpful to identify patients who are at high risk of relapse and to guide early clinical intervention for these patients.

Authors’ contributions
LZ and YM designed the study and drafted the manuscript. LG, HZ, YS and SL were responsible for the collection and analysis of the experimental data. AW, XZ, JS, JZ and KX revised the manuscript critically for important intellectual content evaluating literature data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Affiliated Hospital of Xuzhou Medical University (XYFY2016-KL002-01). Patient informed consent was waived due to the retrospective nature of the present study.

Patent consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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