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The role of 18F-FDG PET/CT-derived metabolic parameters in the early evaluation and prognostic assessment of diffuse large B-cell lymphoma

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► ***Original article***

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ABSTRACT

Background: To investigate the dynamic changes in 18F-FDG PET/CT (18F)-derived metabolic parameters throughout the entire chemotherapy process for diffuse large B-cell lymphoma (DLBCL), and to analyze their clinical value in early diagnosis, curative effect evaluation, and prognosis stratification. ***Materials and Methods:*** One hundred and sixty-five patients with suspected DLBCL admitted from April 2022 to May 2023 were included. 18F scans were performed before chemotherapy (baseline), after 3-4 courses of chemotherapy (interim), and 6-8 weeks following chemotherapy completion (post-therapy). SUVmax, SUVmean, and TLG were calculated by delineating the metabolic tumor volume (MTV). Therapeutic efficacy was evaluated using the Deauville 5-point scale. Patients were followed up for 2 years to record their survival outcomes. A combined diagnostic model was constructed using Logistic regression, with its predictive efficiency analyzed using ROC curves. ***Results:*** Baseline SUVmax, SUVmean, MTV, and TLG were higher in DLBCL patients than in non-DLBCL cases ($P<0.05$). The combined model demonstrated an AUC of 0.972, with 93.15% sensitivity and 89.13% specificity. The interim metabolic parameters were highly correlated with Deauville scores. Higher SUVmax, MTV, and TLG levels were observed in the poor-efficacy group than in the good-efficacy group ($P<0.05$). Besides, the death group exhibited SUVmax, MTV, and TLG elevations compared to the survival group ($P<0.05$). The area under the ROC curve for the combined detection in predicting the prognostic mortality of DLBCL patients was 0.942 ($P<0.001$). ***Conclusion:*** The temporal variations of metabolic parameters derived from 18F prove valuable for the early detection, therapeutic effect assessment, and prognostic prediction of DLBCL.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) stands as the predominant subtype of non-Hodgkin lymphoma (NHL), representing roughly 30–40% of all new NHL cases globally [1]. Despite significantly improved survival rates by the Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP) regimen in recent years, about 30%-40% of patients experience poor prognosis due to drug resistance or disease progression [2]. Early and accurate assessment of treatment efficacy and prognostic risk in DLBCL patients is crucial for optimizing treatment regimens, reducing treatment-emergent toxicities, and improving survival rates [3].

Currently, the prognosis assessment of DLBCL mainly relies on clinical staging systems (e.g., Ann Arbor staging) and the International Prognostic Index (IPI), but these indicators are difficult to dynamically reflect the changes in the tumor's biological behavior [4]. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT, 18F), as an imaging technique combining function and anatomy, has seen its maximum standardized uptake value (SUVmax) widely used to assess therapeutic responses in lymphoma [5]. SUVmax has been shown to be closely related to tumor metabolic activity, but the limitations of this single metric have become increasingly apparent [6]. Recent studies suggest that comprehensive metabolic parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) can reflect tumor load and heterogeneity more comprehensively, which is expected to improve the accuracy of prognosis evaluation [7]. However, most of the existing literature focuses on the static assessment of SUVmax, with insufficient longitudinal exploration of the dynamic changes in metabolic parameters during the treatment process. Moreover, there are still gaps in the multi-parameter joint analysis and long-term follow-up data for DLBCL [8].

This study's novelty lies in three aspects: first, it dynamically tracks four core metabolic parameters (SUVmax, SUVmean, MTV, TLG) throughout the entire chemotherapy process (baseline, interim, post-therapy), filling the gap of insufficient longitudinal exploration in existing studies; second, it constructs a multi-parameter combined model instead of relying

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on single metrics, improving the accuracy of diagnosis and prognosis stratification; third, it combines 2-year long-term follow-up data to verify the persistent predictive value of metabolic parameters, providing more reliable evidence for clinical translation.

MATERIALS AND METHODS

Research sample size estimation

The participants of this prospective cohort study were patients with suspected DLBCL admitted between April 2022 and May 2023. The target sample size was estimated based on overall survival (OS). The 3-year OS of patients was assumed to be 70%, with a pre-detected intergroup difference of hazard ratio (HR)=2, α=0.05, and 1-β=80%, considering a 15% dropout rate. Sample size estimation was performed using PASS 15 software (NCSS LLC, USA), a total of 165 subjects were finally included. Ethical approval was obtained from Affiliated Hospital of Hebei University's ethics committee (No. 2022-11-55).

Inclusion and exclusion criteria

To be included, patients were required to meet all the following criteria: in line with the clinical manifestations of DLBCL [9]; aged 18-80 years; undergoing 18F after admission; without other malignant tumors; demonstrating basically normal heart, liver, and kidney functions. Fulfilling any of the exclusion criteria below indicated ineligibility: pregnant or lactating status; active infection or serious complications; contraindications to PET/CT examination; previous radiotherapy or targeted therapy before enrollment; failure to complete 3 courses of chemotherapy or loss to follow-up.

Imaging inspection

All patients underwent 18F examinations upon admission (defined as baseline/early chemotherapy stage), with the contrast medium (18F-FDG) purchased from China Isotope & Radiation Corporation (China). For patients pathologically confirmed with DLBCL, the identical examination was repeated within 1 week after 3-4 chemotherapy cycles (interim stage) and 6–8 weeks after full chemotherapy completion (post-therapy stage) to assess tumor recurrence.

Pre-examination preparations included: ≥6 hours of fasting, pre-scan blood glucose measurement, and pre-adjustment of hypoglycemic medications for diabetic patients to maintain blood glucose ≤11.1 mmol/L. Radiopharmaceutical dosage was calculated by body weight (3.7 MBq/kg, conventional adult dosage: 200-300 MBq) and slowly injected via the cubital vein, with 5 minutes of pressure applied to the puncture site to prevent leakage.

Scans were performed using a GE Discovery MI PET/CT integrated machine (GE Healthcare, USA), covering the range from skull vertex to mid-thigh, with targeted scanning added for identified lesions. CT parameters: 120 kV tube voltage, 0.984:1 pitch, 3.75 mm slice thickness, 3.27 mm reconstruction interval. PET parameters: 2.5–3.5 mm/s scanning speed, 25 cm axial field of view. PET/CT images were rigidly registered via Syngo.via software (Siemens Healthineers, Germany) to ensure anatomical-functional spatial consistency.

Two nuclear medicine physicians independently delineated regions of interest (ROIs) with long diameter ≥1 cm, extracting lesion SUVmax (maximum standardized uptake value) and ROI SUVmean (mean standardized uptake value). Metabolic tumor volume (MTV) was automatically segmented using a ≥41% SUVmax threshold, and total lesion glycolysis (TLG) was calculated as TLG = MTV × SUVmean (unit: g).

Prognostic follow-up

All enrolled patients completed a 2-year prospective prognostic follow-up, conducted via monthly regular re-examinations. Follow-up assessments included clinical symptom inquiry, physical examination, and necessary auxiliary examinations (e.g., routine blood tests, lactate dehydrogenase detection, and targeted 18F scans for suspected recurrence) to comprehensively monitor disease progression and survival status. Follow-up data were recorded in a dedicated electronic data collection system (EDC) and cross-validated by two researchers to ensure accuracy.

Endpoints

Changes in metabolic 18F-derived parameters during chemotherapy were analyzed. Subsequently, according to the baseline, interim, and post-therapy parameter results, the diagnostic performance of DLBCL, and the evaluation effect on clinical efficacy and prognosis mortality were explored. Clinical efficacy was evaluated according to the Deauville 5-point scale [10] after the completion of chemotherapy. Scores of 1-3 and 4-5 represent ‘good efficacy' and ‘poor efficacy’, respectively.

Quality control

The injection dose (3.7 MBq/kg), scanning range (vertex to the mid-thigh) and acquisition time (60min) were all strictly standardized. An electronic data collection system (EDC) was established, and the data was independently entered and cross-checked by two different personnel.

Statistical analysis

The data were analyzed and processed using SPSS 30.0 software (IBM Corporation, USA). The comparison of counting and measurement data was conducted using the chi-square test and the independent sample t-test, respectively. The joint detection model was established by Logistic

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regression modeling, and the diagnostic effect was analyzed by ROC curve analysis. Statistical significance was declared if the P-value was < 0.05.

RESULTS

Inspection results

Pathological examination confirmed DLBCL (Ann Arbor stage: II-IV) in 73 cases. All of them received standard R-CHOP chemotherapy: Rituximab (Roche Group, Switzerland) + Cyclophosphamide (Jiangsu Hengrui Medicine Co., Ltd., China) + Doxorubicin (Pfizer Inc., China) Us) + Vincristine (Qilu Pharmaceutical Co., Ltd., China) + Prednisone (Merck & Co., Inc., USA). Figures 1 and 2 show the changes in neck and liver lesions before and after chemotherapy in a patient (a 47-year-old woman). After chemotherapy, it can be seen that the lesion size of the patient is significantly reduced.

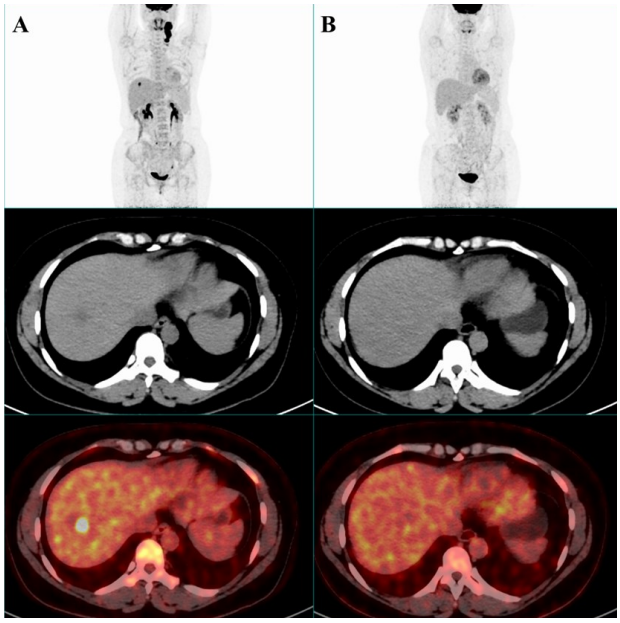

Figure 1. Changes in cervical lesions before and after chemotherapy in a given patient. After treatment, the patient's cervical lymph nodes were significantly reduced and partially disappeared. **(A)** before treatment. **(B)** after treatment.

Dynamic changes in 18F-derived metabolic parameters in DLBCL patients during chemotherapy

In the process of chemotherapy, SUVmax, SUVmean, MTV, and TLG in patients with DLBCL showed a gradual decrease, with their levels reaching the lowest levels post-therapy (figure 3).

Diagnostic performance of baseline 18F-derived metabolic parameters for DLBCL

Compared with non-DLBCL patients, DLBCL patients showed increased SUVmax, SUVmean, MTV, and TLG (P<0.05). Through Logistic regression analysis, a combined detection model of 18F-derived metabolic parameters was established: -26.006 +0.386×SUVmax+0.333×SUVmean+0.018×MTV+0.003×TLG. ROC curve analysis showed that this model had a diagnostic sensitivity of 93.15% and specificity of 89.13% for DLBCL (P<0.001), with an AUC of 0.972 (95%CI=0.953-0.992), indicating good reference value (figure 4).

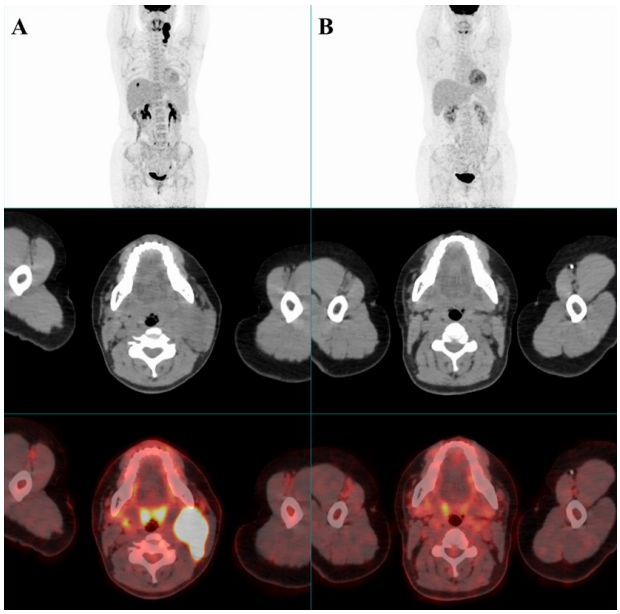

Figure 2. Changes in liver lesions before and after chemotherapy in a given patient. After treatment, the patient's liver lesions disappeared. **(A)** before treatment. **(B)** after treatment.

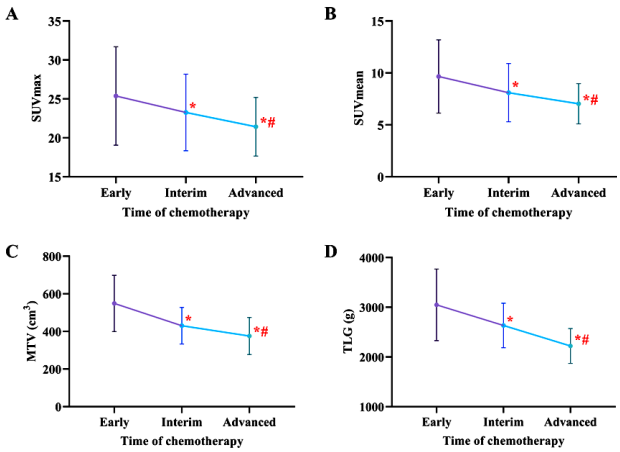

Figure 3. Changes in 18F parameters during chemotherapy in DLBCL patients. **(A)** changes in SUVmax. **(B)** changes in SUVmean. **(C)** changes in MTV. **(D)** changes in TLG * indicates P<0.05 compared with early chemotherapy, and # indicates P<0.05 compared with middle chemotherapy.

Evaluation of clinical efficacy using interim 18F-derived metabolic parameters

According to the Deauville 5-point survey results, 45 DLBCL patients showed good efficacy and 28 showed poor efficacy. Compared with patients with good efficacy, those with poor efficacy exhibited higher SUVmax, SUVmean, MTV, and TLG during mid-chemotherapy (P<0.05). The combined formula was -20.159+0.355×SUVmax+0.467×SUVmean+0.007×MTV+0.002×TLG. ROC analysis indicated that 18F had

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excellent predictive value for clinical efficacy, sensitivity was 89.29%, specificity was 77.78%, AUC=0.903, 95%CI=0.835-0.972 (P<0.001) (figure 5).

Evaluation of the prognostic effect of post-therapy 18F-derived metabolic parameters

Prognostic follow-up successfully tracked all patients, with a total of 19 deaths. Higher SUVmax, SUVmean, MTV, and TLG levels were determined in deceased patients versus survivors post-therapy (P<0.05). The combined formula was -30.447+0.408×SUVmax+0.674×SUVmean+0.011×MTV+0.005×TLG. ROC indicated the excellent predictive performance of 18F for adverse prognosis, sensitivity and specificity were 78.95% and 94.44%, respectively, AUC=0.942, 95%CI=0.886-0.997 (P<0.001) (figure 6).

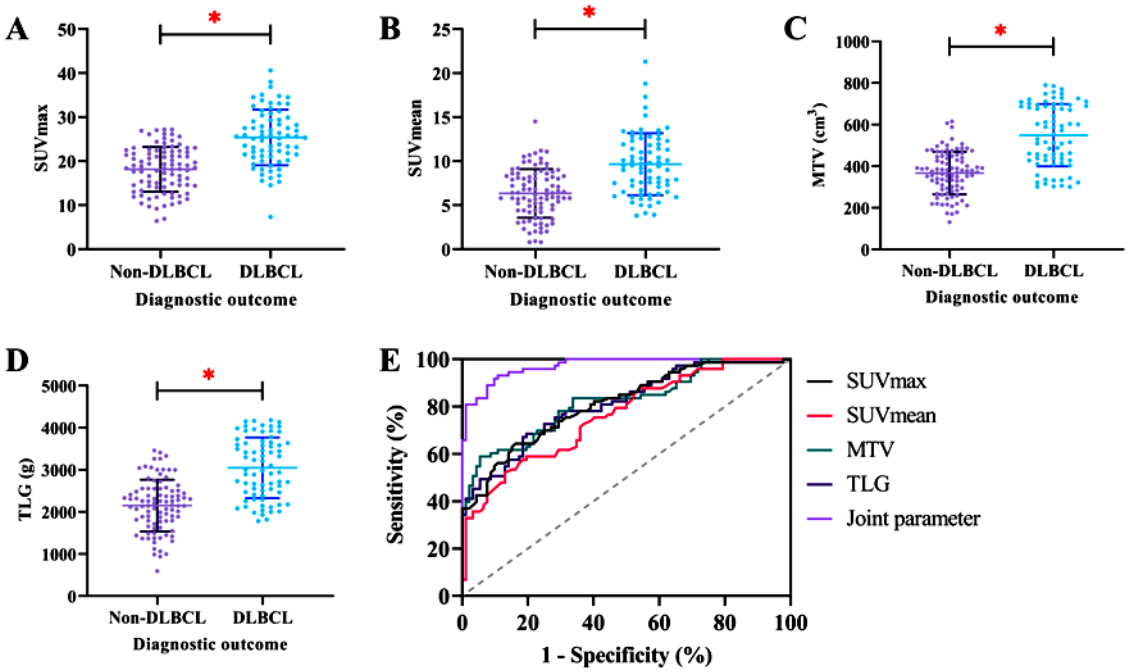

Figure 4. Diagnostic performance of baseline 18F-derived metabolic parameters for DLBCL. **(A)** comparison of SUVmean. **(B)** comparison of MTV. **(C)** comparison of SUVmax. **(D)** comparison of TLG. **(E)** ROC curve of 18F-derived metabolic parameters for diagnosing DLBCL. *P<0.05.

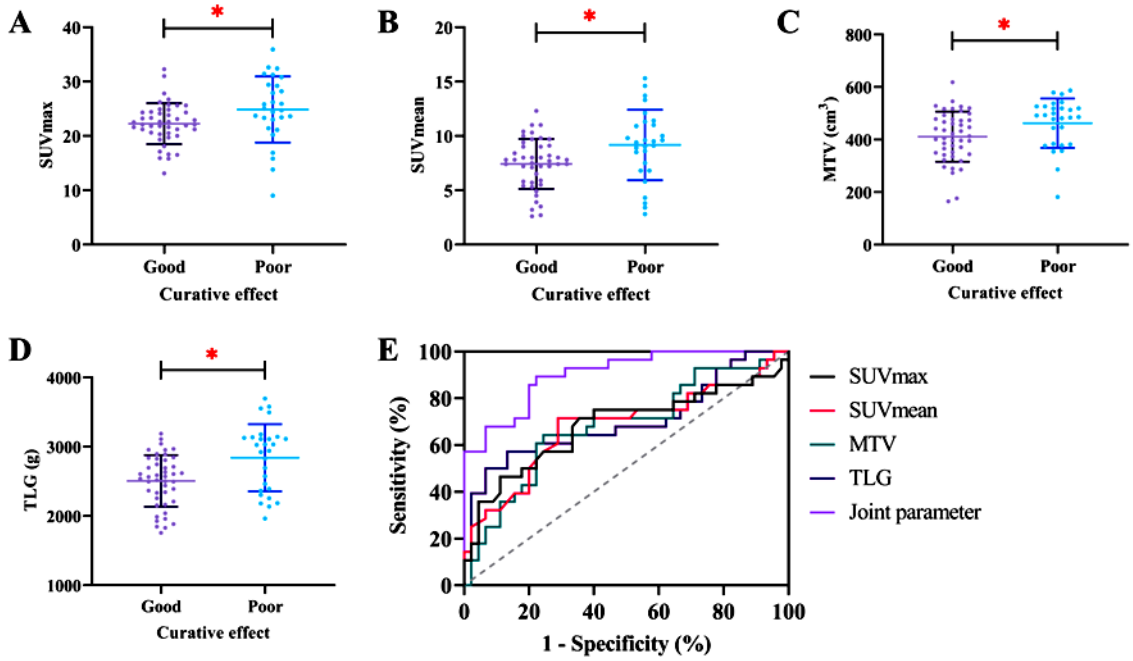

Figure 5. Evaluation of clinical efficacy using interim 18F-derived metabolic parameters. **(A)** comparison of SUVmean. **(B)** comparison of MTV. **(C)** comparison of SUVmax. **(D)** comparison of TLG. **(E)** ROC curve of 18F-derived metabolic parameters for evaluating clinical efficacy. *P<0.05.

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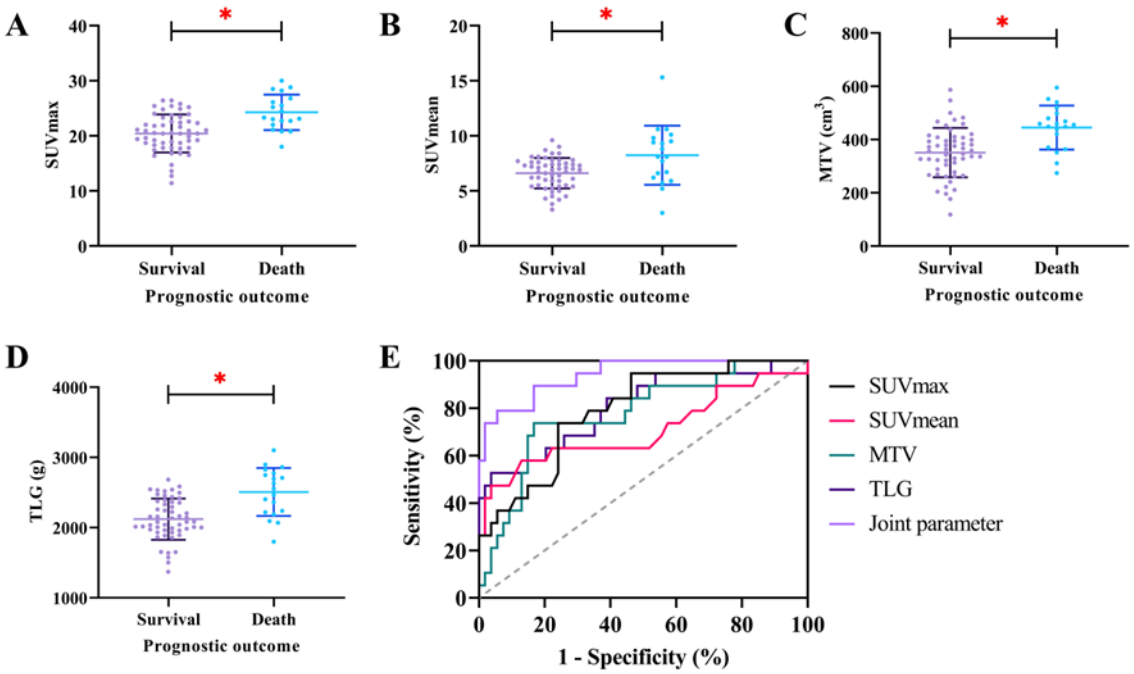

Figure 6. Evaluation of the prognostic effect of post-therapy 18F-derived metabolic parameters. **(A)** comparison of SUVmean. **(B)** comparison of MTV. **(C)** comparison of SUVmax. **(D)** comparison of TLG. **(E)** ROC curve of 18F-derived metabolic parameters for predicting prognostic death. *P<0.05.

DISCUSSION

As the most common subtype of NHL, DLBCL exhibits significant heterogeneity, which leads to notable differences in patient prognosis [11]. PET/CT, a functional imaging technique, quantifies tumor activity through 18F-FDG metabolic parameters (SUVmax, SUVmean, MTV, and TLG), providing a new perspective for the precise assessment of treatment efficacy and prognosis [12]. In this study, through a prospective cohort design, we integrated the changes in metabolic parameters throughout the entire chemotherapy process for the first time, aiming to reveal their value in the early diagnosis, treatment efficacy prediction, and prognosis stratification of DLBCL and to provide evidence-based support for the development of individualized treatment strategies.

This study demonstrated that at baseline, the SUVmax, SUVmean, MTV, and TLG of DLBCL patients were higher than those of non-DLBCL counterparts. The AUC of the combined model reached 0.903, with a sensitivity of 93.15% and a specificity of 89.13%. This result is consistent with previous studies, confirming that the multi-parameter combined model can enhance diagnostic accuracy. For example, Dondolin *et al*. found that SUVmax was associated with the high metabolic activity of DLBCL [13], and Zhao *et al*. indicated that an MTV >500 cm^3 suggested a high-risk status [14]. As the product of SUVmean and MTV, TLG combines the dual characteristics of tumor burden and metabolic activity [15]. Therefore, the combined diagnostic model established based on the above metabolic parameters shows a trend of outperforming single parameters, suggesting its potential clinical application value.

Additionally, the changes in metabolic parameters during mid-chemotherapy are of great value for predicting therapeutic efficacy. The longitudinal study by Xie W et al. confirmed that a decrease in interim MTV indicated an increased probability of complete remission (CR) [16], aligning with our findings that a decrease in interim MTV corresponded to good efficacy.

Finally, the post-therapy SUVmax, SUVmean, MTV, and TLG in deceased patients were higher than those in the survival group. ROC analysis indicated that the combined detection also had a good predictive effect on patient outcomes. This was consistent with the conclusion of Wen *et al*., that is, an increase in TLG indicated a heightened risk [17]. The results of this study further supported that the dynamic changes in metabolic parameters of 18F could be used as real-time indicators for monitoring therapeutic efficacy.

Compared with traditional imaging, the advantages of 18F are as follows: (1) It quantifies tumor activity through metabolic parameters, compensating for the lag in morphological assessment; (2) It can identify the risk of treatment failure in the middle stage of chemotherapy, avoiding ineffective treatment; (3) With the synergy of multiple parameters, it improves the specificity of early diagnosis of DLBCL. However, its drawbacks can also not be ignored. For example, regarding the issue of radiation exposure, the effective dose of whole-body PET/CT is approximately 8-12 mSv, which may limit repeated examinations for high-risk patients. Moreover, the cost of a single PET/CT examination is relatively high, resulting in a low penetration rate in primary medical institutions. Additionally, differences in SUV calibration among

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different devices may lead to result bias. These issues remain the main limitations affecting the clinical promotion of 18F.

Of course, there are still many limitations in this study. Although the sample size reached 165 cases, it was limited to a single center. The consistency of region and equipment may affect the generalizability of the results. Second, the follow-up time was only 2 years, and long-term survival data (such as 5-year OS) were not fully mature. Third, the influence of biochemical indicators such as pre-treatment lactate dehydrogenase (LDH) levels and β2-microglobulin was not corrected, making it impossible to completely eliminate the impact of confounding factors. Fourth, the study did not consider DLBCL molecular subtypes (e.g., germinal center B-cell-like vs. activated B-cell-like), which may affect the association between metabolic parameters and prognosis. Fifth, the SUV threshold for MTV segmentation lacks unified standards, which may lead to result bias among different centers. Sixth, the sample included mostly Ann Arbor stage II-IV patients, with insufficient representation of early-stage cases, limiting the generalizability to all DLBCL populations. In subsequent studies, we need to conduct more in-depth and comprehensive research and analysis to address these limitations as soon as possible.

CONCLUSION

18F-derived metabolic parameters (SUVmax, SUVmean, MTV, TLG) exhibit dynamic decreases during DLBCL chemotherapy. Their combined model effectively enhances early diagnosis, efficacy evaluation, and prognostic stratification. Multicentre, large-sample studies are needed to validate cross-platform consistency and associations with molecular subtypes, promoting precise DLBCL management.

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***Ethical consideration*:** The study was conducted in compliance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Affiliated Hospital of Hebei University (No. 2022-11-55). Written informed consent was obtained from all participants.

***Conflicts of interest*:** The authors report no conflict of interest.

***Availability of data and materials*:**The data that support the findings of this study are available from the corresponding author upon reasonable request.

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***Author contributions*:** N.F., designed the study,X.D. wrote the and revised manuscript; WY.G. and SH.L., collected and analyzed data, All authors read and approved the final submitted manuscript.

***AI Usage Statement*:** None of the authors used artificial intelligence tools for manuscript preparation, data analysis, or image processing.

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