Original Article

Predictive value of clinical characteristics and baseline ^{18}F-FDG PET/CT quantization parameters in primary adrenal diffuse large B-cell lymphoma: a preliminary study

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Background: Primary adrenal diffuse large B-cell lymphoma (PA-DLBCL) is a rare occurrence, has a very poor prognosis, and is marked by a high risk of relapse. Accurate prediction of patient prognosis before treatment initiation, along with timely adjustment of the treatment plan, holds paramount importance. 2-Deoxy-2-[fluorine-18]-fluoro-D-glucose (^{18}F-FDG) positron emission tomography combined with computed tomography (PET/CT) imaging techniques are conventionally performed prior to treatment initiation in DLBCL patients, offering indispensable functional and metabolic insights into lymphoma lesions.

Methods: We conducted a retrospective case-control study using data collected from January 2014 to December 2022, including 24 patients diagnosed with PA-DLBCL. Clinical information of patients was collected based on inpatient medical records, including age, gender, B symptoms, adrenocorticotropic hormone (ATCH), lactate dehydrogenase (LDH), β_2-microglobulin, albumin (Alb), ferritin (Fe), blood calcium, Eastern Cooperative Oncology Group performance status (ECOG-PS), International Prognostic Index, Ann Arbor staging, number of involved organs, and Hans' algorithm. Prior to treatment, all patients underwent baseline ^{18}F-FDG PET/CT, and the metabolic parameters of the tumor were calculated using a threshold of 41% of maximum standardized uptake value (SUVmax), including metabolic tumor volume (MTV) and total lesion glycolysis (TLG). Prognostic analysis of overall survival (OS) was performed using Kaplan-Meier survival analysis, as well as univariate and multifactor Cox proportional hazards regression models.

Results: The 24 enrolled patients comprised 16 men and 8 women (median age 65 years, range 51–90 years). The median follow-up period was 17.5 months (range, 1–107 months). In univariate analysis, Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, regions of lymph node involvement, treatment, chemotherapy cycles, SUVmax, MTV, and TLG showed association with OS ($P<0.1$). In multivariate analysis, Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, and treatment were shown to be independent prognostic factors for OS. We found that SUVmax, MTV, and TLG correlated with Ann Arbor staging ($P<0.05$), mean standardized uptake value (SUVmean) and TLG

correlated with the number of involved organs (P<0.05).

Conclusions: PA-DLBCL is characterized by a low incidence and a poor prognosis. Baseline ^{18}F-FDG PET/CT quantization parameters showed correlations with Ann Arbor staging and number of involved organs. Increasing the sample size or prolonging the follow-up period may reveal the predictive value of PET/CT quantization parameters.

Keywords: Adrenal; diffuse large B-cell lymphoma (DLBCL); ^{18}F-fluorodeoxyglucose (^{18}F-FDG); positron emission tomography/computed tomography (PET/CT); prognosis

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Introduction

Diffuse large B-cell lymphoma (DLBCL), constituting around 30% of all newly diagnosed non-Hodgkin lymphomas (NHL), is the predominant subtype of aggressive NHL in adults, with an estimated annual incidence of 150,000 cases worldwide (1,2). DLBCL can manifest in various extra-nodal sites, including the gastrointestinal tract, skin, soft tissues, bone, genitourinary tract, and others. Among these, primary adrenal diffuse large B-cell lymphoma (PA-DLBCL) is a rare occurrence, comprising 3% of extra-nodal DLBCL cases (3,4). Until now, no more than 200 cases have been reported in the literature (5-7). PA-DLBCL was reported to frequently have clinicopathologic features, including elevated lactate dehydrogenase (LDH) levels, the presence of B symptoms, a non-germinal center B-cell-like (non-GCB) subtype, and Bcl-6 gene rearrangement (8). The prognosis of PA-DLBCL is notably poor, with a high risk of relapse, as evidenced by a 2-year overall survival (OS) rate of only 68.3% following the first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone regimen (R-CHOP) (3,9,10). Consequently, accurate prediction of patient prognosis prior to treatment initiation and timely adjustment of the treatment plan are of paramount importance. However, the identification of high-risk patients using existing prognostic scoring systems, such as the International Prognostic Index (IPI), is currently limited and hindered by a lack of comprehensive biological and imaging data (11-13).

Positron emission tomography/computed tomography (PET/CT) imaging techniques are typically performed before treatment initiation in patients with DLBCL, providing indispensable functional and metabolic information regarding lymphoma lesions. This imaging method serves multiple purposes, including staging, restaging, evaluating disease aggressiveness, and monitoring treatment response, and has been incorporated into the revised International Workshop Criteria (IWG) (1,14-25). PET/CT is included in the staging of lymphomas due to its higher sensitivity compared to CT, enabling a more accurate assessment of treatment response against a baseline (21). Exploring quantitative imaging parameters as potential prognosticators for assessing disease burden and response is crucial. The standardization of PET/CT application is mandatory for quantitative analysis and highly desirable for optimal clinical practice (26). Quantitative parameters derived from ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET, including maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), have demonstrated predictive value for assessing outcomes in patients with DLBCL (27-29). However, the prognostic utility of ^{18}F-FDG PET/CT in PA-DLBCL remains unstudied.

Therefore, in this retrospective study, we reviewed the medical records of PA-DLBCL patients from two institutions, aiming to assess the potential value of ^{18}F-FDG PET/CT and related factors in predicting prognosis. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-803/rc).

Methods

Patients

We retrospectively collected data from 594 patients diagnosed with DLBCL through pathological histological examination at Peking University First Hospital and the First Affiliated Hospital of Zhengzhou University. The

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Peking University First Hospital and the First Affiliated Hospital of Zhengzhou University, and the requirement for individual consent for this retrospective analysis was waived. The data was collected from January 2014 to December 2022. As there is no unified guideline standard for PA-DLBCL, we developed inclusion criteria by combining the criteria adopted by most studies with the actual situation of the hospitals (5,30,31). The inclusion criteria were as follows: (I) pathological diagnosis of unilateral or bilateral PA-DLBCL (n=62); (II) no previous history of lymphoma at other sites (n=53); (III) if lymph node or organ involvement at other sites was present, lesions at the adrenal site were considered the main lesions (n=47); (IV) no abnormal blood cells were observed in routine blood or bone marrow examinations (n=45); (V) patients had complete clinical information (n=45); (VI) all patients underwent ^{18}F-FDG PET/CT examination (n=40). The exclusion criteria were as follows: (I) patients who had received treatment (including chemotherapy, radiation therapy, surgery, etc.) before the PET examination (n=4); (II) patients with concomitant other malignant tumors (n=2); (III) patients lost to follow-up (n=4); and (IV) involvement of kidney or peripheral lymph nodes that were difficult to measure with ^{18}F-FDG PET/CT parameters (n=6).

Clinical information of patients was collected based on inpatient medical records, including age, gender, B symptoms, adrenocorticotropic hormone (ATCH), LDH, β_2-microglobulin, albumin (Alb), ferritin (Fe), blood calcium, Eastern Cooperative Oncology Group performance status (ECOG PS), IPI (11), Ann Arbor staging (32), number of involved organs, and Hans' algorithm (33).

FDG PET/CT acquisition

Patients were instructed to abstain from smoking, alcohol, coffee, and tea for 24 hours before the examination and to avoid strenuous exercise. They were also required to fast for at least 6 hours prior to the examination in order to maintain their blood glucose below 11.1 mmol/L. The ^{18}F-FDG PET/CT scan [utilizing Philips GXL-16 PET/CT (Philips Healthcare, Chicago, IL, USA) and Siemens Biograph Truepoint 64 PET/CT (Siemens, Erlangen, Germany) machines] was performed 60–80 minutes after intravenous administration of ^{18}F-FDG (3.70–5.18 MBq/kg, radiochemical purity >95%). Additionally, patients were instructed to consume 500–1,000 mL of water and empty their bladders after 60 minutes of quiet rest. Routine scans were conducted from the head to mid-thigh, with separate acquisitions of the head and torso. Spiral CT scans were initially performed using a tube voltage of 120 kV and a tube current of 100 mA, followed by reconstruction using a soft tissue algorithm with a layer thickness of 5 mm. PET scans were generally acquired in 7–10 beds, with each bed lasting 1.5–2.5 minutes. The PET images were attenuation-corrected using CT data and reconstructed through an iterative method for image reconstruction.

PET/CT image analysis

Transverse, sagittal, and coronal FDG PET/CT images were reviewed. Consensus on the presence of abnormal lesions was reached between two nuclear medicine physicians with 4 and 8 years of experience, respectively. The workstation automatically delineated the region of interest (ROI) for each patient's adrenal lesion, utilizing a threshold of 41% SUVmax (34,35). Manual adjustments were made to exclude physiological uptake from adjacent tissues at each level, and the software automatically calculated CT attenuation value, SUVmax, SUVmean, MTV, and TLG for the lesion.

Follow-up

Follow-up visits are conducted utilizing a combination of telephone communication and inpatient medical records, with a frequency of once every 3 months during the follow-up period. The follow-up deadline was January 2023. OS was defined as the time of diagnosis to death or follow-up cut-off time of the patient.

Statistical analysis

Statistical analysis was performed using IBM SPSS 24.0 software (IBM Corp., Armonk, NY, USA). The Mann-Whitney *U* test, independent samples *t*-test, and chi-square test were used for univariate analyses under the appropriate circumstances. Quantitative data following a normal distribution were expressed as $\bar{x}\pm s$, whereas quantitative data with a non-normal distribution were expressed as M (Q1, Q3). Prognostic analysis of OS was conducted utilizing Kaplan-Meier survival analysis, as well as univariate and multifactor Cox proportional risk regression models. A statistically significant difference was defined as $P<0.1$ in the

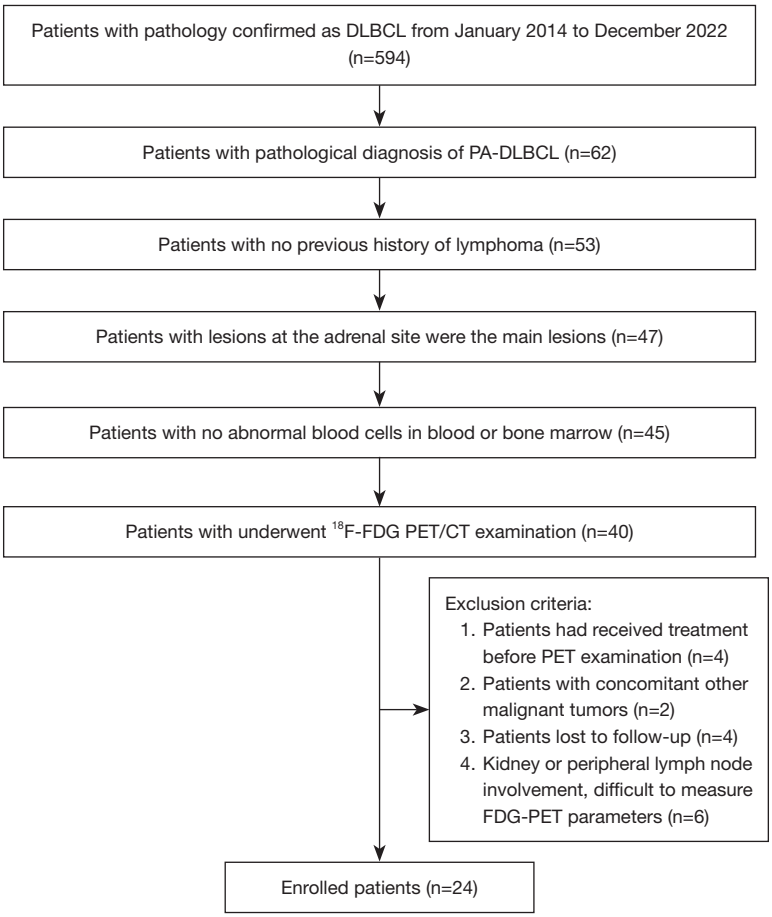

Figure 1 Flow chart of the patient recruitment with inclusion and exclusion criteria. DLBCL, diffuse large B-cell lymphoma; PA-DLBCL, primary adrenal diffuse large B-cell lymphoma; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography.

one-way analysis of factors and P<0.05 in the multifactorial analysis.

Results

Patient characteristics

The 24 enrolled patients comprised 16 men and 8 women (median age 65 years, range, 51–90 years) (*Figure 1*). Among them, lymph node involvement was observed in 18 patients, skeletal involvement in 14 patients, renal involvement in 5 patients, and central nervous system (CNS) involvement as well as intestinal involvement in 4 patients each. Additionally, there were three patients each with spleen involvement and lung involvement, and two patients each with cardiac involvement and reproductive involvement. There was one patient with pleural and pancreatic involvement (*Figure 2*). A total of 18 patients received 4–8 cycles of R-CHOP or a standard CHOP regimen as first-line treatment, high-dose methotrexate-based regimen during chemotherapy in 3 patients with CNS involvement, whereas 1 patient with CNS involvement achieved remission after undergoing six cycles of chemotherapy followed by hematopoietic stem cell transplantation (HSCT). There were six patients who did not receive any treatment. Glucocorticoids were administered to patients with adrenocortical insufficiency before chemotherapy regimen. The median follow-up period was 17.5 months (range, 1–107 months). At the cut-off of follow-up, 16 cases had died. Among them, 15 patients died from disease progression, and 1 patient died due to a lung infection 1 year after autologous HSCT. The clinical data and baseline PET/CT parameters are summarized in *Table 1*.

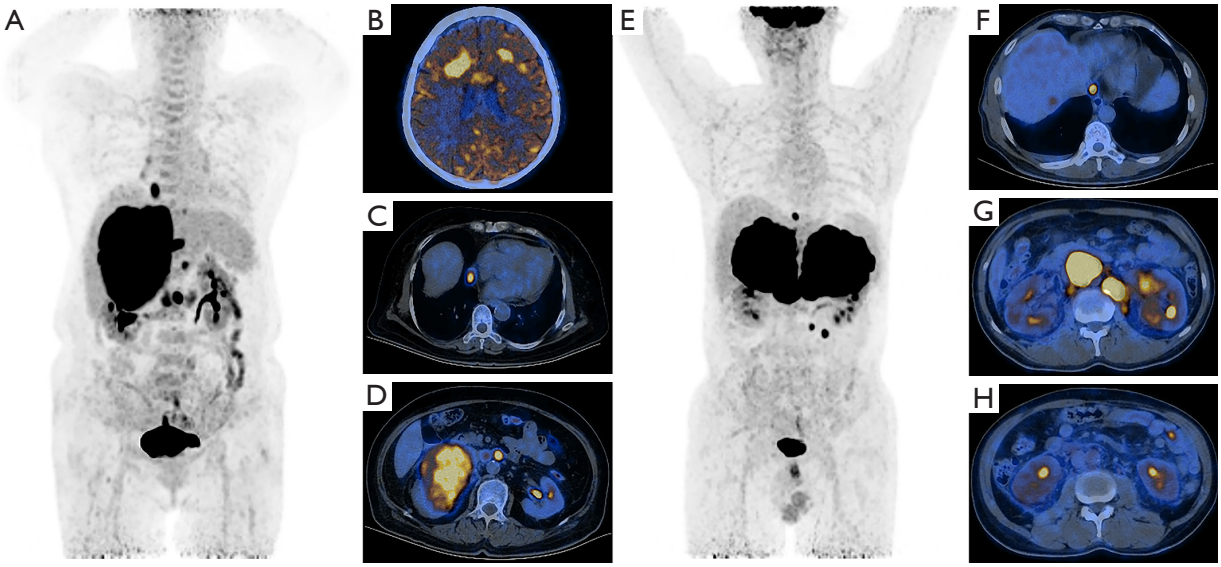

Figure 2 ^{18}F-FDG PET/CT image of primary adrenal diffuse large B-cell lymphoma. (A-D) A 72-year-old woman, who has achieved good survival following 6 cycles of R-CHOP treatment, has currently survived for 9 months. (A) In the patient's MIP image, the SUVmax, MTV, and TLG values for the right adrenal lesion were 38.6, 556.75, and 6,452.76, respectively. (B-D) Fusion images revealed involvement of the patient's right basal ganglia area and left thalamus, lymph nodes in the cardio-diaphragmatic horn region, and retroperitoneal lymph nodes. (E-H) A 75-year-old man, who has achieved good survival after 8 cycles of R-CHOP treatment, has currently survived for 15 months. (E) In the patient's MIP image, the SUVmax, MTV, and TLG of the bilateral adrenal lesion were 32.8, 643.96, and 10,264.89, respectively. (F-H) Fusion images displayed involvement of the patient's paraesophageal lymph nodes, retroperitoneal lymph nodes, and group 2 small bowel. ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; R-CHOP, first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone regimen; MIP, maximum intensity projection; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

Univariate analysis

Of all the clinical indicators and baseline PET/CT parameters, Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, regions of lymph node involvement, treatment, chemotherapy cycles, SUVmax, MTV, and TLG showed association with OS (P<0.1) (*Table 2*, *Figure 3*).

Multivariate analysis

The statistically significant indicators in univariate analysis were included in the multivariate analysis. We established two Cox survival analysis models, each focusing on distinct clinical characteristics: the entire treatment process and the pre-treatment phase. The survival analysis model based on pre-treatment clinical characteristics primarily examines the impact of tumor characteristics on survival analysis, while not accounting for the influence of treatment on survival outcomes. Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, and treatment were shown to be independent prognostic factors for OS in the survival analysis model based on pre-treatment clinical characteristics (P<0.05). Ann Arbor stage, ATCH, and number of involved organs were shown to be independent prognostic factors for OS in the survival analysis model based on entire treatment process (P<0.05) (*Table 3*).

Correlation study analysis

Quantitative PET parameters were correlated with clinical characteristics that were statistically significant in multivariate analysis. We found that SUVmax, MTV, and TLG correlated with Ann Arbor staging (P<0.05). SUVmean and TLG correlated with the number of involved organs (P<0.05) (*Table 4*, *Figure 4*).

Discussion

Identification of the poor prognostic group could be helpful

Table 1 Characteristics and baseline PET/CT parameters of the 24 enrolled patients

Characteristics	Values
Age (years)	
>60	18 (75.00)
≤60	6 (25.00)
Sex	
Male	16 (66.67)
Female	8 (33.33)
Clinical symptoms	
Asymptomatic	3 (12.50)
B symptom	14 (58.33)
Abdominal pain	7 (29.17)
Ann Arbor staging	
III/IV	18 (75.00)
I/II	6 (25.00)
ECOG PS	
2/3/4	8 (33.33)
0/1	16 (66.67)
IPI	
2/3/4	13 (54.17)
0/1	11 (45.83)
β_2-microglobulin	
Elevated	11 (45.83)
Normal	13 (54.17)
ATCH	
Abnormal	14 (58.33)
Normal	10 (41.67)
LDH	
Elevated	14 (58.33)
Normal	10 (41.67)
Albumin	
Low	14 (58.33)
Normal	10 (41.67)
Ferritin	
Elevated	15 (62.50)
Normal	9 (37.50)
Blood calcium	
Reduced	7 (29.17)
Normal	17 (70.83)
Pathologic type	
GCB	8 (33.33)
Non-GCB	16 (66.67)
Ki-67	
>75%	17 (70.83)
≤75%	7 (29.17)
Treatment	
No	6 (25.00)
Yes	18 (75.00)
Chemotherapy time (cycles)	
>6	12 (50.00)
≤6	12 (50.00)
Number of involved organs	
>2	8 (33.33)
≤2	16 (66.67)
Regions of lymph node involvement	
>2	13 (54.17)
≤2	11 (45.83)
SUVmax	26.94±7.37
SUVmean	14.86±4.31
MTV, cm^3	165.71 [54.73, 347.26]
TLG, g	3,324.26 [773.46, 5,658.58]
Maximum diameter, cm	8.02±3.20
CT attenuation value (HU)	33.74±6.29

Data are presented as mean ± standard deviation/median [interquartile range]/n (%) as appropriate. ACTH: normal range is 7.2–63.3 pg/mL; β2-microglobulin: normal range is 0.8–2.4 mg/L; albumin: normal range is 35–51 g/L; ferritin: normal range is 15–200 μg/L; LDH: normal range is 100–240 IU/L. PET/CT, positron emission tomography/computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; ATCH, adrenocorticotropic hormone; LDH, lactate dehydrogenase; GCB, germinal center B-cell-like; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HU, Hounsfield units.

Table 2 Univariate analyses of the clinical characteristics and baseline PET/CT parameters for OS

Variables	β	HR (95% CI)	P value
Age (>60 *vs.* ≤60 years)	0.46	1.58 (0.44–5.62)	0.481
Sex (female *vs.* male)	0.74	2.10 (0.74–5.98)	0.163
Clinical symptoms (asymptomatic)	–	–	0.718
B symptom	–0.020	0.98 (0.21–4.64)	0.979
Abdominal pain	0.432	1.54 (0.30–7.98)	0.607
Ann Arbor staging (III/IV *vs.* I/II)	2.02	7.52 (0.98–57.38)	0.021*
ECOG PS (2/3/4 *vs.* 0/1)	0.51	1.66 (0.59–4.65)	0.333
IPI (2/3/4 *vs.* 0/1)	0.84	2.32 (0.79–6.84)	0.127
β_2-microglobulin (high *vs.* normal)	1.22	3.28 (1.14–10.01)	0.020*
ATCH (abnormal *vs.* normal)	1.11	3.03 (0.96–9.59)	0.046*
LDH (high *vs.* normal)	0.51	1.67 (0.59–4.74)	0.335
Albumin (low *vs.* normal)	0.67	1.96 (0.59–4.74)	0.221
Ferritin (high *vs.* normal)	0.13	1.14 (0.40–3.21)	0.808
Blood calcium	0.35	1.41 (0.45–4.42)	0.554
Pathologic type (GCB *vs.* non-GCB)	–0.36	0.79 (0.24–2.02)	0.507
Ki-67 (>75% *vs.* ≤75%)	–0.71	0.49 (0.17–1.41)	0.185
Treatment (no *vs.* yes)	–1.22	0.30 (0.01–0.89)	0.020*
Chemotherapy cycles (>6 *vs.* ≤6)	–0.92	0.40 (0.14–1.13)	0.072*
Number of involved organs (>2 *vs.* ≤2)	2.02	7.55 (2.19–26.11)	0.001*
Regions of lymph node involvement (>2 *vs.* ≤2)	0.91	2.49 (0.85–7.30)	0.084*
SUVmax (>26.7 *vs.* ≤26.7)	1.14	3.12 (1.11–8.71)	0.022*
SUVmean (>14.3 *vs.* ≤14.3)	0.70	2.01 (0.74–5.45)	0.170
MTV (>165.7 *vs.* ≤165.7 cm^3)	0.89	2.44 (0.86–6.93)	0.082*
TLG (>3,324.3 *vs.* ≤3,324.3 g)	0.89	2.44 (0.86–6.93)	0.082*
Maximum diameter (>7.9 *vs.* ≤7.9 cm)	0.73	2.08 (0.74–5.88)	0.168
CT attenuation value (>35.2 *vs.* ≤35.2 HU)	0.15	1.16 (0.42–3.20)	0.776

*, statistically significant. PET/CT, positron emission tomography/computed tomography; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; ATCH, adrenocorticotropic hormone; LDH, lactate dehydrogenase; GCB, germinal center B-cell-like; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HU, Hounsfield units.

for guiding further treatment strategies in PA-DLBCL patients. Results from our present preliminary study indicate that Ann Arbor stage, β_2-microglobulin, ATCH, the number of involved organs, regions of lymph node involvement, treatment, chemotherapy cycles, SUVmax, MTV, and TLG are associated with OS. In addition, Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, and treatment were shown to be independent prognostic factors for OS in the survival analysis model based on pre-treatment clinical characteristics. Notably no quantitative PET parameters were available in the multivariate analysis as an independent risk factor for OS, but in the correlation analysis, we found that SUVmax, MTV, and TLG correlated with Ann Arbor staging, and

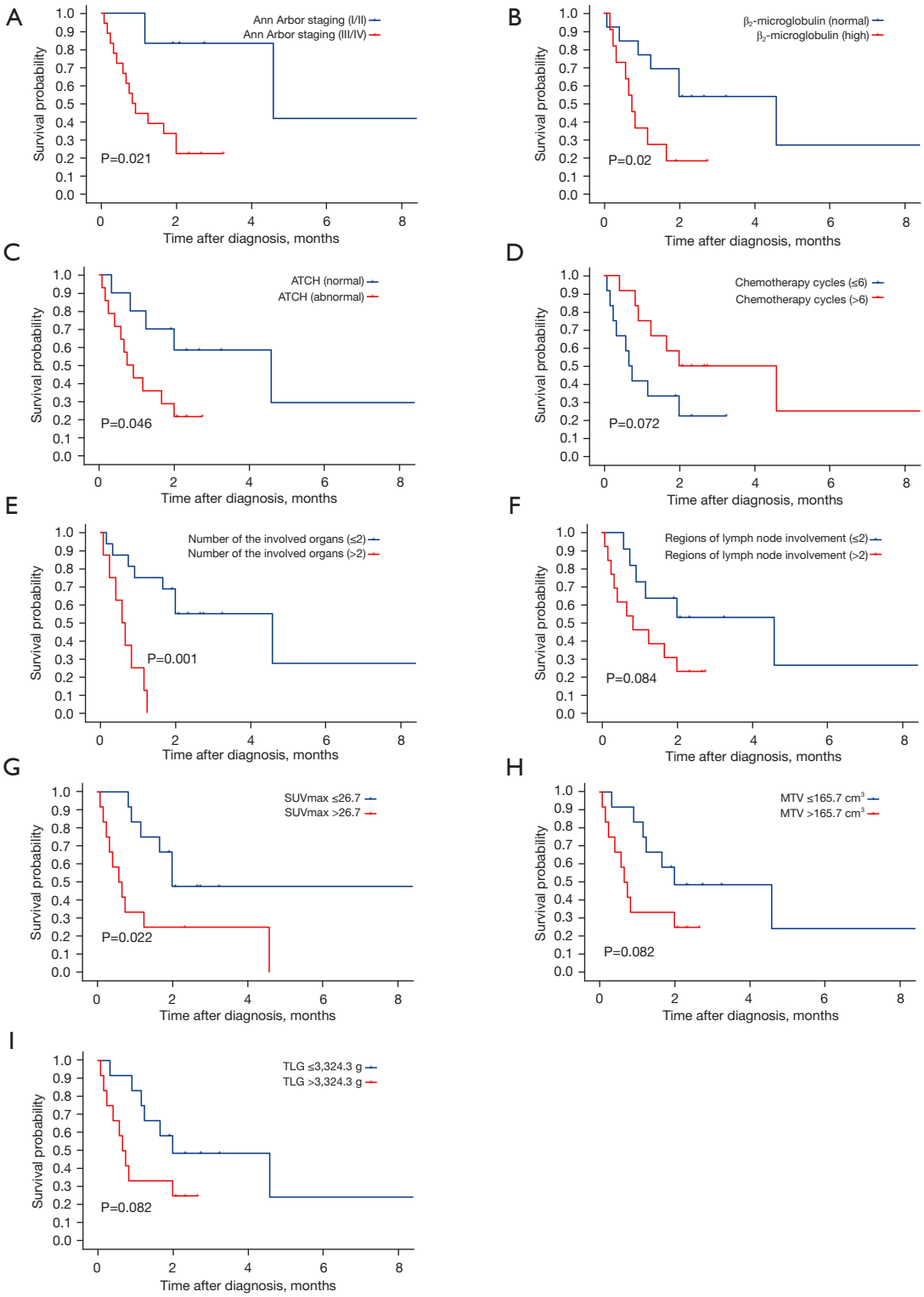

Figure 3 The Kaplan-Meier survival analyses illustrating OS in patents with primary adrenal diffuse large B-cell lymphoma stratified by (A) Ann Arbor staging, (B) β_2-microglobulin, (C) ATCH, (D) chemotherapy cycles, (E) number of the involved organs, (F) regions of lymph node involvement, (G) SUVmax, (H) MTV, (I) TLG. ATCH, adrenocorticotropic hormone; SUVmax, maximum standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; OS, overall survival.

Table 3 Multivariate analyses of clinical characteristics for OS

Variables	Survival analysis model based on entire treatment process			Survival analysis model based on pre-treatment process		
	β	Hazard ratio (95% CI)	P value	β	Hazard ratio (95% CI)	P value
Ann Arbor staging (III/IV *vs.* I/II)	3.29	26.60 (2.40–294.99)	0.008*	2.37	10.94 (1.30–92.19)	0.029*
β_2-microglobulin (abnormal *vs.* normal)	1.65	5.21 (1.47–22.69)	0.024*	–	–	–
ATCH (abnormal *vs.* normal)	–	–	–	1.56	4.81 (1.30–17.80)	0.020*
Treatment (no *vs.* yes)	–1.58	0.21 (0.06–0.76)	0.016*	–	–	–
Number of involved organs (>2 *vs.* ≤2)	1.76	5.77 (1.47–22.69)	0.012*	2.33	10.33 (2.44–43.62)	0.001*

*, statistically significant. OS, overall survival; CI, confidence interval; ATCH, adrenocorticotropic hormone.

Table 4 Correlation of clinical characteristics with baseline PET/CT parameters

Variables	SUVmax	SUVmean	MTV	TLG
Ann Arbor staging				
III/IV	28.94±6.63	15.48±4.08	208.74 (118.42, 420.99)	4,257.75 (1,816.39, 5,303.36)
I/II	20.94±6.52	13.01±4.81	41.38 (18.81, 160.39)	608.95 (236.33, 1,610.94)
P value	0.018*	0.231	0.039*	0.016*
β_2-microglobulin				
High	28.68±8.60	15.70±4.80	181.56 (22.50, 556.75)	3,769.06 (454.50, 6,186.22)
Normal	25.46±6.11	14.16±3.90	149.86 (63.85, 344.61)	2,532.63 (783.52, 5,630.55)
P value	0.312	0.395	0.794	0.794
Number of involved organs				
>2	31.00±6.65	17.32±4.16	338.42 (159.39, 584.81)	5,880.35 (2,923.32, 6,712.76)
≤2	24.91±7.03	13.63±3.94	112.74 (39.26, 310.94)	1,802.98 (531.72, 4,282.22)
P value	0.054	0.045	0.050*	0.027*
ATCH				
Abnormal	28.24±8.04	15.44±4.41	278.21 (118.74, 401.15)	4,257.75 (1,546.71, 5,969.99)
Normal	25.10±6.25	14.06±4.24	90.78 (33.48, 206.49)	1,316.72 (411.38, 3,581.25)
P value	0.313	0.450	0.101	0.089
Treatment				
No	31.90±6.22	16.51±4.11	208.74 (109.88, 329.71)	4,257.75 (2,184.40, 5,393.16)
Yes	25.28±7.11	14.31±4.34	137.30 (43.49, 420.99)	2,181.22 (686.17, 5,717.23)
P value	0.055	0.289	1.000	0.505

Data are presented as mean ± standard deviation/median (interquartile range) as appropriate. *, statistically significant. PET/CT, positron emission tomography/computed tomography; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; ATCH, adrenocorticotropic hormone.

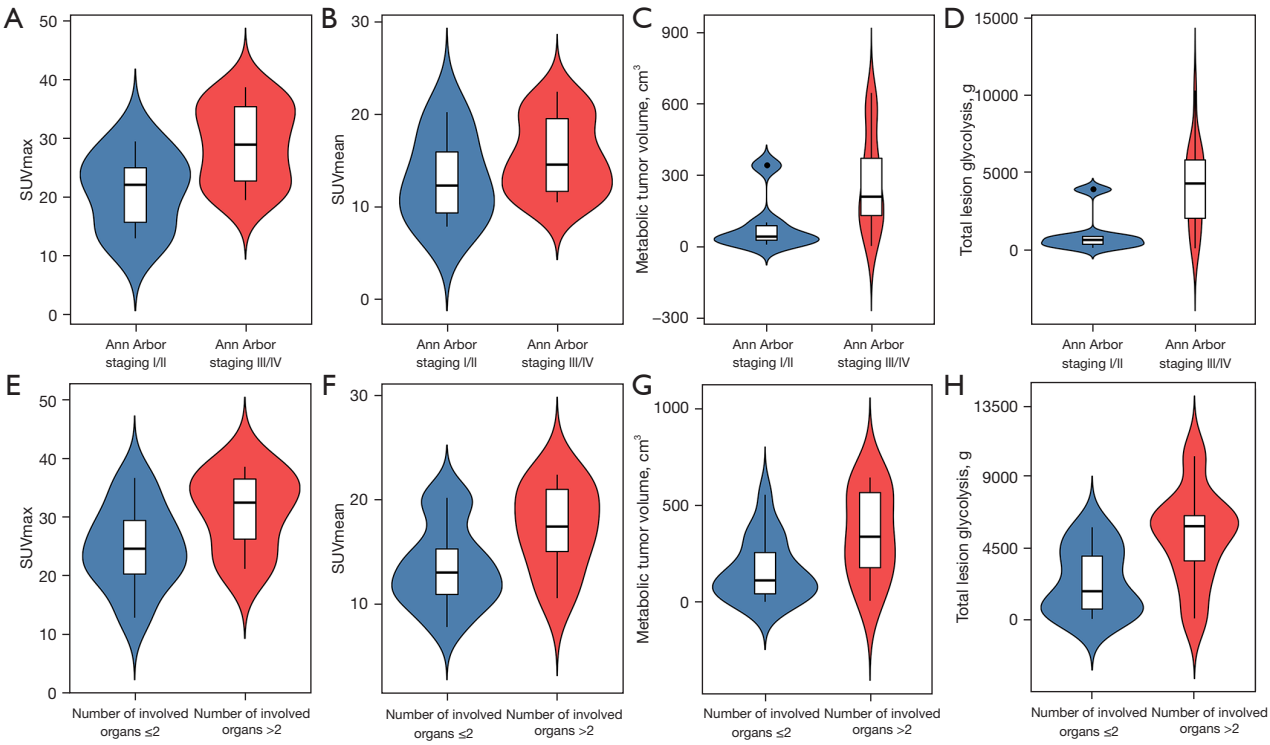

Figure 4 The violin plot shows the differences of SUVmax, SUVmean, MTV, and TLG in different Ann Arbor staging (A-D) and the number of involved organs (E-H). SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

that SUVmean and TLG correlated with the number of involved organs.

Numerous clinical studies have reported prognostic factors associated with DLBCL, and it is crucial to identify high-risk groups before initiating treatment for selecting appropriate clinical strategies. Compared to other DLBCL subtypes, PA-DLBCL carries a worse prognosis. Li *et al.* (36) reported 5- and 10-year OS rates of 19.17% and 3.33%, respectively, for patients with adrenal DLBCL. In this study, the median survival of patients with PA-DLBCL was 17.5 months, which suggests a possible correlation with the rapid disease progression. Compared to patients who received no treatment, we found that undergoing chemotherapy was a positive prognostic factor for predicting OS. Previous studies have reported that the most commonly used chemotherapy regimens were CHOP or R-CHOP (37-40). Zhang *et al.* conducted a series tracking the outcomes of 14 patients with PA-DLBCL and endorsed the use of the R-CHOP regimen, reporting that achieving complete remission (CR) following R-CHOP was predictive of improved survival (41). Similarly, Kim *et al.* suggested that R-CHOP combination chemotherapy was an effective first-line regimen for PA-DLBCL (9). The findings of Lu *et al.* (42) suggest that specific extranodal involved sites have significant prognostic value in DLBCL patients treated with R-CHOP. Hui *et al.* (43) also identified the number of extranodal involvement sites as an important prognostic factor in DLBCL patients treated with R-CHOP. Similarly, our study found that the number of extra nodal lesions other than adrenal is associated with poorer OS rates. Secondary CNS involvement in DLBCL, including relapse or progression, significantly impacts treatment efficacy (44-46). Some researchers have reported prophylactic treatments to reduce the recurrence of CNS relapse, including intrathecal (IT) injection chemotherapy alone and high-dose methotrexate-based regimens and/or cytarabine (47). However, the lack of effective biological therapies due to the impermeability of the blood-brain barrier results in an unclear optimal prophylactic strategy (48). Our study only included four patients with CNS involvement, with worse prognosis than those without CNS involvement, with only 1 case currently alive.

Existing prognostic scoring systems such as the IPI can assess the prognosis of most patients with DLBCL, but some patients with similar IPI scores still have different long-term survival rates (49). Quantitative parameters derived from ^{18}F-FDG PET have demonstrated predictive value for assessing outcomes in patients with DLBCL (27-29,49-51). The standardized uptake value (SUV) is a widely utilized semiquantitative index of ^{18}F-FDG metabolic rate, known for its ease of calculation and noninvasive nature (52). Chihara *et al.* (51) assessed the prognostic significance of baseline SUVmax in 169 DLBCL patients undergoing R-CHOP treatment. Multivariate analysis revealed that high SUVmax is a significant adverse prognostic factor for both progression-free survival (PFS) and OS. Positive findings on interim PET performed between 2 and 4 cycles of chemotherapy indicate a higher likelihood of disease relapse in patients with DLBCL. Fuertes *et al.* (53) conducted an assessment to determine whether interim PET could serve as a prognostic indicator for OS and PFS in DLBCL patients. Their findings revealed that ΔSUVmax cut-off value of 76% [95% confidence interval (CI): 62.7–89.2%] and 75% (95% CI: 54.6–95.4%) was optimal for predicting differences in PFS and OS, respectively. Lin *et al.* (52) reported that assessing therapeutic response using SUV during initial chemotherapy enhances the prognostic value of early ^{18}F-FDG PET in patients with DLBCL. Our results also demonstrate the prognostic value of SUVmax, indicating that patients with PA-DLBCL have a more favorable prognosis when SUVmax is ≤26.7 compared to >26.7, and correlating with Ann Arbor staging. However, it is susceptible to measurement variability caused by factors such as imaging delay after ^{18}F-FDG injection, partial volume effects, and the applied normalization scheme (54-56).

Following the development of software programs, the MTV and TLG on PET/CT serve as measures of tumor metabolic activity, offering valuable information for assessing efficacy and prognosis in patients with DLBCL (57,58). In a meta-analysis conducted by Xie *et al.* (59), involving 703 patients from seven retrospective trials, it was observed that high MTV is significantly associated with decreased survival among DLBCL patients undergoing R-CHOP treatment. Malek *et al.* (60) conducted a comparison between gradient- or threshold-based methods for measuring MTV and SUVmax on interim PET analyses to assess their predictive ability for PFS in patients with DLBCL following initial therapy. The results demonstrated that patients who achieved a ΔSUVmax of 472% on interim PET, and those with a ΔMTV of 452% exhibited a significantly improved PFS (P=0.02). Similarly, Shagera *et al.* (1) and Song *et al.* (23) identified pretreatment MTV as an independent predictor of survival in DLBCL patients. All of these findings suggest that MTV and TLG hold significant potential for predicting the prognosis of patients with DLBCL. However, it is worth noting that the measurement methods for MTV and TLG are relatively complex, and a consensus on the most accurate segmentation method has not been reached. Standardization and operational specifications need to be established (61,62). In previous literature, Ann Arbor staging and the number of involved organs have been reported as poor prognostic factors for DLBCL. In our study, we observed correlations between MTV and TLG with Ann Arbor staging and number of involved organs (42,63-65). However, in the multifactorial analysis, MTV and TLG were not identified as independent predictors. This observation may be attributed to the presence of large adrenal lesions with internal necrosis in the majority of patients in our study group. The necrotic condition within the tumor significantly affects the magnitude of MTV and TLG measurements. The absence of FDG uptake in the internal necrotic area results in lower MTV and TLG values, leading to an underestimation of the true tumor burden and a reduction in their predictive efficacy. Subsequent studies with increased sample sizes or prolonged follow-up periods may reveal the predictive value of MTV and TLG. We are actively working on this task. Given the potential prognostic value of these FDG-PET parameters, it is essential to carefully consider treatment approaches for patients with higher values. In clinical practice, a more aggressive treatment strategy may indeed be considered for patients with poor prognostic FDG-PET parameters to improve their outcomes (7). Aggressive treatment options may include intensified chemotherapy regimens, targeted therapies, radiation therapy, or stem cell transplantation, depending on individual patient characteristics and disease stage. However, it is crucial to emphasize that treatment decisions should be made on a case-by-case basis, taking into account the overall health status of the patient, disease extent, presence of comorbidities, and treatment-related toxicities. Additionally, further research and prospective studies are needed to validate the predictive value of FDG-PET parameters. In recent years, there has been growing interest in the role of radiomics, particularly in the context of artificial intelligence, as a potential tool for predicting treatment outcomes in various malignancies, including DLBCL. Eertink *et al.* (28) demonstrated the value of

^{18}F-FDG PET baseline radiomics features in improving the prediction of treatment outcomes in DLBCL. The authors reported promising results, suggesting that radiomics analysis may offer valuable prognostic insights. Therefore, we encourage further investigation into the role of radiomics in the prognosis of this specific lymphoma subtype.

The present study has certain limitations, and no quantitative FDG-PET parameters indicated predictive factors in our multivariate analysis. We recognize the potential biases that could be addressed by a prospective study. Firstly, patients from two centers were included in our study, the low prevalence of PA-DLBCL and limited data posed challenges in conducting further investigations. To reduce this limitation, future studies will focus on expanding the sample size, potentially through multi-center collaborations, to enhance the statistical power and generalizability of our findings. Secondly, variations in PET/CT imaging equipment between two centers could have introduced variability in the imaging results. Standardization of imaging protocols is crucial to ensure consistent and reliable measurements across different centers. In a prospective study, it would be feasible to implement standardized imaging protocols from the outset, leading to more robust and comparable data. Thirdly, our study had 6 patients who did not receive treatment, and this could have influenced the prognosis analysis. To address this issue, we established two Cox survival analysis models, each focusing on distinct clinical characteristics: the entire treatment process and the pre-treatment phase. Additionally, the follow-up time for some cases in this study was relatively short, with only 15 patients completing more than 2 years of follow-up. Meanwhile, we have plans to conduct further analysis on the 3- and 5-year PFS, which would allow for longer and more comprehensive follow-up periods, providing a clearer understanding of the long-term outcomes of PA-DLBCL patients. Lastly, advancements in PET/CT technology and the emergence of artificial intelligence could influence the prognostic value of PET/CT in PA-DLBCL in the future. Prospective studies could incorporate these technological advancements, enabling more refined and accurate prognostic predictive information for the evaluation of PA-DLBCL during the chemotherapy.

Conclusions

PA-DLBCL is characterized by a low incidence and a poor prognosis, encompassing cases with isolated involvement of adrenal tissue as well as cases with additional extra-adrenal organ manifestations. Prognostic factors for OS include Ann Arbor stage, β_2-microglobulin, ATCH, number of involved organs, and treatment. Baseline ^{18}F-FDG PET/CT quantization parameters showed correlations with Ann Arbor staging and number of involved organs. Increasing the sample size or prolonging the follow-up period may reveal the predictive value of PET/CT quantization parameters. There is a need to enhance FDG-PET examinations for improved prognostic evaluation of tumors, which would be valuable for standardizing treatment.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-803/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of Peking University First Hospital and the First Affiliated Hospital of Zhengzhou University, and individual consent for this retrospective analysis was waived.

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