Correlation Analysis Between Hematological Toxicity and Body Composition in Patients With Diffuse Large B Cell Lymphoma Treated With CHOP±R Regimen

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Abstract

**Purpose:** The tolerance of patients with diffuse large B cell lymphoma (DLBCL) receiving CHOP±R regimen was significantly different, and grade 3~4 hematologic toxicity after chemotherapy in some patients resulted in prolonged hospital stay, increased risk of infection, delayed treatment, and directly or indirectly affected short-term efficacy and long-term prognosis. Lean body mass (LBM) and L3 skeletal muscle index (L3SMI) obtained from abdominal CT of DLBCL patients were analyzed to determine whether they could be used as independent predictors of hematological toxicity of CHOP±R regimen in DLBCL patients.

**Methods:** The patients with DLBCL who underwent CHOP±R regimen at the Cancer Center of the First Hospital of Jilin University from January 2015 to November 2018 were retrospectively analyzed. The abdominal CT of the patient was analyzed by sliceOmatic5.0 software. The third lumbar disc planar imaging was selected, and two consecutive images were taken to calculate LBM and L3SMI. Single factor and multivariate analysis were performed on the correlation of LBM, L3SMI and chemotherapy-related grade 3~4 hematologic toxicity. The ROC curve was drawn to investigate the predictive value of various human indicators on the hematologic toxicity of grade 3~4 related to chemotherapy.

**Results:** The L3 skeletal muscle index is associated with the occurrence of grade 3~4 hematologic toxicity (leukocyte and neutropenia) in patients with diffuse large B-cell lymphoma treated with CHOP±R regimen. Those with lower L3SMI are prone to grade 3~4 hematologic toxicity. LBM is associated with the occurrence of grade 3~4 hematologic toxicity (leukopenia) in patients with diffuse large B-cell lymphoma treated with CHOP±R regimen. This with lower LBM is prone to grade 3~4 hematologic toxicity. The L3 skeletal muscle index can be used as an independent predictor of grade 3~4 hematologic toxicity (leukocyte and neutropenia) in patients with diffuse large B-cell lymphoma treated with CHOP ± R regimen. The cut-off value can be defined as 39.91 cm$^2$/m$^2$.

**Conclusion:** We can draw the following conclusions: The L3 skeletal muscle index is associated with the occurrence of grade 3~4 hematologic toxicity (leukocyte and neutropenia) in patients with diffuse large B-cell lymphoma treated with CHOP±R regimen. Those with lower L3SMI are prone to grade 3~4 hematologic toxicity. LBM is associated with the occurrence of grade 3~4 hematologic toxicity (leukopenia) in patients with diffuse large B-cell lymphoma treated with CHOP±R regimen. This with lower LBM is prone to grade 3~4 hematologic toxicity. The L3 skeletal muscle index can be used as an independent predictor of grade 3~4 hematologic toxicity (leukocyte and neutropenia) in patients with diffuse large B-cell lymphoma treated with CHOP ± R regimen. The cut-off value can be defined as 39.91 cm$^2$/m$^2$.

**Introduction**

Diffuse large B-cell lymphoma is the most common NHL, accounting for about 30% of all NHL cases$^{[1,2]}$. At present, chemotherapy is still the main means of treating the disease. The standard first-line
chemotherapy for DLBCL is CHOP ± R. Grade 3 to 4 hematologic toxicity in patients with DLBCL treated with CHOP ± R regimen can directly and indirectly affect short-term efficacy and long-term prognosis. DLBCL has a better therapeutic effect and a longer survival time. It is especially important to strengthen the research on the dose and prognosis of chemotherapy drugs.

The use of BSA for drug dose calculations has been questioned, and studies have shown that calculating drug doses based on BSA does not reduce differences in pharmacokinetics between individuals\(^3,4\). Small differences in doses can cause severe toxicity in some patients, leading to drug reduction or even delay in treatment, and in some cases, the drug exposure of some patients is relatively insufficient, thereby directly and indirectly affecting the disease outcome. At present, there are few studies on the body composition of hematological tumors and the hematological toxicity of chemotherapy, and there is no good dose measurement index, and more powerful evidence is needed to further prove the calculation.

As a high-precision analysis method at the organizational/system level, CT is considered to be the “gold standard” for the analysis of human body components in cancer patients\(^5\). Studies have shown that the third lumbar vertebrae is the marker of body composition. The ratio of skeletal muscle to adipose tissue in this area is similar to that of whole body tissue. According to the CT scan image of the third lumbar vertebrae level, the skeletal muscle, lean body mass and distribution of the whole body can be calculated by using image analysis software and regression formula\(^6,7\). Abdominal CT is a routine examination item during the treatment of patients with DLBCL. Abdominal CT resources can be used for body composition analysis to further analyze the correlation between body composition and hematological toxicity of chemotherapy. In CT images, the density values of the components are different (skeletal muscle density values are usually between −29HU and +150HU; subcutaneous tissue and visceral tissue density values are −190 to -30HU and −150 to -50HU, respectively). Good anatomical and imaging recognition of various components of the body. The body lean body mass content was assessed by calculating the skeletal muscle area in the selected layer. LBM (kg) = 0.3 × [L3 vertebral skeletal muscle area (cm\(^2\))] + 6.06; L3SMI (cm\(^2\) / m\(^2\)) = L3 vertebral skeletal muscle area (cm\(^2\)) / height \(^2\) (m\(^2\))\(^8-10\).

This study retrospectively analyzed patients with DLBCL who underwent CHOP ± R regimen at the First Hospital of Jilin University from January 2015 to November 2018, and analyzed the relevant data. The use of abdominal CT analysis of L3SMI, LBM, in order to further analyze its relationship with the patient’s chemotherapy hematological toxicity, provide a reference for the choice and calculation of drug dosage, and further improve the prognosis of cancer patients.

**Methods**

**Patient and trial design**

A retrospective analysis was performed on 60 patients with DLBCL who were admitted to the Cancer Center of the First Hospital of Jilin University from January 2015 to November 2018. Inclusion criteria: (1) Age is greater than 18 years old. (2) The pathological examination was initially diagnosed as DLBCL and
received standard dose of CHOP ± R regimen. (3) There is no pre-existing liver disease, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal. (4) Total bilirubin ≤ upper limit of normal value. (5) The heart function is normal. (6) There is no pre-existing kidney disease, creatinine ≤ 1.5 times the upper limit of normal. (7) Long-acting whitening drugs are not prophylactically applied during the intermittent period of chemotherapy. (8) There is no intervention (such as surgery) between the CT scan date and the start of chemotherapy to alter body composition. Exclusion criteria: (1) Inverted lymphoma transformation. (2) Double tumors. (3) ECOG score > 2 points. (4) Concomitant HIV or active hepatitis. (5) The combination of cimetidine and other drugs that may affect the metabolism of epirubicin.

All subjects were recorded within 24 hours of admission, height and weight were recorded according to standard methods, laboratory biochemical tests were performed, and abdominal CT or PET-CT examinations were performed within 30 days prior to the start of the first course of chemotherapy. Peripheral blood tests were performed every 3 to 4 days between the end of the first course of chemotherapy and the start of the second course of chemotherapy. When the patient was admitted to the hospital, he was uniformly dressed in a thin and sick suit, and the height and weight were measured on an empty stomach. The formula was used to calculate BMI and BSA. BMI = weight (kg) / height^2 (m^2). BSA (m^2) = [height (cm) + body weight (kg) − 60] / 100. The patient was admitted to the hospital on the second day of the morning. The fasting sterile venous blood was sent to the hospital for examination. The records included Alb, AST, ALT, cholinesterase, creatinine, urea nitrogen, bilirubin, peripheral blood leukocytes, and peripheral blood neutrophils. Laboratory test indicators such as absolute cell value, peripheral blood hemoglobin, and peripheral blood platelets.

**Assessing Hematologic Toxicity In Patients**

Peripheral blood routine testing was performed every 3 to 4 days between the end of the first course of chemotherapy and the start of the second course of chemotherapy. Peripheral blood leukocytes, peripheral blood neutrophils, peripheral blood hemoglobin, peripheral blood were recorded. The lowest value of platelets, according to CTCAE4.2 for hematological toxicity grading. The general hematologic toxicity of patients with chemotherapy is mainly manifested by leukopenia and neutropenia, so we mainly analyze leukocyte hematological toxicity and neutrophil hematological toxicity.

**Measurement Of Body Composition**

The patient’s abdominal CT was analyzed by SliceOmatic5.0 software produced by TOMOVISION of Canada. According to the patient’s abdominal CT scan, the third lumbar disc planar imaging was selected, and two consecutive images were taken in the L3 plane to calculate the skeletal muscle (including the psoas muscle, The sum of the cross-sectional areas of the erector spinae, the lumbar muscles, the transverse abdominis muscles, the external oblique muscles, and the intra-abdominal
oblique muscles was calculated using a regression formula. LBM (kg) = 0.3 × [L3 vertebral skeletal muscle area (cm²)] + 6.06; L3SMI (cm² / m²) = L3 vertebral skeletal muscle area (cm²) / height² (m²).

**Data analysis**

The data was analyzed using SPSS 22.0 statistical software. Measurement data are described as mean ± standard deviation. Univariate analysis of influencing factors of hematologic toxicity was performed by t test, and multivariate analysis was performed by logistic regression. And the ROC curve was drawn to explore the diagnostic value of various human indicators for hematological toxicity. All tests were performed on both sides, and P < 0.05 indicated that the difference was statistically significant.

**Result**

**Basic characteristics of patients**

A total of 60 patients with diffuse large B-cell lymphoma were used for this study based on patient inclusion and exclusion criteria. The basic characteristics of the patients are as follows: 27 males and 33 females, with an average age of (55.83 ± 13.33) years. The distribution of clinical features among different hematological toxicity groups was balanced. See Table 1 for details.

**Anthropometric Indicators**

The BMI of the included patients was (23.21 ± 3.78) kg/m², and the BMI of the patients with < 3 grade neutrophil count reduction group and ≥ 3 grade neutrophil count reduction group were (23.57 ± 4.02) kg/m² and (22.73, respectively). ±3.45) kg/m², the difference was not statistically significant. See Table 1 for details. The BMI of patients in the grade 3 leukopenia group and the grade 3 leukopenia group were (24.27 ± 4.26) kg/m² and (21.73 ± 2.33) kg/m², respectively, and the difference was statistically significant (P < 0.05). See Table 2 for details. The calculated BSA was (1.77 ± 0.36) m², and the BSA of the < 3 grade neutrophil count reduction group and the ≥ 3 grade neutrophil count decrease group were (1.78 ± 0.36) m² and (1.75 ± 0.37)m², respectively. The difference was not statistically significant. See Table 1 for details. The BSA of the < 3 grade leukopenia group and the grade 3 leukopenia group were (1.81 ± 0.33) m² and (1.71 ± 0.40) m², respectively, and the difference was not statistically significant. See Table 2 for details.

**Laboratory Test Indicators**

According to patient test data, Alb was (38.37 ± 5.55) g/L. <3 grade neutrophil count reduction group was (38.58 ± 5.64) g/L, ≥ 3 grade neutrophil count reduction group was (38.09 ± 5.52) g/L, and the two groups of Alb were not statistically significant. See Table 1 for details. <3 grade leukopenia group was (39.43 ±
5.63) g/L, and grade 3 grade leukopenia group was (36.93 ± 5.20) g/L. There was no significant difference between the two groups. See Table 2 for details.

**Body Composition Index**

The slice CT image of the patient’s abdomen was analyzed by sliceOmatic 5.0 software, and L3SMI and LBM were derived, which were (42.34 ± 8.79) cm²/m², (40.54 ± 8.66) kg, respectively. <3 grade neutrophil count reduction group and ≥ 3 grade neutrophil count reduction group L3SMI were (44.79 ± 9.11) cm²/m² and (39.13 ± 7.36) cm²/m², ≥ 3 grade neutrophils, respectively. The L3SMI of patients with reduced count was significantly lower than that of patients with lower neutrophil counts than < 3, the difference was statistically significant (P < 0.05). See Table 1 and Fig. 1 for details. The L3SMI of the patients in the grade 3 leukopenia group and the grade 3 leukopenia group were (45.60 ± 9.23) cm²/m² and (37.76 ± 5.67) cm²/m², respectively. The patients with ≥ 3 grade leukopenia had significantly lower L3SMI than < 3 grade leukocytes. In the reduction group, the difference was statistically significant (P < 0.001). The LBM of the grade 3 neutrophil count reduction group and the ≥ 3 grade neutrophil count reduction group were (42.17 ± 8.84) kg and (38.41 ± 8.10) kg, respectively, and the difference was not statistically significant. The LBM of the grade 3 leukopenia group and the grade 3 leukopenia group were (43.31 ± 9.18) kg and (36.67 ± 6.19) kg, respectively, and the difference was statistically significant (P < 0.05). See Table 2 and Fig. 2 for details.
Table 1
General information on neutrophil count reduction and univariate analysis results

| Relevant factors | Mean ± standard deviation | A              | B              | t     | P      |
|------------------|---------------------------|-----------------|-----------------|-------|--------|
| Age              | 55.8 ± 13.33              | 54.35 ± 15.15   | 57.77 ± 10.48   | -0.98 | 0.330  |
| LBM              | 40.54 ± 8.66              | 42.17 ± 8.84    | 38.41 ± 8.10    | 1.69  | 0.097  |
| L3SMI            | 42.34 ± 8.79              | 44.79 ± 9.11    | 39.13 ± 7.36    | 2.59  | 0.012  |
| BSA              | 1.77 ± 0.36               | 1.78 ± 0.36     | 1.75 ± 0.37     | 0.34  | 0.735  |
| BMI              | 23.21 ± 3.78              | 23.57 ± 4.02    | 22.73 ± 3.45    | 0.85  | 0.398  |
| Alb              | 38.37 ± 5.55              | 38.58 ± 5.64    | 38.09 ± 5.52    | 0.33  | 0.740  |
| Creatinine       | 68.9 ± 18.27              | 67.87 ± 15.41   | 70.39 ± 21.61   | -0.52 | 0.603  |
| Urea nitrogen    | 5.61 ± 2.13               | 5.53 ± 2.01     | 5.71 ± 2.32     | -0.40 | 0.692  |
| AST              | 24.71 ± 8.18              | 25.38 ± 7.83    | 23.85 ± 8.67    | -0.32 | 0.754  |
| ALT              | 21.0 ± 13.44              | 23.19 ± 15.70   | 18.33 ± 9.46    | 1.39  | 0.170  |
| Cholinesterase   | 7637.71 ± 2545.01         | 7809.36 ± 2475.30 | 6855.26 ± 2613.11 | 1.18 | 0.245  |

A: < Class 3 hematological toxicity; B: < Grade 3 hematological toxicity
Table 2
General information on leukopenia and univariate analysis results

| Relevant factors | Mean ± standard deviation | A             | B             | t      | P     |
|-----------------|---------------------------|---------------|---------------|--------|-------|
| Age             | 55.83 ± 13.33             | 53.37 ± 14.39 | 59.28 ± 11.06 | -1.72  | 0.091 |
| LBM             | 40.54 ± 8.66              | 43.31 ± 9.18  | 36.67 ± 6.19  | 3.347  | 0.001 |
| L3SMI           | 42.34 ± 8.79              | 45.60 ± 9.23  | 37.76 ± 5.67  | 4.07   | < 0.001 |
| BSA             | 1.77 ± 0.36               | 1.81 ± 0.33   | 1.71 ± 0.40   | 1.14   | 0.261 |
| BMI             | 23.21 ± 3.78              | 24.27 ± 4.26  | 21.73 ± 2.33  | 2.97   | 0.004 |
| Alb             | 38.37 ± 5.55              | 39.43 ± 5.63  | 36.93 ± 5.20  | 1.74   | 0.087 |
| Creatinine      | 68.98 ± 18.27             | 68.49 ± 15.72 | 69.66 ± 21.60 | -0.24  | 0.810 |
| Urea nitrogen   | 5.61 ± 2.13               | 5.52 ± 2.02   | 5.74 ± 2.31   | -0.40  | 0.692 |
| AST             | 24.71 ± 8.18              | 24.62 ± 7.63  | 24.84 ± 9.04  | -0.10  | 0.920 |
| ALT             | 21.05 ± 13.44             | 23.96 ± 15.51 | 17.08 ± 8.79  | 2.16   | 0.036 |
| Cholinesterase  | 7292.±2545.01             | 7809.2 ± 2380.80 | 6590.2 ± 2639.56 | 1.86   | 0.069 |

Multivariate Analysis Results

Univariate analysis of neutrophil counts showed that L3SMI was associated with a decrease in grade 3 ~ 4 neutrophil counts, age, BMI, BSA, Alb, LBM, creatinine, urea nitrogen, ALT, AST, choline esters. The enzyme is not associated with a decrease in neutrophil count. Multivariate logistic regression analysis was performed on the factors affecting the reduction of grade 3 ~ 4 neutrophil count. The inclusion factors included L3SMI, BMI, Alb, creatinine, urea nitrogen, AST, ALT, cholinesterase. The results showed: L3SMI Statistically significant, it is an independent predictor of decreased neutrophil count in patients with diffuse large B-cell lymphoma treated with the CHOP ± R regimen. The risk of chemotherapy-related grade 3~4 neutrophil count was significantly higher in patients with low L3SMI than in the control group (OR: 0.893, 95% CI [0.818–0.975], P = 0.012). See Table 3 for details. Univariate analysis of leukopenia showed that L3SMI, LBM, BMI, and ALT were associated with grade 3~4 leukopenia. Age, BSA, Alb, creatinine, urea nitrogen, AST, and cholinesterase were not associated with leukopenia. Multivariate logistic regression analysis was performed on the factors affecting the occurrence of grade 3 ~ 4 leukopenia. The inclusion factors included L3SMI, BMI, Alb, creatinine, urea nitrogen, AST, ALT, and cholinesterase. The results showed that L3SMI was statistically significant. Is an independent predictor of leukopenia in patients with diffuse large B-cell lymphoma treated with the CHOP ± R regimen. The risk of
chemotherapy-related grade 3–4 leukopenia was significantly higher in patients with low L3SMI than in the control group (OR: 0.871, 95% CI [0.785–0.966], P = 0.009). See Table 4 for details.

### Table 3
Logistic multivariate analysis results of neutrophil count reduction of grade ≥ 3

| Variables    | β     | SE   | Wald  | P     | OR   | 95%CI Lower | 95%CI Upper |
|--------------|-------|------|-------|-------|------|-------------|-------------|
| L3SMI        | -0.113| 0.045| 6.368 | 0.012 | 0.893| 0.818       | 0.975       |
| BMI          | 0.066 | 0.097| 0.454 | 0.500 | 1.068| 0.882       | 1.292       |
| Alb          | 0.059 | 0.069| 0.730 | 0.393 | 1.061| 0.926       | 1.215       |
| Creatinine   | 0.031 | 0.024| 1.599 | 0.206 | 1.031| 0.983       | 1.081       |
| Urea nitrogen| -0.128| 0.208| 0.382 | 0.537 | 0.880| 0.585       | 1.322       |
| AST          | 0.008 | 0.045| 0.028 | 0.867 | 1.008| 0.923       | 1.100       |
| ALT          | -0.016| 0.030| 0.293 | 0.588 | 0.984| 0.927       | 1.044       |
| Cholinesterase| 0     | 0    | 2.031 | 0.154 | 1    | 0.999       | 1.000       |

### Table 4
Logistic Multivariate Analysis Results for Leukopenia of Grade ≥ 3

| Variables    | β     | SE   | Wald  | P     | OR   | 95%CI Lower | 95%CI Upper |
|--------------|-------|------|-------|-------|------|-------------|-------------|
| L3SMI        | -0.138| 0.053| 6.789 | 0.009 | 0.871| 0.785       | 0.966       |
| BMI          | -0.092| 0.119| 0.604 | 0.437 | 0.912| 0.723       | 1.151       |
| Alb          | 0.015 | 0.076| 0.038 | 0.845 | 1.015| 0.875       | 1.177       |
| Creatinine   | 0.050 | 0.028| 3.163 | 0.075 | 1.052| 0.995       | 1.111       |
| Urea nitrogen| -0.332| 0.242| 1.875 | 0.171 | 0.718| 0.447       | 1.151       |
| AST          | 0.083 | 0.054| 2.364 | 0.124 | 1.086| 0.977       | 1.207       |
| ALT          | -0.050| 0.038| 1.727 | 0.189 | 0.951| 0.883       | 1.025       |
| Cholinesterase| 0     | 0    | 2.127 | 0.145 | 1    | 0.999       | 1.000       |

**Diagnostic value of different body composition indicators for grade 3 ~ 4 hematological toxicity**

According to the results of multivariate logistic regression analysis, L3SMI is an independent predictor of decreased neutrophil count and leukopenia in patients with diffuse large B-cell lymphoma treated with CHOP ± R regimen. According to the reduction of ≥ 3 grade neutrophil count as the cut-point value, ROC
analysis of BMI, BSA, L3SMI, LBM, Alb, creatinine, urea nitrogen, ALT, AST, cholinesterase reduced the absolute value of neutrophils Diagnostic value. The area under the L3SMI curve was 0.681, P = 0.018. L3SMI has a good diagnostic effect on the reduction of neutrophil count. In addition, the ROC curve analysis showed that the ≥ 3 grade neutrophil count decreased and the < 3 grade neutrophil count reduction group had a L3SMI cutoff value of 39.91 cm²/m², and its sensitivity was 0.65, and the specificity was 0.70. See Fig. 3, Table 5 and Table 6 for details. According to ≥ 3 grade leukopenia as the cut-point value, ROC curve was used to analyze the diagnostic value of BMI, BSA, L3SMI, LBM, Alb, creatinine, urea nitrogen, ALT, AST and cholinesterase on leukopenia. The area under the L3SMI curve is 0.74, P = 0.002. The area under the LBM curve was 0.705, P = 0.007. L3SMI and LBM have a good diagnostic effect on leukopenia. In addition, the ROC curve analysis showed that the critical values of L3SMI and LBM of ≥ 3 leukopenia and < 3 grade leukopenia were 39.91 cm²/m², 40.50 kg, the sensitivity of L3SMI was 0.68, and the specificity was 0.71. The sensitivity is 0.80 and the specificity is 0.56. See Fig. 4, Table 7 and Table 8 for details.

| Relevant factors | AUC   | Standard error | P    | 95%   | Confidence interval |
|------------------|-------|----------------|------|-------|---------------------|
| L3SMI            | 0.681 | 0.07           | 0.018| 0.54  | 0.82                |
| BMI              | 0.576 | 0.08           | 0.321| 0.43  | 0.72                |
| BSA              | 0.505 | 0.08           | 0.95 | 0.35  | 0.66                |
| LBM              | 0.622 | 0.07           | 0.111| 0.48  | 0.77                |
| Alb              | 0.529 | 0.08           | 0.703| 0.38  | 0.68                |
| Creatinine       | 0.485 | 0.08           | 0.843| 0.33  | 0.64                |
| Urea nitrogen    | 0.496 | 0.08           | 0.957| 0.35  | 0.65                |
| AST              | 0.581 | 0.08           | 0.29 | 0.43  | 0.73                |
| ALT              | 0.568 | 0.08           | 0.372| 0.42  | 0.72                |
| Cholinesterase   | 0.540 | 0.08           | 0.60 | 0.39  | 0.69                |
### Table 6
Threshold, sensitivity and specificity of neutrophil count reduction of grade $\geq 3$

| Relevant factors | Threshold | Sensitivity | Specificity |
|------------------|-----------|-------------|-------------|
| L3SMI            | 39.91     | 0.65        | 0.70        |
| BMI              | 26.52     | 0.92        | 0.27        |
| BSA              | 1.67      | 0.35        | 0.79        |
| LBM              | 35.50     | 0.42        | 0.79        |
| Alb              | 33.50     | 0.27        | 0.85        |
| Creatinine       | 51        | 0.19        | 0.91        |
| Urea nitrogen    | 5.8       | 0.77        | 0.36        |
| AST              | 24.05     | 0.73        | 0.55        |
| ALT              | 40.6      | 1.00        | 0.18        |
| Cholinesterase   | 5909      | 0.35        | 0.85        |

### Table 7
ROC curve value of $\geq 3$ leukopenia

| Relevant factors | AUC    | Standard error | P     | 95% Confidence interval |
|------------------|--------|----------------|-------|-------------------------|
| L3SMI            | 0.74   | 0.06           | 0.002 | 0.62 - 0.87             |
| BMI              | 0.689  | 0.07           | 0.14  | 0.56 - 0.82             |
| BSA              | 0.541  | 0.08           | 0.59  | 0.39 - 0.70             |
| LBM              | 0.705  | 0.07           | 0.007 | 0.574 - 0.84            |
| Alb              | 0.646  | 0.07           | 0.056 | 0.50 - 0.79             |
| Creatinine       | 0.511  | 0.08           | 0.890 | 0.36 - 0.66             |
| Urea nitrogen    | 0.482  | 0.08           | 0.818 | 0.33 - 0.63             |
| AST              | 0.512  | 0.08           | 0.88  | 0.36 - 0.66             |
| ALT              | 0.621  | 0.07           | 0.12  | 0.48 - 0.76             |
| Cholinesterase   | 0.608  | 0.08           | 0.16  | 0.46 - 0.76             |
Table 8
Threshold, sensitivity and specificity of ≥ 3 leukopenia

| Relevant factors | Threshold | Sensitivity | Specificity |
|------------------|-----------|-------------|-------------|
| L3SMI            | 39.91     | 0.68        | 0.71        |
| BMI              | 22.98     | 0.72        | 0.62        |
| BSA              | 1.67      | 0.40        | 0.82        |
| LBM              | 40.50     | 0.80        | 0.56        |
| Alb              | 40.65     | 0.76        | 0.50        |
| Creatinine       | 67.85     | 0.60        | 0.53        |
| Urea nitrogen    | 5.80      | 0.76        | 0.35        |
| AST              | 24.05     | 0.68        | 0.50        |
| ALT              | 14.40     | 0.56        | 0.68        |
| Cholinesterase   | 5909      | 0.40        | 0.88        |

Discuss

DLBCL is the most common NHL, accounting for about 30% of all NHL cases\(^1,2\). Grade 3 to 4 hematologic toxicity in patients with DLBCL treated with CHOP ± R regimen can directly and indirectly affect short-term efficacy and long-term prognosis. However, the study found that the widely used clinically based doses of chemotherapeutic drugs based on BSA did not adequately account for individual differences in body composition between different patients and their effects on pharmacokinetics\(^11,12\). Calculating drug doses based on BSA does not reduce the difference in pharmacokinetics between individuals\(^3,4\). Studies have shown that body composition is closely related to pharmacokinetics in the body. Human body composition analysis as a component of body composition and function can better predict the toxicity and efficacy of anti-tumor drugs.

Univariate analysis showed that the L3SMI of the patients with < 3 grade neutrophil count reduction group and ≥ 3 grade neutrophil count decreased group were (44.79 ± 9.11) cm\(^2\)/m\(^2\) and (39.13 ± 7.36) cm\(^2\)/m\(^2\). The L3SMI of patients with ≥ 3 grade neutrophil count reduction was significantly lower than that of patients with < 3 grade neutrophil count reduction. The difference was statistically significant. The L3SMI of the patients with <3 leukopenia group and ≥ 3 grade leukopenia group were (45.60 ± 9.23) cm\(^2\)/m\(^2\) and (37.76 ± 5.67) cm\(^2\)/m\(^2\), respectively. The L3SMI of patients with ≥ 3 leukopenia was significantly lower than that of patients with <3 grade leukopenia, and the difference was statistically significant. The LBM of the < 3 grade leukopenia group and the ≥ 3 grade leukopenia group were (43.31 ± 9.18) kg and (36.67 ± 6.19) kg, respectively, which were statistically significant (\(P < 0.05\)). Multivariate analysis showed that L3SMI was an independent predictor of decreased neutrophil count and leukopenia in diffuse large B-cell...
lymphoma chemotherapy. The results of single factor and multivariate analysis are consistent with most existing studies. In the analysis of patients participating in Phase I clinical trials, low SMI was the only factor associated with the discovery of DLT regardless of tumor or drug type, and patients with severe toxic events had significantly lower SMI (42.4 vs. 48.4 cm²/m²)[13]. A single factor and multivariate analysis of chemotherapy toxicity in patients receiving stage III rectal cancer treated with FOLFOX showed that the lumbar skeletal muscle index predicts all grade 3–4 toxicity and grade 3–4 neutropenia[14]. In addition, in a cohort of patients with advanced recurrent ovarian cancer treated with liposomal doxorubicin and trobeidine, it was concluded that lean body soft tissue is the only important predictor of DLT in normal-weight patients[15]. The results of this study show that L3SMI and LBM are associated with hematologic toxicity and are consistent with previous results. Importantly, according to our findings, the L3 skeletal muscle index can be used as an independent predictor of grade 3–4 hematologic toxicity (leukocyte and neutropenia) in patients with diffuse large B-cell lymphoma treated with CHOP ± R regimen.

Analysis by ROC curve showed that L3SMI has a good diagnostic effect on the reduction of neutrophil count. The ≥ 3 grade neutrophil count decreased and the < 3 grade neutrophil count reduction group had a L3SMI cutoff value of 39.91 cm²/m², with a sensitivity of 0.65 and a specificity of 0.70. L3SMI and LBM have a good diagnostic effect on leukopenia. The critical values of L3SMI and LBM in ≥ 3 leukopenia and < 3 grade leukopenia were 39.91 cm²/m², 40.50 kg, the sensitivity of L3SMI was 0.68, the specificity was 0.71, the sensitivity of LBM was 0.80, and the specificity was 0.56. It has been reported in the literature that the ROC curve shows that the BMI of the SMI-predicted DLT is 43.1 cm²/m², which is similar to our findings[16]. We predict that the exact role of body composition will become clearer in clinical work. Since previous studies consistently show clinical relevance, we expect to push the body composition to calculate the dose of chemotherapy. The definition or threshold for sarcopenia may vary between people of different ages or races. Quantification of body muscle mass will help to understand the interaction between these parameters and drug distribution and side effects. Overall, this will enable clinicians to get more precise individualized treatment options.

Declarations

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest relevant to this manuscript.

Ethical approval This is a retrospective study. This article does not contain any studies with human participants or animals performed by any of the authors.
**Statements**

All methods were carried out in accordance with relevant guidelines and regulations.

All experimental protocols were approved by The First Affiliated Hospital of Jilin University.

Informed consent was obtained from all subjects, and all subjects were older than 18 years.

**References**

1. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001[J]. Blood. 2006;107(1):265–76.

2. Swerdlow S, Campo E, Harris N, et al. World Health Organization classification of tumours of haematopoietic and lymphoid tissues[M]. 4th ed. Lyon: IARC Press; 2008.

3. Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area[J]. Eur J Cancer. 2002;38(13):1677–84.

4. Baker SD, Verweij J, Rowinsky EK, et al. Role of body surface area in dosing of investigational anticancer agents in adults, 1991–2001[J]. J Natl Cancer Inst. 2002;94(24):1883–8.

5. Prado CM, Birdsell LA, Baracos VE. The emerging role of computerized tomography in assessing cancer cachexia[J]. Curr Opin Support Palliat Care. 2009;3(4):269–75.

6. Prado CM, Cushen SJ, Orsso CE, et al. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact[J]. Proc Nutr Soc. 2016;75(2):188–98.

7. Di Sebastiano KM, Mourtzakis M. A critical evaluation of body composition modalities used to assess adipose and skeletal muscle tissue in cancer[J]. Appl Physiol Nutr Metab. 2012;37(5):811–21.

8. Cruz,Jentoft AJ, Baeyens JP, Bauer. JM, et al. Sarcopenia: Europol consensus oH definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People[J]. Age Aging. 2010;39(4):412–23.

9. Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism [J]. Kidney Int. 2013;84(6):1096–107.

10. Prado CM, Lieffers JR, McCargar U, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population—based study[J]. Lancet Oncol. 2008,9(7):629–635.

11. Heaf J. The origin of the 1·73-m2 body surface area normalization: problems and implications[J]. Clin Physiol Funct Imaging. 2007;27:135–7.

12. Gurney HP, Ackland S, Gebski V, et al. Factors affecting epirubicin pharmacokinetics and toxicity: evidence against using body-surface area for dose calculation[J]. J Clin Oncol. 1998;16(7):2299–304.
13. Sjoblom B, Benth JS, Gronberg BH, et al. Drug dose per kilogram lean body mass predicts hematologic toxicity from carboplatin doublet chemotherapy in advanced non-small-cell lung cancer[J]. Clin Lung Cancer. 2017;18(12):129–36.

14. Ali R, Baracos VE, Sawyer MB, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens[J]. Cancer Med. 2016;5(6):607–16.

15. Yip C, Goh V, Davies A, et al. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer[J]. Eur Radiol. 2014;24(5):998–1005.

16. Huillard O, Mir O, Peyromaure M, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients[J]. Br J Cancer. 2013;10(8):1034–41.

**Figures**

Figure 1

Relationship between L3 SMI and decreased neutrophil count
Figure 2

Relationship between L3 SMI and leukopenia

Figure 3

ROC curve with $\geq 3$ grade neutrophil count reduction
Figure 4

ROC curve for leukopenia of grade ≥3