# Prognostic value of metabolic parameters in baseline 18F-FDG PET/CT for pediatric lymphoblastic lymphoma

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**Abstract**

Purpose: This retrospective study aimed to evaluate the prognostic value of metabolic parameters in baseline fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) for pediatric lymphoblastic lymphoma (LBL). Method: Thirty patients with LBL who underwent baseline 18F-FDG PET/CT from April 2013 to November 2018 were enrolled. Their metabolic parameters including maximum standardized uptake value (SUVmax), total metabolic tumor volume (TMTV), and total lesion glycolysis (TLG) were measured and compared with those from different clinical characteristic groups. Event-free survival (EFS) and overall survival (OS) curves were constructed using the Kaplan–Meier method and compared with the log-rank test. Results: The patients with stage IV had higher TMTV than stage III (mean 580.66cm$^3$ vs. 176.52cm$^3$; p=0.031). No statistical significance in SUVmax and TLG was observed between patients with stages III and IV (p=0.061; p=0.291). After a median follow-up of 41.5 months (range of 1–86 months), the patients with a low TMTV (<242.91cm3) had better 3-year EFS rate compared with those with a high TMTV (88.9% vs. 56.3%; p=0.036). However, SUVmax and TLG were not predictive of EFS(p=0.874; p=0.152). Conclusions: TMTV may be a potential PET/CT metabolic parameter for predicting the prognosis of pediatric lymphoblastic lymphoma. A high TMTV indicates a poor outcome. However, SUVmax and TLG are not related to the prognosis of pediatric lymphoblastic lymphoma.

## 2. Methods

### 2.1 Patients

Thirty patients with lymphoblastic lymphoma diagnosed between April 2013 and November 2018 were retrospectively enrolled. Inclusion criteria were as follows: (1) age under 18 years; (2) with pathologically confirmed LBL; (3) without lymphoma-related treatment before$^{18}$F-FDG PET/CT scan; (4) receive standard and consecutive treatment in the department of pediatric cancer in Tianjin Medical University Cancer Institute and Hospital; and (5) has complete clinical information and follow-up result. Exclusion criteria were as follows: (1) receive any anti-tumor treatment (including chemotherapy or surgery) before the first PET/CT examination; and (2) have previous history of other malignancies. Sixteen patients were registered to NHL-2010 regime, and fourteen patients were registered to CCCG-LBL-2016 regime.

Patient's characteristics, including age at diagnosis, gender, stage according to St Jude staging system[11], immunophenotyping including T-LBL and B-LBL, BM infiltration, CNS involvement, and serum lactate dehydrogenase (LDH) and albumin levels at diagnosis were carefully recorded. This study was approved by the Tianjin Medical University Cancer Institute Hospital, and written informed consent was obtained from every patient prior to the treatment.

### 2.2 $^{18}$F-FDG PET/CT scans

The patients were fasted for at least 4 h while maintaining normal blood glucose levels prior to $^{18}$F-FDG PET/CT examination.$^{18}$F-FDG with radiochemical purity of more than 95% was provided by the PET/CT center of our institute, manufactured by USA GE Mini trace cyclotron, and synthesized by Tracerlab FN-FDG synthesizer. GE Discovery Elite PET/CT was used for imaging. The PET/CT image was obtained 60 min after the intravenous injection of 3.7-4.8 MBq/kg $^{18}$F-FDG. CT examination was performed with pitch 0.75 and slice thickness of 3.75 mm, followed by PET acquired from the skull to the mid-thigh for 2 min per bed position. 3D PET images were reconstructed using iterative method.

### 2.3 Image analysis

Images were analyzed by two experienced nuclear medicine physicians to determine lesions by using the Advantage Workstation 4.6 (AW4.6). Focal or diffuse $^{18}$F-FDG uptake above the background excluding normal physiological uptake in PET was considered as a positive lesion as confirmed by the presence of morphologic changes on CT imaging[12]. A focal bone marrow uptake was considered as bone marrow infiltration[13 14]. PET VCAR software was used to delineate the region of interest (ROI). The computer program automatically calculated the metabolic parameters including $SUV_{max}$, metabolic tumor volume (MTV), and TLG. A $SUV_{max}$ threshold of 41%[8] was used to determine MTV. Total MTV (TMTV) was calculated as the sum of MTV of all lesions, and TLG was calculated as the sum of the products of metabolic tumor volume and the mean SUV for each lesion.

### 2.4 Follow-up

All patients were followed until the end of April 2020. The primary endpoint was event-free survival (EFS) defined as the duration from diagnosis to last contact or first event. Events were defined as death for any reason, progression, or relapse. Overall survival (OS) was defined as the duration from diagnosis to last contact or death.

### 2.5 Statistical analysis

Statistical analyses were performed using SPSS 25 software (Chicago, Illinois, USA). Mann–Whitney U-test was used to compare the metabolic parameters of different clinical characteristic groups. Quantitative metabolic parameters ($SUV_{max}$, TMTV, and TLG) were analyzed using receiver operating characteristic (ROC) curve and area under curve (AUC) to estimate the optimal cut-off value. EFS and OS curves were constructed using the Kaplan–Meier method and compared with the results of log-rank test. A P value of $<0.05$ was considered statistically significant.

## 3. Results

### 3.1 Characteristics and outcomes of pediatric patients with LBL

The patient's characteristics are shown in Table 1. Thirty patients (23 males and 7 females) with age range of 17–180 months and a median age of 78 months were included. All the patients were at stages III–IV, among which 18 (60.0%) had the immunophenotype of T-LBL, and 12 (40.0%) had the immunophenotype of B-LBL. Bone marrow infiltration was seen in 10 (33.3%) patients, and CNS involvement was seen in only 3 (10%) patients (Table1).

**TABLE 1** The characteristics of patients with LBL

| Characteristics | Total |
|---|---|
| Gender | |
| Male | 23(76.7%) |
| Female | 7(23.3%) |
| Age median (range) | 78(17-180 months) |
| St. Jude Stage | |
| III | 20(66.7%) |
| IV | 10(33.3%) |

| Characteristics | Total |
|---|---|
| Immunophenotyping | |
| T | 18(60.0%) |
| B | 12(40.0%) |
| Bone marrow infiltration | |
| Yes | 10(33.3%) |
| No | 20(66.7%) |
| CNS involvement | |
| Yes | 3(10%) |
| No | 27(90.0%) |
| Mediastinal involvement | |
| Yes | 11(36.7%) |
| No | 19(63.3%) |
| Serum Alb levels | |
| Normal | 21(70.0%) |
| Reduced | 9(30.0%) |
| Serum LDH levels | |
| >2N | 12(40.0%) |
| <2N | 18(60.0%) |

CNS, Central Nervous System; Alb, Albumin; LDH, lactate dehydrogenase;

2N, double times of normal value

After a median follow-up of 41.5 months (range of 1–86 months), six patients suffered recurrence or progression with a median time of 19.0 months (range of 1.0–57.1 months), and five patients died with a median time of 12.7 months (range of 2.4–30.3 months). Two patients died out of progressive infection during the induction chemotherapy regime (both at 1 month). The 2-year EFS of all patients was 83.3% (95%CI 70.0% to 96.6%) and the 3-year EFS was 75.4% (95%CI 59.4% to 91.3%). The 2-year OS was 86.7% (95%CI 74.5% to 98.9%), and the 3-year OS was 78.4% (95%CI 62.9% to 93.9%). The median EFS and OS were both 41.5 months (range of 1–86 months) (Fig. 1).

### 3.2 Comparison of metabolic parameters among different clinical characteristics

The clinical characteristics and $^{18}$F-FDG PET/CT metabolic parameters are shown in Table 2. The median $SUV_{max}$, TMTV, and TLG were 7.1, 172.13 $cm^3$, and 521.90 g, respectively. As displayed in Table 3, no significant difference in $SUV_{max}$ was found among various clinical characteristics ($P$ >0.05). However, the patients at stage IV had significantly higher TMTV than those at stage III (176.52 $cm^3$ vs. 580.66 $cm^{3;}$ $P$ = 0.031). The patients with T-LBL and mediastinal involvement had a high TMTV ($P$ <0.05) and TLG ($P$ <0.05).

**TABLE 2** The Characteristics of baseline PET/CT metabolic parameters

| Characteristic | Median | Range |
|---|---|---|
| $SUV_{max}$ | 7.1 | 2.66-25.78 |
| TMTV ($cm^{3)}$) | 172.13 | 10.09-2145.81 |
| TLG (g) | 521.90 | 47.59-5930.88 |

**TABLE 3** Comparison of PET/CT metabolic parameters among different clinical Characteristics

| | $SUV_{max}$ | $SUV_{max}$ | $SUV_{max}$ | TMTV ($cm^3$) | TMTV ($cm^3$) | TMTV ($cm^3$) | TLG(g) | TLG |
|---|---|---|---|---|---|---|---|---|
| | Mean | U | *p* | Mean | U | *P* | Mean | U |
| Gender | | | | | | | | |
| Male | 10.12 | 59.50 | 0.303 | 308.97 | 72.00 | 0.677 | 1174.74 | 79.0 |
| Female | 8.14 | | | 318.66 | | | 944.99 | |
| St. Jude Stage | | | | | | | | |
| III | 11.48 | 57.50 | 0.061 | 176.52 | 51.00 | 0.031[a] | 1001.99 | 76.0 |
| IV | 6.00 | | | 580.66 | | | 1359.41 | |
| Immunophenotyping | | | | | | | | |
| T | 10.30 | 97.00 | 0.641 | 337.42 | 51.00 | 0.016[a] | 1304.02 | 50.0 |
| B | 8.70 | | | 271.95 | | | 846.79 | |
| Bone marrow infiltration | | | | | | | | |
| Yes | 6.81 | 71.50 | 0.210 | 408.23 | 55.00 | 0.048[a] | 993.98 | 81.0 |
| No | 11.08 | | | 262.73 | | | 1184.70 | |
| CNS involvement | | | | | | | | |
| Yes | 5.78 | 26.00 | 0.316 | 795.59 | 36.00 | 0.756 | 2192.06 | 35.0 |
| No | 10.09 | | | 257.41 | | | 1002.14 | |
| Mediastinal involvement | | | | | | | | |
| Yes | 11.43 | 79.50 | 0.282 | 347.19 | 48.00 | 0.015[a] | 1337.42 | 49.0 |
| No | 8.63 | | | 290.41 | | | 995.91 | |
| Serum Alb levels | | | | | | | | |
| Normal | 9.59 | 84.00 | 0.635 | 329.99 | 85.00 | 0.667 | 1147.14 | 84.0 |
| Reduced | 9.81 | | | 267.46 | | | 1060.44 | |
| Serum LDH levels | | | | | | | | |
| ¿2N | 10.07 | 78.00 | 0.204 | 374.05 | 92.00 | 0.498 | 1475.51 | 62.0 |
| ¡2N | 9.38 | | | 269.35 | | | 884.87 | |

[a], Statistical significance

### 3.3 Role of $^{18}$F-FDG PET/CT in outcome prediction

For EFS, ROC curves showed that 5.14, 242.91 $cm^3$, and 978.03 g were the optimal cut-off value (Table 4). Given the small AUC at $SUV_{max}$, the median of 7.1 was considered as the suitable cut-off point. The EFS of patients with a low TMTV (<242.91 $cm^3$) was significantly better than that of patients with a high TMTV (>242.91 $cm^3$) with 3-year EFS rates of 88.9% and 56.3%, respectively ($P = 0.036$; Figure 2). $SUV_{max}$ and TLG were not significantly predictive of EFS ($P$ >0.05; Table5; Figure3-4).

For OS, ROC curves revealed that 10.15, 165.14 $cm^3$, and 978.03 g were the optimal cut-off value (Table 4). However, $SUV_{max}$, TMTV, and TLG were not associated with OS ($P$ >0.05; Table 5, Figures 2-4).

**TABLE 4** Receiver operating characteristic (ROC) curve analysis of PET/CT metabolic parameters

| | EFS | EFS | EFS | EFS | EFS | EFS |
|---|---|---|---|---|---|---|
| | AUC (95% CI) | AUC (95% CI) | Cut-off | Sensitivity | Specificity | *p* |
| $SUV_{max}$ | 0.509(0.279-0.738) | 5.14 | 5.14 | 0.875 | 0.320 | 0.944 |
| TMTV | 0.716(0.527-0.904) | 242.91 | 242.91 | 0.750 | 0.727 | 0.075 |
| TLG | 0.682(0.479-0.885) | 978.03 | 978.03 | 0.625 | 0.727 | 0.133 |

| OS | OS | OS | OS | OS |
|---|---|---|---|---|
| AUC (95% CI) | Cut-off | Sensitivity | Specificity | *p* |

| | OS | OS | OS | OS | OS |
|---|---|---|---|---|---|
| $SUV_{max}$ | 0.569(0.305-0.834) | 10.15 | 0.500 | 0.708 | 0.604 |
| TMTV | 0.694(0.479-0.910) | 165.14 | 0.833 | 0.542 | 0.147 |
| TLG | 0.694(0.458-0.931) | 978.03 | 0.667 | 0.708 | 0.147 |

**TABLE 5** Analysis of 3-year EFS and OS according to cut-off values of parameters

| | 3-years EFS | 3-years EFS | 3-years EFS | 3-years EFS | 3-years OS | 3-years OS | 3-years OS |
|---|---|---|---|---|---|---|---|
| | Value | *P* | *P* | $\chi^2$ | Value | *P* | $\chi^2$ |
| $SUV_{max}$ | | | | | | | |
| Low | 80.0% | 80.0% | 0.874 | 0.025 | 85.0% | 0.454 | 0.560 |
| High | 73.3% | 73.3% | | | 70.0% | | |
| TMTV | | | | | | | |
| Low | 88.9% | 88.9% | 0.036[a] | 4.388 | 92.9% | 0.119 | 2.428 |
| High | 56.3% | 56.3% | | | 66.5% | | |
| TLG | | | | | | | |
| Low | 84.2% | 84.2% | 0.152 | 2.049 | 89.5% | 0.120 | 2.419 |
| High | 61.4% | 61.4% | | | 61.4% | | |

[a], Statistical significance

## 4. Discussion

In this study, we retrospectively investigated the prognostic value of baseline $^{18}$F-FDG PET/CT metabolic parameters in pediatric LBL and found that TMTV has a potential role in predicting the outcome of this disease, whereas $SUV_{max}$ and TLG show no value.

FDG PET/CT has been widely used in pediatric HL[6 15 16]. Compared with conventional methods, PET has advantages of sensitivity and specificity in detecting lesions[17] and has become an indispensable technique to evaluate the spread of diseases[6 15]. Many studies have been dedicated to response-adapted treatment based on PET/CT in pediatric HL[18-20]. However, the research on PET/CT in pediatric NHL is limited[9]. Elhussein et al.'s[10] study involved 18 children with LBL and showed that all lesions are FDG-avid, and PET/CT plays a useful role in assessing the spread of disease. Park et al.[21]reported the feasibility of identifying the extent of T-LBL in adults by using PET/CT. Becker et al.[8] investigated the prognostic value of PET/CT metabolic parameters in adults with T-LBL and revealed that $SUV_{max}$ has a substantial prognostic value.

Various PET/CT metabolic parameters, including $SUV_{max}$, SUV normalized by lean body mass (SUL or $SUV_{LBM}$), TMTV, and TLG, have been used in oncologic studies[7]. Among which, the most commonly used is $SUV_{max}$, the maximum voxel value of SUV in the tumor that represents the most aggressive fragment of lesions[22] and is advantageous in distinguishing benign or malignant tumor[23 24]. However, the prognostic value of $SUV_{max}$ is still controversial. $SUV_{max}$ is not predictive of the outcomes in multiple adult lymphomas including diffuse large B-cell lymphoma[22], Burkitt lymphoma[25], and mantle cell lymphoma[26]. Some studies showed that $SUV_{max}$ could be an important prognostic factor for NK/T cell lymphoma[27 28] and Ewing Sarcoma[29]. Most previous investigations reported that a high initial $SUV_{max}$ indicates a poor outcome. Becker et al. [8] showed that baseline $SUV_{max}$is predictive of outcomes in adults with T-LBL. However, the patients with a low baseline $SUV_{max}$ have poor outcomes. They speculated that the correlation between *NOTCH* mutation status and $SUV_{max}$ may be responsible for this result. In a study involving forty seven children, Zhou et al. [12] found that $SUV_{max}$ fails to predict the outcome of pediatric lymphoma. Similar result is shown in our study, in which the $SUV_{max}$ of baseline PET/CT was unrelated to the EFS and OS of children with LBL. Owing to its limits, the inefficiency of $SUV_{max}$ for predicting prognosis can be

interpreted as the following reasons. First, many factors, including injection time, administered FDG dose, residual activity in the syringe, decay of the injected dose, can affect the reliability of SUV[30]. Second, $SUV_{max}$ can only reflect the characteristics of the most aggressive cell components without considering the volume, that represents the burden of the tumor.

Compared with the prognostic factors that roughly describe tumor burden, including stage, LDH level, bone marrow infiltration, and CNS involvement, the metabolic parameters TMTV and TLG in PET/CT can directly measure the whole-body tumor burden[7 31]. Our study revealed that patients with stage IV had a high TMTV, indicating a high tumor burden. Furthermore, patients with T-LBL, bone marrow infiltration, or mediastinal involvement had a high TMTV. The patients with T-LBL mostly present with mediastinal involvement[1] and suffered from disseminated disease (stages III–IV)[32]. In addition, the patients with bone marrow infiltration were subjected to stage IV. These clinical characteristics may contribute to this result. Therefore, we believe that TMTV can accurately represent tumor burden.

TMTV is correlated to prognosis[22 28 33]. Contrary to our results, Becker et al.[8] believed that TMTV is not predictive of the outcome in adult T-LBL. This discrepancy can be explained by the following reasons. First, extrapolating adult conclusions to children is unreasonable. Second, our study included patients with T-LBL and B-LBL all at stages III–IV. Conversely, the previous research only contained T-LBL distributed in all stages. In our study, the patients with a low TMTV had good EFS, which is in accordance with the study of Zhou et al.[12]. Although not significantly, the patients with a high TMTV had a poor OS. Nevertheless, the measurement method for TMTV in our study was different: as recommended by the European Association of Nuclear Medicine[34], a $SUV_{max}$ threshold of 41% was used to determine the TMTV. Meanwhile, a fixed $SUV_{max}$ threshold of 2.5 was used in the study of Zhou et al. Given the extensive lesions with diverse sizes in lymphoma and varied intensities of nodal FDG uptake[10], the former method was considered more suitable for pediatric LBL compared with the latter. Meignan et al.[35] reported that the $SUV_{max}$ threshold of 41% may overestimate the volume of tumors $< 5.6$ $cm^3$ but had a limited effect on TMTV. It is worth mentioning that there is no standard method for calculating MTV[12]. In the current work, an optimal cut-off of 242.91 $cm^3$ for TMTV was reported for pediatric LBL.

TLG reflects the tumor metabolic activity and volume [7]and calculated as the sum of the MTV*$SUV_{mean}$ (mean SUV) of all lesions. The prognostic value of TLG is still vague. Some studies believed that TLG is relevant to the outcomes in various lymphomas[12 25 26 36]. Our result coincides with the study of Park et al.[37] who showed that the TMTV of baseline PET/CT is an independent prognostic factor in patients with NHL patients, whereas TLG is not remarkably related to the outcomes. By contrast, Becker et al.[8] reported that TMTV is not predictive of the outcome in adult T-LBL. As mentioned above, many factors affect SUV value, and the discrepancy may be attributed to this result.

This study has some limitations. First, with its single-center retrospective design, this work assigned patients to different treatment regimes. Furthermore, a small number of patients were enrolled, and multivariate analysis was not suitable. Therefore, multi-center prospective studies with large population are necessary to determine the optimal role of TMTV.

## 5. Conclusion

TMTV may be a potential PET/CT metabolic parameter for predicting the prognosis of pediatric LBL. A high TMTV indicates a poor outcome. However, $SUV_{max}$ and TLG are not related to the prognosis of this disease.

## Conflict of Interest

The authors declare no conflict of interest.

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## DATAAVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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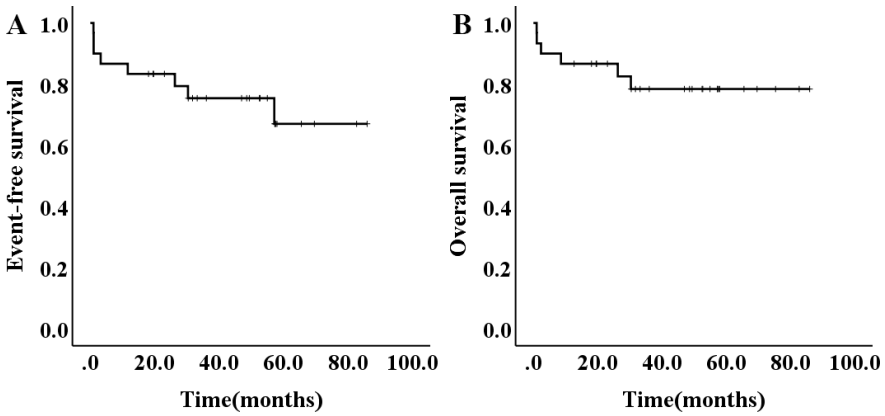

FIGURE 1 Kaplan Meier Curve for event-free Survival (A) and overall survival (B)

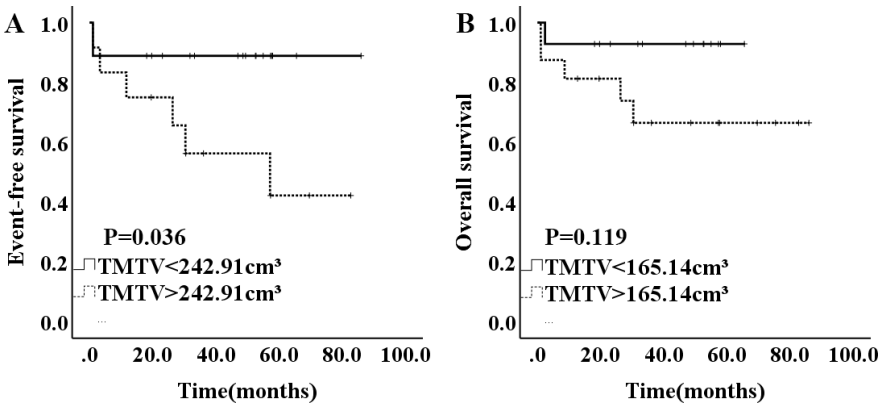


FIGURE 2 Kaplan Meier Curve for event-free Survival (A) and overall survival (B) according to TMTV. TMTV was associated with EFS, while a high TMTV predicted a poor EFS. However, TMTV was not predictive for OS.

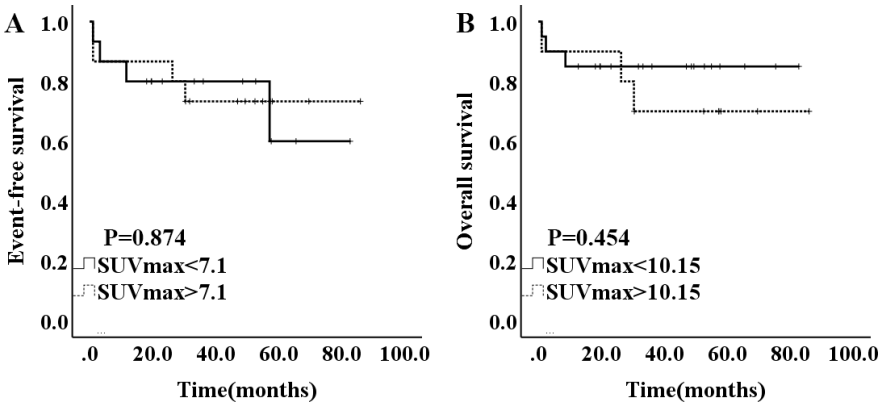


FIGURE 3 Kaplan Meier Curve for event-free Survival (A) and overall survival (B) according to SUVmax. SUVmax was not predictive for EFS and OS.

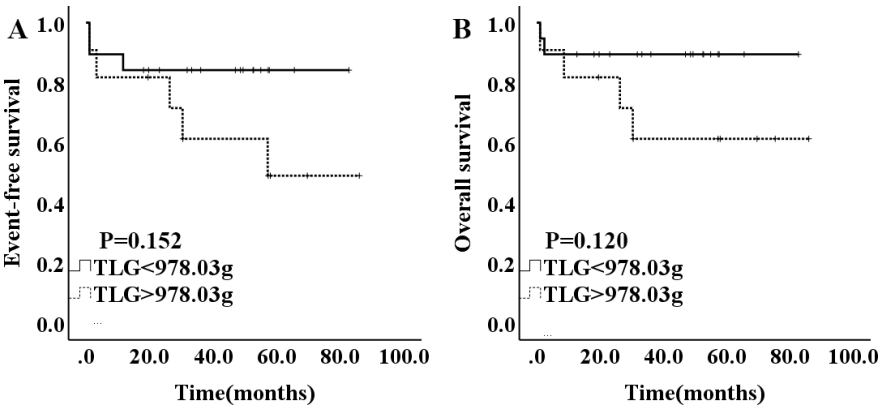

FIGURE 4 Kaplan Meier Curve for event-free Survival (A) and overall survival (B) according to TLG. TLG was not associated with EFS and OS.

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