The value of 18 F-FDG PET/CT quantitative indexes in the diagnosis of non-destructive PTLD after pediatric liver transplantation

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September 5, 2022

Abstract

Rationale: Post-transplant lymphoproliferative disease (PTLD) is a serious complication after pediatric liver transplantation (pLT), which may lead to death. ^{18}F-FDG PET/CT is rarely considered in PTLD after pLT and lacks clear diagnostic guidelines, especially in the differential diagnosis of non-destructive PTLD. The aim of this study was to find a quantifiable ^{18}F-FDG PET/CT index to identify non-destructive PTLD after pLT. **Materials and Methods:** This retrospective study collected the data of patients who underwent pLT, postoperative lymph node biopsy, and ^{18}F-FDG PET/CT at Tianjin First Central Hospital from January 2014 to December 2021. Quantitative indexes were established using lymph node morphology and the maximum standardized uptake value (SUVmax). **Results:** A total of 83 patients met the inclusion criteria and were included in this retrospective study. To distinguish between PTLD-negative cases and non-destructive PTLD cases, according to the receiver operating characteristic curve, [the shortest diameter of the lymph node at the biopsy site (SDL)/the longest diameter of the lymph node at the biopsy site (LDL)]*[SUVmax at the biopsy site (SUVmaxBio)/SUVmax of the tonsils (SUVmaxTon)] had the maximum area under the curve (0.923; 95% confidence interval, 0.834–1.000), and the cut-off value was 0.264 according to the maximum value of Youden's index. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 93.6%, 94.7%, 97.8%, 85.7%, and 93.9%, respectively. **Conclusions:** (SDL/LDL)*(SUVmaxBio/SUVmaxTon) has good sensitivity, specificity, positive predictive and negative predictive values, and accuracy, and can be used as a good quantitative index for the diagnosis of non-destructive PTLD.

Introduction

Liver transplantation is the most effective treatment for end-stage liver disease in children. Due to the use of immunosuppressants, infection by the Epstein–Barr virus (EBV) is common after pediatric liver transplantation (pLT)(1), and post-transplant lymphoproliferative disease (PTLD) related to EBV is a serious complication with a poor prognosis that can lead to death after pLT(2, 3).

Compared to adults, children with PTLD show obvious characteristics in terms of incidence rate and performance. The incidence of PTLD after solid organ transplantation in children is higher than that in adults(4). With the growing number of pLT procedures in recent years, the number of pediatric cases of EBV-related PTLD has also increased year by year. Different from the 80%–90% rate of EBV infection in adults, only about 20%–50% of children are EBV carriers by the age of 5 years, and their symptoms may be hidden or they may show symptoms of EBV infection (fever, night sweats, and weight loss), lymph node hyperplasia, or graft dysfunction(5-8).

Histopathological examination is the gold standard for the diagnosis and classification of PTLD after pLT. According to the World Health Organization classification of lymphomas (2017) revised edition, PTLD can be divided into the following categories: (I) non-destructive PTLD, including plasmacytic hyperplasia PTLD, infectious mononucleosis PTLD, and florid follicular hyperplasia PTLD; (II) polymorphic PTLD; (III) monomorphic PTLD, including B- and T-/natural killer cell types; and (IV) classical Hodgkin's lymphoma PTLD(9-11). However, as an invasive assessment, histopathological examination will inevitably do some harm to patients. As a non-invasive method,^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) imaging has been widely used in adult PTLD, but its application in children is less commonly reported. A recent study involving 28 children with PTLD showed that ^{18}F-FDG PET/CT has a good positive predictive value (PPV) and specificity, but its sensitivity and negative predictive value (NPV) were poor. This may be because children grow and develop rapidly, and there are high metabolic regions such as the brain, kidneys, and heart that render^{18}F-FDG PET/CT unable to detect PTLD that can be confirmed by histology in these regions(12). Studies have shown that the median peak standardized uptake value (SUVpeak) at the biopsy site of monomorphic PTLD is significantly higher than those of the polymorphic and non-destructive subtypes of PTLD. However, it is difficult to distinguish between PTLD-negative cases and non-destructive PTLD cases using SUVpeak due to the significant SUV overlap of the different subtypes(13). Therefore, it is of significant interest to find an index that can distinguish PTLD-negative cases and non-destructive PTLD cases with high sensitivity, specificity, PPV, NPV, and accuracy; confirm or refute the clinical suspicion of PTLD; and identify suggestive lesions accessible for biopsy. This study reviewed and collected clinical and pathological data of pLT patients who underwent^{18}F-FDG PET/CT and lymph node biopsy, explored the indicators that can effectively distinguish PTLD-negative cases and non-destructive PTLD cases, and evaluated their effects.

Materials and Methods

Patient selection

This retrospective analysis included consecutive pLTs performed between January 2014 and December 2021 at the Department of Pediatric Transplantation, Tianjin First Central Hospital, Tianjin, China. The inclusion criteria were as follows: (I) the patient's age at the time of operation was <14 years and (II) ^{18}F-FDG PET/CT and lymph node biopsy were performed simultaneously in patients with clinically suspected PTLD. This study was approved by the Tianjin First Central Hospital Medical Ethics Committee (approval no. 2022N140KY).

Interpretation and examination of^{18}F-FDG-PET/CT scans

All patients fasted for [?]6 h. ^{18}F-FDG was purchased from Tianjin Atom High Science Isotopes Medicine Co., Ltd. According to the manufacturer's test, the radiochemical purity of^{18}F-FDG is 98%. The dose of ^{18}F-FDG was adjusted according to the body weight of the patient. Sixty minutes after intravenous injection, the whole-body PET/CT examination was performed using a Biograph mCT 64 system (Siemens Healthineers, Erlangen, Germany) in the supine position. Whole-body CT images were obtained for attenuation mapping and lesion localization (94–140 mAs, 120 kVp, 5-mm-wide section). We reconstructed a 3.0-mm-thick section for attenuation correction and then performed subsequent image fusion. PET images of the same area were acquired following CT scans in a 3-dimensional mode, with 6–7 bed positions. We used an iterative algorithm to reconstruct the image, transferred the image to a dedicated workstation (syngoMMWP VE40A; Siemens Healthineers), and used the syngo TrueD software program (TRUED_ SYSLATEST_VE10A40; Siemens Healthineers) for analysis. Main outcome measures included the location, quantity, and size of abnormal ^{18}F-FDG uptake. During quantitative analysis, the maximum standardized uptake value (SUVmax) and the maximum standardized uptake value of the posterior wall of tonsil or nasopharynx (SUVmaxTon) were measured or calculated using TrueD software.

Lymph node biopsy

The pathological results of lymph node biopsy are the gold standard for the diagnosis of PTLD. A true-positive (true-negative) result means that the ^{18}F-FDG PET/CT scan or judgment index is positive (neg-

ative) for PTLD and the pathological diagnostic result is positive (negative) for PTLD. A false-positive (false-negative) means that the ^{18}F-FDG PET/CT scan or judgment index is positive (negative) for PTLD but the pathological diagnostic result is negative (positive) for PTLD.

Statistical analysis

Categorical variables are expressed in frequency and proportion. Continuous variables that conformed to the positive distribution are expressed as mean and standard deviation (SD) values, while continuous variables that did not conform to the positive distribution are expressed as median and interquartile range (IQR) values. The Chi-squared test or Fisher's exact test was used to analyze the categorical variables, when appropriate. The Mann–Whitney U test or independent-samples t test was used to assess the continuous variables, when appropriate. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the discriminative ability. The AUC varied from 0.5 to 1.0, with 0.5 representing a random chance and 1.0 representing a perfect fit. Sensitivity, specificity, PPV, NPV, and accuracy were calculated with a 95% confidence interval (CI). Statistical analyses were conducted using SPSS, version 26.0.0.2 (IBM Corporation, Armonk, NY, USA) and R version 4.2.1 (*http://www.R-project.org*; The R Foundation for Statistical Computing, Vienna, Austria). $P< 0.05$ was considered to be statistically significant.

Results

Patients' basic information

From January 2014 to December 2021, 1431 children underwent pLT at the Department of Pediatric Transplantation, Tianjin First Central Hospital. A total of 76 patients were diagnosed with PTLD by lymph node biopsy, for an incidence rate of 5.31%. A total of 83 patients were <14 years old at the time of pLT and underwent lymph node biopsy and ^{18}F-FDG PET/CT in the same period. According to the results of lymph node biopsy, 19 patients (22.9%) were PTLD-negative cases, 47 patients (56.7%) were diagnosed with non-destructive PTLD, 5 patients (6.0%) were diagnosed with polymorphic PTLD, 11 patients (13.3%) were diagnosed with monomorphic PTLD, and 1 patient (1.2%) was diagnosed with classical Hodgkin's lymphoma PTLD (**FIGURE 1**). See **TABLE 1** for the patient characteristics. There were 44 boys (53%) and 39 girls (47%), with a median age of 7.27 (range, 5.85–8.70) months. Among these patients, 73 (88%) underwent pLT for biliary atresia and 10 (12%) underwent pLT for other reasons. Sixty-four patients (77.1%) received LDLT and 19 patients (22.9%) received DDLT. The EBV result was positive in 60 cases (72.3%) and negative in 23 cases (27.7%). The median time between transplantation and ^{18}F-FDG PET/CT was 735 (range, 448–829) days.

PTLD-negative and non-destructive PTLD cases

In this cohort study, 19 patients were PTLD-negative cases and 47 patients were diagnosed with non-destructive PTLD by biopsy.**TABLE 2** shows the clinical baseline characteristics of the two groups. There were no significant differences between the two groups in terms of age at surgery, gender, diagnosis, donor type, EBV status of the tumor, time between transplant and ^{18}F-FDG PET/CT, the longest diameter of the lymph node at the biopsy site (LDL), and SUVmaxTon ($P > 0.05$). In contrast, there were significant differences in the shortest diameter of the lymph node at the biopsy site (SDL), SDL/LDL, SUVmaxBio, SUVmaxBio/SUVmaxTon, and (SDL/LDL)*(SUVmaxBio/SUVmaxTon) between the groups ($P < 0.05$).

^{18}F-FDG-PET/CT index for judging non-destructive PTLD

ROC curve analysis was used to evaluate the value of each index in diagnosing non-destructive PTLD. The results showed that (SDL/LDL)*(SUVmaxBio/SUVmaxTon) had the largest AUC (0.923; 95% CI, 0.834–1.000) (Supplementary Figure 1 and Supplementary Table 1), and the cut-off value was 0.264 (**FIGURE 2**) at the maximum value of Youden's index. According to the cut-off value, the patients were divided into [?] cut-off value group and > cut-off value group, including 21 patients in the [?] cut-off value group and 45 patients in the > cut-off value group. Lymph node biopsy confirmed that 44 cases (66.7%) were true positive, 18 cases (27.3%) were true negative, 1 case (1.5%) was false positive, and 3 cases (4.5%) were false negative (**TABLE 3**). Using (SDL/LDL)*(SUVmaxBio/SUVmaxTon) for the detection of non-destructive

PTLD, the sensitivity was 93.6%, the specificity was 94.7%, the PPV was 97.8%, the NPV was 85.7%, and the accuracy was 93.9% (**TABLE 4**).

Specific information of false-positive and false-negative cases according to the new index judgment of PTLD

The results of non-destructive PTLD diagnosis predicted by the cut-off value showed that there were three false negatives and one false positive. See **TABLE 5** for specific results. The final diagnosis of the false-positive patient was reactive hyperplasia of the lymph nodes, but the SUVmaxBio was too high; so, it was misjudged as PTLD. The final diagnosis of the three false-negative cases was non-destructive PTLD, and their SUVmaxBio or SDL/LDL values were too low; so, they were misjudged as being PTLD-negative cases. **FIGURE 3** shows^{18}F-FDG-PET/CT and lymph node biopsy results of the false-negative and false-positive cases.

Discussion

PTLD is a proliferative disease that results in abnormal cloning of lymphocytes or plasma cells after solid organ transplantation or stem cell transplantation due to immunosuppression of the recipient, and it can eventually progress to malignant invasive lymphoma. At present, it is believed that the occurrence of PTLD is closely related to postoperative EBV infection(14). The incidence of PTLD after pLT can reach 2%–20%(15-17). In pLT, EBV serological negativity before transplantation is considered to be a major risk factor for PTLD. In adult liver transplantation, there are fewer EBV-seronegative recipients(18), which is one of the reasons why the incidence of PTLD after pLT is higher in children than in adults(19). In addition, another major cause of EBV-related PTLD after pLT is the use of immunosuppressive regimens of high intensity and long duration.

There is limited research on the clinical application of^{18}F-FDG PET/CT in children with PTLD, who are usually combined with adult PTLD cohorts(19-23). The results of an adult cohort showed that ^{18}F-FDG PET/CT is a feasible imaging method for the diagnosis of PTLD. However, the sensitivity values and NPVs of ^{18}F-FDG PET/CT in the detection of PTLD were not high in children(21, 24). At present, there are three problems in the study of ^{18}F-FDG PET/CT in children with PTLD. First, most existing studies were descriptive studies, meta-analyses, or reviews(22, 25, 26) or involved comparisons of other non-pathological examination methods using ^{18}F-FDG PET/CT(27). Second, the numbers of cases in studies on ^{18}F-FDG PET/CT and PTLD in children have been small(28), and there are few studies on PTLD after pLT.

The third problem involves the use of ^{18}F-FDG PET/CT in the diagnosis of PTLD in children. At present,^{18}F-FDG PET/CT has no definite quantitative index in the diagnosis of PTLD in children, and it relies more on the experience of nuclear medicine doctors without a formal guideline(29). When reading the report, the nuclear medicine physician will more or less refer to the patient's reasons for seeing a doctor and cannot complete the^{18}F-FDG PET/CT diagnosis of PTLD in a completely independent manner. In this study, ^{18}F-FDG PET/CT reports from nuclear medicine doctors for the diagnosis of non-destructive PTLD had high sensitivity values and NPVs, but the specificity values and PPVs were not high. Considering that low uptake of non-destructive or low-grade PTLD may lead to false-negative results, while high uptake related to infection or inflammatory process may lead to false-positive results, the application of SUV in differentiating benign and malignant lesions is still controversial(22, 30). Therefore, finding a quantifiable ^{18}F-FDG PET/CT index to judge PTLD after pLT was the focus of this study.

Unlike traditional tumor-induced lymphadenopathy, our experience found that there was no significant difference in the longest diameter of lymph nodes between PTLD-negative cases and non-destructive PTLD cases. Moreover, the longest diameter of lymph nodes in different parts of the body also varies. Clinically, we are not concerned about the longest diameter of lymph nodes in PTLD patients in the early stage but instead with the morphology of lymph nodes. We found that the lymph nodes of patients with non-destructive PTLD were rounder than those of PTLD-negative cases. This was reflected in the ratio of the shortest diameter of the lymph node to the longest diameter of the lymph node; if the ratio was closer to 1, it meant that the shape of the lymph node was more spherical, while, if it was closer to 0, it meant that the

shape of the lymph node was closer to an ellipse. Another problem we found in clinical practice pertains to the SUVmax value. The SUVmax value in our data can effectively distinguish between monomorphic PTLD and polymorphic or non-destructive PTLD. However, although there was a statistical difference in SUVmax between PTLD-negative and non-destructive PTLD cases, the sensitivity, specificity, PPV, NPV, and accuracy obtained using this index were poor. In clinical practice, we have found that there are many reasons that can lead to increased uptake of ^{18}F-FDG in tonsils, posterior pharyngeal wall, or adenoids, such as a high EBV DNA load or tonsil hypertrophy(31, 32). Moreover, ^{18}F-FDG uptake also increases in patients with other conditions after transplantation, such as postoperative inflammation, infection, bone marrow activation, or transplant rejection(19). Therefore, we used the ratio of SUVmaxBio to SUVmaxTon to numerically validate our reasoning in the above clinical practice.

Through our calculation, we found that (SDL/LDL)*(SUVmaxBio/SUVmaxTon) had the largest AUC in each combination, and the cut-off value calculated by this index can effectively judge the non-destructive PTLD in children. Using this cut-off value, the sensitivity, specificity, PPV, and accuracy can reach >90%, and the NPV can also reach 85.7%. However, according to this index, there will still be errors. In the data of our center, there were three false-negative cases and one false-positive case. We found that SUVmaxBio was high in the false-positive case, but the high uptake sites of^{18}F-FDG were concentrated in the neck or supraclavicular lymph nodes, and there was no abnormal uptake of^{18}F-FDG in other parts of the body. In the three false-negative cases, the SUVmaxBio or SDL/LDL was too low, resulting in an incorrect prediction. However, in these three cases, abnormally high uptake of ^{18}F-FDG could be seen in many parts of the patient's body, including the neck, supraclavicular fossa, armpit, retroperitoneal para-aortic, and inguinal lymph nodes. Therefore, the use of (SDL/LDL)*(SUVmaxBio/SUVmaxTon) and the subjective judgment of nuclear medicine physicians can further improve the accuracy of diagnosing PTLD-negative and non-destructive PTLD cases. It is worth noting that one false-negative case underwent inguinal lymph node biopsy. The inguinal lymph node SUVmax was 1.25, while the cervical lymph node SUVmax was 6.81. If the cervical lymph node SUVmax value was used, the result of this quantitative index would have been PTLD positivity, which was consistent with the pathological results.

It is undeniable that this study has some limitations. First, this study was a retrospective study, necessitating prospective and multicenter studies for internal and external validation in the future. Second, since the gold standard for the diagnosis of PTLD in this study is lymph node biopsy, the selection of lymph node biopsy site became key. The longest and shortest diameters and SUVmax values of lymph nodes involved in this study were those at the biopsy site. Due to clinical limitations, we selected superficial and easily accessible lymph nodes as much as possible. Therefore, some selected lymph nodes were not the most typical lymph nodes used in ^{18}F-FDG PET/CT reports.

Conclusions

We found that, through ^{18}F-FDG PET/CT, (SDL/LDL)*(SUVmaxBio/SUVmaxTon) can be used as a good quantitative index to distinguish PTLD-negative and non-destructive PTLD cases. The sensitivity, specificity, PPV, NPV, and accuracy were 93.6%, 94.7%, 97.8%, 85.7%, and 93.9%, respectively. (SDL/LDL)*(SUVmaxBio/SUVmaxTon) can improve the diagnosis of non-destructive PTLD after pLT in the future.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Wei Gao and Zhongyang Shen contributed to conception and design, revising the manuscript and approving the final content of the manuscript; Zhuyuan Si, Dongyan Lu, Lili Zhai, Weiping Zheng, Chong Dong, Chao Sun, Kai Wang, Wei Zhang, Zhixin Zhang and Shengqiao Zhao contributed to acquiring data, drafting the manuscript and approving the final content of the manuscript. Xinzhe Wei contributed to analyzing and

interpreting data, revising the manuscript and approving the final content of the manuscript.

Acknowledgments

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

Funding

This study is funded by Tianjin Key Medical Discipline (Specialty) Construction Project; National Natural Science Foundation of China (grant number 82170672) and Project ELITE: A Special Supportive Program for Organ Transplantation by COTDF (No. 2019JYJH03).

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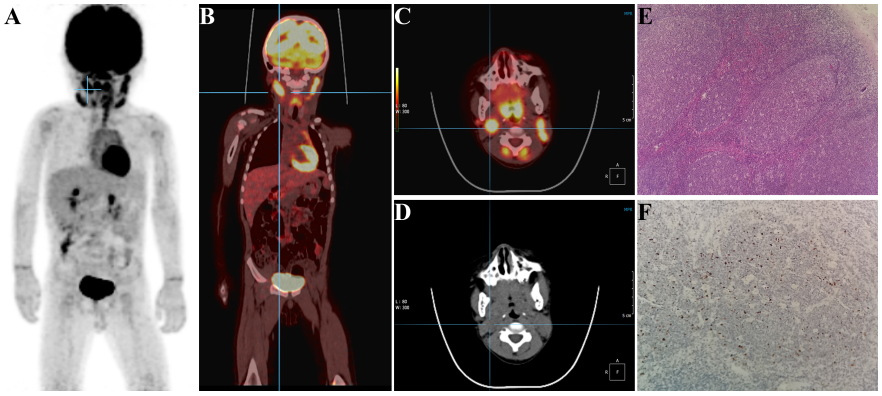
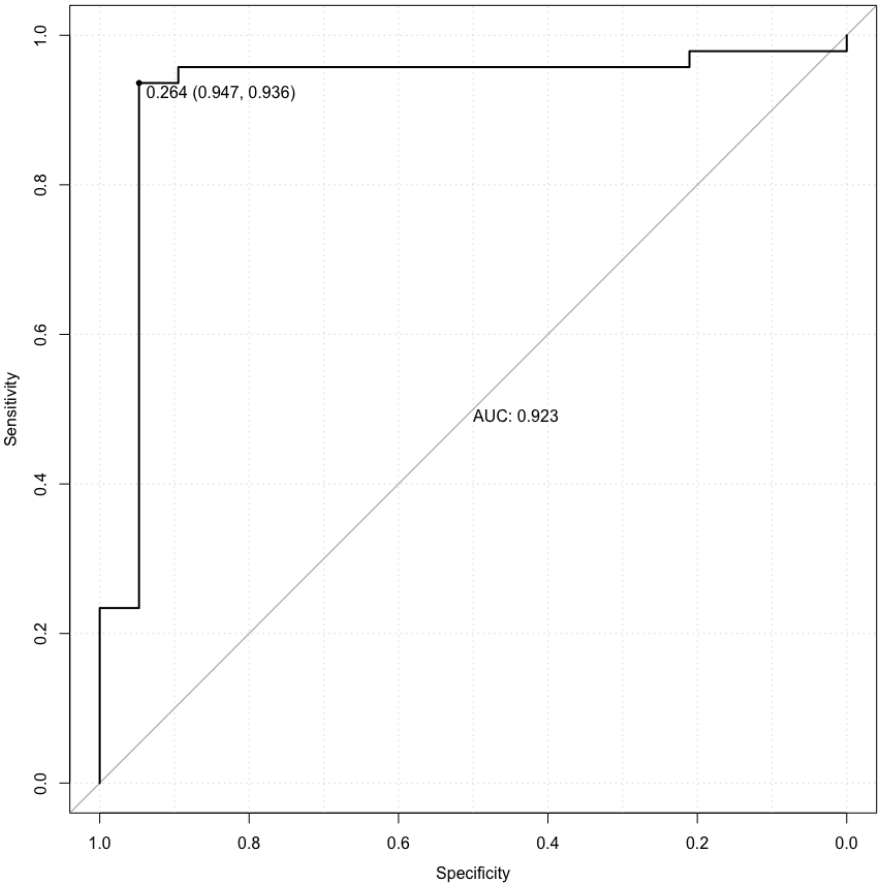
Figure Legends

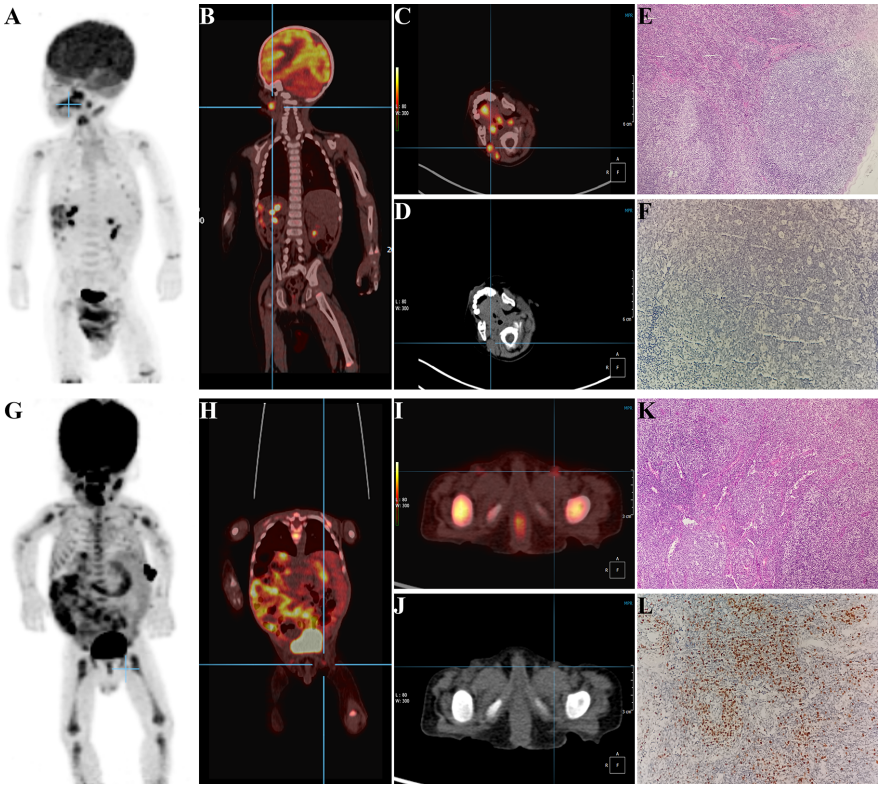
FIGURE 1 A 6-month-old boy received pLT for biliary atresia.^{18}F-FDG PET/CT was performed 2 years and 6 months after the operation due to long-term fever and lymphadenopathy. Key findings of the ^{18}F-FDG PET/CT scan report include the following. First, there were multiple enlarged lymph nodes in the cervical, bilateral parapharyngeal space and right supraclavicular fossa, with abnormally high metabolism, and PTLD was considered. Second, the wall of the nasopharynx was diffusely thickened and the metabolism was abnormally increased; additionally, the morphology of the bilateral tonsils is plump, and the metabolism is diffusely and abnormally high; so, inflammation was considered in our conclusion. (A and B) Maximum-intensity projection and fusion of ^{18}F-FDG PET/CT at the lymph node biopsy site. (C) Axial fusion^{18}F-FDG PET/CT imaging revealed high uptake in the right cervical lymph node. (D) During diagnostic CT imaging, a spherical mass was seen in the right side of the neck. (E) Hematoxylin and eosin staining (×100 magnification) showed lymphoid infiltration. (F) EBV-encoding region in situ hybridization (×200 magnification) showed a positive result.

FIGURE 2 ROC curve. The AUC of the ROC curve was 0.923 (95% confidence interval, 0.834–1.000). The cut-off value at the maximum value of Youden's index was 0.264, and the sensitivity and specificity were 93.6% and 94.7%, respectively.

FIGURE 3 False-positive and false-negative cases. (A–F) False-positive case. A 7-month-old boy received pLT for biliary atresia.^{18}F-FDG PET/CT imaging was performed 8 months after the operation due to lymphadenopathy. Key findings of the^{18}F-FDG PET/CT scan report include the following. First, the top and posterior walls of the nasopharynx were thickened, and the metabolism was abnormally increased. Second, there were multiple cervical enlarged lymph nodes and abnormal metabolism; the above considerations are consistent with PTLD. (A and B) Maximum-intensity projection and fusion of ^{18}F-FDG PET/CT at the lymph node biopsy site. (C) Axial fusion ^{18}F-FDG PET/CT imaging showed high uptake in the right cervical lymph node. (D) During diagnostic CT imaging, a spherical mass was seen in the right side of the neck. (E) Hematoxylin and eosin staining (×100 magnification) showed lymphoid infiltration. (F) EBV-encoding region in situ hybridization (×200 magnification) showed a negative result. (G–L) False-negative case. A 5-month-old boy received pLT for biliary atresia.^{18}F-FDG PET/CT imaging was performed 8 months after the operation due to long-term fever and lymphadenopathy. Key findings of the ^{18}F-FDG PET/CT scan report include the following. First, there were multiple enlarged lymph nodes in the cervical, mediastinum (anterior trachea), bilateral axial, retroperitoneal autonomous aorta and bilateral inguinal areas, with increased metabolism to varying degrees. Second, the wall of the nasopharynx was significantly thickened, and the metabolism was abnormally increased. Third, the soft tissue nodule under the right diaphragm in the abdominal cavity exhibited an abnormally increased metabolism; these findings were consistent with PTLD. (G and H) Maximum-intensity projection and fusion of ^{18}F-FDG PET/CT at the lymph node biopsy site. (I) Axial fusion^{18}F-FDG PET/CT imaging showed high uptake in the inguinal lymph node. (J) During diagnostic CT imaging, a spherical mass could be seen in the groin. (K) Hematoxylin and eosin staining (×100 magnification) showed lymphoid infiltration. (L) EBV-encoding region in situ hybridization (×200 magnification) showed a positive result.







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