論文の内容の要旨

論文題目　Noninvasive monitoring of allograft rejection in a modified rat lung transplant model: Application of machine learning-based 18F- fluorodeoxyglucose positron emission tomography radiomics
(改良ラット肺移植モデルを用いた非侵襲的肺移植後拒絶反応モニタリングの試み：18F-fluorodeoxyglucose positron emission tomography の Radiomics 解析における機械学習の利用)

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Background and Objectives: Lung transplantation (LTx) is the only therapeutic option for end-stage lung diseases. Allograft rejection (AR) is a significant complication limiting the survival of patients after surgery, even though new and effective immunosuppressive drugs have been introduced. It is a substantial complication after LTx without a satisfactory noninvasive method for early detection. The 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) has the potential for lung AR detection, but the accuracy is controversial. Radiomics is a new and developing field in medical imaging, and can quantify spatial relationships among image voxels with the aim of relating imaging information to clinical outcomes. Because of its high-dimensional nature, the field of radiomics needs powerful analytical tools. Machine learning (ML), a branch of artificial intelligence, appears to be a potential candidate for this purpose, having shown powerful capabilities in radiological research. Currently, studies reporting the use of ML algorithms for the detection of lung AR are low in number, and no study has yet reported the performance of ML-based radiomics for monitoring lung AR. It may be applied in a preclinical investigation. Nevertheless, preclinical research needs an ideal animal model as an essential condition. However, the difficulties and disadvantages of this model still exist and remain technically challenging. This study preliminarily investigated the noninvasive method of AR detection using ML-based PET radiomics and had two main aims: (1) To propose modifications of orthotopic LTx in a rat model which achieved the advantages easy mastery, expeditiousness, low complication rate and high success rate. (2) To construct ML-based PET radiomics models for predicting AR, and evaluated their potential for further prediction of AR in comparison with the maximum standardized uptake value (SUVmax) in a rat model.
Methods: Initially, 180 consecutive rats underwent orthotopic left LTx using our modified devices and procedures for various experimental use. Of these, twenty-eight rats were served in the PET experiment. Among this study, four groups were set as follows: isograft,

allograft-cyclosporinecontinuous (CsAcont), allograft-CsAdelayed, and allograft-CsA1week. Rats in the isograft group (n = 8) received no immunosuppressive drugs after LTx. In the allograft- CsAcont group (n = 8), rats were subcutaneously administered CsA until the study endpoint. In the allograft-CsA1week group (n = 8), CsA administration was ceased after the first week. In the allograft-CsAdelayed group (n = 4), CsA was ceased after the first week, but then recommenced after three weeks. The allograft-CsAdelayed group was developed mainly to a mimic the clinical situation of therapeutic process for AR. 18F-FDG PET scans were acquired at weeks 3 and 6 post-procedure, and a pre-set number of rats in each group were sacrificed for pathological evaluation after each scan. Segmentation of the lung graft was performed on each PET image using 3D slicer software. The region of interest (ROI) was manually delineated on the slice with the highest SUV. Subsequently, the radiomics features were extracted from the ROI using the PyRadiomics package in Python. The least absolute shrinkage and selection operator algorithm was used to select AR-related radiomic features and calculate a radiomics score (Rad-score). Correlations between histopathology and image parameters (SUVmax and Rad-score) were assessed. Six subsets of feature selection methods were used by each of the eight modeling algorithms. Therefore, a total of 48 models, including 42 ML models and 6 logistic regression (LR) models, were developed. The performance of these models was assessed using the area under the curves (AUCs). The optimal model was determined by the AUC value. Additionally, we calculated the AUC on SUVmax for making a comparison with the optimal model. ML-based radiomics models for monitoring AR were further validated using leave-one-out cross-validation.

Results: A special cuff-preparation plate was created using a petri dish and two foam blocks which stabilized the cuff preparation and prevented donor lung compression. A "⊥"-shaped incision was carved into the front wall of the pulmonary artery. "V"-shaped incisions were made from the inferior-to-superior branches of the pulmonary vein and bronchus. A "pendulum model" was proposed at implantation to make the hilar anastomosis tension-free and technically easier to perform. There were no intraoperative complications. Ten rats (5.6%) experienced partial or full pulmonary atelectasis. Five deaths (2.8%) due to pleural effusion occurred during the follow-up period. The operative times for heart-lung block retrieval, cuff preparation, cold ischemia, warm ischemia, and total procedure time were 8.4±0.8 min, 11.6±1.5 min, 25.1±2.2 min, 8.1±1.2 min, and 46.7±2.8 min, respectively. Based on the modified cuff technique, we have evaluated the correlation between PET radiomics and lung AR. At week 3, the allograft-CsA1week group showed significantly worse rejection outcomes than both the isograft and allograft-CsAcont groups ($P < 0.05$). At week 6, the allograft-CsA1week group showed significantly

higher AR criteria than the isograft group ($P < 0.05$). Compared with the allograft-CsAdelayed group, the allograft-CsA1week group exhibited a higher value in both A-grade rejection and Fibrosis-(%) ($P < 0.05$). Furthermore, significant decreases in A-grade rejection and Fibrosis-(%) were found from week 3 to week 6 in the allograft-CsAdelayed group ($P < 0.05$). The SUVmax in the allograft-CsA1week group was significantly higher than that in the isograft group ($P = 0.011$) at week 3, and significantly higher than those in the isograft ($P = 0.002$) and allograft-CsAdelayed ($P = 0.001$) groups at week 6. There was a significant decline in SUVmax between week 3 and week 6 in the allograft-CsAdelayed group ($P = 0.014$). The SUVmax was correlated with the AR criteria of A-grade rejection ($r = 0.686$, $P < 0.001$), B-grade rejection ($r = 0.573$, $P = 0.002$), and Fibrosis-(%) ($r = 0.681$, $P < 0.001$). From the PET images, a total of 837 radiomics features were extracted. A large number of radiomic features showed an acceptable correlation with the histopathological results. The Rad-score calculated using seven selected AR-related radiomics features showed significant positive correlations with histopathology ($P<0.05$). The 48 models were developed for predicting AR. The median AUC of 42 ML models was 0.944 (range: 0.878-0.978) which was superior than that of LR models (AUC = 0.794, range: 0.756-0.897). The random forest (RF) modeling algorithm with features selected by the RF (RF-RF) was the optimal model (AUC = 0.978), which significantly outperformed SUVmax (AUC = 0.783). Multidimensional scaling analysis showed rats with or without AR had a different distribution predicted by the RF-RF model. The original_GLDM_GLN presented the most significant among the selected features in the RF-RF model. In the DCA plot, the net benefit of the RF-RF model was greater than the SUVmax over all threshold.

Conclusions: The key tricks and improvements we made in the cuff technique for rat LTx provided the advantages of expeditiousness, a low complication rate, and a high success rate. Following this excellent animal model, we successfully demonstrated that both SUVmax and PET radiomics showed good correlations with AR, and ML-based PET radiomics can further the value of functional imaging with 18F-FDG PET for monitoring AR in a rat LTx model. Our current study supports further evaluation of the utility of this noninvasive method for detecting AR and monitoring the effectiveness of treatment for AR in clinical LTx.