Can the BMI-based dose regimen be used to reduce injection activity and to obtain a constant image quality in oncological patients by \(^{18}\)F-FDG total-body PET/CT imaging?

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Abstract
Purpose PET image quality is influenced by the patient size according to the current guideline. The study aimed to propose an optimized dose regimen to yield a constant image quality independent of patient habitus to meet the clinical needs.

Methods A first patient cohort of 78 consecutive oncological patients (59.7 ± 13.7 years) who underwent a total-body PET/CT scan were retrospectively enrolled to develop the regimen. The patients were randomly distributed in four body mass index (BMI) groups according to the World Health Organization (WHO) criteria. The liver SNR (signal-to-noise ratio, SNRL) was obtained by manually drawing regions of interest (ROIs) and normalized (SNR\(_{\text{norm}}\)) by the product of injected activity and acquisition time. Fits of SNR\(_{\text{norm}}\) against different patient-dependent parameters were performed to determine the best correlating parameter and fit method. A qualitative assessment on image quality was performed using a 5-point Likert scale to determine the acceptable threshold of SNRL\(_{\text{L}}\). Thus, an optimized regimen was proposed and validated by a second patient cohort consisted of prospectively enrolled 38 oncological patients.

Results The linear fit showed SNR\(_{\text{norm}}\) had the strongest correlation (R\(^2\) = 0.69) with the BMI than other patient-dependent parameters and fit method. The qualitative assessment indicated a SNR\(_{\text{L}}\) value of 14.0 as an acceptable threshold to achieve sufficient image quality. The optimized dose regimen was determined as a quadratic relation with BMI: injected activity (MBq) = 39.2 (MBq)/(−0.03*BMI + 1.49)\(^2\). In the validation study, the SNR\(_{\text{L}}\) no longer decreased with the increase of BMI. There was no significant difference of the image quality regarding the value of SNR\(_{\text{L}}\) between different BMI groups (\(p > 0.05\)). In addition, the injected activity was reduced by 75.6 ± 2.9%, 72.1 ± 4.0%, 67.1 ± 4.4%, and 64.8 ± 3.5% compared with the first cohort for the four BMI groups, respectively.

Conclusion The study proposed a quadratic relation between the \(^{18}\)F-FDG injected activity and the patient’s BMI for total-body \(^{18}\)F-FDG PET imaging. In this regimen, the image quality can maintain in a constant level independent of patient habitus and meet the clinical requirement with a reduced injected activity.

Keywords Image quality · Dose optimization · Patient habitus · Total-body PET · FDG · PET/CT imaging
F-18-fluorodeoxyglucose positron emission tomography/computed Tomography ($^{18}$F-FDG PET/CT) has been widely used in tumor diagnosis, staging, restaging, and response evaluation. Meanwhile, this hybrid imaging modality has shown the potential value in prognosis prediction and image-guided biopsy, providing both anatomic and functional information for clinical management [1–5]. The total-body PET/CT, uEXPLORER (United Imaging Healthcare, China), with an increased geometric coverage to encompass the entire body, can dramatically improve the PET sensitivity by a factor of about 40 over existing PET scanners for imaging the entire body. This predicted gain in sensitivity has various implications, such as to improve the image quality to reconstruct images with higher resolution and allow detection of smaller or lower-contrast structures. In addition, it can be used in the clinical practice with the reduced injected activity or short PET acquisition duration while maintaining the image quality [6].

Previously, our team has conducted a series of research on PET image quality with the uEXPLORER. Zhang et al [7] found that oncological patients with an injected activity of 4.4 MBq/kg and an acquisition time of 30–60 s could obtain an acceptable image quality for total-body PET imaging. Furthermore, our previous results showed that total-body PET/CT with half-dose (1.85 MBq/kg) $^{18}$F-FDG of 2-min acquisition could achieve an equivalent image quality to that of whole-body PET/CT with full-dose (3.7 MBq/kg) in lung cancer [8]. Recently, Liu et al reported that dynamic PET imaging of ultra-low-dose (0.37 MBq/kg) injected activity achieved relevant kinetic metrics of $^{18}$F-FDG and comparable image contrast with full-dose imaging [9].

However, these studies have all adopted a weight-based injected activity as recommended in the European Association of Nuclear Medicine (EANM) Guideline [10]. It is well-known that the linear weight-based dose regimen had several deficiencies for a stable and reliable PET image quality, especially in obese patients with a significantly high amount of body fat, resulting in low FDG accumulation [11]. Thus, this study aimed to further investigate the influence of patient habitus on PET image quality and propose a personalized dose regimen to yield a more constant image quality.

**Materials and methods**

**Patients**

The study included two cohorts to develop and validate the new dose regimen for total-body PET imaging. We retrospectively enrolled 78 consecutive patients as the first patient cohort, who were referred to our center for $^{18}$F-FDG PET/CT examinations from September 2019 to July 2020. They were randomly selected from the database of our center. Patients with severe fatty liver, cirrhosis, and multiple liver metastases were excluded. The included patients were equally distributed in each BMI group according to the criteria of the WHO [12], with 20 patients in the underweight group, 19 patients in the normal-weight group, 19 patients in the overweight group, and 20 patients in the obese group. Subsequently, the second patient cohort consisting of 38 patients with known or suspected malignancy were prospectively enrolled to validate the proposed dose regimen, including 7 patients, 10 patients, 11 patients, and 10 patients for each BMI group, respectively. Exclusion criteria for the second patient cohort are those with diabetes or younger than 18 years old. The demographic characteristics of patients in the two cohorts were extracted from the database, including gender, age, body mass (BM), and height (H). BMI (kg/m$^2$) was calculated by dividing the BM (kg) by the square of height (m). Considering human body composition, lean body weight (LBW, kg) and fat mass (FM, kg) were also investigated as the patient-dependent parameters in the study. LBW for male and female as well as FM was calculated as follows (Eqs. 1–3, respectively) [13].

\[
LBW_{\text{male}} = 28.27 \times H + 0.359 \times BM - 0.032 \times \text{age} - 21.83
\]

\[
LBW_{\text{female}} = 26.12 \times H + 0.253 \times BM - 0.022 \times \text{age} - 19.58
\]

\[
FM = BM - LBW
\]

In Eqs. 1 and 2, LBW is the lean body weight in kilograms, H is the height in meters, BM is the body weight in kilograms, and age is patient age in years. In Eq. 3, FM is the fat mass in kilograms, BM is the body weight in kilograms, and LBW is the lean body weight in kilograms. This study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University. Informed consent was waived to the patients in the first cohort due to the retrospective nature and all patients in the second cohort signed an informed consent prior to the PET/CT scan.

**PET/CT examination**

All patients were instructed to fast and avoid strenuous exercise at least 6 h prior to the $^{18}$F-FDG injection, and blood glucose level was measured and recorded. In the study on the first patient cohort, a bolus injection of $^{18}$F-FDG (3.7 MBq/kg) was intravenously administered. In the study of the second patient cohort, the injection activity was strictly following the proposed dose regimen. All images were acquired on the uEXPLORER. A CT scan was performed before PET imaging for attenuation correction and anatomical localization with a dose modulation technique. Subsequently, a total-body PET imaging was performed with 5-min acquisition with arms down positioning.
PET raw data was segmented into 30, 45, 60, and 120 s from the 300 s list-mode data, referred as G30, G45, G60, G120, and G300. All the PET images were reconstructed using a 3D ordered subset expectation maximization algorithm with the following parameters: 3 iterations, 20 subsets, a matrix of 192 × 192, slice thickness of 1.443 mm, time of flight and point spread function modeling. A Gaussian filter with a full width at half maximum of 3 mm was applied to the reconstructed images.

### Image analysis

In PET clinical studies, the signal-to-noise ratio in the liver (SNR_L) was used as a measure of image quality as it is the organ with a relatively homogeneous uptake of FDG in the human body. It is well-known that various factors, such as the patient weight, injected activity, and acquisition time, can impact the SNR_L.

For a given situation on a PET scanner, SNR in PET images is dominated by the Poisson statistics inherent in radionuclide decay detection and is proportional to the square root of the detected events. In the first-order approximation we expect that [7].

\[
\text{SNR} \approx k \sqrt{S \times A \times t} \tag{4}
\]

where \(k\) is a constant, \(S\) is the effective sensitivity of the scanner, \(A\) is the injected activity (MBq), and \(t\) is the acquisition time per bed position (min). Here, the dose-time product (DTP, MBq·min) is the product of the injected activity (MBq) and the acquisition time per bed position (min). If the SNR in the liver is normalized by the square root of the DTP, it can be assumed to be independent of the injected activity and the acquisition time (Eq. 5) [14]. Therefore, \(\text{SNR}_{\text{norm}} (1/\sqrt{\text{MBq} \cdot \text{min}})\) can be regarded as a function of patient-dependent parameters and investigated in the study.

\[
\text{SNR}_{\text{norm}} = \frac{\text{SNR}_L}{\sqrt{\text{DTP}}} \tag{5}
\]

In the first part of the study, the slice with the largest cross section in the liver on the CT transverse slice was determined. In the corresponding PET slice and two adjacent slices, a circular region of interest (ROI) with a diameter of 20 ± 1 mm was manually drawn in a lesion-free and homogenous region of the right liver lobe with care to avoid large blood vessels and the partial volume effect (Supplementary Fig. 1). The ROIs were identical in all the three slices. Liver standard uptake value (SUV) and its standard deviation (SD) were measured and recorded and determined as the average of three ROIs. The \(\text{SNR}_L\) was obtained by dividing the liver SUV\text{mean} by its SD (Eq. 6) [15].

\[
\text{SNR}_L = \frac{\text{SUV}_{\text{mean}}}{\text{SD}} \tag{6}
\]

Both linear and non-linear fits were performed with the \(\text{SNR}_{\text{norm}}\) vs. the patient-dependent parameters. The highest coefficient of determination \((R^2)\) was used to determine the best-correlated parameter and fit method. In addition, the relation between the \(\text{SNR}_{\text{norm}}\) and the patient-dependent parameters, referred as \(\text{SNR}_{\text{fit}}\) were obtained from the fit function (Eq. 7).

\[
\text{SNR}_{\text{norm}} \approx \text{SNR}_{\text{fit}} = a(p + b)^c \tag{7}
\]

where \(p\) indicated the best-correlated parameter and \(a, b,\) and \(c\) were constants derived from the fit function.

In order to determine the acceptable \(\text{SNR}_L\) threshold \((\text{SNR}_{\text{acc}})\), a qualitative analysis on image quality was performed. The image quality was independently assessed by two experienced nuclear medicine physicians on a dedicated workstation (uWS, United Imaging Healthcare, Shanghai, China). For each patient, the reading order of PET images was randomized by an independent operator. The patient’s history and the acquisition time were blinded to the readers. Image quality was assessed with a 5-point Likert scale \((1 = \text{non-diagnostic image quality}; 2 = \text{poor image quality}; 3 = \text{moderate image quality}; 4 = \text{good image quality}; 5 = \text{excellent image quality})\). Figure 1 shows reference images with different Likert scores. The score of 3 was equivalent to the image quality to meet the clinical need in our department and served as the reference to determine the acceptable threshold \((\text{SNR}_{\text{acc}})\). The \(\text{SNR}_{\text{acc}}\) was obtained by calculating the mean value of \(\text{SNR}_L\) from all the images scored with 3 points. Finally, the dose regimen was determined as follows (Eq. 8).

\[
\text{Injected activity} = \left(\frac{\text{SNR}_{\text{acc}}}{\text{SNR}_{\text{fit}}}\right)^2 \tag{8}
\]

where \(t\) indicated the acquisition duration and \(\text{SNR}_{\text{fit}}\) was the determined function of the fit to the \(\text{SNR}_{\text{norm}}\) vs. patient-dependent parameter.

Subsequently, the proposed dose regimen was validated with a newly enrolled patient cohort. In the validation group, the patient was injected strictly following the proposed regimen. Image quality was assessed qualitatively using the same criteria by the same nuclear medicine physicians. Quantitative analysis was performed to compare the liver SUV\text{mean}, SD, as well as \(\text{SNR}_L\) between the two cohorts. For each patient, the lesion with the highest uptake was selected for analysis. A volume of interest (VOI) was manually drawn on each selected lesion and SUV\text{max} was obtained and compared between the two cohorts.
Statistical analysis

All statistical analysis was performed using SPSS Statistics Version 26 (IBM Inc., Chicago, IL, USA) and GraphPad Prism 8 (GraphPad Software Inc., San Diego, California, USA). Data were described as mean ± SD. Differences in quantitative variables were assessed by analysis of variance (ANOVA) with post hoc Bonferroni adjustment for pairwise comparison. Independent t test was performed to compare the quantitative variables between the two cohorts. Categorical variables were compared using the Chi-square test. Cohen’s kappa analysis was performed to evaluate the inter-reader agreement. Wilcoxon signed rank test was used to compare the qualitative scores between different BMI groups. Statistical significance was considered if p value is less than 0.05.

Results

Patient characteristics

The demographic and clinical characteristics of the two patient cohorts are listed in Table 1. In the first patient cohort, a total number of 78 oncological patients (Male: 51/Female: 27) with an average age of 59.7 ± 13.7 years (range: 19–81 years) were retrospectively studied. The location of the primary tumor of the enrolled patients included the head and neck (n = 4), the chest (n = 19), the abdomen and pelvic cavity (n = 54), and the retroperitoneum (n = 1). In the second patient cohort, 38 patients (Male: 29/Female: 9) with an average age of 61.3 ± 14.1 years were enrolled, including 1 patient with primary tumor located in the head and neck, 12 in the chest, and 25 in the abdomen and pelvic cavity. The blood glucose level for all the enrolled patients was under 6.1 mmol/L with an uptake time of 74.9 ± 21.0 min (range: 45.0–121.0 min) and 77.3 ± 16.1 min (range: 46.0–120.0 min) for the two cohorts, respectively. There were no significant differences in gender, age, BMI, BMI, LBW, FM, BSA, blood glucose level, and uptake time between the two cohorts (all p > 0.05).

The development of the dose regimen

The SNRL increased along with the increase of acquisition duration with a significant difference to that in G300 (as shown Fig. 2). Moreover, SNRL showed significant difference between BMI groups (all p < 0.01), as listed in Table 2. The SNRL decreased along with the increase of the BMI groups for a given group, as observed in the clinical practice. Compared with that in the normal weight group, the SNRL in other BMI groups were significantly different (all p < 0.05). As expected, the SNRL of the obese group had the lowest value, indicating the worst image quality.

The SNR norm, the normalized SNRL, was fitted with the different patient-dependent parameters using a linear and non-linear fit method, as illustrated in Fig. 3. It was found that the SNR norm was best fitted with BMI with a linear fit function, with the highest coefficient (R^2 = 0.69) and slightly lower coefficient in a non-linear fit with BMI (R^2 = 0.68). Therefore, BMI was determined as the best-correlated parameter, with a linear fit function (Eq. 9).
The new dose regimen was validated with a second patient cohort consisting of 38 oncological patients both
In the qualitative analysis, there was no significant difference between the BMI groups (as shown in Fig. 4), indicating a constant image quality. Compared with that in the weight-based regimen, the proposed regimen can improve the image quality of the patients with a BMI no less than 25, as shown in Fig. 5.

In the quantitative analysis, there were no significant differences in the liver $SUV_{\text{mean}}$ and lesion $SUV_{\text{max}}$ between the patient cohorts ($p > 0.05$, as shown in Table 4). The liver SD in the second patient cohort showed a significantly larger value than that in the first patient cohort due to the reduced injected activity. The $SNR_L$ was plotted vs. the BMI, as shown in Table 2.

**Table 2** Comparison of liver SNR ($SNR_L$) between BMI groups

| BMI groups       | Underweight | Normal weight | Overweight | Obese  | $F$  | $p$ value |
|------------------|-------------|---------------|------------|--------|------|-----------|
| G30              | 12.2±2.3    | 12.7±2.8      | 11.6±2.8   | 10.0±1.3 | 4.8  | <0.001*   |
| G45              | 13.8±2.8    | 14.4±2.9      | 12.8±2.6   | 11.1±1.3 | 6.8  | <0.001*   |
| G60              | 15.1±2.8    | 15.5±2.7      | 13.9±3.0   | 12.5±2.0 | 5.2  | 0.003*    |
| G120             | 19.1±4.3    | 18.1±4.2      | 16.0±3.0   | 13.7±2.9 | 8.6  | <0.001*   |
| G300             | 24.1±4.9    | 23.4±4.9      | 20.1±4.6   | 18.2±3.4 | 7.8  | <0.001*   |

*, $p < 0.01$ in one-way analysis of variance (ANOVA); ☆, $p < 0.05$ in Dunnett’s multiple comparison test. Δ the control group of Dunnett’s multiple comparison test. $SNR_L$, signal noise ratio of the liver.

Data are presented as the mean ± standard deviation.

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Fig. 3 The linear fits (a-g) and non-linear fits (a1-g1) of the $SNR_{\text{norm}}$ against the patient-dependent parameters, including height (a, a1), BM (body mass, b, b1), body mass per height (BM/H, c, c1), lean body weight (LBW, d, d1), fat mass (FM, e, e1), body surface area (BSA, f, f1) and body mass index (BMI, g, g1). Note: $SNR_{\text{norm}}$, normalized signal-to-noise ratio.
Compared with the first patient cohort, the reduction of the injected activity in the second cohort was up to $69.2 \pm 5.4\%$.

**Discussion**

The current EANM guideline recommended a linear weight-based regimen for $^{18}$F-FDG PET examinations [16]. A quadratic relationship between the $^{18}$F-FDG administered activity, PET acquisition time, and patient BM was also described in the guideline [10]. In this regimen, the SNR for the patient with a BM $\geq 75$ kg will be decreased, indicating a degraded image quality due to excessive attenuation and scatter. Thus, an experienced technician is required to modify the acquisition scheme in the clinical scenario for specific situations, which inevitably complicates the operations. Previous studies utilized a higher $^{18}$F-FDG activity per kilogram for patients with a body mass $\geq 90$ kg to compensate for attenuation, while SNR still decreased with body mass in the overweight group [15]. In previous studies, SNR of 9.6 and 10.0 could yield a good image quality [15, 17]. Tan et al. reported that the SNR of 11.7 in the half-dose total-body group with a 2-min duration was higher than the SNR of 8.3 in full-dose whole-body group. However, in this study, the subjective assessment of image quality found that a SNR of 14.0 could obtain a sufficient image quality. A reason for the higher SNR in this study may be bias from different raters. A quadratic relation between the BMI and injected $^{18}$F-FDG activities was determined in this study, which contributes to more constant image quality not affected by BMI. Although this regimen is less convenient than a linear relation in clinical practice, it can be easily overcome by an automatic calculator or a look-up table.

It has been known that the patient-dependent parameters can influence the PET image quality, which is the initial motivation of this study. The fits of SNR with different parameters showed that both the quadratic and linear fitting with BMI had the highest $R^2$ (0.68 and 0.69, respectively). Other parameters, such as the BM, height, body mass per height, LBW, FM, and BSA showed a lower value of $R^2$ than the parameters discussed in previous studies [14, 15]. Based on the results, a linear fit with BMI was selected. The findings were inconsistent with previous studies which suggested a quadratic dose regimen of BM. This may be due to the difference of the subjects selected in the studies. The BM range and number of the enrolled patients may impact the results. Moreover, the population body shape varies with races, which might also induce a bias to the results.

In the proposed regimen, the injected activity was with a $69.2 \pm 5.4\%$ reduction compared with that in the weight-based regimen (3.7 MBq/kg). In addition, the injected activity was reduced by $75.6 \pm 2.9\%$, $72.1 \pm 4.0\%$, $67.1 \pm 4.4\%$, and $64.8 \pm 3.5\%$ for the underweight, normal weight,
overweight, and obese patient group, respectively. The injected activity of normal weight group (68.0 ± 8.3 MBq) according to the proposed regimen in our study was lower than the half-dose (119.5 ± 18.8 MBq) study for lung cancer [8]. It is due to the high sensitivity of the total-body PET scanner which is about 40-fold of that for a conventional PET scanner [10]. This helps to propose the regimen with a reduced injected activity while maintaining the image quality feasible for clinical practice. Obviously, the proposed regimen had limited application in patients due to the methodology. The patient with a BMI ≥ 35 was not enrolled in the study due to the limited patient weight in our site. Actually, the obese patient referred a PET/CT scan in our center were scarce. Therefore, extrapolation was simply used to develop the regimen. Due to the mathematical nature of the quadric expression, the injected activity was dramatically increased with the increase of BMI values. Therefore, an upper limit should be determined for safety concern. Here, we simply investigated the SNRL against BMI in a linear relationship: 

\[ \text{SNRL} = -0.5 \times \text{BMI} + 33.1 \]

Since the acceptable of the SNRL should be more than 14.0 to meet the need of image quality, the upper limit of BMI was determined as 38.2 kg/m². Thus, the proposed regimen may be not feasible for the patient with a BMI larger than the upper limit.

In this study, SNR measured in the liver was selected as a measure to assess the image quality since the liver has a relatively homogeneous uptake of 18F-FDG. However, SNR could be influenced by several physiological factors, such as blood glucose levels, uptake time, plasma clearance, and drinking water status. Blood glucose

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**Table 4** Comparison of Liver SUV mean, SD and lesion SUV mean between the patient cohorts

| Measurement      | Developing dataset | Validation dataset | \( p \) value |
|------------------|--------------------|--------------------|--------------|
| Liver SUVmean    | 2.56 ± 0.58 [1.36–4.84] | 2.55 ± 0.46 [1.64–3.66] | 0.97         |
| SD               | 0.14 ± 0.06 [0.05–0.43] | 0.19 ± 0.04 [0.10–0.30] | <0.001*     |
| Lesion SUVmax    | 12.92 ± 9.66 [0.56–59.92] | 13.39 ± 9.87 [1.08–41.47] | 0.81         |

Independent t test was used to compare the difference between the two patient cohorts, and an asterisk indicated a significant difference. SUV, standardized uptake value

Data were presented as mean ± standard deviation

**Fig. 5** Comparison of patient images in a linear weight-based (a, b) and the proposed BMI-based dose regimen (c, d). Compared with the linear weight-based regimen, MIP and transverse images of the total-body 18F-FDG PET images showed an improved image quality for patients with a BMI = 25 kg/m² (subfigure a vs. c) and 30 kg/m² (subfigure b vs. d)
levels affects liver uptake of the activity as reported in other studies [18]. To minimize the influence factor, the glucose level was controlled within a normal range (3.9–6.1 mmol/L) for both cohorts. Further study should be performed with the glucose level in a wider range. Additionally, plasma clearance can be influenced by water consumption before the scan and the distribution of FDG may be changed. According to our experience, although the patients were recommended to drink 0.5–1L of water after the injection of FDG, not all the enrolled patients strictly followed this instruction. The uptake time of FDG also influenced the level of plasma clearance and the liver SNR. A previous study reported that liver SUV remains constant if the uptake time is in the range of 50–110 min [19]. The uptake time varied from 45 to 121 min in the study, and the results may be biased.

The study has several limitations. Firstly, both cohorts do not include subjects with a BMI larger than 35. Secondly, it is a single-center preliminarily study, and the number of patients in the validation cohort was limited. The proposed regimen should be further validated in a multi-center large scale study. Thirdly, this study just simplified the regimen as a function of the injected activity. In future study, the combination of personalized acquisition time and injected activity should be further explored.

Conclusion

The study recommended a quadratic relation between the 18F-FDG injected activity and the patient’s BMI and proposes a regimen for total-body PET imaging. In the regimen, the image quality can maintain in a constant level independent of patient habitus and meet the clinical requirement even with a reduced injected activity.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00259-021-05462-5.

Authors’ contributions

Jie Xiao was involved in the statistical analysis and manuscript writing. Haojun Yu contributed to data acquisition and reconstructions. Xiuli Sui and Yan Hu contributed to data analyses and image interpretation. Guobing Liu and Yanyan Cao helped with data processing. Yiqiu Zhang and Pengcheng Hu supervised the study. Ying Wang and Chenwei Li were with editing English grammar. Hongcheng Shi and Baixuan Xu designed the study and contributed to editing and reviewing the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-
tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest  Ying Wang and Chenwei Li are employees of United Imaging Healthcare. The other authors who are working in Zhongshan Hospital or Chinese PLA General Hospital have full control of the data and declare that they have no conflicts of interest.

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