Original Article

A preliminary study on the effect of renal function on the metabolism of ^{18}F-FDG in the human cerebellum

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Background: The cerebellum is less affected by normal aging or neurodegenerative diseases, the aim of this paper is to investigate the effect of renal function status on uptake of 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) in human cerebellum based on independent creatinine (CRE) or blood urea nitrogen (BUN) levels.

Methods: A total of 253 patients who underwent ^{18}F-FDG PET/CT scans were included. The patients were divided into groups according to renal function status: 201 patients with normal renal function, 16 patients with increase CRE, 36 patients with decrease CRE, and 31 patients with abnormal BUN. The maximum standardized uptake values were obtained in regions of interest (ROIs) for multiple tissue types (right cerebellum, right lobe of liver, right lung, bone marrow and psoas muscle at the level of the fourth lumbar vertebra). Moreover, the selected normal CRE groups were pair-matched with CRE decrease group with respect to age, sex, body mass index and glucose, respectively.

Results: Among 253 patients who met the inclusion/exclusion criteria, the final analysis included 967 ROIs (244 cerebellum, 191 lungs, 230 muscles, 145 bone marrow, and 157 liver) from ^{18}F-FDG PET/CT scans. Among patients grouped by CRE or BUN levels, the uptake of ^{18}F-FDG by cerebellum was significantly decreased in patients with CRE decrease level (P=0.001). There were no statistically significant differences between the other groups. Matched-pair analysis indicated there were no significant changes in outcomes between the CRE decrease group and the age-, sex-, BMI-, and glucose-matched controls compared to pre-matching.

Conclusions: In patients with normal renal function and reduced CRE concentration, decrease cerebellar glucose metabolism was observed; however, no abnormal uptake of ^{18}F-FDG was found in the cerebellum and other normal tissues of patients with impaired renal function. Consequently, in the study of cerebellar ^{18}F-FDG metabolism, it may be necessary to consider the influence of blood CRE level.

Keywords: Renal function; fluorodeoxyglucose; cerebellum; positron emission tomography/computed tomography (PET/CT); creatinine (CRE)

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Introduction

Positron emission tomography/computed tomography (PET/CT) is a diagnostic method commonly used in oncology, cardiovascular disease or neurological disease with applications ranging from disease diagnosis to treatment planning and monitoring of treatment response (1). Chronic kidney disease is a major public health threat, and its incidence rate in cancer patients is higher than that in non-cancer patients. The study of Renal Insufficiency and Anticancer Medications conducted by Launay-Vacher and colleagues showed that 50–60% of cancer patients had lower renal function than normal, or estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (2). In addition, anticancer drugs carry the risk of renal dysfunction during treatment (3).

At present, the most widely used positron tracer is 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG). Although several factors including blood glucose, sex and body mass index (BMI) will affect the accuracy of ^{18}F-FDG standardized uptake values (SUV) measurement (4), it is well known that renal clearance is an important component of ^{18}F-FDG metabolism, and Kobayashi *et al.* confirmed the partial reabsorption of FDG by the proximal tubules (5). Some researchers believe that renal function affects ^{18}F-FDG uptake (6,7); however, there are papers that do not support this view (8,9). Of course, it is generally believed that the kidney clears the ^{18}F-FDG activity from the blood pool, which in turn clears the background activity in normal tissues. Most previous studies have been based on the effect of renal function or eGFR on ^{18}F-FDG uptake, and there is limited information in the literature on the effect of ^{18}F-FDG uptake directly based on independent creatinine (CRE) or blood urea nitrogen (BUN) levels. Minamimoto *et al.* (6) found that ^{18}F-FDG brain accumulation decreased and blood pool accumulation increased in patients with high plasma CRE level. However, there is no report on the effect of serum CRE reduction on ^{18}F-FDG metabolism in the literature. Since the possible relationship between low serum CRE and type 2 diabetes has been confirmed (10), low serum CRE may affect the metabolism of ^{18}F-FDG. In addition, the cerebellum is less affected by normal aging or neurodegenerative diseases than the cerebral cortex, and its metabolism is relatively stable (11).

In this study, we believe that low serum CRE is also a state of renal function and attempt to elucidate the effect of renal function on ^{18}F-FDG uptake in the cerebellum or other normal tissues based on independent CRE or BUN levels.

Methods

Patients selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the First Affiliated Hospital, Dalian Medical University (No. PJ-KY-2021-280) and individual consent for this retrospective analysis was waived. The anonymity and confidentiality of patients were maintained. The inclusion/exclusion criteria were as follows: (I) No signs suggestive of any inflammatory disease on ^{18}F-FDG PET/CT imaging. (II) Blood sugar level at acceptable range (3.9–9.0 mmol/L) for ^{18}F-FDG PET/CT examination. (III) Measurement of CRE and BUN within two weeks of ^{18}F-FDG PET/CT. (IV) Ability to empty the bladder prior to PET/CT scan. This study initially enrolled 283 patients who underwent standard protocol ^{18}F-FDG PET/CT. A total of 30 patients were excluded, including one patient with kidney transplant, two patients from injection to PET/CT scan for more than 70 minutes, two patients with diffuse brain injury, two patients with cerebrovascular disease, five patients with diffuse liver metastasis, one patient with biliary dilation, three patients with lung infection, two patients with fibrotic lung disease, four patients with diffuse bone malignant tumor, two patients with diffuse inflammatory disease and six patients with lesions on the selected area of interest (ROI) during the image analysis. Finally, a total of 253 patients met the criteria and were included in the analysis. Several factors including blood glucose, sex and BMI would affect the accuracy of SUV measurement, so the basic data were collected including gender, weight, BMI and laboratory tests including blood glucose, CRE, and BUN level.

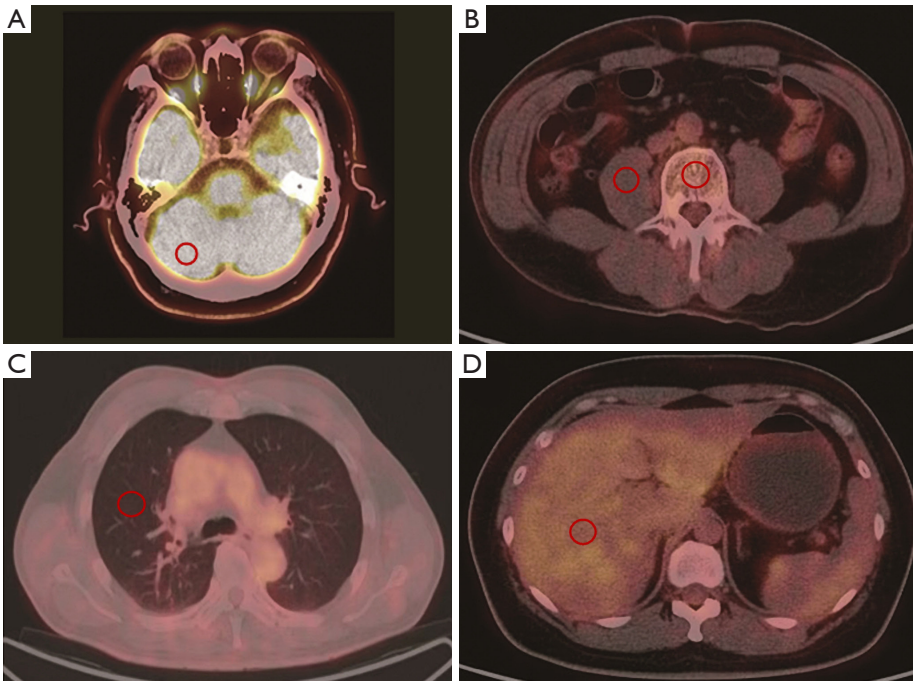

Figure 1 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) image ROI analysis. Circular regions of interest (ROIs, red circles) for measuring the standardized uptake value (SUV) were placed, 10 mm ROIs on cerebellum (A); 20 mm ROIs on psoas muscle, bone marrow at the level of the L4 vertebral body (B), lungs (upper lobe) (C) and liver (D), as shown.

Patient preparation

On the day of the examination, all patients fasted for more than six hours prior to receiving the radiopharmaceutical injection. The alcohol, caffeine, and sweets were avoided, blood glucose was within the acceptable range. Patients were injected 5.55 MBq/kg (0.15 mCi/kg) ^{18}F-FDG intravenously. During the uptake phase prior to ^{18}F-FDG PET/CT scan, the patient sat in a quiet room without speaking and avoided other physical exercise for 55–68 minutes.

PET/CT scanning equipment and image reconstruction

The experiment utilized a Siemens Biograph true point PET/CT scanner (Siemens Molecular Imaging, healthcare China), with lutetium oxyorthosilicate crystal, and 64-slice CT scanner.^{18}F-FDG was synthesized by a cyclotron (Siemens Molecular Imaging, China) and an automated synthesizer (PET Biotechnology, China). Radiochemical purity was >95%. The scanning parameters were as follows: voltage 120 kV, tube current automatic mA/s adjustment (preset: 170 mA/s), slice thickness 2 mm, the average scanning time per bed was 1 min. After reconstructing CT images, the PET images attenuated by CT data were reconstructed by the sequential subset thickness (true x) algorithm, repeated three times, with 21 subsets and 3-D Gaussian filtering. Finally, the reconstructed PET images were fused with CT images.

PET/CT image analysis

^{18}F-FDG PET/CT images were evaluated on the Siemens workstation. On the fused PET/CT images, a 20 mm circular ROI was used to record the SUVmax from right hepatic lobe, right lung (upper lobe), bone marrow and psoas muscle at the level of the fourth lumbar vertebra, and a 10 mm circular ROI was placed at the right cerebellum. For lung, the ROI was placed in area without nodules, major blood vessels, or inflammatory changes; for liver, the ROI was placed on the right lobe dome with the largest cross-sectional area orther than CT abnormalities or large vessels. Quantitative analysis of the data was performed to obtain the SUVmax normalized by body weight. A representative image illustrating the ROI is shown in *Figure 1*. Each ROI was carefully placed so as not to include any disease or adjacent organs. Finally, the results of SUVmax of each

group based on CRE or BUN levels were obtained. To rule out other possible confounding factors affecting ^{18}F-FDG uptake, in the normal group, the patients with the same blood glucose, age and BMI as those in the corresponding groups were selected for one-to-one matching, then the age, gender, BMI and glucose levels pair-matched groups were analyzed.

Statistical analysis

All statistical analyses were performed using SPSS-26 (IBM SPPS, Chicago, IL, USA). Data were checked for normality using the Shapiro-Wilkes test. Descriptive analysis was used to obtain sample characteristics, including gender, age and diagnosis. Continuous data were presented as mean and standard deviation. Based on the CRE level, the multiple independent samples Kruskal-Wallis test was used to analyze the SUV values of the three groups. If there was a significant difference, post-hock testing was performed on the specific tissue. Based on the BUN level, the Mann-Whitney U test was used. For matched-pair analysis, the explore command of SPSS tested for normality of data in each group, the data were normally distributed and were analyzed using the independent samples *t*-test.

A P value less than 0.05 was considered statistical significance. All P values were two-sided.

Results

Clinical features

A total of 253 patients were finally included, 125 males and 128 females, with an age range of 27–84 years (mean 54 years). Among them, breast cancer patients dominated the most, 18.20% (46/253); followed by gastrointestinal cancer with 17.80% (45/253) and lung cancer with 13.8% (35/253). The remaining 50.19% (127/253) of patients had one of the following diagnoses: liver cancer, gallbladder cancer, gynecological cancer, pancreatic cancer, urinary tract cancer, lymphoma, head and neck cancer, prostate cancer, malignant fibroids, soft tissue tumors, sarcoidosis, malignant melanoma, plasmacytoma, liposarcoma, and other undiagnosed diseases. The CRE levels were normal in 201 cases, decrease in 36 cases, and increase in 16 cases (gender, age, blood glucose, and BMI are shown in *Table 1*). Based on BUN, patients were divided into normal group (n=222, male/female: 109/113) and abnormal group (n=31, male/female: 16/15), overall age: 27–84 years (mean 56).

In our institutional laboratory, the normal range of CRE was 47–110 μmol/L, regardless of gender. The CRE reduction level in this study ranged from 35–47 μmol/L, and the CRE level greater than 110 μmol/L was considered to be abnormally high. The normal range of BUN was 2.90–8.20 mmol/L.

Comparison of ^{18}F-FDG uptake based on CRE or BUN levels

Based on CRE level, the SUVmax of the cerebellum was lower in the group with decrease CRE level, 7.85±2.19, while it was 9.01±1.75 and 8.63±1.18 in the group with normal and increase level, respectively. The multiple independent samples Kruskal-Wallis test showed statistically significant differences in cerebellum (Test Statistic H(2)=12.86, P=0.002). Among other groups, there was no statistical difference in the SUVmax of cerebellum, lung, liver, lumbar muscle and bone marrow (*Table 2*). Bonferroni-corrected post hoc test was performed on the SUVmax of cerebellum in three groups, and showed a significant difference in cerebellar SUVmax between the CRE-reduced group and the normal group (P=0.001), but not the other two groups (P value 0.420 for decrease level *vs.* increase level; P value 1.000 for increase level *vs.* normal level). When classifying patients according to BUN level, there was no significant difference between normal and abnormal group (*Table 3*).

Matched-pair analysis

To rule out other possible confounding factors affecting ^{18}F-FDG uptake, such as a range of age, gender, BMI and glucose levels, the selected normal CRE groups were pair-matched with CRE decrease level group with respect to age, sex, BMI and blood glucose, respectively (1:1 nearest-neighbor matching). A comparison of matching variables between the controls and CRE decrease level group showed no significantly changed from the results before matching (*Table 4*).

Discussion

Among several factors that may affect SUV measurement, the blood glucose and renal function may be two important factors affecting ^{18}F-FDG uptake. After controlling blood glucose level to a certain range, the importance of renal function status on ^{18}F-FDG uptake was highlighted.

Table 1 Patient characteristics based on CRE level

Characteristics	Normal level	Decrease level	Increase level
Total	201 (100.00)	36 (100.00)	16 (100.00)
Gender			
Female	112 (55.70)	14 (38.90)	2 (12.50)
Male	89 (44.30)	22 (61.10)	14 (87.50)
Age, years			
27–35	8 (4.00)	1 (2.80)	0 (0)
36–55	61 (30.30)	10 (27.80)	2 (12.50)
56–84	132 (65.70)	25 (69.00)	14 (87.50)
Blood glucose, mmol/L			
3.9–5.4	92 (45.80)	15 (41.70)	9 (56.30)
5.5–9.0	109 (54.20)	21 (58.30)	7 (43.80)
BMI, kg/m^2			
<18.5	5 (2.50)	1 (2.80)	0 (0)
18.5–24.9	115 (57.20)	32 (88.90)	8 (50.00)
25.0–29.9	68 (33.80)	2 (5.60)	8 (50.00)
≥30.0	13 (6.50)	1 (2.80)	0 (0)

The data of each group was represented in numbers and frequencies. BMI, body mass index; CRE, creatinine.

Table 2 ^{18}F-FDG PET/CT SUVmax comparison based on CRE levels

CRE levels	Cerebellum	Lung	Liver	Psoas muscle	Bone marrow
Normal level	9.01±1.75	0.63±0.12	3.04±0.41	0.89±0.21	2.30±0.35
Decrease level	7.85±2.19	0.58±0.09	3.05±0.31	0.87±0.26	2.28±0.27
Increase level	8.63±1.18	0.58±0.11	3.06±0.30	0.97±0.19	2.28±0.33
Test statistic (H)	12.86	5.50	0.08	4.74	0.46
Degree of freedom	2	2	2	2	2
P value	0.002	0.064	0.956	0.093	0.791

The data of each group was represented as mean ± standard deviation. The multiple independent samples Kruskal-Wallis test was used to analyze the SUVmax values of the three groups, and showed statistically significant differences in cerebellar tissue (P=0.002). So the post-hock testing was performed on the SUVmax of cerebellum in three groups. ^{18}F-FDG PET/CT, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/computed tomography; SUV, standardized uptake values; CRE, creatinine.

Unlike glucose, a high portion of ^{18}F-FDG was excreted through the urine. In dogs, 60 min and 135 min after intravenous injection, the excretion rate of ^{18}F-FDG through urine was 16% and 50% of each injection dose, respectively (12). Kobayashi *et al.* confirmed the partial reabsorption of FDG by the proximal tubules (5). These indicate that renal function has an impact on the metabolism of ^{18}F-FDG. For the evaluation of renal function, CRE and BUN are two important indicators in clinical practice. Akers *et al.* reported the study of ^{18}F-FDG PET/CT in patients with renal function impairment classified according to the level of eGFR (8). However, it is worth noting that eGFR is not a perfect test, the calculation formula of eGFR usually needs to be revised and adjusted, several factors

Table 3 ^{18}F-FDG PET/CT SUVmax comparison based on BUN levels

BUN levels	Cerebellum	Lung	Liver	Psoas muscle	Bone marrow
Normal level	8.80±1.90	0.62±0.12	3.06±0.38	0.90±0.22	2.30±0.34
Abnormal level	8.98±1.26	0.60±0.11	2.89±0.42	0.89±0.20	2.25±0.30
P value	0.381	0.243	0.117	0.927	0.791

The data of each group was represented as mean ± standard deviation. ^{18}F-FDG PET/CT, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/computed tomography; SUV, standardized uptake values; BUN, blood urea nitrogen.

Table 4 Comparison of ^{18}F-FDG PET/CT SUVmax between CRE decrease level group and age-, gender-, BMI- and glucose-matched controls

Matched groups	n	Cerebellum	Lung	Liver	Psoas muscle	Bone marrow
Age-matched						
Normal level	36	9.15±1.39	0.63±0.10	3.13±0.44	0.94±0.20	2.19±0.35
Decrease level	36	7.85±2.19	0.58±0.09	3.05±0.31	0.87±0.26	2.28±0.27
P value		0.004*	0.073	0.492	0.242	0.357
Gender-matched						
Normal level	36	9.78±1.53	0.66±0.10	3.04±0.40	0.84±0.21	2.37±0.44
Decrease level	36	7.85±2.19	0.58±0.09	3.05±0.31	0.87±0.26	2.28±0.27
P value		0.000*	0.004*	0.910	0.491	0.509
BMI-matched						
Normal level	36	9.30±1.95	0.64±0.14	2.97±0.40	0.84±0.19	2.27±0.42
Decrease level	36	7.85±2.19	0.58±0.09	3.05±0.31	0.87±0.26	2.28±0.27
P value		0.004*	0.089	0.427	0.438	0.928
Glucose-matched						
Normal level	36	9.37±1.95	0.64±0.13	3.16±0.47	0.92±0.23	2.27±0.31
Decrease level	36	7.85±2.19	0.58±0.09	3.05±0.31	0.87±0.26	2.28±0.27
P value		0.003*	0.062	0.360	0.548	0.861

The data of each group was represented as mean ± standard deviation. *P<0.05, a P value less than 0.05 was considered to indicate statistical significance. ^{18}F-FDG PET/CT, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography/computed tomography; SUV, standardized uptake values; BMI, body mass index; CRE, creatinine.

affect its accuracy. For example, the eGFR calculation based on CRE levels are only accurate if a person's kidney function is stable, however, the test is generally not accurate enough for acutely ill patients, including those with severe comorbidities (13).

Amyloidosis is one of the earliest changes in patients with Alzheimer's disease (AD). Its AD neuropathological level is at intermediate or high level, and more than 15 years before the occurrence of cognitive impairment (14). Amyloid-β (Aβ) is the major component of senile plaques in the brain of AD. The senile plaques are usually observed in the cerebral cortex of AD patients rather than in the cerebellum (15); and from the biological point of view, cerebellum is a suitable reference area for PET quantification. Therefore, the cerebellum was selected as the main research area of interest in this study.

The SUVmax of cerebellum, lung, liver, psoas major muscle and bone marrow of each group were compared,

and there was no statistical difference in ^{18}F-FDG uptake between groups with elevated CRE level and abnormal BUN level, which was consistent with the previous report (8). In contrast to glomerular filtration rate and CRE clearance, it is generally accepted that blood BUN levels are not a specific indicator of impaired renal function. Therefore, we would not further discuss its impact on ^{18}F-FDG uptake here.

At the same time, we noticed a statistically significant difference in the SUV of the cerebellum, i.e. patients with reduced CRE had lower cerebellar SUV than those with normal CRE. These results suggest that a reduction in CRE may affect ^{18}F-FDG PET quantitative analysis in cerebellum. However, we have not yet retrieved reports of reduced ^{18}F-FDG uptake in patients with reduced CRE levels.

In this study, some patients with fever and special tumors that may affect the liver and bone marrow SUV value were excluded, the vast majority of patients enrolled were cancer patients. In some of these patients, the disease was associated with low muscle quality due to infrequent exercise and muscle atrophy. This could partly explain the decline of CRE level. In addition, CRE, a marker of kidney function, is a chemical waste product of creatine phosphate, and creatine is a ubiquitous non-protein amino acid that is synthesized mainly in the liver (16). In chronic liver disease, the decrease of serum creatinine pool is due to the reduction of liver creatine production by 50%; generally, the baseline serum creatinine concentration of patients with chronic liver disease is significantly lower than that of the general population (17,18). Liver metastases have been reported in approximately 5% of cancer patients at diagnosis; at the same time, cancer treatments, such as certain types of chemotherapy, radiation therapy, and immunotherapy, may also lead to liver problems (19-21). All of these factors may reduce creatine production, then resulting in lower CRE.

Importantly, patients with liver damage have significant insulin resistance (22). Insulin promotes microvascular blood flow, glucose uptake, and glucose oxidation to adenosine-5'-triphosphate (23,24). Insulin resistance is defined as decrease tissue responsiveness to insulin. Furthermore, a possible relationship between low serum CRE and type 2 diabetes has been demonstrated (10,25). Several studies have shown a link between reduced ^{18}F-FDG metabolism in the brain and insulin resistance (26,27). In addition, in this study, the majority of the patients in the group with decrease CRE level were aged and had a BMI below the normal range, and it is generally believed that renal function gradually declines with age (28), and decreased ^{18}F-FDG metabolism in the brain was observed in normal aging or neurodegenerative diseases (AD or dementias) (29,30).

Taken together, the decrease of CRE level may be directly or indirectly related to insulin resistance and impaired glucose metabolism, and the cerebellum is relatively less affected by neurodegenerative diseases or normal aging. These pathophysiological processes can partly explain the reason for the decrease of cerebellar SUV in the group with CRE-reduced level in this study.

Sprinz *et al.* reported that higher blood glucose levels were significantly associated with lower brain ^{18}F-FDG uptake (31). By controlling the influence of all other characteristics, matching samples can obtain better and accurate output when determining significant differences (32). Our matched-pair analysis showed that there was no significant difference in the outcomes between the group with CRE decrease level and the age-, sex-, BMI- and glucose-matched control group compared to the results before matching.

At present, to the best of our knowledge, there is no report to evaluate ^{18}F-FDG uptake in patients with reduced CRE level. The limitation of this paper is that it is a single-center study, and the inclusion conditions are relatively strict, resulting in a relatively small sample size of this study. More data accumulation and analysis are needed in the future. On another hand, the reasons why renal function status affects ^{18}F-FDG uptake may be quite complex and further studies are needed to deepen the understanding and consensus on its molecular mechanisms.

Conclusions

In patients with normal renal function and reduced CRE concentration, decrease cerebellar glucose metabolism was observed; however, no abnormal uptake of ^{18}F-FDG was found in the cerebellum and other normal tissues of patients with impaired renal function. Consequently, in the study of cerebellar ^{18}F-FDG metabolism, it may be necessary to consider the influence of blood CRE level.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-917/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of The First affiliated Hospital, Dalian Medical University (No. PJ-KY-2021-280) and individual consent for this retrospective analysis was waived.

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