Application of [68Ga]Ga-citrate PET/CT for Differentiating Prosthetic Joint Infection from Aseptic Loosening After Joint Replacement Surgery

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Abstract

Purpose

Preoperative differentiation of prosthetic joint infection (PJI) and aseptic loosening (AL) is challenging. We aimed to evaluate the utility of visual analysis and semi-quantitative parameters of $[^{68}\text{Ga}]$Ga-citrate positron emission tomography/computed tomography (PET/CT) in the differentiation of PJI and AL.

Methods

Sixteen patients with suspected PJI or AL underwent $[^{68}\text{Ga}]$Ga-citrate PET/CT imaging. Results were evaluated by three nuclear medicine doctors based on (1) visual analysis of the attenuation correction (AC) and non-attenuation correction (NAC) based on tracer uptake intensity and range; (2) maximum standard uptake value (SUVmax) of lesions and the SUVmax of the target area/SUVmax of the non-target area (bone and muscle; T/NT [bone] and T/NT [muscle]). The final diagnosis was based on the Musculoskeletal Infection Society criteria, intraoperative findings, and histopathological and microbiological examinations.

Results

Overall, 10 (62.5%) and 6 (37.5%) patients were diagnosed with PJI and AL, respectively. Receiver operating characteristic analysis revealed that the areas under the curve for SUVmax, T/NT (bone), and T/NT (muscle) were 0.617 (cut-off = 2.243, $P = 0.4312$), 0.850 (cut-off = 2.844, $P = 0.0052$), and 0.850 (cut-off = 5.983, $P = 0.0003$), respectively. AC, NAC, and T/NT (bone) exhibited high differential diagnostic values (sensitivity, specificity, and accuracy of 90.0%, 83.3%, and 87.5%, respectively). The diagnostic efficacy of T/NT (muscle) was the second highest (sensitivity, specificity, and accuracy of 60.0%, 100%, and 75.0%, respectively). SUVmax demonstrated the poorest diagnostic efficacy (sensitivity, specificity, and accuracy of 70.0%, 66.7%, and 68.8%, respectively).

Conclusion

Our results suggest that $[^{68}\text{Ga}]$Ga-citrate may differentiate PJI and AL.

Introduction

The causes of pain following joint replacement include aseptic loosening (AL), prosthetic joint infection (PJI), periprosthetic fracture, and heterotopic ossification[1]. Of these, AL and PJI are the commonest complications[2], and accurately distinguishing between the two is essential for the optimal treatment of patients with pain following joint replacement because treatment approaches for the two conditions differ substantially. In the presence of AL, a one-stage revision arthroplasty is typically successful, whereas for PJI a two-stage revision arthroplasty is usually necessary[3, 4]. In addition, further treatment including amputation can be required if the first-line treatment for PJI fails[5]. Therefore, an accurate and timely diagnosis can ensure that the correct treatment strategy is selected; it can also maximise the patient's long-term quality of life and clinical outcomes. However, the differentiation of AL and PJI remains a challenge due to the similarities in their associated symptoms[6]. Further, most infections that are identified are chronic and low-grade, lacking the typical clinical symptoms and signs associated with an infection[4, 6].

Various clinical assessment methods are currently used in the preoperative diagnosis of AL and PJI, including laboratory testing, X-rays, computed tomography (CT) imaging, magnetic resonance imaging (MRI), $[^{99}\text{m}\text{Tc}]$Tc-MDP and $[^{18}\text{F}]$NaF bone scans, triple-phase bone scintigraphy, $[^{67}\text{Ga}]$Ga-citrate imaging, radioactive-labelled leukocyte scintigraphy, $[^{18}\text{F}]$FDG positron emission tomography/CT (PET/CT) imaging, joint aspiration, and microbial culture[3, 4, 7]. However, there is no unified diagnostic protocol for the evaluation of AL and PJI, and each of these clinical assessment methods has shortcomings[8]. Laboratory testing often provides non-specific results[3]. Joint aspiration and microbial culture may provide false-negative results and, when the sample is contaminated, false-positive results may occur[9]. Conventional X-rays typically appear normal[10]. The quality of CT and MRI scans is degraded by metal artefacts around the implant[5, 10]. $[^{99}\text{m}\text{Tc}]$Tc-MDP and $[^{18}\text{F}]$NaF bone imaging usually lacks the specificity to distinguish between various complications after the implantation of a prosthesis, and the tracer uptake caused by physiological bone remodelling following implantation may be present for several years[3, 10–12]. Triple-phase bone scintigraphy is limited by the fact that the results obtained are dependent on the diagnostic criteria applied[3]. The disadvantages of leukocyte scintigraphy include its complex operation, time-intensive labelling process, poor spatial resolution, and limited availability[7, 8]. The use of $[^{67}\text{Ga}]$Ga-citrate is limited by the long half-life ($T_{1/2} = 78.3\text{ h}$) and the need for repeated imaging over several days[10, 13]. It is still difficult to distinguish between PJI and AL on $[^{18}\text{F}]$FDG PET/CT, and its high cost and the requirement for fasting before PET imaging limit its clinical application[4, 9].
At present, the diagnosis of PJI and AL depends predominantly on methods facilitated by surgery such as histological analysis and intraoperative microbial culture[14]. The preoperative diagnostic process may provide insufficient information for a definite diagnosis prior to surgery, and this can affect treatment decisions; this highlights the importance of an accurate preoperative diagnosis for planning effective treatment strategies. Gallium-68 is an isotope of Gallium-67 with similar physical and chemical properties[15]. As a positron radionuclide, [$^{68}$Ga]$^3+$-citrate can be combined with PET/CT imaging to obtain a high-resolution image; its half-life is short (68 min), and it can be used for early imaging[15]. Furthermore, Gallium-68 is obtained by a Germanium-68/Gallium-68 generator, which is convenient, fast, and has a significantly lower cost than that of cyclotron-generated Gallium-67. Therefore, [$^{68}$Ga]$^3+$-citrate has superior performance to that of traditional [$^{67}$Ga]$^3+$-citrate. The preliminary data on the ability of [$^{68}$Ga]$^3+$-citrate PET imaging to identify bone infections are promising[16, 17]. Salomäki et al. [17] demonstrated that [$^{68}$Ga]$^3+$-citrate was able to distinguish between bone infections and physiological bone healing following surgery to the bone. Data from Tseng et al.[16] suggested that [$^{68}$Ga]$^3+$-citrate PET/CT may distinguish infectious from non-infectious diseases after joint replacement. However, research on the efficacy of [$^{68}$Ga]$^3+$-citrate PET/CT in distinguishing between PJI and AL is limited.

We hypothesised that [$^{68}$Ga]$^3+$-citrate can distinguish between periprosthetic infection and AL, especially in the early postoperative period, and explored the effectiveness of [$^{68}$Ga]$^3+$-citrate as an auxiliary diagnostic tool for PJI and AL following joint replacement surgery. The purpose of this study was two-fold: (1) to evaluate any differences in the semi-quantitative analysis of the maximum SUV (SUVmax) of the target area, SUVmax of the target area/SUVmax of the non-target area (bone or muscle; T/NT [bone] and T/NT [muscle]) between PJI and AL; and (2) to compare the differential diagnostic performance of visual analysis and semi-quantitative analysis for PJI and AL.

Material And Methods

Patients

A total of 23 patients that were clinically suspected of having PJI or AL underwent [$^{68}$Ga]$^3+$-citrate PET/CT imaging in the Department of Nuclear Medicine at the Affiliated Hospital of Southwest Medical University between August 2019 and May 2020. All patients underwent bone imaging within 1 week prior to [$^{68}$Ga]$^3+$-citrate PET/CT imaging. The inclusion criteria of the study were as follows[16, 18]: (1) a history of hip or knee arthroplasty; and (2) pain that was suspected to be due to PJI or AL and the patient was planned for treatment. The exclusion criteria of the study were as follows[16, 18, 19]: (1) the presence of another inflammatory arthropathy or osteopathy; (2) treatment with antibiotics before the study; (3) infection or inflammation of other body parts; (4) critical illness or unstable vital signs; and (5) pregnancy or lactation.

The diagnostic standards used in this study were based on the previous literature[4, 12, 18, 20, 21], as follows: PJI was diagnosed when the patient met the 2013 Musculoskeletal Infection Society (MSIS) criteria[22], or when at least one of three features was positive (intraoperative findings including the occurrence of pus or purulent fluid around the prosthesis, histological analysis, and surgical microbiological culture); AL was only diagnosed when the patient was excluded from the MSIS criteria and the intraoperative findings, histological analysis, and microbial culture results were negative. Those who did not meet the MSIS criteria and were not confirmed to have AL through surgery were considered to have insufficient criteria for the diagnosis of AL and were excluded from our cohort.

Of the 23 cases that were clinically suspected of having PJI or AL, diagnosis could be confirmed in 17; 13 of these were diagnosed through an operation (seven and six cases of PJI and AL, respectively), and 4 cases of PJI met the non-operative criteria of MSIS. We excluded 6 patients whose final diagnosis was uncertain. In addition, one patient with anaemia underwent [$^{68}$Ga]$^3+$-citrate imaging two days after receiving a blood transfusion; in this patient, we observed that the uptake of the imaging agent in the bone marrow of the patient bilaterally was much higher than that in the lesion. This patient was excluded from our analysis in order to prevent the potential effects of the bone marrow uptake of the imaging agent on our results. Therefore, 16 patients were included in the final analysis. Variables including age, sex, involved joint, cause of implant, time after implant, and main symptoms were recorded. This study met the requirements of the Declaration of Helsinki. All patients provided written informed consent after the nature and significance of the imaging study had been fully explained to them.

Synthesis and quality control of [$^{68}$Ga]$^3+$-citrate

An ITG Germanium-68/Gallium-68 generator was purchased from China Isotope and Radiation Corporation (Beijing, China). The generator was washed with 0.05 M HCl, and a 5 mL Gallium-68$^{3+}$ solution was obtained for radioactive labelling. In the process of washing, the Gallium-68$^{3+}$ solution was divided into five tubes, each containing 1 mL of the solution. The second to fourth tubes of Gallium-68$^{3+}$ (20 mCi) containing 3 mL in total were used. Sodium citrate solution (0.2 M) was prepared, and 2 mL sodium citrate was added to Gallium-68$^{3+}$. The mixture was allowed to react at room temperature for 15 min. Microorganisms were filtered through a 0.22-μm filter membrane. With 0.1 M ammonium acetate and methanol (1:1, v/v) as the developing solvent, the radiochemical purity of [$^{68}$Ga]$^3+$-citrate was analysed by thin layer chromatography. The final radiochemical purity of the product was confirmed to be > 97%, with a pH ranging from 6 to 8.

PET/CT scanning
The injection dose of $^{68}$Ga-citrate used was 2.59–3.7 MBq/Kg. Local PET/CT scanning of the hip or knee joint was performed on a Philips Gemini TF 16 scanner (Philips Healthcare, Best, Netherlands) 60 minutes after the injection of the intravenous tracer. A 16-slice spiral CT scan was performed initially (field-of-view 600 mm, 120 kV, 100 mA, layer thickness 0.3 mm, and pitch 0.813 mm). After the CT scanning was complete, three-dimensional PET was performed for 3 min per bed position (two to five beds). The resulting images were corrected by attenuation and reconstructed iteratively using the ordered subset expectation maximization method (three iterations, 33 subsets, image size $144 \times 144$ matrix) to obtain transverse, sagittal, and coronal views of the PET/CT scans.

Image analysis

Three experienced PET/CT doctors performed visual analysis and semi-quantitative analysis of the PET/CT images. Any areas with increased uptake were identified and the location of the uptake was recorded. The imaging features of the lesions were observed and recorded, including the location, surrounding soft tissue, and anatomical morphology. Interobserver differences in the interpretation of the PET images were resolved through consensus.

Visual analysis

Visual analysis was performed on PET/CT images with attenuation correction (AC) and non-attenuation correction (NAC). Based on background muscle uptake and macrovascular activity, the degree of lesion uptake was divided into three grades\cite{4, 12, 23}: I, no uptake or uptake close to that of the background muscles; II, higher than the background muscle uptake and lower than the background macrovascular activity; and III, close to or more than the background macrovascular activity. The lesions were divided into focal or diffuse uptake based on the range of uptake and regardless of the intensity\cite{4, 12, 24}. Focal uptake referred to focal uptake at the bone-prosthesis interface that did not extend along the femur, tibia, or fibula. Diffuse uptake was defined as: diffuse uptake at the bone-prosthesis interface; and/or uptake extending along the femur, tibia, or fibula; and/or abnormal uptake in the soft tissue around the prosthesis or bone. The possible outcomes following evaluation of the visual analysis were: the degree of uptake was III and/or diffuse uptake was considered to be positive for PJI, and the degree of uptake was I-II with a focal range of uptake for AL.

Semi-quantitative analysis

The indices of the semi-quantitative analyses were SUVmax of the target area, T/NT [bone], and T/NT [muscle]. Evaluating SUVmax of the target area involved delineating the highest uptake area of the bone-prosthesis interface, bone-bone interface, or soft tissue around the region of interest (ROI) and measuring the maximum standard uptake value of the ROI after excluding the radioactivity of the large blood vessels. In patients with multiple lesions, only images exhibiting the highest SUVmax were included in the analysis. Non-target area SUVmax was acquired as the average SUVmax of five regions of contralateral normal bone or muscle. The location of the lesions was determined by bone imaging when no obvious uptake abnormalities were identified on PET/CT imaging.

Statistical analysis

SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The data are presented as median. The SUVmax, T/NT (bone), and T/NT (muscle) of the PJI and AL groups were compared with a nonparametric rank sum test (Wilcoxon test). Receiver operating characteristic (ROC) analysis was performed to determine the best cut-off and area under the curve (AUC) for SUVmax, T/NT (bone), and T/NT (muscle) with MedCalc software version 19.0.5 (MedCalc Software Ltd., Ostend, Belgium). A 2 × 2 contingency table with four diagnostic outcomes (true positive, false positive, true negative, and false negative) was constructed based on the final diagnostic results. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of three semi-quantitative indices were calculated. The significance level was set at $P < 0.05$.

Results

Patient characteristics

The 16 patients comprised 11 males and 5 females (median age: 63.5 years; range: 19–73 years), with nine cases of artificial hip joints and seven cases of artificial knee joints. The median time since surgery was 1 year (range: 1 month–10 years). A total of 10 cases of PJI and six cases of AL were diagnosed. Details of the patients are presented in Table 1.
Table 1
Clinical and imaging features of 16 patients.

| Patient No. | Age (year) | Sex | Replacement site + type | Surgical time | Surgical reason | Symptom | Final diagnosis | SUVmax | T/NT (bone) | T/NT (muscle) |
|-------------|------------|-----|--------------------------|---------------|----------------|---------|----------------|--------|-------------|---------------|
| 1           | 60         | Female | LH + PI                  | 10 Year       | Osteonecrosis | Pain    | Aseptic loosening | 2.242  | 1.651       | 2.166         |
| 2           | 66         | Male   | LK + PI                  | 10 Year       | Osteonecrosis | Pain and swelling | 1.498  | 5.220       | 3.360         |
| 3           | 63         | Female | LH + PI                  | 9 Month       | Osteonecrosis | Pain    | Aseptic loosening | 4.422  | 1.711       | 3.363         |
| 4           | 69         | Male   | LK + PI                  | 3 Year        | Trauma        | Pain    | Infection        | 1.955  | 2.734       | 2.303         |
| 5           | 56         | Male   | RH + PI                  | 6 Year        | Osteonecrosis | Pain    | Infection        | 1.805  | 2.781       | 3.574         |
| 6           | 67         | Female | BK + PI                  | 9 Month       | Osteonecrosis | Pain    | Infection        | 5.942  | 6.137       | 7.145         |
| 7           | 59         | Male   | RH + PI                  | 7 Year        | Osteonecrosis | Pain and swelling | 3.120  | 4.376       | 3.288         |
| 8           | 52         | Male   | LH + RI                  | 5 Month       | Osteonecrosis | Pain    | Infection        | 6.412  | 11.574      | 6.026         |
| 9           | 64         | Female | RH + PI                  | 6 Month       | Trauma        | Pain    | Aseptic loosening | 2.243  | 2.065       | 3.732         |
| 10          | 67         | Male   | LH + PI                  | 5 Month       | Trauma        | Pain and swelling | 3.919  | 8.034       | 9.287         |
| 11          | 73         | Male   | RK + RI                  | 3 Year        | Osteoarthritis | Pain    | Infection        | 2.341  | 7.783       | 6.512         |
| 12          | 46         | Female | RH + PI                  | 2 Year        | Osteonecrosis | Pain    | Infection        | 3.870  | 7.316       | 6.418         |
| 13          | 70         | Male   | RK + PI                  | 4 Month       | Osteoarthritis | Pain and swelling | 1.694  | 8.223       | 4.982         |
| 14          | 59         | Male   | RH + RI                  | 1 Year        | Trauma        | Pain and swelling | 1.473  | 2.844       | 2.580         |
| 15          | 19         | Male   | LK + PI                  | 1 Year        | Osteosarcoma  | Pain    | Infection        | 5.096  | 9.199       | 11.675        |
| 16          | 69         | Male   | LK + PI                  | 1 Month       | Osteoarthritis | Pain    | Aseptic loosening | 4.308  | 8.285       | 5.983         |

LH, left hip; LK, left knee; RH, right hip; RK, right knee; PI, primary implant; RI, revised implant; SUVmax, the maximum standard uptake value; T/NT, SUVmax of target area/SUVmax of non-target area.

Visual Analysis Results

The AC and NAC visual evaluation results are compared with the final diagnosis in Table 2.

Table 2
Comparison between visual analysis results of AC and NAC and final diagnosis.

| Group               | I    | II   | III  |
|---------------------|------|------|------|
|                     | Focal Diffuse | Focal Diffuse |
| Aseptic loosening   | AC   | 1    | 4    | 0    |
|                     | NAC  | 3    | 2    | 0    |
| Infection           | AC   | 0    | 1    | 2    |
|                     | NAC  | 0    | 1    | 2    |

AC, attenuation correction; NAC, non-attenuation correction.
Semi-quantitative Analysis Results

A comparison of three semi-quantitative indices between the infection and aseptic loosening groups is shown in Fig. 1. There was no significant difference between the two groups in terms of SUVmax (P = 0.448). However, significant differences were observed in T/NT (bone) and T/NT (muscle) between the two groups (P = 0.023 and P = 0.023, respectively). The ROC curves of the three semi-quantitative indices are shown in Fig. 2. The AUCs of SUVmax, T/NT (bone), and T/NT (muscle) were 0.617 (cut-off = 2.243, P = 0.4312), 0.850 (cut-off = 2.844, P = 0.0052), and 0.850 (cut-off = 5.983, P = 0.0003), respectively.

Sensitivity, specificity, accuracy, PPV, and NPV of the visual analysis and semi-quantitative analysis indices

AC, NAC, and T/NT (bone) had high differential diagnostic value (Table 3), with a sensitivity, specificity, and accuracy of 90.0%, 83.3%, and 87.5%, respectively. The diagnostic efficacy of T/NT (muscle) was the second highest, with a sensitivity, specificity, and accuracy of 60.0%, 100%, and 75.0%, respectively. SUVmax had the worst differential diagnosis ability, with a sensitivity, specificity, and accuracy of 70.0%, 66.7%, and 68.8%, respectively.

### Table 3

| Method                  | TP | FP | TN | FN | Sen (%) | Spe (%) | Acc (%) | PPV (%) | NPV (%) |
|-------------------------|----|----|----|----|---------|---------|---------|---------|---------|
| **Visual analysis**     |    |    |    |    | 90.0    | 83.3    | 87.5    | 90.0    | 83.3    |
| AC                      | 9  | 1  | 51 |    |         |         |         |         |         |
| NAC                     | 9  | 1  | 51 |    | 90.0    | 83.3    | 87.5    | 90.0    | 83.3    |
| SUVmax (cut-off 2.243)  | 7  | 2  | 4  | 3  | 70.0    | 66.7    | 68.8    | 77.8    | 57.1    |
| T/NT (bone) (cut-off 2.844) | 9  | 1  | 5  | 1  | 90.0    | 83.3    | 87.5    | 90.0    | 83.3    |
| T/NT (muscle) (cut-off 5.983) | 6  | 0  | 6  | 4  | 60.0    | 100.0   | 75.0    | 100.0   | 60.0    |

AC, attenuation correction; NAC, non-attenuation correction; SUVmax, the maximum standard uptake value; T/NT, SUVmax of target area/SUVmax of non-target area; TP, true positive; FP, false positive; TN, true negative; FN, false negative; Sen, sensitivity; Spe, specificity; Acc, accuracy; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Accurate distinction of AL and PJI is essential for the optimal treatment of patients with painful lower limb joint replacements because the two conditions are treated differently[10]. AL usually requires only one revision arthroplasty to be successful[3, 4]. However, treatment for PJI is more complex, typically requiring two-stage surgery; the first stage includes implant removal, debridement, and antibiotic treatment, followed by a second-stage revision arthroplasty after control of the infection[3, 4]. Therefore, treatment for PJI is protracted, the medical costs are high, and the patients’ function and quality of life are significantly decreased[11]. An accurate and timely diagnosis is crucial for implementing the correct treatment strategy. However, AL and PJI can result in similar symptoms such as pain, swelling, and difficulty walking[6, 19, 25]; in addition, chronic and low-grade infections are more common than acute PJI in the clinical environment and such patients lack the typical clinical symptoms and signs of an infection[4, 6, 9]. This makes differentiating between AL and PJI challenging. Various clinical assessment methods are currently used to confirm the diagnosis, including laboratory examination, X-ray examination, CT imaging, MRI, bone scan, $^{67}$GaGa-citrate imaging, radioactive-labelled leukocyte scintigraphy, $^{18}$F$^{18}$FDG PET/CT imaging, joint aspiration, and microbial culture[3, 4, 7, 25]. However, routine laboratory tests and imaging examinations often provide non-specific results, and joint aspiration may not be successful[1, 3, 5, 9, 26]. Nuclear medicine imaging is considered one of the most valuable methods for the diagnosis of PJI and AL[3]. However, at present, various nuclear medicine methods such as $^{99m}$Tc$^{99m}$Tc-MDP bone imaging, leukocyte scintigraphy, and $^{67}$GaGa-citrate have shortcomings which limit their clinical application.

Preliminary data on the use of $^{68}$GaGa-citrate PET/CT to identify bone infections are promising[16, 17]. Importantly, these studies have shown that $^{68}$GaGa-citrate PET/CT may differentiate between bone infection and physiological bone healing after bone surgery[17], and distinguish infectious from non-infectious diseases after joint replacement[16]. $^{18}$F$^{18}$FDG is one of the most widely studied positron imaging agents for the diagnosis of complications after prosthesis replacement. It has the advantages of high spatial resolution, good image quality, low radiation dose, and the potential for accurate anatomical localization[4, 10, 11]. Extensive literature has compared $^{18}$F$^{18}$FDG with $^{68}$GaGa-citrate for the diagnosis of bone infection-related diseases, and showed different results[13, 16, 17, 27, 28]. However, distinguishing bone infection from AL or physiological inflammation with $^{18}$F$^{18}$FDG remains challenging[4, 9]. In addition, studies by Salomäki et al[17] and Tseng et al[16] have demonstrated that $^{18}$F$^{18}$FDG is unable to distinguish between bone infection and physiological healing or non-infectious complications after bone surgery. Therefore, our study focused on the ability of $^{68}$GaGa-citrate to distinguish between PJI and AL rather than performing a further assessment of $^{18}$F$^{18}$FDG.
Conclusions

Evaluation standard is needed in future studies. Small amount of existing studies of (quantitative analysis) were formulated comprehensively based on experience from relevant studies of [16]. For T/NT (bone) and T/NT (muscle), the Wilcoxon test showed that there was a significant difference between PJI and AL (both P = 0.023); in the ROC analysis, the AUC of T/NT (bone) and T/NT (muscle) were 0.850 (cut-off = 2.844, P = 0.0052) and 0.850 (cut-off = 5.983, P = 0.0003), respectively. These data indicated that T/NT (bone) and T/NT (muscle) were able to effectively distinguish PJI from AL. In addition, we observed that T/NT (bone) has a good sensitivity, specificity, and accuracy (90.0%, 83.3%, and 87.5%, respectively); and the differential diagnostic efficacy of T/NT (muscle) was slightly lower than that of T/NT (bone), with a sensitivity, specificity, and accuracy of 60.0%, 100%, and 75.0%, respectively. Therefore, T/NT (bone) may be a better semi-quantitative index with excellent potential for differentiating between PJI and AL.

Our preliminary results also revealed that visual assessment (AC and NAC) of [68Ga]Ga-citrate PET/CT may be used to distinguish AL (Figs. 3 and 4) from PJI (Figs. 5 and 6) with high sensitivity, specificity, and accuracy (90.0%, 83.3%, and 87.5%, respectively, for both), which is equivalent to the diagnostic effectiveness of T/NT (bone). However, two patients in our study exhibited artefacts on PET images after AC, which mimicked a slight uptake of the imaging agent by the prosthesis; these artefacts were effectively avoided in the NAC images. It is well-known that AC can cause increased tracer uptake artefacts around the prosthesis of patients with metal implants [29]. This may significantly impact the reliability of PET image interpretation in patients suspected of implant complications [29]. Therefore, we evaluated AC and NAC images in order to ensure that the lesions after AC were not imaging artefacts. Although the artefacts of the two patients examined by AC did not affect the final results of our study, we suggest that future [68Ga]Ga-citrate PET examinations in these patients should be combined with AC and NAC.

In our study, we observed a high uptake of imaging agents in the bone marrow cavities bilaterally of an elderly patient with PJI, which was significantly higher than that of the lesion. The patient had severe anaemia and received a blood transfusion two days before the examinations described in this study. This phenomenon can be explained by the fact that adults mainly rely on bone marrow for haematopoiesis, and bone marrow is active after blood transfusion or when it is in a state of self-anæmia; [68Ga]Ga-citrate is an iron analogue, which can be absorbed by active bone marrow and is therefore associated with abnormal uptake of imaging agent. In the patient who underwent a blood transfusion, although the visual analysis of the infection was unaffected it was unclear whether the SUVmax and T/NT values at the infected site were affected by bone marrow uptake. We therefore excluded this patient from the study cohort. In addition, a false-positive result occurred in one of our patients with AL one month following surgery, potentially due to the short postoperative time and the presence of a severe inflammatory reaction in the operative area. This suggests that [68Ga]Ga-citrate may not be suitable for patients who have undergone surgery recently. Similar to [67Ga]Ga-citrate, [68Ga]Ga-citrate is an inflammatory imaging agent which accumulates in the presence of both aseptic and infectious inflammation [10]. Possible mechanisms of [68Ga]Ga-citrate accumulation in such lesions includes: binding to transferrin, binding to ferritin in bacteria and lactoferrin in neutrophils, direct absorption by siderophores with a high affinity for Gallium-68, and enhanced capillary permeability at the lesion site [17, 26, 30]. AL is described as a loss of fixation of the implant that can occur as a result of inadequate initial fixation and mechanical loss of fixation over time [31, 32]. In addition, particles of wear debris may lead to macrophage activation, which in turn releases bone-resorbing products [32, 33]. This results in bone osteolysis around the implant, resulting in the biologic loss of fixation [23, 32]. Therefore, AL may be accompanied by an inflammatory immune reaction to the prosthetic material, which makes it possible for the imaging of patients with AL to show the uptake of [68Ga]Ga-citrate to a certain extent. However, the inflammatory reaction associated with AL may be significantly lower than that of infectious inflammation. In addition, neutrophils are common in PJI, but the proportion of AL cases associated with nonspecific inflammation is small (< 10%) [34]. The difference in cell composition and inflammatory reaction between AL and PJI may explain the difference in [68Ga]Ga-citrate uptake, but the overlap of cytology and histology may also explain the diagnostic difficulties encountered in this study. However, the sample size of this study was limited, and it was not possible to define the specific time period for which postoperative inflammation had a significant impact on [68Ga]Ga-citrate uptake.

With regards to the use of other imaging agents such as [18F]NaF and [18F]FDG for the diagnosis of PJI or AL, some previous studies [11, 12, 35–38] evaluated the relationship between the uptake site and final diagnosis. However, we did not evaluate this in our study. As our study involved a comprehensive assessment of complications after hip and knee arthroplasty, we employed unified diagnostic criteria to diagnose postoperative complications in two different locations. In addition, we were limited by the current sample size.

There were some limitations to our study. First, it was a single-centre study and the sample size was limited. In the current study, it was impossible to evaluate the specific period of time during which postoperative inflammation affects the uptake of the imaging agent, and it was not possible to assess the relationship between uptake sites and final diagnosis; these important issues need to be addressed in future research. Secondly, there are a few current research studies involving [68Ga]Ga-citrate, and our image analysis standards (including visual analysis and semi-quantitative analysis) were formulated comprehensively based on experience from relevant studies of [18F]NaF and [18F]FDG, combined with the small amount of existing studies of [68Ga]Ga-citrate. Given that different evaluation criteria may be associated with different results, a unified evaluation standard is needed in future studies.

Conclusions
In conclusion, our current analysis demonstrated that $^{68}$Ga-citrate has potential as a diagnostic method to distinguish AL and PJI following joint replacement surgery. Visual methods (AC and NAC) and semi-quantitative analysis indices (T/NT [bone] and T/NT [muscle]) were effective for the differential diagnosis of these conditions. However, it is not appropriate to perform this examination until at least one month after the operation, and it is also not suitable for patients with severe anaemia or a recent blood transfusion. A study with a larger sample size and more detailed assessment of the utility of $^{68}$Ga-citrate in patients with pain after joint replacement surgery is warranted.

**Abbreviations**

CT  
Computed tomography  

PET/CT  
Positron emission tomography/computed tomography  

MRI  
Magnetic resonance imaging  

SUVmax  
The maximum standardized uptake value  

AC  
Attenuation correction  

NAC  
Non-attenuation correction  

T/NT  
SUVmax of target area/SUVmax of non-target area  

PJI  
Prosthetic joint infection  

AL  
Aseptic loosening  

MSIS  
Musculoskeletal Infection Society  

ROC  
Receiver operating characteristic  

AUC  
Area under the curve  

LH  
Left hip  

LK  
Left knee  

RH  
Right hip  

RK  
Right knee  

PI  
Primary implant  

RI  
Revised implant  

TP  
True positive  

FP  
False positive  

TN  
True negative  

FN  
False negative  

Sen  
Sensitivity  

Spe  
Specificity
Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written consent after the nature and significance of the imaging study had been fully explained.

Consent for publication

All patients consented to the publication of this manuscript.

Availability of data and material

The datasets and materials during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

TX, YZ, and HY contributed equally to this work and shared joint first authorship. YC and FJ shared joint corresponding author.

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