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Labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography fails in diagnosing chronic periprosthetic shoulder joint infection

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Background: Shoulder periprosthetic joint infections (PJI) caused by low-virulent bacteria pose a diagnostic challenge. Combined labeled leukocyte (WBC) and technetium 99m sulfur colloid bone marrow imaging (WBC/BM) is considered the radionuclide imaging gold standard for diagnosing lower limb PJI. However, it is laborious and expensive to perform, and documentation on shoulder arthroplasties is lacking. This study investigated WBC/BM single-photon emission computed tomography-computed tomography diagnostic performance in shoulder PJI.

Method: All patients with a failed arthroplasty referred to a highly specialized shoulder department were scheduled for a diagnostic program including a WBC/BM. If an arthroplasty was revised, biopsy specimens were obtained and cultured for 14 days. The diagnostic performance of WBC/BM imaging was determined using biopsy specimens as a reference.

Results: Of the 49 patients who underwent a WBC/BM scan, 29 (59%) were revised. Infection was present in 11 patients, in whom 2 WBC/BM scans were true positive. The WBC/BM scan in 9 patients was false negative. The remaining 18 patients all had a true negative WBC/BM scan. WBC/BM showed a sensitivity 0.18 (95% confidence interval [CI], 0.00-0.41) and specificity 1.00 (95% CI, 1.00-1.00) in detecting shoulder PJI. The positive predictive value was 1.00 (95% CI, 1.00-1.00), and negative predictive value

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The Local Ethical Committee of Central Region Denmark approved this study (Ethical Board approval: ref. no. 217/2013).

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was 0.67 (95% CI, 0.49-0.84). No patients infected with *Cutibacterium* (formerly *Propionibacterium*) *acnes* resulted in a positive WBC/BM, nor had they preoperative or perioperative signs of infection.
Conclusion: A positive WBC/BM was found only in patients with obvious PJI. Hence, the scan added nothing to the preoperative diagnosis. The WBC/BM single-photon emission computed tomography–computed tomography scan cannot be recommended as a screening procedure when evaluating failed shoulder arthroplasties for possible infection.
Level of evidence: Level III; Diagnostic Study

Keywords: Revision; shoulder arthroplasty; periprosthetic infection; nuclear medicine; cultures; revision shoulder arthroplasty; hybrid imaging

When patients present with a failed shoulder arthroplasty, surgeons are often put in a difficult position. Are symptoms caused by infection or is it aseptic failure? Fulminant infections caused by high-virulent bacteria presenting with swelling, erythema, fever, or a draining sinus will often reveal the diagnosis. Unfortunately, symptoms of chronic low-grade infection of a shoulder arthroplasty caused by low-virulent bacteria, such as *Cutibacterium* (formerly *Propionibacterium*) *acnes*, can be equally subtle. Patients often present with pain and stiffness as the only complaints. Such symptoms mimic aseptic failure and rarely are any obvious symptoms of infection observed.[2,13] In such situations, the diagnosis of infection can be extremely difficult to obtain preoperatively.

Accurately distinguishing between the different causes of failure preoperatively is important because the choice of treatment and prognosis after revision differ considerably.[10]

No exact diagnostic approach has yet been established despite extensive research in biomarkers, radionuclide imaging, and the use of consensus infectious criteria such as developed by the Musculoskeletal Infection Society (MSIS) or the American Academy of Orthopaedic Surgeons (AAOS).[5,8,19]

Combined labeled leukocyte (WBC) and technetium 99m sulfur colloid bone marrow (WBC/BM) imaging is currently regarded as the gold standard of radionuclide imaging for detecting periprosthetic joint infections (PJI).[6] Most studies investigating WBC/BM imaging have been performed using conventional scintigraphy (planar imaging), which detects tracer activity in 2-dimensions. Technical innovation has made single-photon emission computed tomography (SPECT) possible. A SPECT scan is a scintigraphic technique in which tracer activity is detected in 3-dimensions, making the spatial resolution superior to the planar detection. Furthermore, when SPECT is coupled to a low-dose computed tomography (CT) scan (SPECT CT), the tracer activity can be located both spatially and related to specific anatomic structures.

This enhanced spatial and anatomic resolution makes SPECT CT the current technique of choice in diagnosing infections of the skeletal system. Based on lower extremity PJI, several studies have reported sensitivity and specificity above 90%.[12,14] Despite the promising results, WBC/BM has drawbacks that limit its usefulness. It involves handling of blood products, labeling of blood cells requires 2 work days to complete, exposes the patient to a high level of radiation, and is expensive.

If the high diagnostic precision reported in lower limb PJI can be achieved in shoulder PJI, it could, despite the limitations of the WBC/BM, be a valuable help to shoulder surgeons. No formal study using WBC/BM on failed shoulder arthroplasties has yet been published.

The objective of this study was to establish the diagnostic performance of WBC/BM SPECT CT when used to diagnose chronic infection in a consecutive cohort referred with a failed shoulder arthroplasty. We hypothesized that WBC/BM SPECT CT would have similar specificity and sensitivity in detecting shoulder PJI as seen in lower limb PJI.

Materials and methods

This prospective cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline in designing and reporting of observational studies.[21]

In Denmark, all citizens (5.7 million) have free access to health care because of tax funding; thus, only public hospitals treat patients with a failed shoulder arthroplasty. Two departments are appointed by the Danish National Board of Health as the only units to perform revision shoulder arthroplasty surgery in Denmark. Approximately 140 patients are annually referred to the 2 centers with this condition. We included all patients regularly referred with a failed shoulder arthroplasty for evaluation of a possible revision arthroplasty. A failed shoulder arthroplasty was defined as patient-reported unsatisfactory result of any cause after shoulder replacement causing the patient to consult a physician and resulting in a referral to the highly specialized The plan was to include 50 revised patients in the study starting April 1, 2014.

A standardized preoperative workup consisting of 3 visits was set up to identify potential infected arthroplasties in the referred patients. At the first visit, a number of diagnostic tests were scheduled, including blood tests (erythrocyte sedimentation rate, WBC count, and C-reactive protein), ultrasonography with aspiration, x-ray imaging, and a thorough clinical assessment conducted by the surgeon.

At the second visit, a WBC/BM SPECT CT was performed. If the patient was on antibiotic treatment, it was paused, and the scan scheduled after at least 14 days to reduce the risk of false negative scans due to suppression of bacterial activity. At the last visit, the patient was informed of the results of the diagnostic tests, upon which the surgeon recommended revision surgery or nonsurgical treatment. Revision surgery was recommended if our modified MSIS criteria indicated infection (Fig. 1), or if signs of component loosening, obvious mechanical failure (eg, cranial migration), glenoid

attrition, or tubercular resorption were observed. The surgeon made an individual recommendation in cases with severe pain or significant functional limitation without the aforementioned findings or if the patient suffered from severe comorbidities.

The decision of surgery was ultimately left to the patient, even when the surgeon found surgery was indicated. Only when the surgeon suspected deep infection were the patients strongly advised to undergo surgery. Some patients choose not to undergo surgery after receiving information of pros, cons, and expected results after revision surgery. If the latter was the case, and the patient decided to live with the current limitations, no further actions were taken and the patient was omitted from the study.

Patients planned for surgical revision were paused for any antibiotic treatment for at least 14 days before surgery, and perioperative antibiotics were withheld until all biopsy specimens were obtained. During the revision procedure, biopsy specimens were obtained according to the definition of Kamme-Linberg.[11] Five individual samples were acquired with clean instruments from areas showing sign of infection and from the prosthesis surface. If no infection or suspicious signs were observed, samples were obtained from different intra-articular spots. The samples were cultured 4 days for aerobic bacteria and 14 days for anaerobic bacteria to detect bacteria such as *C acnes*.

After 1 year, the results were reviewed. Studies have reported that 1% to 4% of primary shoulder arthroplasties are infected.[17,18] Because the referred population exclusively consisted of patients with a failed arthroplasty, the prevalence was suspected to be even higher. With an infection rate of 38% (11 of 29), our data confirm this. The interim results led to a running discussion of the justification to continue the study among the nuclear medicine department and the orthopedic surgeons, especially owing to the substantial patient and economic resources needed to perform the scans as a screening procedure. The conclusion was that even in this high-prevalence cohort, the WBC/BM SPECT CT was not cost-effective. As a consequence, enrollment stopped on May 15, 2015, before the planned number of patients was reached.

Definition of infection

Our primary definition of infection was set to be at least 3 positive tissue cultures with the same bacteria or if a sinus tract communicating to the prosthesis was present. This definition was based on publications from Kamme-Lindberg[11] and the Oxford group.[1] This more rigorous definition than is typically used in published reports was chosen to reduce the risk of erroneously diagnosing skin contamination from especially *C acnes* as PJI.

To evaluate whether increased diagnostic power could be obtained by adding advanced radionuclide imaging and shoulder-specific signs of infection (stiffness and unexplained pain) as minor signs of infection (Fig. 1), we modified the existing MSIS definition of PJI. In this modified MSIS definition, the primary signs remain the same as in the original MSIS definition, but the number of secondary signs needed to diagnose infection were reduced to 2, compared with 4 in the original MSIS definition. The latter was done to reduce the risk of underdiagnosing low-virulent PJI. Because immediate histology of perioperative specimens was presently not available to us, we choose to omit such findings as secondary signs of infection.

Labeling and imaging protocol of WBC/BM SPECT CT

^{111}Indium-labelled WBC imaging is a 2-day procedure. On the first day, 50 mL whole blood is extracted from the patient, and leucocytes

MSIS 2013 criteria	Modified MSIS criteria (modifications marked with underscore)
PJI Positive if at least one primary sign exists OR at least three secondary signs exist.	**PJI Positive if at least one primary sign exists OR at least <u>two</u> secondary signs exist.**
Primary signs 1)There is a sinus tract communicating with the prosthesis; OR 2)A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; OR	**Primary signs** 1)There is a sinus tract communicating with the prosthesis; OR 2)A pathogen is isolated by culture from at least three separate tissue or fluid samples obtained from the affected prosthetic joint; OR
Secondary signs a) Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR) b) Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip c) Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) d) Positive histological analysis of periprosthetic tissue e) A single positive culture	**Secondary signs** a) <u>Elevated serum C-reactive protein (CRP) OR erythrocyte sedimentation rate (ESR) OR WBC</u> b) A single positive culture c) <u>Positive radionucleide imaging</u> d) <u>Unexplained nightly pain OR excessive joint stiffness</u>

Figure 1 Musculoskeletal Infection Society (*MSIS*) periprosthetic joint infection (*PJI*) definition and modified MSIS PJI definition.

are labeled with 30 MBq ^{111}indium-tropolone and then reinjected. Images are acquired approximately 24 hours later.

At the second day, 400 MBq freshly prepared ^{99m}Tc-sulfur colloid is injected intravenously to depict the bone marrow. Patients are scanned within 1 hour after the injection, using a gamma-camera with simultaneous dual-isotope imaging. A Symbia (T16) scanner (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) equipped with medium-energy collimators were used with a 15% window centered on 140 keV, a 15% window centered on 174 keV, and a 15% window centered on 247 keV in a 128×128 matrix. Planar imaging of thorax and shoulders in anterior and posterior projection in a 128×128 matrix with 20 minutes per view were performed. To locate pathologic foci in 3D, a SPECT with low-dose CT (50 mAs) was performed in a 64×64 matrix with 32 views of 40 seconds per view. The same collimator and energy windows were used performing both planar and tomographic imaging.

Image analysis

A senior nuclear radiologist reviewed all scans. A positive scan was defined as any mismatch activity between the BM scan and WBC scan in close relation to the arthroplasty, regardless of intensity or location, providing a positive or negative answer. Examples of positive WBC/BM SPECT CT are shown in Fig. 2.

Microbiologic culture protocol

Specimens were cultured on 5% blood agar plates (SSI, Copenhagen, Denmark), anaerobic agar plates (SSI), BLL chromagar orientation medium (Becton Dickinson, Heidelberg, Germany), and inoculated in semisolid agar + pepsis blood + thioglycollate (SSI) and serum broth (SSI).

Agar plates were inspected for growth up to 4 days. Semisolid agar and serum broth was visually inspected for signs of growth on day 4 and day 14. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Bruker, Bremen, Germany) was used for identification of strains.

Study population

During the 1-year inclusion period, 71 patients were referred to the center with a failed arthroplasty, all of whom completed the first visit. WBC/BM SPECT CT was performed on 49 patients. A detailed description of patient enrollment is shown in the flowchart (Fig. 3). Nine patients were at the surgeon's discretion assessed not to be candidates for surgery. This assessment was based on comorbidities, expected relief of symptoms, and patient's acceptance of the course of rehabilitation after surgery. In all cases, the surgeon had no suspicion of infection.

Statistical analysis

The sample size for a reasonable estimation of sensitivity and specificity was calculated using binominal proportions. The microbiologically confirmed infection rate in the revised population was estimated to be 25% and hypothesizing a WBC/BM SPECT CT sensitivity and specificity of 0.9. Based on these assumptions and including 50 patients, we expected an estimation of sensitivity ± 0.19 and specificity ± 0.09, which we considered acceptable.

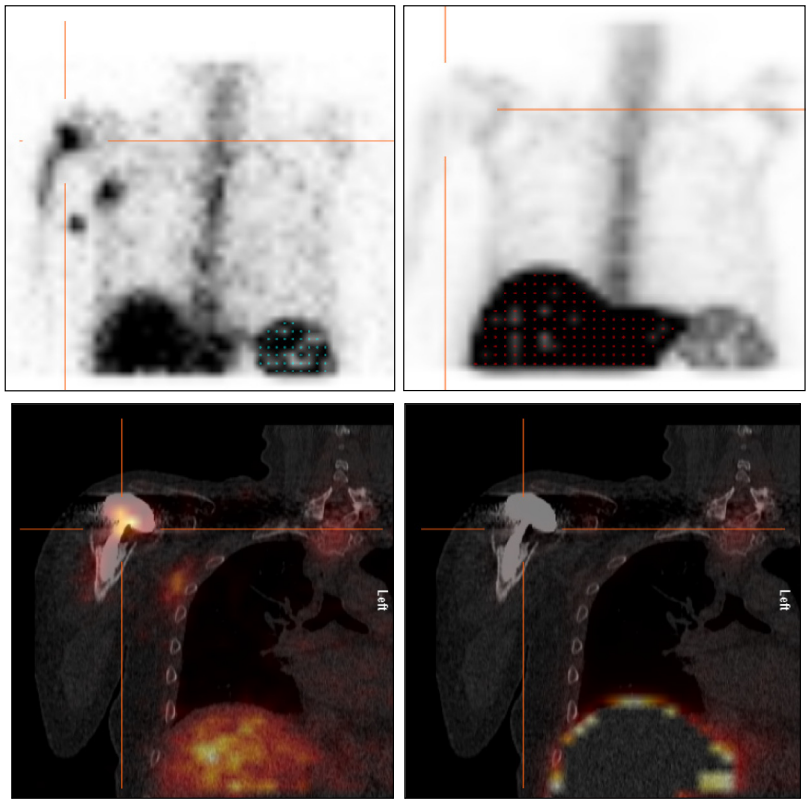

Figure 2 Example of a positive WBC/BM SPECT CT scan.

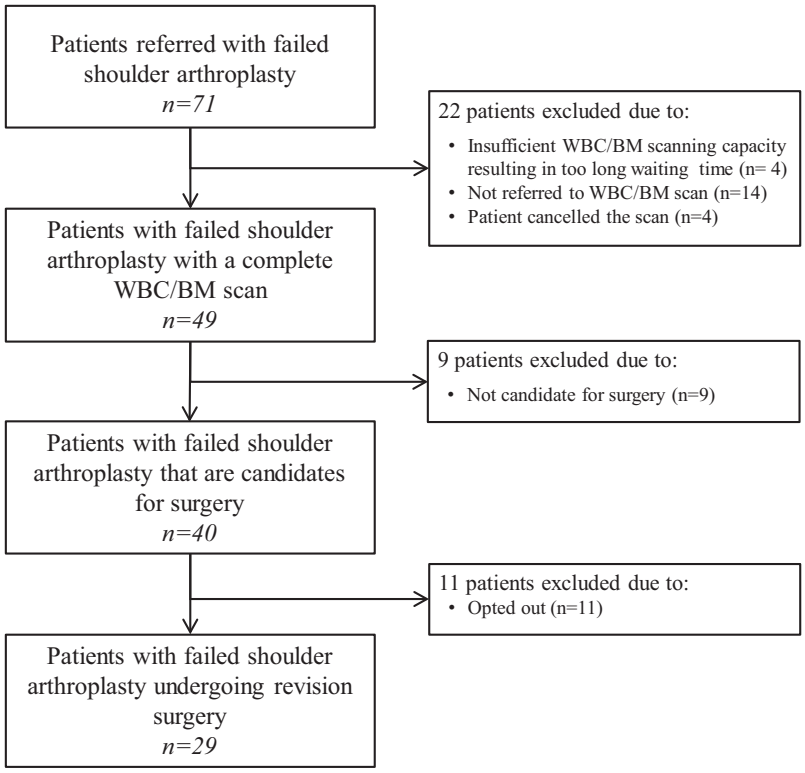

Figure 3 Flowchart of patient inclusion. *WCB/BM*, labeled leukocyte and technetium 99m sulfur colloid bone marrow.

Sensitivity, specificity, accuracy, and positive and negative predictive value (PPV and NPV, respectively) of WBC/BM SPECT CT were calculated using the microbial diagnosis as the true infection status. The same values were calculated and compared for the MSIS and modified MSIS definitions. All results are reported as fractions with 95% confidence intervals (CI). Data were analyzed using STATA 15 software (StataCorp, College Station, TX, USA).

Results

The demographics of the referred cohort and study population are described in Table I. No statistical differences between the dropout population and study cohort were found when testing for sex, mean age, or prosthesis age. No patient was being treated with antibiotics at the time of referral. A summary of the preoperative test results can be found in Table II.

Of the 49 performed WBC/BM SPECT CT studies, 2 (4%) were positive, and 47 (96%) were negative. One positive scan showed increased activity along the stem and in several lymph nodes in the axilla. The other positive scan showed intense increased activity in the shoulder joint and around the proximal part of humerus. The 2 positive WBC/BM SPECT CT studies were also culture positive.

Activity was recorded in 3 patients with negative scans, but not in areas related to the shoulder prosthesis. None of the 3 underwent operations.

Table I Demographics

Variable	Referred (n = 71)	Dropped out (n = 22)	WBC/BM SPECT CT (n = 49)	Study cohort (n = 29)
Age, mean (range), yr	65 (29-88)	67 (54-88)*	64 (29-88)	63 (29-84)
Sex, No.				
Female	33	8*	25	10
Male	38	14*	24	19
Prosthesis age, median (range), yr	3 (0-29)	5.5 (0-13)*	4 (0-13)	5 (0-13)
Revision rate		0.68 (15/22)*	0.59 (29/49)	1.00 (29/29)
Infection rate		0.2 (3/15)*	0.22 (11/49)	0.38 (11/29)

WBC/BM, labeled leukocyte and technetium 99m sulfur colloid bone marrow; *SPECT*, single-photon emission computed tomography; *CT*, computed tomography. Data are presented as median (range) or as number of patients.

* No significant difference between dropout and study cohort ($P > .05$).

Table II Results of preoperative diagnostic tests

Variable	Referred (n = 71)	Dropped out (n = 22)	Opted out and excluded (n = 20)	Study cohort (n = 29)
Indication for primary arthroplasty				
Arthrosis	25	8	8	13
Fracture/fracture sequelae	33	8	8	14
Rheumatoid arthritis	4	1	2	1
Other	9	5	2	1
Arthroplasty type				
Hemi	45 (cemented 20)	13 (cemented 8)	12 (cemented 8)	15 (cemented 13)
Total shoulder replacement	8 (cemented 3)	4 (cemented 3)	4 (cemented 3)	3 (cemented 1)
Resurfacing (hemi)	14 (uncemented)	3 (uncemented)	3(uncemented)	10 (uncemented)
Reverse	4 (cemented 4)	2 (cemented 2)	1 (cemented 1)	1 (cemented 1)
Radiologic findings				
Normal	10	2	4	4
Surgical error*	12	3	3	6
Loosening of components or osteolysis	10	4	1	5
Other†	39	13	12	14
Serologic findings				
≥1 elevated infectious marker§	21	8	8	5

* Surgical error consisted of malpositioning of implant, oversized implant.
† Other consisted of superior migration, resorption of tuberculi, glenoid attrition, dislocation, bent humoral implant.
§ C-reactive protein, white blood cell count, erythrocyte sedimentation rate.

Biopsy samples were obtained in all 29 surgically treated patients according to the protocol. In 10 patients (34%), infection was diagnosed with least 3 positive cultures. One patient had a fistula, and 2 of 5 cultures were positive with coagulase-negative staphylococci but a negative WBC/BM. This patient was classified as infected because of the fistula. Infection was ruled out in 18 patients (66%; Table III). Of the noninfected patients, all-negative cultures were found in 12 patients, and a growth pattern with less than 3 positive cultures with the same microbe or mixed flora on several plates was judged to be contamination was found in 6 patients.

The shortest interval between the latest operation to the arthroplasty and our revision was 5 months; thus, all infection can be categorized as chronic infection. The predominant organism isolated was *C acnes* found in 6 patients, followed by coagulase-negative staphylococci in 4 patients and *Peptostreptococcus* found in 1 patient. An overview of the culture results can be found in Supplementary Table S1.

Table III Summarized results of WBC/BM scan and infections status

Variable	Infected	Not infected	Total
WBC/BM SPECT CT			
Negative	9	18	27
Positive	2	0	2
Total	11	18	29

WBC/BM, labeled leukocyte and technetium 99m sulfur colloid bone marrow; *SPECT*, single-photon emission computed tomography; *CT*, computed tomography.

During surgery, only 1 of the 2 patients with a positive WBC/BM SPECT CT showed clinical signs of infection such as intra-articular purulence, membranes, stem loosening, or bone loss. For the remaining patients with positive WBC/BM SPECT CT or positive microbiological diagnosis, the surgeon did not find findings suspicious for infection preoperatively (fever, sinus, erythema, elevated blood tests) or during surgery.

The overall diagnostic values of WBC/BM SPECT CT in relation to cultures and MSIS criteria are summarized in Table IV.

Discussion

The use of radionuclide imaging to screen for low-virulent infection in the shoulder has not previously been described. A review by Yue and Tang[23] reported that WBC/BM SPECT imaging diagnosed lower extremity PJI with a high specificity and sensitivity, but large variations in estimates of diagnostic performance between studies exist. Whether a high diagnostic power can be achieved in shoulder arthroplasties is a valid question, especially keeping in mind that chronic low-grade infections (eg, caused by *C acnes*) are the most frequent cause of PJI of the shoulder.

In our study, WBC/BM SPECT CT showed a sensitivity 0.18, specificity 1.00, PPV of 1.00, NPV of 0.67, and an accuracy of 0.69 in detecting a chronic infected shoulder arthroplasty. This is in contrast to Love et al[12] who found an accuracy of 0.95, a sensitivity of 1.00, specificity of 0.91, PPV of 0.89, and NPV of 1.00 using WBC/BM scintigraphy to detect lower limb PJI in a population of both postoperative and chronic

Table IV Diagnostic performance of WBC/BM SPECT CT based on cultures, MSIS, and modified MSIS definition of periprosthetic joint infection

Variable	WBC/BM imaging (95% CI)	Modified MSIS criteria (95% CI)	MSIS criteria (95% CI)
Sensitivity	0.18 (0.00-0.41)	0.20 (0.00-0.45)	0.15 (0.0-0.35)
Specificity	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
PPV	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (0.00-0.00)
NPV	0.67 (0.49-0.84)	0.70 (0.53-0.88)	0.59 (0.41-0.78)
Accuracy	0.69 (0.52-0.86)	0.72 (0.56-0.89)	0.62 (0.44-0.80)

WBC/BM, labeled leukocyte and technetium 99m sulfur colloid bone marrow; *SPECT*, single-photon emission computed tomography; *CT*, computed tomography; *MSIS*, Musculoskeletal Infection Society; CI, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value.

infections. Their study was performed on 59 hip and knee arthroplasties, and infection was defined as growth in least 1 biopsy sample or >5 neutrophils per high-power field in a synovial sample. The difference in results could partly be explained by the population and the definition of PJI.

If an arthroplasty is infected postoperatively, an aggressive organism like *Staphylococcus aureus* is often the pathogen. This type of infection causes severe soft tissue reactions compared with the more indolent course a chronic infection can have. As a consequence, leucocyte aggregation is marked and expected to be detected more reliably using WBC/BM. Our study group consisted of chronic infections only. Most infections in the shoulder are caused by *C acnes*, and this bacterium was not identified in the hip or knee infections. Studies of *C acnes* have shown that it can escape the immune system by surviving inside macrophages and resisting phagocytosis.[22] Grosso et al[7] examined the aggregation of leucocytes in frozen sections from shoulder revisions. They concluded that fewer leucocytes were present in frozen sections from *C acnes* infections compared with other infections. This could indicate that *C acnes* might not trigger the immune system adequately to be detected by the WBC/BM SPECT CT. In consequence, this would explain the decreased sensitivity in our cohort compared with the study by Love et al.[12]

To minimize the risk of overdiagnosing PJI, our definition requires identification of the same bacteria in at least 3 of 5 separate tissue cultures. However, it is possible that 1 or 2 positive cultures represent a true infection because bacterial load may not be evenly spread throughout the joint. Thus, our definition of 3 or more positive samples could potentially underestimate the infection rate and sensitivity and overestimate the NPV in this study. Nevertheless, because no difference in WBC/BM SPECT performance could be detected using our definitions compared with the MSIS criteria requiring only 2 positive cultures to define infection, an underestimation of infection in our study seems unlikely.

Furthermore, some organisms, such as *C acnes*, exist in 2 states, biofilm and planktonic. The biofilm is found on surfaces of an implant and the planktonic form in tissue and joint fluid. It is accepted that the planktonic form can be detected with regular tissue cultures, but sonication of the extracted implant is often needed to dislodge the bacteria from the biofilm.[20] Sonication was not available to us during the study period, and biopsy samples from the implant surface were obtained by scraping any material off the implant. This could potentially have reduced the number of infected patients in our study group, resulting in even lower sensitivity than observed. However, a recent report by Grosso et al[9] found no benefits of sonication vs. standard intraoperative cultures in diagnosing shoulder PJI.

A limitation of any study investigating PJI diagnostics is the lack of a gold standard criteria for shoulder PJI.[4] Any test of a diagnostic modality can never outperform the chosen gold standard against which the modality is compared. The MSIS adopted in 2013 is a consensus criteria of PJI primarily based on lower limb arthroplasties.[15] Because numerous authors argue that excessive stiffness and nightly pain of a shoulder without any apparent explanation can be a sign of PJI, we modified the MSIS criteria to incorporate both symptoms as secondary criteria and lowered the number of secondary symptoms needed to fulfill the criteria of infection.

Using our modified MSIS criteria of infection compared with the original MSIS criteria, we could not detect a difference in diagnostic power definition (Table V). Perioperative histology was not available to us during the study period; furthermore, despite ultrasound guidance, aspiration in nearly all cases were dry taps. As a consequence, the MSIS criteria can only be positive when a primary sign is present. Because MSIS requires only 2 separate biopsy samples as a primary sign to indicate infection, and our biopsy-based definition requires 3 or more samples to indication infection, the overlap between the 2 definitions is considerable. All 3 definitions exhibit the same limitation, the difficulty of making a precise preoperative diagnosis.

All but one of our infections can be classified as unexpected positive cultures. This is a common finding in shoulder revision surgery, and the clinical implications of this is still uncertain.[3] Because *C acnes* is an abundant commensal around the shoulder girdle, this bacterium is a highly possible contaminant introduced during the revision procedure.[16] If the latter is the case, the WBC/BM SPECT CT would show significantly different results, with specificity and sensitivity near 100%. We believe that using the principle of at least 3 positive cultures from 5 separate biopsy samples as a marker of

true infection substantially lowers the risk of contamination being diagnosed as an infection.

Another limitation of this study is the low number of patients included, which is attributed to 2 factors. The first is a high dropout rate. Twenty-two patients (36% of the patients) were never referred to WBC/BM SPECT CT. This dropout was partly a consequence of far more patients than expected being referred to our center, causing an unacceptably long wait to perform the assay. A potential selection bias could have been introduced if surgeons omitted referral to WBC/BM SPECT CT of patients with low suspicion of infection. An analysis of the patients who dropped out showed no difference in demographics, revision, or infection rate. Thus, we do not believe an influential bias was introduced.

Furthermore, 11 patients who completed the preoperative diagnostics and were offered revision surgery choose to opt out. Four patients stated that due to recent non-shoulder-related surgery, they had no surplus mental and physical resources to undergo major surgery and rehabilitation. For the rest of the group, no specific reason for refusal of surgery was recorded. However, this relatively high number can partly be explained by the long rehabilitation and the sometimes limited gain in function and pain reduction after revision surgery.

Another factor for the high dropout could be attributed to the Danish health care system. In Denmark, treatment is fully paid by the government. As a consequence, a patient who opted out could, without any implications, return to the hospital for surgery at any given time.

The second limitation is the premature closure of the study after the analysis of the results after 1 year, as described in Materials and Methods. If the study had continued, the most likely effect would be more precise estimates of specificity, NPV, and accuracy.

Conclusion

Our study found a low NPV, a high PPV, and a poor accuracy using WBC/BM SPECT CT in screening a failed shoulder arthroplasty for chronic infection. Despite the premature shutdown of the study and the limitations of patient recruitment, the results of WBC/BM SPECT CT in this study are significantly inferior to similar studies of lower limb arthroplasties.

Because of the high risk of an inconclusive result, WBC/BM SPECT CT cannot currently be recommended as a method of screening a failed shoulder arthroplasty for PJI. Thus, future research in functional imaging of shoulder arthroplasties should focus on modalities that can detect chronic low-grade infections or even target specific molecules produced by the most frequent disease-causing bacteria. Furthermore, studies investigating preoperative diagnostic tools should incorporate histologic analysis of biopsy samples.

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Supplementary data

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