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Original Research

Serum CD64 as a Marker for Chronic Periprosthetic Joint Infection

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ABSTRACT

Background: Serum cluster of differentiation 64 (CD64) has emerged as a diagnostic test for musculoskeletal infections. The purpose of this study was to evaluate the utility of serum CD64 in diagnosing periprosthetic joint infections (PJIs) compared to conventional markers like white blood count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6).

Methods: A prospective case-control study on patients undergoing revision hip or knee arthroplasty surgery >6 weeks after their index surgery was performed at a single institution. Whole blood samples were drawn within 24 hours prior to revision surgery for white blood count, ESR, CRP, IL-6, and CD64. Intraoperative cultures were obtained during the revision, and PJI was defined using the major criteria from the 2018 Musculoskeletal Infection Society criteria. Two-sample Wilcoxon rank-sum test and Fisher's exact test were used to determine if there were significant differences in serum laboratory values between patients with and without infection. The sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy of each test were calculated.

Results: With an average age of 67 years, 39 patients with 15 revision THAs and 24 TKAs, were included. 19 patients (48.7%) were determined to have PJI. Patients with PJI had significantly higher CD64 ($P = .036$), CRP ($P = .016$), and ESR ($P = .045$). CD64 had the highest specificity (100%) and PPV (100%), moderate accuracy (69.2%), but low sensitivity (37.0%) and negative predictive value (62.5%).

Conclusions: Given the high specificity, PPV, and accuracy, CD64 may be an excellent confirmatory test to help diagnose PJI.

Introduction

Periprosthetic joint infection (PJI) is a disastrous condition, and its prevalence has continued to rise for both total hip arthroplasty (THA) and total knee arthroplasty (TKA) [1,2]. PJI is the leading cause of primary TKA failure and the third leading cause of primary THA failure [3]. These infections are associated with significant complications, and patients undergoing revision arthroplasty for infection have significantly increased mortality rates compared to patients undergoing revision for aseptic causes [4-6]. Additionally, hospital costs related to PJI are double that of their aseptic counterparts, and recent studies are projecting the United States' economic burden of PJI to reach $1.85 billion by 2030 [7,8].

Prompt diagnosis of PJI is critical but can be difficult due to variable symptoms on presentation. Multiple criteria have been developed in order to diagnose PJI, with the Musculoskeletal Infection Society (MSIS) 2018 update being the most recognized [9,10]. Although these criteria together have been validated to have 97.7% sensitivity and 99.5% specificity for the diagnosis of PJI, they require synovial fluid in order to establish a diagnosis. Current conventional serum parameters, including white blood count (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), are not specific to musculoskeletal infection [11]. More recently, newer studies have sought to evaluate the ability of various serum biomarkers to diagnose PJI. Shahi et al. demonstrated serum D-dimer to have a sensitivity of 89% and a specificity of 94% in the diagnosis of PJI [12], and a meta-analysis study for serum leukocyte esterase testing showed 81% sensitivity and 97% specificity for PJI [13]. Serum levels of interleukin-6 (IL-6) have also been shown to have both high sensitivity and specificity in detecting periprosthetic hip and knee infections [14]. However, IL-6

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can also be elevated in inflammatory conditions, immunocompromised individuals, and patients with multiple sclerosis [14,15].

The expression of cluster of differentiation 64 (CD64) has come into the spotlight as a potential marker for orthopedic infections [16]. CD64 is a surface protein typically expressed on macrophages, monocytes, and dendritic cells, with minimal neutrophil expression at the physiological baseline. During infection, however, neutrophils and lymphocytes upregulate CD64 in response to inflammatory cytokines [17-19]. Tanaka et al. evaluated serum neutrophil CD64 expression and found a sensitivity of 60.9% and a specificity of 97.9% in the detection of general musculoskeletal infections [20]. Additionally, Qin et al. evaluated synovial fluid CD64 expression and found a sensitivity of 92% and a specificity of 96% for the diagnosis of PJI [21].

The purpose of this study was to compare serum CD64 expression to more conventional serum markers. We hypothesized that CD64 expression would have increased sensitivity, specificity, and accuracy compared to serum WBC, ESR, CRP, and IL-6 in the diagnosis of PJI.

Material and methods

This was a prospective case-control study on patients undergoing revision THA or TKA. The study was conducted over a period of 24 months at a single academic institution. Reasons for revision included aseptic loosening, suspected PJI, polyethylene wear, or instability. Our institutional review board approved the study, and all patients gave their written informed consent prior to participating. Inclusion criteria included patients undergoing revision for TKA or THA at least 6 weeks after their index procedure. Patients were excluded if they had any previous history of revision surgery on the index joint, received antibiotics prior to obtaining intraoperative cultures, or had a history of chronic inflammatory disease, malignancy, or blood dyscrasias. Whole blood samples were drawn within 24 hours prior to revision surgery to determine the WBC, ESR, CRP, IL-6, and CD64. Preoperative antibiotics were held until after intraoperative cultures were obtained. At least 4 intraoperative cultures were obtained, and all cultures were held for at least 14 days. A positive infection was diagnosed if a single organism was grown from 2 or more cultures and/or a draining sinus was present, in accordance with the most recent major MSIS criteria. These were chosen as the gold standard as the MSIS criteria were designed to be tested against these 2 major criteria [9]. All diagnosed infections were considered PJIs, and they were treated with irrigation, debridement, explant of components, and antibiotic cement spacer placement. All other patients were treated with either a partial or complete revision of their arthroplasty implant components.

The WBC, ESR, CRP, and IL-6 were drawn and measured using standard laboratory protocols as established at our institution. The WBC was measured on the Sysmex XE-5000 hematology analyzer (Sysmex, Lincolnshire, IL). The erythrocyte sedimentation rate was measured on the Excyte 40 and Excyte 10 ESR analyzers (Clinical Data, Smithfield, RI) based on the Westergren method. The C-reactive protein level was measured with the use of the Tina-quant C-Reactive Protein Gen.3 (CRPL3) kit (Roche Diagnostics, Indianapolis, IN) on the Roche/Hitachi Modular System (Roche Diagnostics, Indianapolis, IN). The IL-6 sample was sent to Quest Diagnostics with the use of the Human IL-6 Quantikine ELISA kit (R&D Systems, Minneapolis, MN). For the CD64 sample, 5 mL of whole blood was drawn into an EDTA tube. The blood samples were all tested within 24 hours of being drawn without any refrigeration in between. 20 uL of QuantiBrite CD64PE/CD45PerCP (Becton-Dickinson, San Diego, CA) was added to 50 uL of whole blood and incubated for 60 minutes in the dark at room temperature. After the erythrocytes had been lysed with 2 ml of 1X NH4Cl solution, the samples were incubated for an additional 15 minute at room temperature and then centrifuged at 1500 rpm for 5 minutes. The samples were then washed with 1X phosphate buffered saline and centrifuged again at 1500 rpm for 5 minutes. The supernatant was discarded after each centrifuge. 500 uL of cold phosphate buffered saline were added to the samples and mixed thoroughly. The expression of CD64 was examined using a Navios flow cytometer (Beckman Coulter, Miami, FL) calibrated with QuantiBrite phycoerythrin (PE) beads (Becton-Dickinson, San Diego, CA) which contain 4 different beads with known numbers of PE molecules that make it possible to create a standard curve for determining the mean number of PE molecules present on a cell. Each CD64-PE antibody was designed to bind one PE molecule per antibody. The mean number of CD64 molecules present on neutrophils was then calculated using the PE fluorescence quantification kit with QuantiBrite PE beads. Neutrophils were identified by their CD45 and side scatter properties.

Statistical analysis

Positive infection was confirmed if 2 positive intraoperative cultures grew out the same organism and/or a draining sinus was present. Two-sample Wilcoxon rank-sum (Mann-Whitney) tests for the continuous variables and Fisher's exact tests for the categorial variables were then used to determine the differences between patients diagnosed with PJI and patients without PJI in the values of WBC, ESR, CRP, IL-6, and CD64. Finally, the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for each test were also calculated. Accuracy was calculated as true positives plus true negatives divided by the total number of cases.

Results

A total of 39 patients met the study criteria. There were 19 females and 20 males, with an average age of 67 years. Within this group, 15 patients underwent revision THA and 24 patients underwent revision TKA. Revision surgery occurred at a mean 4.98 years after the index arthroplasty. Of the 39 patients studied 19 patients (48.7%) were determined to have PJI. The most common pathogens grown were methicillin-sensitive Staphylococcus aureus in 5 patients, Staphylococcus epidermidis in 3 patients, and methicillin-resistant Staphylococcus aureus in 2 patients (Table 1). All studies were obtained on all patients except for IL-6, which was not able to be analyzed in 5 patients due to the blood sample coagulating during transport.

The diagnostic threshold for a positive value was determined for WBC ($N < 10{,}800$ cells/mm^3), ESR ($N < 30$ mm/hour), CRP ($N < 10$ mg/L), IL-6 ($N < 10$ pg/mL), and CD64 ($N < 2000$ molecules/cell) in accordance with previously published studies [14,18]. Patients with PJI had significantly higher ESR ($P = .045$), CRP ($P = .016$), and CD64 ($P = .036$) (Table 2). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for WBC ($N > 10{,}800$ cells/mm^3), ESR ($N > 30$ mm/hour), CRP ($N > 10$ mg/L), IL-6 ($N > 5$ pg/mL), and CD64 ($N > 2000$ molecules/cell) are highlighted in Table 3. Specifically, CD 64 had the highest specificity and positive predictive value out of all tests included at 100.0% each, but sensitivity was low at 36.8%. CRP was found to have the highest sensitivity and negative predictive value at 68.4% and 70.0%, respectively. CD64 and CRP were found to have the highest accuracy at 69.2%.

Table 1
Culture-positive subjects.

Implant	WBC (cells/mm^3)	ESR (mm/h)	CRP (mg/L)	IL-6 (pg/mL)	CD64 (molecules/cell)	Bacteria
THA	7.07	23	10.3	3.88	2112	MRSA
THA	9.75	92	268.8	347.41	14,590	MRSA
THA	11.93	11	2.1	3.34	3105	Parvimonas vicra
THA	22.5	110	360.8	61.7	3562	MSSA
THA	6.32	9	49.5	14.1	483	Cutibacterium acnes
THA	13.5	125	4.8	19.5	545	MSSA
THA	8.82	83	32.3	32.8	955	Clostridium clostridioforme
THA	11.2	130	0.75	3.2	596	Cutibacterium acnes
TKA	10.4	44	20.2	2.85	620	MSSA
TKA	3.4	7	3.3		592	Staphylococcus epidermidis
TKA	6.2	14	3.3		711	Streptococcus gordonii
TKA	6.63	103	25.4	18.58	740	Staphylococcus epidermidis
TKA	7.48	94	31.2	3.2	961	Corynebacterium striatum
TKA	5.92	30	33	12.9	747	MSSA
TKA	21.72	34	17.4	22.8	2531	Streptococcus dysgalactiae
TKA	16.99	28	21.5		4607	Staphylococcus epidermidis
TKA	13.18	130	335.5	77.8	3963	MSSA
TKA	8.97	24	2.47	3.2	1417	Pseudomonas aeruginosa
TKA	5.02	130	86.8	6.6	1132	Staphylococcus lugdunensis

WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin 6; CD64, serum cluster of differentiation 64; THA, total hip arthroplasty; TKA, total knee arthroplasty; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus.

Discussion

Accurate diagnosis of PJI is paramount, and yet none of the available preoperative tests are 100% accurate in the diagnosis of PJI [9-15]. We hypothesized that CD64 expression would have increased sensitivity, specificity, and accuracy compared to serum WBC, ESR, CRP, and IL-6 in the diagnosis of PJI. We found that CD64 had a very high specificity (100%) and PPV (100%), moderate accuracy (69.2%), but also a low sensitivity (37.0%) and NPV (62.5%).

As total joint replacements become more common, the prevalence of PJIs will continue to increase. Assessing patients for PJI remains particularly difficult, especially in patients with mild symptoms. Often the only complaint that patients will present with after a total joint replacement is pain, and infection must always be considered in the differential. While modern surgical aseptic techniques have reduced rates of PJIs, they continue to place a large burden on healthcare resources due to the increasing incidence of total joint replacement surgery [2]. Failure to diagnose infection around the implant can result in implant failure, sepsis, and even death. Standard treatment for chronic PJIs frequently requires multiple surgeries, IV antibiotics, and prolonged hospital stays.

Evaluation of a potential PJI usually includes standard radiographs, serum laboratory studies (WBC, ESR, and CRP), and a possible joint aspiration. Previous studies have shown that WBC,

Table 2
Positive vs negative cultures.

	Total	Cultures		*P*-value
	n = 39	Negative n = 20	Positive n = 19	
Implant				.747
THA	15 (38.5%)	7 (35.0%)	8 (42.1%)	
TKA	24 (61.5%)	13 (65.0%)	11 (57.9%)	
WBC (cells/mm^3)	8.8 (6.1, 10.4)	8.2 (5.2, 9.5)	9.0 (6.3, 13.2)	.148
WBC (>10.8 cells/mm^3)				.064
Yes	9 (23.1%)	2 (10.0%)	7 (36.8%)	
No	30 (76.9%)	18 (90.0%)	12 (63.2%)	
ESR (mm/h)	30.0 (14.0, 90.0)	24.0 (10.0, 68.0)	44.0 (23.0, 110.0)	**.045**[a]
ESR (>30 mm/h)				.343
Yes	19 (48.7%)	8 (40.0%)	11 (57.9%)	
No	20 (51.3%)	12 (60.0%)	8 (42.1%)	
CRP (mg/L)	7.6 (2.4, 32.3)	3.0 (1.8, 12.7)	21.5 (3.3, 49.5)	**.016**[a]
CRP (>10 mg/L)				**.025**[a]
Yes	19 (48.7%)	6 (30.0%)	13 (68.4%)	
No	20 (51.3%)	14 (70.0%)	6 (31.6%)	
IL-6 (pg/mL) missing	6.4 (3.2, 31.3) 5	5.0 (3.2, 31.3) 2	13.5 (3.3, 27.8) 3	.305
IL-6 (>5 pg/mL)				.509
Yes	19 (55.9%)	9 (50.0%)	10 (62.5%)	
No	15 (44.1%)	9 (50.0%)	6 (37.5%)	
Missing	5	2	3	
CD64 (molecules/cell)	860.0 (592.0, 1338.0)	745.5 (501.0, 1020.5)	961.0 (620.0, 3105.0)	**.036**[a]
CD64 (>2000 molecules/cell)				**.003**[a]
Yes	7 (17.9%)	0 (0.0%)	7 (36.8%)	
No	32 (82.1%)	20 (100.0%)	12 (63.2%)	

THA, total hip arthroplasty; TKA, total knee arthroplasty; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin 6; CD64, serum cluster of differentiation 64.
Continuous variables were compared using Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test.
[a] Denotes a statistically significant value with a *P*-value of <.05.

Table 3
Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of tests.

Tests	Youden index	Significant on continuous	Sensitivity	Specificity	PPV	NPV	Accuracy	*P*-value on cut point
WBC>10.8 cells/mm^3	10.4	No	36.8%	90.0%	77.8%	60.0%	64.1%	.064
ESR>30 mm/h	92.1	Yes	57.9%	60.5%	57.9%	60.0%	59.0%	.343
CRP>10 mg/L	17.4	Yes	68.4%	70.0%	68.4%	70.0%	69.2%	.025
IL-6>5 pg/mL	6.6	No	62.5%	50.0%	52.6%	60.0%	55.9%	.509
CD64 > 2000 molecules/cell	1418	Yes	36.8%	100.0%	100.0%	62.5%	69.2%	.003

PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IL-6, interleukin 6; CD64, serum cluster of differentiation 64.

ESR, and CRP are all nonspecific markers for infection, and they can be elevated in the presence of any inflammatory condition. One study demonstrated ESR to be variable before and after surgery in uncomplicated total hip arthroplasties, with some patients having an elevated ESR even 1 year after the surgery [22]. While CRP has been shown to be more specific than ESR, it remains an acute-phase reactant, which makes it unreliable in detecting many chronic infections. Other modalities have also been used to detect infection, such as WBC scans, joint aspirations, and gram stains. However, more recent studies have confirmed that no single study is able to reliably detect the presence of infection in every case [23].

CD64 has gained recent attention for its ability to detect musculoskeletal infections, and it has even found novel use as a synovial marker for PJI [20,21]. CD64, also known as an FcγR1 or Fc-gamma receptor 1, is an integral membrane glycoprotein with an Fc receptor that binds IgG antibodies. It is commonly expressed on macrophages, monocytes, and eosinophils, and it has been found to be upregulated on neutrophils in response to bacterial cell wall products [17]. It participates in the clearance of foreign targets opsonized by IgG antibodies, and there is also evidence to show that it plays a role in the release of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-α [20]. It is clear CD64 plays an important role in modulating the physiological inflammatory response.

This study showed serum CD64 to be a highly specific but poorly sensitive marker in the diagnosis of PJI. Of the 19 positively identified infections, only 7 had CD64 levels higher than 2000 molecules per cell (sensitivity of 36.8%). Despite this, every patient with elevated CD64 levels had positive intraoperative cultures (specificity of 100.0%), indicating that this test may be beneficial as a preoperative confirmatory test. The high positive predictive value (100.0%) of CD64 in this study also shows that it may still be effective as a diagnostic marker in the general arthroplasty population, where the prevalence of PJI is much lower [1,2]. CD64 and CRP were also both found to have the highest accuracy among the tested markers (69.2%). Finally, ESR, CRP, and CD64 were the only markers to show any significant difference between positive and negative infections. The sensitivities and specificities of all the markers in our study fell within or were close to the ranges of previously published numbers [14,24-26].

CD64 has several distinct advantages over other diagnostic studies. Compared to obtaining a joint aspiration, obtaining serum CD64 is less invasive. Whereas a knee aspiration can easily be performed with minimal equipment, not every surgeon is comfortable performing hip aspirations in an office setting. Interventional radiology is routinely required to perform image-guided aspirations, which can add time, cost, and morbidity to the patient. Synovial WBC has been found to be highly dependent on the cutoff used for the diagnosis of infection [27]. CD64 is easily performed in-house with a turnaround time of about 1 hour. In many institutions, IL-6 requires delivery to an outside lab for analysis with a turnaround time of about 1 week. This poses a problem with arranging timely transport, as was seen in this study, where 5 of the 39 IL-6 samples were deemed unusable upon arrival at the outside lab facility. CD64 can also be used to monitor the resolution of an infection, as it rises within 4 hours and starts to drop 48 hours after the eradication of an infection [28]. CRP and IL-6 are both acute phase reactants which have the disadvantage of increasing in the setting of major surgery, but CD64 has been shown to be reliable in distinguishing between postoperative inflammation and acute infection [19]. This may allow CD64 to aid in the diagnosis of acute PJIs.

This study has several limitations. First, the patients selected for this study are not truly representative of the general arthroplasty population, and it was a small sample size limiting the study's external validity. The infection rate in this study was ~49%, whereas previously reported rates of infection after total joint arthroplasty are around 1%-2% [1,2]. Given the relatively low incidence of PJI, it's likely our study would be underpowered if applied to the general population. Another weakness is using just the MSIS major criteria to establish a positive infection, as not all infections have a draining sinus and culture-negative PJI rates have been reported to range from 7% to 42.1% [27,29,30]. Cultures are also highly dependent on previous antibiotic use, and CD64 levels have been found to be affected by antibiotic use [31]. This was addressed by excluding any patients who received antibiotics prior to obtaining intraoperative cultures. Finally, this study may have been predisposed to selection bias. Only patients who underwent revision arthroplasty were included in this study, and patients with clinically silent PJIs may have been inadvertently excluded.

Conclusions

Serum CD64 appears to have utility as a confirmatory test due to its high specificity and positive predictive value. Given its low measured sensitivity, it is likely ineffective as a screening marker. Large, multicenter validation studies will need to be performed to confirm these findings. Until then, it does appear serum CD64 has clinical value in the diagnosis of chronic PJIs when used in conjunction with more conventional inflammatory markers.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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