



A commentary by Lawrence D. Dorr, MD, is linked to the online version of this article at jbjs.org.

The Effectiveness of Blood Metal Ions in Identifying Patients with Unilateral Birmingham Hip Resurfacing and Corail-Pinnacle Metal-on-Metal Hip Implants at Risk of Adverse Reactions to Metal Debris

Gulraj S. Matharu, BSc(Hons), MBChB, MRCS, MRes, Fiona Berryman, BSc(Hons), PhD, Lesley Brash, MSc, RN, Paul B. Pynsent, PhD, Ronan B.C. Treacy, FRCS(Tr&Orth), and David J. Dunlop, FRCS(Tr&Orth)

Investigation performed at the Royal Orthopaedic Hospital, Birmingham, United Kingdom

Background: We investigated whether blood metal ions could effectively identify patients with metal-on-metal hip implants with two common designs (Birmingham Hip Resurfacing [BHR] and Corail-Pinnacle) who were at risk of adverse reactions to metal debris.

Methods: This single-center, prospective study involved 598 patients with unilateral hip implants (309 patients with the BHR implant and 289 patients with the Corail-Pinnacle implant) undergoing whole blood metal ion sampling at a mean time of 6.9 years. Patients were classified into two groups, one that had adverse reactions to metal debris (those who had to undergo revision for adverse reactions to metal debris or those with adverse reactions to metal debris on imaging; $n = 46$) and one that did not ($n = 552$). Three metal ion parameters (cobalt, chromium, and cobalt-chromium ratio) were compared between groups. Optimal metal ion thresholds for identifying patients with adverse reactions to metal debris were determined using receiver operating characteristic analysis.

Results: All ion parameters were significantly higher ($p < 0.0001$) in the patients who had adverse reactions to metal debris compared with those who did not. Cobalt maximized the area under the curve for patients with the BHR implant (90.5%) and those with the Corail-Pinnacle implant (79.6%). For patients with the BHR implant, the area under the curve for cobalt was significantly greater than that for the cobalt-chromium ratio ($p = 0.0005$), but it was not significantly greater than that for chromium ($p = 0.8483$). For the patients with the Corail-Pinnacle implant, the area under the curve for cobalt was significantly greater than that for chromium ($p = 0.0004$), but it was similar to that for the cobalt-chromium ratio ($p = 0.8139$). Optimal blood metal ion thresholds for identifying adverse reactions to metal debris varied between the two different implants. When using cobalt, the optimal threshold for identifying adverse reactions to metal debris was $2.15 \mu\text{g/L}$ for the BHR group and $3.57 \mu\text{g/L}$ for the Corail-Pinnacle group. These thresholds had good sensitivities (88.5% for the BHR group and 80.0% for the Corail-Pinnacle group) and specificities (84.5% for the BHR group and 76.2% for the Corail-Pinnacle group), high negative predictive values (98.8% for the BHR group and 98.1% for the Corail-Pinnacle group), and low positive predictive values (34.3% for the BHR group and 20.0% for the Corail-Pinnacle group). The authority thresholds proposed by the United States

continued

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(3 µg/L and 10 µg/L) and the United Kingdom (7 µg/L) missed more patients with adverse reactions to metal debris at 2.0% to 4.7% (twelve to twenty-eight patients) compared with our implant-specific thresholds at 1.2% (seven patients missed).

Conclusions: Patients who underwent metal-on-metal hip arthroplasty performed with unilateral BHR or Corail-Pinnacle implants and who had blood metal ions below our implant-specific thresholds were at low risk of adverse reactions to metal debris. These thresholds could be used to rationalize follow-up resources in asymptomatic patients. Analysis of cobalt alone is acceptable. Implant-specific thresholds were more effective than currently recommended fixed authority thresholds for identifying patients at risk of adverse reactions to metal debris requiring further investigation.

Level of Evidence: Diagnostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Adverse reactions to metal debris have resulted in high failure rates of most metal-on-metal hip designs¹⁻³, with poor outcomes also reported following the revision procedure for adverse reactions to metal debris⁴. To identify adverse reactions to metal debris early, regulatory authorities recommend regular follow-up of patients with metal-on-metal hip implants⁵⁻⁷.

Blood metal ion levels reflect in vivo metal-on-metal bearing wear⁸ and are used for follow-up. The United Kingdom Medicines & Healthcare products Regulatory Agency (MHRA) was the first to publish blood metal ion thresholds for concern in 2010, recommending cross-sectional imaging in patients with metal-on-metal hip implants if cobalt and/or chromium were >7 µg/L⁹. Optimal cobalt and chromium thresholds for identifying poorly functioning metal-on-metal hip implants have ranged from 3.5 to 7 µg/L in subsequent studies, with thresholds having higher specificity than sensitivity¹⁰⁻¹⁴. A recent consensus statement from the United States focused on risk-stratifying patients with metal-on-metal implants to assist management, with blood metal ion results divided into groups of low risk (<3 µg/L), moderate risk (3 to 10 µg/L), and high risk (>10 µg/L)¹⁵.

A recent study of 597 patients with unilateral Articular Surface Replacement (ASR) hip implants (DePuy Orthopaedics) showed different diagnostic test characteristics for blood metal ion levels between resurfacings and total hip replacements, with cobalt raised out of proportion to chromium in failed total hip replacements¹⁴. The blood cobalt-chromium ratio may therefore be useful in patients with metal-on-metal total hip replacements, although, to our knowledge, it has not been investigated. Although the recent work by Hart et al. was the first to assess diagnostic test characteristics of blood metal ions in total hip replacements, there were some important limitations¹⁴. The four main limitations were: (1) blood sampling during the bearing running-in phase¹⁶, (2) including all symptomatic patients who may have had no evidence of adverse reactions to metal debris in the failed group, (3) including patients whose revisions were performed for reasons other than adverse reactions to metal debris in the failed group, and (4) using arbitrary thresholds to assess blood metal ion diagnostic test characteristics. However, the authors recognized that their findings were only applicable to ASR hip implants, which represent the worst-performing device^{17,18}. Given that implant failure rates vary among metal-on-metal hip designs¹⁷, we hypothesized that blood metal ion thresholds for identifying adverse reactions to metal debris would also differ among implant designs.

This study involved patients with two commonly implanted metal-on-metal hip designs: Birmingham Hip Resurfacing (BHR;

Smith & Nephew) and Corail-Pinnacle (DePuy Synthes) total hip replacement. The study had two aims: (1) to investigate whether blood metal ion thresholds could effectively identify patients at risk of adverse reactions to metal debris, and (2) to determine whether the cobalt-chromium ratio, when compared with using cobalt and chromium alone, was any more effective for identifying patients with adverse reactions to metal debris.

Materials and Methods

A prospective, single-center, cohort study of consecutive patients receiving current-generation metal-on-metal hip replacements was performed. This study was registered with the hospital board. Ethical approval was not required because patients were assessed according to published guidelines⁵ and were not specifically evaluated for this study.

Metal-on-Metal Hip Replacement

Between August 1997 and May 2013, 3988 patients at one specialist center received 4816 primary metal-on-metal hip implants (3792 resurfacing and 1024 total hip replacement). Of the 3792 resurfacing implants, 87% (3299) were BHR implants, which are produced from an as-cast high-carbon cobalt-chromium-molybdenum alloy and represent the most commonly implanted resurfacing device worldwide¹⁹. Five different metal-on-metal total hip replacement designs were implanted at this center on the basis of surgeon preference; the majority (578 [56%]) of these 1024 total hip replacements were Corail-Pinnacle implants. The Corail femoral stem is a fully hydroxyapatite-coated titanium alloy stem with a 12/14 taper onto which a cobalt-chromium alloy femoral head is impacted, which articulates with a metal liner. The BHR implant and Corail-Pinnacle total hip replacement were the only implant designs assessed in this study, with information regarding patient selection, operative technique, and routine follow-up described previously²⁰⁻²².

Follow-up

This institution's routine follow-up of patients with metal-on-metal hip implants was adapted according to MHRA alerts^{5,9}. In addition to clinical assessment (history, examination, anteroposterior pelvic radiographs, and Oxford Hip Score questionnaire²³), all symptomatic patients underwent blood metal ion sampling and cross-sectional imaging. All asymptomatic patients who underwent total hip replacement and asymptomatic patients with BHR implants who had adverse reactions to metal debris risk factors (small femoral components, malpositioned acetabular components, radiographic evidence suggesting implant failure) underwent clinical assessment with blood metal ions^{22,24,25}. In line with MHRA guidance, all asymptomatic patients with blood cobalt and/or chromium ion levels of >7 µg/L (the MHRA upper limit) underwent cross-sectional imaging⁵. The institution's protocol recommends ultrasound for symptomatic patients and metal artifact reduction sequence magnetic resonance imaging (MRI) for asymptomatic patients. As asymptomatic patients were likely to require repeat imaging, serial MRIs were considered easier to compare than ultrasound images. If MRI was contraindicated, ultrasound was used. By May 2013, 1336 patients with 1557 metal-on-metal hip implants had undergone blood metal ion sampling. These patients were initially eligible for study inclusion.

TABLE I Patient Demographic Characteristics for the Study Cohort (N = 598)

Parameter	All Patients	Patients with Adverse Reactions to Metal Debris	Patients without Adverse Reactions to Metal Debris	P Value
All patients (100%)				
No. of patients	598 (100%)	46 (8%)	552 (92%)	
Sex*				0.0226†
Female	313	32	281	
Male	285	14	271	
Age at the time of the blood test‡ (yr)	61.7 (19.6 to 93.8)	58.8 (32.8 to 77.0)	62.0 (19.6 to 93.8)	0.0552
Time between primary arthroplasty and blood test‡ (yr)	6.9 (1.0 to 16.2)	7.3 (2.1 to 14.3)	6.9 (1.0 to 16.2)	0.3367
BHR group (52%)				
No. of patients	309 (100%)	26 (8%)	283 (92%)	
Sex*				0.0001†
Female	145	22	123	
Male	164	4	160	
Age at the time of the blood test‡ (yr)	57.2 (19.6 to 78.7)	54.3 (32.8 to 74.0)	57.4 (19.6 to 78.7)	0.0641
Time between primary arthroplasty and blood test‡ (yr)	7.8 (1.0 to 16.2)	8.9 (3.5 to 14.3)	7.6 (1.0 to 16.2)	0.0742
Corail-Pinnacle group (48%)				
No. of patients	289 (100%)	20 (7%)	269 (93%)	
Sex*				0.5967
Female	168	10	158	
Male	121	10	111	
Age at the time of the blood test‡ (yr)	66.6 (40.7 to 93.8)	64.7 (47.2 to 77.0)	66.8 (40.7 to 93.8)	0.4912
Time between primary arthroplasty and blood test‡ (yr)	6.0 (1.9 to 10.1)	5.3 (2.1 to 8.9)	6.0 (1.9 to 10.1)	0.1163

*The values are given as the number of patients. †There was a significant difference between the sex ratios of the patients with adverse reactions to metal debris and those without adverse reactions to metal debris. ‡The values are given as the mean, with the range in parentheses.

TABLE II Blood Metal Ion Parameters for All Study Groups

Parameter	All Patients	Patients with Adverse Reactions to Metal Debris	Patients without Adverse Reactions to Metal Debris	P Value
All patients* (100%)	598 (100%)	46 (8%)	552 (92%)	
Cobalt† ($\mu\text{g/L}$)	1.36 (0.71 to 3.13)	5.96 (2.96 to 47.26)	1.24 (0.71 to 2.77)	<0.0001‡
Chromium† ($\mu\text{g/L}$)	1.40 (0.99 to 2.44)	4.37 (1.68 to 27.99)	1.40 (0.94 to 2.18)	<0.0001‡
Cobalt-chromium ratio†	0.92 (0.56 to 1.46)	1.73 (1.04 to 2.86)	0.86 (0.55 to 1.35)	<0.0001‡
BHR group* (52%)	309 (100%)	26 (8%)	283 (92%)	
Cobalt† ($\mu\text{g/L}$)	1.06 (0.71 to 2.01)	11.95 (2.71 to 61.12)	1.00 (0.71 to 1.56)	<0.0001‡
Chromium† ($\mu\text{g/L}$)	1.56 (1.09 to 2.50)	9.91 (3.12 to 35.36)	1.46 (1.04 to 2.16)	<0.0001‡
Cobalt-chromium ratio†	0.71 (0.52 to 1.00)	1.16 (0.78 to 1.94)	0.69 (0.51 to 0.95)	<0.0001‡
Corail-Pinnacle group* (48%)	289 (100%)	20 (7%)	269 (93%)	
Cobalt† ($\mu\text{g/L}$)	2.18 (0.77 to 3.72)	4.66 (3.66 to 9.56)	2.12 (0.71 to 3.54)	0.0001‡
Chromium† ($\mu\text{g/L}$)	1.30 (0.88 to 2.29)	1.69 (0.76 to 3.49)	1.30 (0.88 to 2.27)	0.1950
Cobalt-chromium ratio†	1.25 (0.81 to 2.15)	2.71 (1.63 to 4.85)	1.16 (0.79 to 2.01)	0.0001‡

*The values are given as the number of patients, with the percentage in parentheses. †The values are given as the median, with the interquartile range in parentheses. ‡There was a significant difference between patients with adverse reactions to metal debris and those without adverse reactions.

TABLE III Summary of ROC Analysis for All Study Groups

	Ion Parameter		
	Cobalt	Chromium	Cobalt-Chromium Ratio
All patients (n = 598)			
AUC* (%)	85.4 (79.2 to 91.6)	75.3 (65.7 to 84.8)	73.8 (66.5 to 81.1)
Optimal threshold	3.57 µg/L	4.11 µg/L	0.99
Sensitivity* (%)	71.7 (58.7 to 82.6)	52.2 (37.0 to 67.4)	80.4 (69.6 to 91.3)
Specificity* (%)	84.6 (81.7 to 87.5)	92.9 (90.6 to 94.9)	58.7 (54.7 to 62.7)
Positive predictive value* (%)	28.0 (20.7 to 36.7)	38.1 (27.1 to 50.4)	14.0 (10.3 to 18.7)
Negative predictive value* (%)	97.3 (95.4 to 98.4)	95.9 (93.9 to 97.3)	97.3 (94.9 to 98.6)
Misclassification of patients (%)	16.4	10.2	39.6
Positive likelihood ratio*	4.66 (3.57 to 6.08)	7.39 (4.90 to 11.13)	1.95 (1.64 to 2.32)
Negative likelihood ratio*	0.33 (0.21 to 0.53)	0.52 (0.38 to 0.70)	0.33 (0.19 to 0.60)
BHR group (n = 309)			
AUC* (%)	90.5 (82.8 to 98.1)	90.3 (82.5 to 98.1)	76.3 (65.8 to 86.8)
Optimal threshold	2.15 µg/L	2.47 µg/L	1.12
Sensitivity* (%)	88.5 (76.9 to 100)	88.5 (76.9 to 100)	57.7 (38.5 to 76.9)
Specificity* (%)	84.5 (80.2 to 88.3)	79.2 (74.2 to 83.8)	87.3 (83.4 to 90.8)
Positive predictive value* (%)	34.3 (24.1 to 46.3)	28.0 (19.5 to 38.6)	29.4 (18.7 to 43.0)
Negative predictive value* (%)	98.8 (96.4 to 99.6)	98.7 (96.2 to 99.5)	95.7 (92.5 to 97.6)
Misclassification of patients (%)	15.2	20.1	15.2
Positive likelihood ratio*	5.69 (4.19 to 7.72)	4.24 (3.25 to 5.54)	4.54 (2.90 to 7.11)
Negative likelihood ratio*	0.14 (0.045 to 0.40)	0.15 (0.05 to 0.42)	0.49 (0.31 to 0.76)
Corail-Pinnacle group (n = 289)			
AUC* (%)	79.6 (68.8 to 90.4)	57.2 (41.7 to 72.8)	78.2 (68.8 to 87.7)
Optimal threshold	3.57 µg/L	9.08 µg/L	1.81
Sensitivity* (%)	80.0 (60.0 to 95.0)	20.0 (5.0 to 40.0)	75.0 (55.0 to 90.0)
Specificity* (%)	76.2 (70.6 to 81.0)	99.6 (98.9 to 100)	71.0 (65.4 to 76.2)
Positive predictive value* (%)	20.0 (12.7 to 30.0)	80.0 (37.6 to 96.4)	16.1 (9.9 to 24.7)
Negative predictive value* (%)	98.1 (95.2 to 99.3)	94.4 (91.0 to 96.5)	97.4 (94.1 to 98.9)
Misclassification of patients (%)	23.5	5.9	28.7
Positive likelihood ratio*	3.36 (2.48 to 4.57)	53.8 (6.31 to 459)	2.59 (1.87 to 3.50)
Negative likelihood ratio*	0.26 (0.11 to 0.63)	0.80 (0.65 to 1.00)	0.35 (0.17 to 0.76)

*The values are given as the mean percentage, with the 95% CI in parentheses.

Inclusion and Exclusion Criteria

Patients with unilateral, primary large-diameter (≥ 36 -mm) BHR and Corail-Pinnacle total hip replacement designs with blood sampling performed at least one year following arthroplasty were included. Patients who underwent revision after blood sampling and who did not have evidence of adverse reactions to metal debris (infection, periprosthetic fracture, aseptic loosening, unexplained pain, dislocation) were excluded to reduce the risk of confounding factors when devising thresholds specific for adverse reactions to metal debris. In all such cases, the intraoperative revision findings, histopathology, and microbiology confirmed the absence of adverse reactions to metal debris.

Definitions

Patients eligible for final inclusion (n = 598) were divided into two groups based on their status in September 2014. The group with adverse reactions to metal debris (n = 46) included all patients who underwent revision to treat such adverse reactions (n = 30), those awaiting revision to treat such adverse reactions (n = 2), and those with adverse reactions to metal debris confirmed on

cross-sectional imaging (evidence of periprosthetic effusions and pseudotumors)²⁶⁻²⁸ who were under surveillance but not listed for revision because of clinician and/or patient preference (n = 14). A revision surgical procedure was recommended on the basis of findings from the clinical assessment, radiographs, and cross-sectional imaging. Blood metal ions alone were not used to decide on revision, as previously recommended¹⁴. The group without adverse reactions to metal debris (n = 552) consisted of all patients with primary metal-on-metal hip implants in situ and no evidence of adverse reactions to metal debris on cross-sectional imaging. Symptoms were not used to stratify patients, given that adverse reactions to metal debris frequently occur in asymptomatic patients^{26,27}.

Blood Metal Ion Analysis

Whole blood was collected from the antecubital vein of patients for metal ion analysis. Venous blood was collected in trace element tubes containing sodium heparin with methods used to minimize contamination risk²⁹. All samples were analyzed in an MHRA-approved laboratory that regularly participates in the

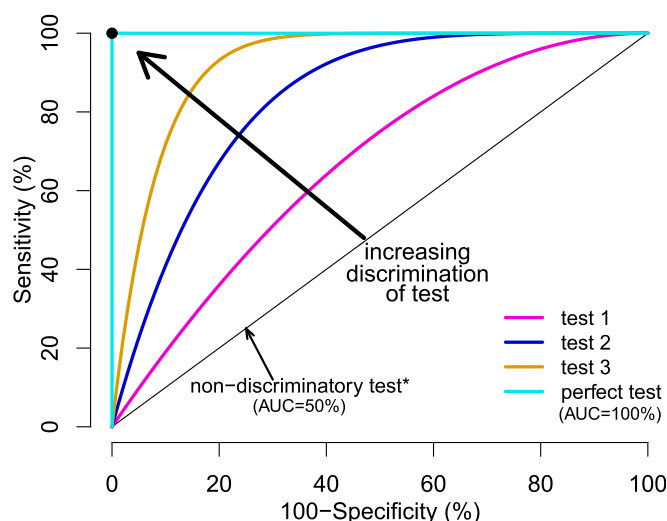


Fig. 1

An explanation of ROC analysis with example lines for varying diagnostic ability. The black solid circle in the top left corner represents the perfect diagnostic threshold, with sensitivity and specificity both equaling 100%. The asterisk indicates that a non-discriminatory test is no better than a chance finding.

Trace Elements External Quality Assessment Scheme, with excellent measurement accuracy and reproducibility reported³⁰. Cobalt and chromium concentrations were measured using an inductively coupled plasma mass spectrometer (Agilent 7500cx; Agilent Technologies). The limit of detection was 0.06 $\mu\text{g/L}$ and the reporting limit was 0.6 $\mu\text{g/L}$.

Statistical Analysis

The three blood metal ion parameters of interest were cobalt, chromium, and the cobalt-chromium ratio. The cobalt-chromium ratio is non-dimensional and was calculated by dividing cobalt concentration by chromium concentration for each patient. To compare the logarithms of the three metal ion parameters between the group that had adverse reactions to metal debris and the group that did not, unpaired t testing was used. Significance was set at $p < 0.05$. The logarithm was necessary to transform the asymmetric blood metal ion distributions to approximately normal distributions as recommended³¹.

Receiver operating characteristic (ROC) analysis is an established method of assessing the performance of a diagnostic test³². The ROC curve is drawn by plotting sensitivity (true positive rate) against $1 - \text{specificity}$ (or $100 - \text{specificity}$ if presented as a percentage; also called a false positive rate) for all possible test thresholds. A useful test will produce a curve that lies to the left of the 45° line (Fig. 1). The further the curve is toward the top left corner, the higher the area under the curve (AUC) and the better the discriminatory performance of the test. An AUC of 100% represents a test with perfect discrimination. An AUC of 50% represents a non-discriminatory test. ROC analysis can also be used to define the optimal threshold to maximize discriminatory ability for any given test.

We used ROC analysis to determine the optimal blood metal ion thresholds for identifying patients with hip implants who had adverse reactions to metal debris. This is a standard method for selecting the threshold maximizing the sum of the specificity and sensitivity. This corresponds to the point on the curve nearest to the top left corner. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated with their 95% confidence intervals (95% CIs) for the optimal thresholds for each of the three blood metal ion parameters. Misclassification rates were also calculated for all thresholds. The DeLong test was used to compare the AUCs among the different metal ion parameters³³.

Results

There were 598 patients with metal-on-metal hip implants (309 BHR implants and 289 Corail-Pinnacle implants) eligible for inclusion (Table I).

Blood Metal Ions

The three blood metal ion parameters were summarized (Table II) and their distribution was illustrated according to implant design (Fig. 2). Patients with the Corail-Pinnacle implant had significantly higher cobalt concentrations ($p = 0.0010$) and cobalt-chromium ratios ($p < 0.0001$) compared with patients with the BHR implant. Patients with the BHR implant had significantly higher chromium concentrations ($p = 0.0012$) compared with patients with the Corail-Pinnacle implant (Fig. 2). For the whole cohort, all three blood metal ion parameters were significantly higher (all $p < 0.0001$) in the group that had adverse reactions to metal debris compared with the group that did not (Table II).

Threshold Analysis

Optimal blood metal ion thresholds for discriminating between patients with hip implants who had adverse reactions to metal debris and those patients who did not varied between the two different implant designs and were also dependent on the specific metal ion parameter used (Table III).

Thresholds for Patients with BHR Implants

Compared with the other two ion parameters, cobalt concentration produced the maximum AUC of 90.5% (95% CI, 82.8% to 98.1%) for patients with BHR implants. The cobalt AUC was significantly greater than the cobalt-chromium ratio AUC ($p = 0.0005$) (Table III and Fig. 3), but not significantly greater than the chromium AUC ($p = 0.8483$). The cobalt threshold for identifying patients in the BHR group with adverse reactions to metal debris providing the optimal diagnostic test characteristics was 2.15 $\mu\text{g/L}$ (88.5% sensitivity, 84.5% specificity, 34.3% positive predictive value, and 98.8% negative predictive value) (Table III, Appendix).

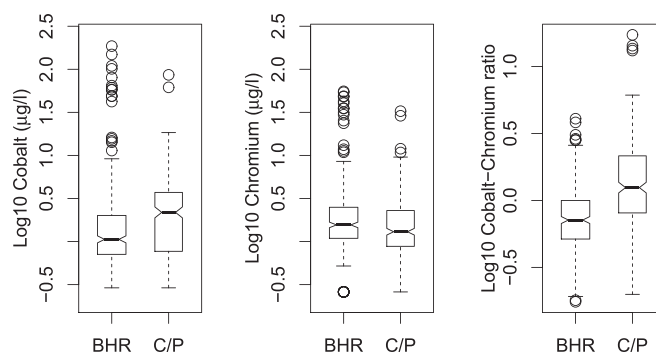


Fig. 2

Box plots showing the median and interquartile range for blood metal ion parameters stratified by implant design. The whiskers show the range covered by data points up to 1.5 times the interquartile range and outliers beyond this range are shown as open circles. BHR = Birmingham Hip Resurfacing and C/P = Corail-Pinnacle total hip replacement.

TABLE IV Summary of ROC Analysis for Various Thresholds of Cobalt Metal Ions for All Study Groups

Group and Threshold	AUC*	Sensitivity*	Specificity*	Positive Predictive Value*
All (n = 598)	85.4 (79.2 to 91.6)			
10 µg/L		39.1 (26.1 to 52.2)	98.9 (98.0 to 99.6)	75.0 (57.6 to 92.3)
7 µg/L		47.8 (32.6 to 60.9)	96.7 (95.1 to 98.0)	55.0 (39.6 to 70.4)
3 µg/L		73.9 (60.9 to 87.0)	76.6 (73.2 to 80.3)	20.9 (14.6 to 27.1)
3.57 µg/L		71.7 (58.7 to 82.6)	84.6 (81.7 to 87.5)	28.0 (20.7 to 36.7)
BHR (n = 309)	90.5 (82.8 to 98.1)			
10 µg/L		50.0 (30.8 to 69.2)	98.6 (97.2 to 99.7)	76.5 (56.3 to 96.6)
7 µg/L		57.7 (38.5 to 76.9)	98.2 (96.5 to 99.7)	75.0 (56.0 to 94.0)
3 µg/L		69.2 (50.0 to 88.5)	88.7 (84.8 to 92.2)	36.0 (22.7 to 49.3)
2.15 µg/L		88.5 (76.9 to 100)	84.5 (80.2 to 88.3)	34.3 (24.1 to 46.3)
Corail-Pinnacle (n = 289)	79.6 (68.8 to 90.4)			
10 µg/L		25.0 (10.0 to 45.0)	99.3 (98.1 to 100)	71.4 (38.0 to 100)
7 µg/L		35.0 (15.0 to 55.0)	95.2 (92.6 to 97.4)	35.0 (14.1 to 55.9)
3 µg/L		80.0 (60.0 to 95.0)	63.9 (58.0 to 69.1)	14.2 (7.7 to 20.6)
3.57 µg/L		80.0 (60.0 to 95.0)	76.2 (70.6 to 81.0)	20.0 (12.7 to 30.0)

*The values are given as the mean percentage, with the 95% CI in parentheses. †The values are given as the ratio, with the 95% CI in parentheses.

Thresholds for Patients with Corail-Pinnacle Implants

Compared with the other metal ion parameters, cobalt concentration produced the maximum AUC of 79.6% (95% CI, 68.8% to 90.4%) for patients with Corail-Pinnacle total hip replacements. The cobalt AUC was significantly greater than that for chromium ($p = 0.0004$), but not significantly different from the cobalt-chromium ratio AUC ($p = 0.8139$) (Table III and Fig. 4). The cobalt threshold for identifying Corail-Pinnacles with adverse reactions to metal debris providing the optimal diagnostic test characteristics was 3.57 µg/L (80.0% sensitivity, 76.2% specificity, 20.0% positive predictive value, and 98.1% negative predictive value) (Table III).

Regulatory Authority Blood Metal Ion Thresholds

Blood metal ion thresholds for concern proposed by the United States (3 µg/L and 10 µg/L)¹⁵ and the U.K. MHRA (7 µg/L)³ were applied to the cohort and were compared with our implant-specific thresholds in terms of the diagnostic test characteristics for identifying patients with adverse reactions to metal debris and the proportion of patients with adverse reactions to metal debris who were not identified by each threshold. As our work demonstrated that cobalt alone provided optimal diagnostic test characteristic and AUC results, we only used cobalt ion data for this comparison.

Compared with fixed regulatory authority thresholds, the implant-specific thresholds for cobalt provided the optimal balance of sensitivity and specificity and higher negative predictive values, but generally lower positive predictive values (Table IV). Applying implant-specific thresholds to the cohort resulted in seven patients with adverse reactions to metal debris being missed (1.2% of the cohort [three patients in the BHR group and four patients in the Corail Pinnacle group]). More patients with adverse reactions to metal debris were missed when using fixed regulatory

thresholds. With the threshold of 3 µg/L, twelve patients (2.0%) were missed; with the threshold of 7 µg/L, twenty-four patients (4.0%) were missed; and with the threshold of 10 µg/L, twenty-eight patients (4.7%) were missed. Using the regulatory authority threshold with the lowest number of missed patients (3 µg/L)

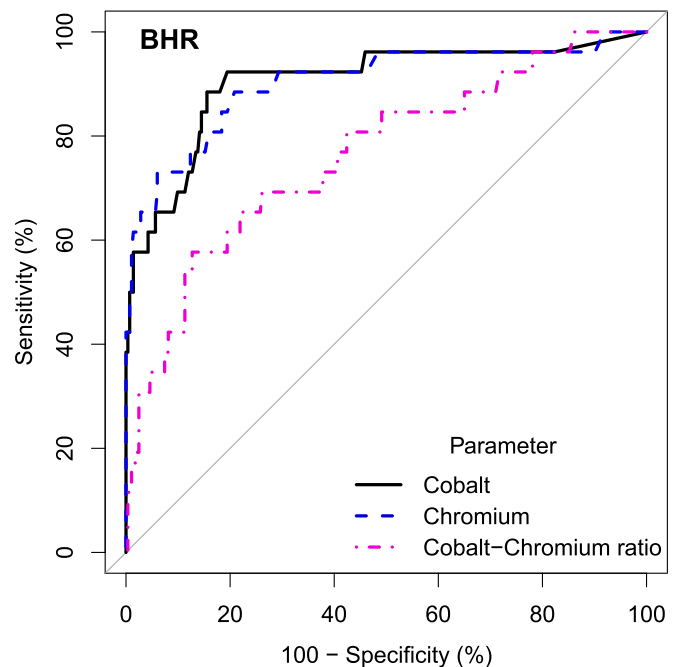


Fig. 3
ROC curve showing the ability of three blood metal ion parameters to distinguish between patients with a Birmingham Hip Resurfacing (BHR) implant who had adverse reactions to metal debris and those who did not.

TABLE IV (continued)

Negative Predictive Value*	Misclassification of Patients	Missed Patients with Adverse Reactions to Metal Debris	Positive Likelihood Ratio†	Negative Likelihood Ratio†
95.1 (93.4 to 96.9)	5.7%	28	36.0 (15.0 to 86.2)	0.62 (0.49 to 0.78)
95.7 (94.0 to 97.4)	7.0%	24	14.7 (8.5 to 25.3)	0.54 (0.41 to 0.71)
97.2 (95.7 to 98.8)	23.6%	12	3.16 (2.52 to 3.98)	0.34 (0.21 to 0.55)
97.3 (95.8 to 98.7)	16.4%	13	4.66 (3.57 to 6.08)	0.33 (0.21 to 0.53)
95.5 (93.2 to 97.9)	5.5%	13	35.4 (12.4 to 100.7)	0.507 (0.35 to 0.75)
96.2 (94.0 to 98.4)	5.2%	11	32.6 (12.9 to 82.7)	0.43 (0.27 to 0.67)
96.9 (94.8 to 99.0)	12.9%	8	6.12 (4.04 to 9.27)	0.35 (0.19 to 0.62)
98.8 (96.4 to 99.6)	15.2%	3	5.69 (4.19 to 7.72)	0.14 (0.05 to 0.40)
94.7 (92.0 to 97.3)	5.9%	15	33.6 (6.96 to 162.5)	0.76 (0.59 to 0.97)
95.2 (92.6 to 97.7)	9.0%	13	7.24 (3.26 to 16.10)	0.68 (0.49 to 0.94)
97.7 (95.5 to 99.9)	34.9%	4	2.22 (1.69 to 2.91)	0.31 (0.13 to 0.75)
98.1 (96.2 to 99.9)	23.5%	4	3.36 (2.48 to 4.57)	0.26 (0.11 to 0.63)

resulted in 71% more missed patients with adverse reactions to metal debris compared with patients missed when using implant-specific thresholds, although this difference was not significant ($p = 0.074$; McNemar test). Significantly more patients with adverse reactions to metal debris were missed when using thresholds of $7 \mu\text{g/L}$ ($p = 0.0001$) and $10 \mu\text{g/L}$ ($p = 0.0001$) compared with patients missed when using implant-specific thresholds.

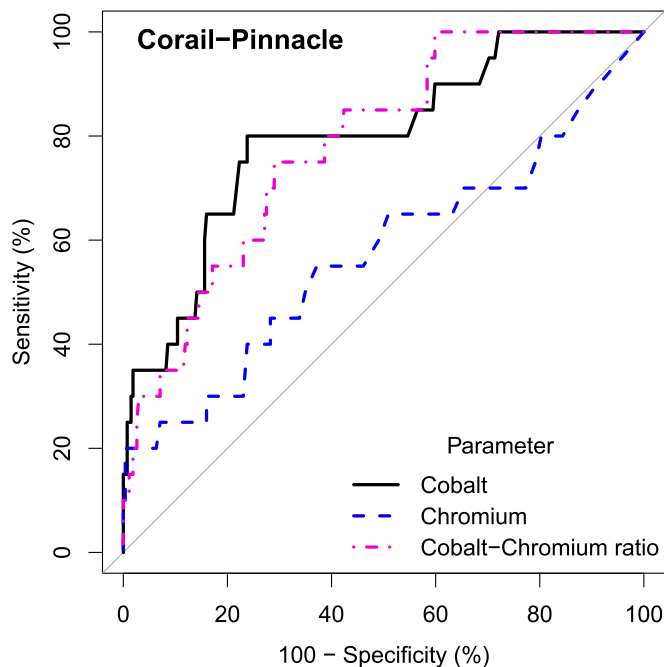


Fig. 4
ROC curve showing the ability of three blood metal ion parameters to distinguish between patients with a Corail-Pinnacle total hip replacement who had adverse reactions to metal debris and those who did not.

Discussion

To our knowledge, this represents the largest study to assess whether blood metal ions could effectively identify patients with metal-on-metal hip implants with two common designs who are at risk of adverse reactions to metal debris, and it also represents the first study to formally analyze the cobalt-chromium ratio. Patients with unilateral BHR and Corail-Pinnacle hip replacements who had blood metal ions below implant-specific thresholds ($2.15 \mu\text{g/L}$ for cobalt for the BHR group and $3.57 \mu\text{g/L}$ for cobalt for the Corail-Pinnacle group) were at low risk of adverse reactions to metal debris. These implant-specific thresholds were more effective compared with the fixed thresholds currently recommended^{5,15}. Cobalt alone produced optimal results for identifying adverse reactions to metal debris in both implant systems.

The observation that implant-specific thresholds exist for identifying patients with metal-on-metal hip implants who have adverse reactions to metal debris is novel. Of the three blood metal ion parameters assessed, cobalt proved to be the best ion to test for in both the BHR group and the Corail-Pinnacle group. Our data demonstrated that cobalt ions were most effective for identifying patients at a low risk of adverse reactions to metal debris, rather than identifying patients with adverse reactions to metal debris. We consider this to be the most important finding because clinically we wish to rule out patients with this complication to allow us to focus on the subgroup of patients who may have adverse reactions to metal debris. Those asymptomatic patients above the implant-specific thresholds require cross-sectional imaging; however, those patients below the implant-specific thresholds are at a low risk of adverse reactions to metal debris. Provided that patients have normal clinical examinations and radiographs, they can be reassured and can be excluded from regular follow-up regimens⁵⁻⁷. In the current study, 78% of patients with BHR implants had a cobalt level below the new implant-specific threshold of $2.15 \mu\text{g/L}$. As most patients with

BHR implants are asymptomatic, even at long-term follow-up³⁴⁻³⁶, reducing follow-up regularity in this large cohort would yield substantial financial and resource savings.

Our implant-specific thresholds are lower than those previously proposed for a range of poorly functioning metal-on-metal hip designs (3.5 to 7 µg/L)¹⁰⁻¹⁴. These implant-specific thresholds provide more balanced sensitivity and specificity compared with those in previous studies, which showed good specificity but poor sensitivity^{10,13,14}. We consider the definition used for failure to be the main factor explaining these observed differences between studies. The definition of failure in previous reports had included both symptomatic patients, regardless of cause, and patients with implants revised for reasons other than adverse reactions to metal debris^{10,13,14}. Our definition for identifying metal-on-metal hip replacement-related complications was more robust; therefore, the implant-specific thresholds are specific for adverse reactions to metal debris.

The application of fixed metal ion thresholds recommended by U.S. and U.K. authorities^{5,15} missed more patients with hip implants who had adverse reactions to metal debris compared with patients missed when using implant-specific thresholds. The fixed thresholds of 7 µg/L (the U.K. threshold and also recommended recently by Hart et al. in patients with ASR hip implants)¹⁴ and 10 µg/L (the U.S. upper threshold) missed significantly more patients with hip implants who had adverse reactions to metal debris compared with implant-specific thresholds. When using 3 µg/L (the U.S. lower threshold), the difference was not significant; however, this “low-risk” threshold¹⁵ missed 71% more patients with hip implants who had adverse reactions to metal debris compared with patients missed when implant-specific thresholds were used. We consider this difference clinically important given the potentially destructive nature of adverse reactions to metal debris and poor outcomes reported following revision of both metal-on-metal hip resurfacings and stemmed total hip replacements⁴. It is important not to miss patients with this potentially destructive condition; therefore, minimizing the false-negative rate is clinically beneficial. Although current guidelines recommend using fixed blood metal ion thresholds^{5,15}, we observed that implant-specific thresholds provided more accurate information for the two implant systems assessed in this study. In light of these findings, it is hoped that implant-specific thresholds will be developed for other implant designs in the future.

Of the three blood metal ion parameters investigated, cobalt was the best ion to test for in both the BHR implant group and the Corail-Pinnacle implant group. Differences in chromium and the cobalt-chromium ratio between arthroplasties are likely to relate to implant design, with previous studies demonstrating that wear debris and/or corrosion at the taper-head junction in metal-on-metal total hip replacements produces cobalt preferentially over chromium³⁷⁻³⁹. Our data suggest that measuring blood chromium in patients with unilateral BHR and Corail-Pinnacle replacements provides no additional information compared with cobalt alone. Given the financial burden associated with follow-up for patients with metal-on-metal implants⁴⁰, we recommend measuring only blood cobalt, which

confirms the recommendations of others⁶. Sampling cobalt alone would save one-third of blood test costs at our laboratory (saving \$15.40 per test).

This study had limitations. The proposed implant-specific thresholds only apply to patients with unilateral BHR and Corail-Pinnacle implants. These two implant groups were also heterogeneous given the different patient selection criteria described for each procedure²⁰⁻²². Furthermore, this was a cross-sectional study with blood metal ions sampled once. Although we cannot make recommendations regarding intervals for repeat blood testing, current evidence suggests that annual blood sampling would be the most frequent for asymptomatic patients with metal-on-metal total hip replacements⁴¹; however, patients with BHR implants who have low initial ion levels are unlikely to need repeat testing within this time frame, if at all, provided that they are asymptomatic⁴². It is also recognized that there is currently a lack of interlaboratory standardization for blood metal ion analysis that may limit the generalizability of our findings. Finally, in line with current recommendations^{5,6} and other centers^{13,43,44}, not all asymptomatic patients underwent cross-sectional imaging. Only asymptomatic patients with blood metal ions of >7 µg/L underwent such imaging. Although this reflects modern follow-up programs in which resources must be rationalized, some asymptomatic patients not undergoing cross-sectional imaging may have had silent adverse reactions to metal debris, although they would have been classified as patients without adverse reactions to metal debris. However, this effect was mitigated by including patients with adverse reactions to metal debris on imaging but still under surveillance as arthroplasty failures.

In conclusion, patients who underwent metal-on-metal hip arthroplasty with unilateral BHR and Corail-Pinnacle implants and who had blood metal ions below our proposed implant-specific thresholds were at a low risk of adverse reactions to metal debris. These implant-specific thresholds could be used to rationalize follow-up resources in asymptomatic patients with these two implant designs. Analysis of cobalt alone is acceptable for both implant systems. Fixed blood metal ion thresholds currently recommended by regulatory authorities^{5,15} were associated with an increased risk of missing patients who have adverse reactions to metal debris. Implant-specific thresholds were therefore more effective for identifying patients with unilateral BHR and Corail-Pinnacle implants who were at risk of adverse reactions to metal debris and required further investigation.

Appendix

eA A description of an analysis of the male and female cohorts in the BHR group and a table showing a summary of the ROC analysis for cobalt in patients with the BHR implant stratified by sex are available with the online version of this article as a data supplement at jbj.org. ■

Gulraj S. Matharu, BSc(Hons), MBChB, MRCS, MRes¹
Fiona Berryman, BSc(Hons), PhD¹
Lesley Brash, MSc, RN¹

Paul B. Pynsent, PhD¹
Ronan B.C. Treacy, FRCS(Tr&Orth)¹
David J. Dunlop, FRCS(Tr&Orth)¹

¹The Royal Orthopaedic Hospital,
Birmingham, United Kingdom

E-mail address for G.S. Matharu: gsm@doctors.org.uk
E-mail address for F. Berryman: fiona.berryman@nhs.net
E-mail address for L. Brash: lesley.brash@nhs.net
E-mail address for P.B. Pynsent: p.b.pynsent@bham.ac.uk
E-mail address for R.B.C. Treacy: trea40@aol.com
E-mail address for D.J. Dunlop: david.dunlop1@nhs.net

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