

■ HIP

Can blood metal ion levels be used to identify patients with bilateral Birmingham Hip Resurfacings who are at risk of adverse reactions to metal debris?

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Aims

We investigated whether blood metal ion levels could effectively identify patients with bilateral Birmingham Hip Resurfacing (BHR) implants who have adverse reactions to metal debris (ARMD).

Patients and Methods

Metal ion levels in whole blood were measured in 185 patients with bilateral BHRs. Patients were divided into those with ARMD who either had undergone a revision for ARMD or had ARMD on imaging (n = 30), and those without ARMD (n = 155). Receiver operating characteristic analysis was used to determine the optimal thresholds of blood metal ion levels for identifying patients with ARMD.

Results

The maximum level of cobalt or chromium ions in the blood was the parameter which produced the highest area under the curve (91.0%). The optimal threshold for distinguishing between patients with and without ARMD was 5.5 µg/l (83.3% sensitivity, 88.4% specificity, 58.1% positive and 96.5% negative predictive values). Similar results were obtained in a subgroup of 111 patients who all underwent cross-sectional imaging. Between 3.2% and 4.3% of patients with ARMD were missed if United Kingdom (7 µg/l) and United States (10 µg/l) authority thresholds were used respectively, compared with 2.7% if our implant specific threshold was used, though these differences did not reach statistical significance (p ≥ 0.248).

Conclusion

Patients with bilateral BHRs who have blood metal ion levels below our implant specific threshold were at low-risk of having ARMD.

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Adverse reactions to metal debris (ARMD) have contributed to high rates of failure for most metal-on-metal (MoM) hip resurfacing designs.^{1,2} As outcomes following revision arthroplasty for ARMD are reportedly poor,³ worldwide regulatory authorities recommend regular follow-up and monitoring of these patients to identify ARMD early.^{4–6} Monitoring currently includes measurement of the levels of cobalt and chromium ions in the blood, which reflects *in vivo* wear.⁷ The United Kingdom Medical and Healthcare Products Regulatory Agency (MHRA) published thresholds for these levels which should be of concern in 2010, recommending cross-sectional imaging if the levels were > 7 µg/l (µg/l are equivalent to parts per billion).⁸ The thresholds used to identify poorly functioning unilateral MoM hip resurfacings have ranged from 3.5 µg/l to 7 µg/l

in subsequent studies, with thresholds having higher specificity than sensitivity.^{9–13}

Patients with bilateral MoM hip arthroplasties are considered to be at increased risk of ARMD by some authorities.^{6,14} However, little is known in these bilateral patients about the thresholds which might be suggestive of ARMD.¹⁵ One study has assessed the thresholds for identifying patients with poorly functioning bilateral hip resurfacings and concluded that optimal threshold levels were 5.0 µg/l for cobalt and 7.4 µg/l for chromium.¹² This study included 139 patients, but with heterogenous combinations of implants, and only short-term follow-up (a mean follow-up period of 4.3 years). A recent consensus statement from the United States suggested that blood metal ion concentrations of > 10 µg/l represented a high-risk group, which could be

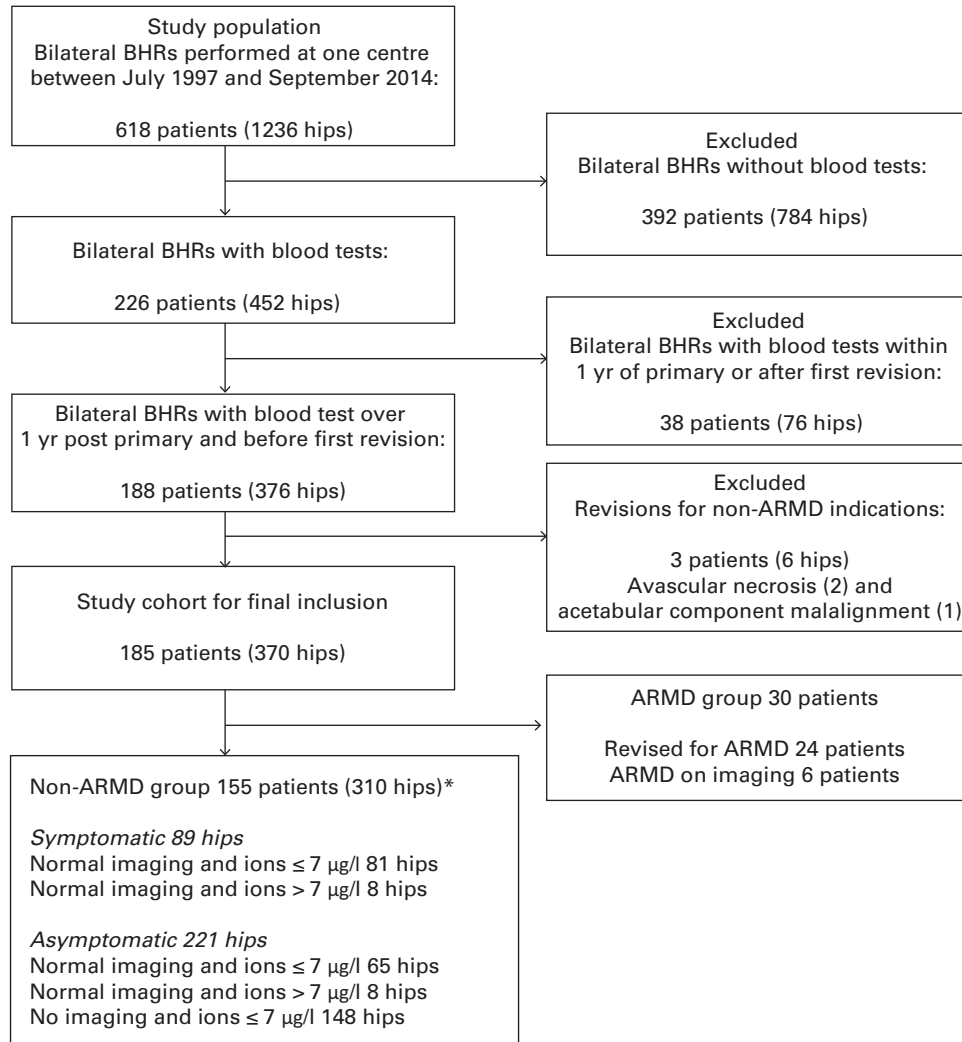


Fig. 1

Flowchart of inclusion and exclusion criteria (ARMD, adverse reactions to metal debris; BHR, Birmingham Hip Resurfacing). *The non-ARMD group is detailed by the number of hips, rather than patients, as hips in the same patient can be in different subgroups.

considered an appropriate threshold for patients with bilateral MoM hip resurfacings.¹⁶

We recently showed that patients with a unilateral MoM hip resurfacing with blood metal ion levels below a newly devised implant specific threshold were at a low-risk of having ARMD.¹⁷ This threshold for patients with a unilateral Birmingham Hip Resurfacing (BHR; Smith & Nephew Ltd, Warwick, United Kingdom), which is the most commonly used hip resurfacing worldwide,¹⁸ was 2.15 µg/l for cobalt.¹⁷ The new implant specific thresholds were more effective for identifying patients with ARMD compared with those recommended by both the MHRA and in the recent United States consensus statement.^{4,16} It was therefore hypothesised that there would also be implant specific thresholds for patients with bilateral hip resurfacings, and that such thresholds could be used to guide the management of these patients.

We investigated whether blood metal ion levels could effectively identify patients with bilateral BHRs who have ARMD.

Patients and Methods

A prospective single-centre cohort study of consecutive patients who underwent MoM hip resurfacings was performed. This study was registered with the hospital board. Ethical approval was not required as patients were assessed according to published guidance.⁴ Between July 1997 and September 2014, 1236 BHRs were implanted in 618 patients (Fig. 1). Information regarding the selection of patients, surgical technique and follow-up for those treated with BHRs at our centre has been described previously.^{19,20}

Our institution's routine follow-up for these patients was adapted in accordance with MHRA guidelines.^{4,8} All patients underwent an updated clinical assessment, anteroposterior

pelvic radiographs and all completed the Oxford Hip Score (OHS) questionnaire.²¹ Measurement of blood metal ion levels and cross-sectional imaging were performed in all symptomatic patients, regardless of the severity of the symptoms. Blood metal ion levels were also measured in specific asymptomatic patients who had risk factors for ARMD including small sizes of the femoral component, malpositioned acetabular components, radiological features suggestive of failure, including osteolysis, radiolucent lines and narrowing of the femoral neck, and noises from the hip including squeaking, clicking, grating, locking and clunking, either reported by the patient and/or elicited during examination.²²⁻²⁶ Blood metal ion levels were also measured in patients with significant concerns as a consequence of media attention. Therefore, blood metal ion levels were measured in a heterogeneous group of patients who were considered to be at risk of ARMD.

In line with MHRA guidance, cross-sectional imaging was performed in all asymptomatic patients with blood metal ion levels of $> 7 \mu\text{g/l}$ (MHRA upper-limit)⁴ and in selected asymptomatic patients with levels which were $\leq 7 \mu\text{g/l}$, where there were clinical concerns about radiological appearances, and in patients in whom the contralateral BHR met the criteria for imaging.

Our protocol for imaging these patients recommends ultrasound for those who are symptomatic and metal artifact reduction sequence MRI for those who are asymptomatic. As asymptomatic patients were likely to need repeat imaging, serial MRIs were chosen to allow comparative analysis given serial ultrasounds are more difficult to compare, especially when different radiologists are performing the examinations. Ultrasound was performed when MRI was contraindicated. This departmental protocol was based on advice from our group of expert musculoskeletal radiologists at the time of the patient recall,^{4,8} with recent evidence confirming that both of these modalities have an important role in assessing MoM hip resurfacings.^{27,28}

As of September 2014, 226 patients with bilateral BHRs (452 hips) had undergone analysis of blood metal ion levels and were considered eligible for inclusion in the study. Patients with bilateral BHRs and measurement of blood metal ion levels, undertaken at least one year after the most recent arthroplasty, were included. This was to allow for the 'running in' phase of the bearing surfaces. The blood metal ion test also needed to be performed before any revision procedure. Patients undergoing these measurements who subsequently underwent a revision for non-ARMD indications, including infection, fracture, aseptic loosening, unexplained pain, dislocation and avascular necrosis were excluded, to reduce the risk of confounding factors when devising specific thresholds for ARMD. There were 185 patients with 370 BHRs who were eligible for final study inclusion (Fig. 1).

Definitions. Blood test results can only be associated with the patient, not with the individual hips. The unit of analysis was therefore patients rather than hips, as recom-

mended previously.¹² Patients were considered to have failed if one or more of their hips failed. Otherwise they were not considered to have failed. When multiple blood test results were available for the same patient, we used the most recent blood test result in patients not undergoing revision surgery, and we used the blood test result immediately prior to revision surgery in those patients who failed.

Eligible patients were divided into two groups based on their status in September 2014. The ARMD group included those who had undergone, or were awaiting, a revision for ARMD, and those with ARMD confirmed on imaging with periprosthetic effusions and pseudotumours²⁹⁻³¹ who were under surveillance but not listed for revision due to clinician and/or patient preference. Revision surgery was recommended based on clinical assessment, blood metal ion levels and imaging findings. Metal ion levels alone were never used as the sole indication for revision.¹³ The non-ARMD group consisted of all the remaining patients, none of whom had undergone, or were awaiting, revision surgery. Therefore, all patients in this group had both primary BHRs *in situ*. This group included all symptomatic and asymptomatic patients with normal imaging, regardless of their blood metal ion levels, and all asymptomatic patients with blood metal ion levels $< 7 \mu\text{g/l}$, but no imaging.

Blood metal ion analysis. Whole blood was collected from the antecubital vein for analysis of the level of metal ions, as previously described.¹⁷ All samples were analysed in a MHRA approved laboratory, regularly participating in the Trace Elements External Quality Assessment Scheme, for which an excellent accuracy of measurement and reproducibility have been reported.³² The levels of cobalt and chromium were measured using an inductively-coupled plasma mass spectrometer (Agilent 7500cx, Agilent Technologies Inc., Santa Clara, California) (limit of detection $0.06 \mu\text{g/l}$ and reporting limit $0.6 \mu\text{g/l}$).

Statistical analysis. The demographic parameters for the ARMD and non-ARMD groups were compared using a chi-squared test with Yates' correction for categorical parameters (gender) and two-sided, unpaired *t*-tests for numerical parameters with normal distributions (mean age at blood test, mean time from last arthroplasty to blood test, and mean cumulative time *in situ* for both hips before blood test).

The four blood metal ion parameters of interest were the levels of cobalt, chromium, the maximum cobalt or chromium (the higher value of the pair) and the cobalt-chromium ratio (cobalt divided by chromium, and non-dimensional). Two-sided, unpaired *t*-tests were used to compare the logarithms of these parameters between ARMD and non-ARMD groups. The logarithm was necessary to transform the asymmetrical distributions of the levels of metal ions to approximately normal distributions as recommended.³³

The analysis of receiver operating characteristic (ROC) curves is an established method of assessing the performance of a diagnostic test.³⁴ A ROC curve is drawn by

Table I. The demographics of the patients in the study (370 BHRs in 185 patients)

Parameter	All patients	ARMD group	Non-ARMD group	p value: ARMD versus non-ARMD
Patients (n, %)	185 (100)	30 (16)	155 (84)	
Gender (f:m)	89:96	19:11	70:85	0.104
Mean age at blood test (range, yrs)	60.4 (27.6 to 79.3)	60.3 (32.1 to 76.4)	60.4 (27.6 to 79.3)	0.949
Mean time from latest BHR to blood test (range, yrs)	7.0 (1.0 to 16.8)	8.6 (2.4 to 15.2)	6.7 (1.0 to 16.8)	0.014
Mean cumulative time <i>in situ</i> for both hips before blood test (range, yrs)	16.9 (2.4 to 33.8)	19.7 (7.9 to 30.4)	16.4 (2.4 to 33.8)	0.009

p-values for all statistically significant results are highlighted in bold text
ARMD, adverse reactions to metal debris; BHR, Birmingham Hip Resurfacing

Table II. Median (interquartile range) blood metal ion parameters for bilateral BHR patients

Parameter	All patients	ARMD group	Non-ARMD group	p value: ARMD versus non-ARMD
Patients (n, %)	185 (100)	30 (16)	155 (84)	
Cobalt (µg/l)	2.24 (1.47 to 4.01)	39.41 (6.83 to 86.18)	1.95 (1.39 to 2.98)	< 0.0001
Chromium (µg/l)	2.70 (1.98 to 4.73)	22.41 (7.36 to 47.74)	2.39 (1.87 to 3.95)	< 0.0001
Maximum cobalt or chromium (µg/l)	2.81 (2.08 to 5.43)	39.41 (9.28 to 86.18)	2.60 (1.92 to 4.11)	< 0.0001
Cobalt-chromium ratio	0.83 (0.67 to 1.12)	1.59 (0.94 to 2.00)	0.78 (0.66 to 1.01)	< 0.0001

p-values for all statistically significant results are highlighted in bold text
ARMD, adverse reactions to metal debris; BHR, Birmingham Hip Resurfacing

plotting sensitivity (true positive rate) against 1-specificity (or 100-specificity if presented as a percentage) for all possible test thresholds. A useful test produces a curve lying to the left of a 45° line. The further the curve is towards the top left corner, the higher the area under the curve (AUC), and the better the discriminatory performance of the test (100% AUC is a perfect discriminatory test; 50% AUC is a non-discriminatory test). The analysis of ROC curves can also be used to define the optimal threshold to maximise discriminatory ability for any test. A ROC curve was used to determine the optimal thresholds of blood metal ion levels for identifying patients with ARMD. The optimum is defined as the threshold corresponding to the point on the curve nearest the top left corner. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated with their 95% confidence intervals (CIs) for the optimal thresholds for each of the four blood metal ion parameters. Rates of misclassification were also calculated for all thresholds. The DeLong test was used to compare the AUCs between the different blood metal ion parameters.³⁵ The McNemar test was used to compare the numbers of patients with ARMD who were not detected when using the different thresholds (our implant specific, MHRA,⁴ and United States consensus statement¹⁶),³⁶ For all the statistical tests, a p-value < 0.05 was considered significant.

Results

The inclusion and exclusion criteria and the demographics of the patients are shown in Figure 1 and Table I. The sizes of the femoral head were grouped into: 38 mm to 44 mm, 54 (14.6%); 46 mm to 50 mm, 230 (62.2%); and 52 mm to 58 mm, 86 (23.2%).

Blood metal ions. Of 185 patients, 155 (84%) were in the non-ARMD group and 30 (16%) were in the ARMD group (Fig. 1 and Table I). The ARMD group had their bilateral resurfacings *in situ* for significantly longer ($p = 0.009$), and had a longer mean time interval from the most recent BHR to blood metal ion testing ($p = 0.014$) compared with the non-ARMD group.

The four blood metal ion parameters are summarised in Table II. All were significantly higher (all $p < 0.0001$) in ARMD compared with non-ARMD patients.

Threshold analysis for bilateral BHRs. Optimal thresholds for the blood metal ion levels in order to discriminate between bilateral BHR patients with and without ARMD depended on the specific ion parameter which was used (Table III).

Compared with the other three parameters, maximum cobalt or chromium produced the highest AUC for BHRs of 91.0% (95% CI 84.5 to 97.4). The maximum cobalt or chromium AUC was significantly greater than the cobalt-chromium ratio AUC ($p = 0.019$) (Table III and Fig. 2), but not significantly greater than the cobalt ($p = 0.574$) or chromium ($p = 0.721$) AUCs. The maximum cobalt or chromium threshold for identifying BHRs with ARMD providing optimal diagnostic test characteristics was 5.5 µg/l (83.3% sensitivity, 88.4% specificity, 58.1% positive predictive value, 96.5% negative predictive value).

As a sensitivity analysis, optimal thresholds for the blood metal ion levels were assessed in a subgroup of patients who all had these measurements and cross-sectional imaging performed. This subgroup included 111 patients (60% of the whole cohort), of whom 30 were in the ARMD group and 81 were in the non-ARMD group. Similar results were obtained in this subgroup as for the whole cohort.

Table III. Summary of the receiver operator characteristic analysis for patients who underwent bilateral Birmingham Hip Resurfacings

Ion parameter	AUC (%) (95% CI)	Optimal thresholds	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Misclassification (%)	+ve LR (95% CI)	-ve LR (95% CI)
Cobalt	90.0 (83.5 to 96.4)	5.7 µg/l	76.7 (60.0 to 90.0)	92.9 (88.4 to 96.8)	67.6 (51.9 to 83.4)	95.4 (92.0 to 98.7)	9.7	10.80 (5.91 to 19.74)	0.25 (0.13 to 0.48)
Chromium	90.6 (83.0 to 98.1)	5.5 µg/l	83.3 (70.0 to 96.7)	91.0 (86.4 to 95.5)	64.1 (49.0 to 79.2)	96.6 (93.6 to 99.5)	10.3	9.23 (5.46 to 15.59)	0.18 (0.08 to 0.41)
Maximum cobalt or chromium	91.0 (84.5 to 97.4)	5.5 µg/l	83.3 (70.0 to 96.7)	88.4 (83.2 to 92.9)	58.1 (43.4 to 72.9)	96.5 (93.4 to 99.5)	12.4	7.18 (4.52 to 11.40)	0.19 (0.08 to 0.42)
Cobalt-chromium ratio	78.9 (68.4 to 89.5)	1.15	73.3 (56.7 to 86.7)	85.2 (79.4 to 90.3)	48.9 (34.3 to 63.5)	94.3 (90.4 to 98.1)	16.8	4.94 (3.20 to 7.63)	0.31 (0.17 to 0.57)

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratios; +ve, positive; -ve, negative

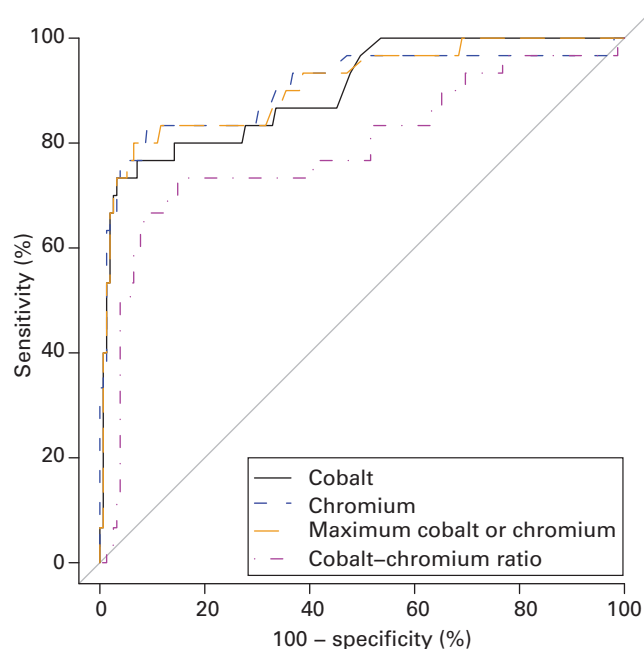


Fig. 2

Receiver operator characteristic curve showing the ability of four blood metal ion parameters to distinguish between patients who have undergone bilateral Birmingham Hip Resurfacings with and without adverse reactions to metal debris.

The AUC for the maximum cobalt or chromium blood parameter was 88.7% (95% CI 81.2 to 96.2) and the optimal threshold was 5.5 µg/l (83.3% sensitivity, 85.2% specificity, 67.6% positive predictive value, 93.2% negative predictive value).

Implant specific thresholds versus regulatory authority thresholds. Fixed blood metal ion thresholds for concern proposed by the United States (10 µg/l, high-risk group),¹⁶ and United Kingdom MHRA (7 µg/l)⁴ were applied to the cohort and compared with our implant specific threshold in terms of the diagnostic test characteristics for identifying patients with ARMD, and the proportion of patients with ARMD who were missed with each threshold. As maximum cobalt or chromium levels provided the optimal AUC and diagnostic test characteristics, only these data were used for comparison.

Compared with fixed regulatory authority thresholds, the maximum cobalt or chromium implant specific

threshold provided the best balance between sensitivity and specificity, higher negative predictive values, and lower positive predictive values (Table IV). Applying the implant specific threshold to the cohort resulted in five patients with ARMD being missed (2.7% of cohort). More patients with ARMD were missed when using fixed regulatory thresholds: 7 µg/l, six patients missed (3.2%); 10 µg/l, eight patients missed (4.3%). However, these differences did not reach statistical significance ($p \geq 0.248$; McNemar test).

Discussion

This represents the largest study assessing whether the measurement of blood metal ion levels could effectively identify patients with bilateral BHRs who have ARMD. Those patients whose levels were below our implant specific threshold (maximum cobalt or chromium, 5.5 µg/l) were at low-risk of having ARMD. This threshold missed fewer patients with ARMD compared with currently recommended fixed regulatory authority threshold.^{4,16} Thus, our implant specific threshold may be useful for managing patients with bilateral BHRs.

This study has a number of limitations, notably selection bias, which was apparent at two stages. The first relates to the subgroup of patients who had measurement of blood metal ion levels which included all symptomatic patients, and asymptomatic patients with risk factors for ARMD and/or concerns about their implants. These patients represent a heterogeneous at-risk group. The second selection bias relates to the use of targeted cross-sectional imaging in asymptomatic patients only with levels of metal ions > 7 µg/l. Despite this approach being in line with current recommendations^{4,5} and the approach used in other centres,^{12,37} some asymptomatic patients in our study not undergoing imaging may have silent ARMD and would have been incorrectly classified in the non-ARMD group. A subgroup analysis was carried out, which involved only patients undergoing cross-sectional imaging, including a number of asymptomatic patients with normal blood metal ion levels. Although this analysis produced similar results to those from the whole cohort, it is acknowledged that the findings may be influenced by selection bias and may not be applicable in centres performing universal measurement of blood metal ion levels and/or cross-sectional imaging in patients with bilateral BHRs, or in institutions where few BHRs were undertaken. This highlights the importance of

Table IV. Summary of the receiver operator characteristic analysis for various thresholds (implant specific and fixed) for maximum blood cobalt or chromium ion concentrations in patients who underwent bilateral BHRs

Threshold	AUC (%) (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Misclassification (%)	Patients (n) with ARMD not identified	+ve LR (95% CI)	-ve LR (95% CI)
10 µg/l	91.0 (84.5 to 97.4)	73.3 (57.5 to 89.20)	96.1 (93.1 to 99.2)	78.6 (63.4 to 93.8)	94.9 (91.5 to 98.3)	7.6	8	18.9 (8.40 to 42.74)	0.28 (0.15 to 0.50)
7 µg/l		80.0 (65.7 to 94.3)	93.6 (89.7 to 97.4)	70.6 (55.3 to 85.9)	96.0 (92.9 to 99.1)	8.6	6	12.4 (6.63 to 23.18)	0.21 (0.10 to 0.44)
5.5 µg/l		83.3 (70.0 to 96.7)	88.4 (83.2 to 92.9)	58.1 (43.4 to 72.9)	96.5 (93.4 to 99.5)	12.4	5	7.18 (4.52 to 11.40)	0.19 (0.08 to 0.42)

AUC, area under the curve; CI, confidence intervals; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratios; +ve, positive; -ve, negative

our implant specific threshold undergoing formal external validation prior to being implemented clinically.

Another limitation is the cross-sectional design of the study with the blood metal ion levels analysed at only one time point (most recent blood test result in patients not undergoing revision surgery, or the blood test result immediately prior to revision surgery in those patients who failed). Therefore, recommendations cannot be made about the intervals for repeat blood testing. Well-designed longitudinal studies are needed to address this issue. Renal function was not assessed at the time of blood sampling, and patients were not specifically questioned about the use of medications and supplements containing trace metals. These factors can influence the interpretation of the levels of metal ions in the blood,³⁸ and this represents another limitation. Finally, our implant specific threshold only applies to patients with bilateral BHRs, and not to patients with other designs of bilateral resurfacings, or those with one BHR and one non-BHR resurfacing.

We recently, for the first time, reported implant specific thresholds for identifying patients with a unilateral BHR with ARMD.¹⁷ The present findings support the initial hypothesis that such a threshold also exists for patients with bilateral BHRs. The measurement of blood metal ion levels was more effective for identifying patients with bilateral BHRs at low risk of ARMD, rather than identifying those with ARMD. This supports our recent findings in patients with a unilateral BHR.¹⁷ We consider this the most important finding, as clinically we wish to exclude patients without ARMD, thereby allowing us to focus on patients who may have ARMD.

Establishing a specific threshold may help in identifying patients who are asymptomatic and at low-risk of developing ARMD, who require less frequent clinical review. If patients with bilateral BHRs are asymptomatic with blood metal ion levels which are below our new implant specific threshold, they can be considered at low risk of ARMD. However, it is uncertain whether patients with sub-threshold measurements of ions in the blood can definitively be excluded from future surveillance, due to a lack of studies with extended follow-up.¹⁵ As most patients who have undergone BHR remain asymptomatic at long-term follow-up,³⁹⁻⁴³ reducing the frequency of review for this

large cohort will have significant savings.¹⁵ Such an approach is supported by a recent study which concluded that asymptomatic patients with a MoM hip resurfacing with normal blood metal ion levels and normal cross-sectional imaging did not require further follow-up within five years of the initial assessment, as no patient developed new ARMD when these investigations were repeated.⁴⁴

Our implant specific threshold for bilateral BHRs (5.5 µg/l) was similar to thresholds reported by Van Der Straeten et al¹² in a smaller cohort of patients who underwent bilateral resurfacings (cobalt, 5.0µg/l; chromium, 7.4µg/l). However, our threshold had much higher sensitivity (83.3% *versus* 43%) and similar specificity (88.4% *versus* 93%). The more favourable diagnostic characteristics observed with our specific threshold may relate to the definition of failure. Previous studies have also included symptomatic patients and revisions for non-ARMD indications as failures.^{9,12,13} Our definition for identifying MoM-related complications was more robust and specific for ARMD. We also included patients who had not undergone a revision, but had ARMD on imaging and were under surveillance as failures, in contrast to some previous studies.^{9,13} Furthermore, the study by Van Der Straeten et al¹² included different combinations of design of hip resurfacings within the same patient, including those designs which have subsequently been withdrawn.⁸

Doubling the optimal thresholds for unilateral BHRs could be considered a crude estimate for bilateral thresholds. Doubling the unilateral specific thresholds from our recent study (4.3 µg/l)¹⁷ gives a different value than that presented here for bilateral BHRs (5.5 µg/l), highlighting the importance of using specific thresholds for patients both with unilateral and bilateral BHRs. Furthermore the bilateral specific threshold is lower than the fixed thresholds recommended by United States (10 µg/l) and United Kingdom (7 µg/l) authorities.^{4,16} Application of these fixed thresholds missed more patients with ARMD than our bilateral specific thresholds, although this did not reach statistical significance ($p \geq 0.248$). These differences may, however, be clinically important, given the potentially destructive nature of ARMD and poor outcomes reported following revision surgery for ARMD.³ It is anticipated that implant specific thresholds will eventually be identified

for other commonly used hip resurfacing designs and that these may also miss fewer patients with ARMD compared with the fixed regulatory thresholds.^{4,16}

The maximum levels of blood cobalt or chromium ions proved to be the best parameter for testing in patients with bilateral BHRs, supporting most studies on patients with unilateral BHRs.^{9,13} However, the level of cobalt alone was recently found to be more effective in a series of patients with unilateral BHRs.¹⁷ This variation may reflect differences in the diameter of the bearings and the position of the components between the two hips within an individual, which is complex, but will affect the overall levels of metal ions in different ways.^{7,26} Some authorities recommend sampling the levels of cobalt alone in all patients who have undergone MoM hip resurfacings.⁵ However, our findings suggest that levels of both cobalt and chromium are required in the assessment of patients with bilateral BHRs. Although the maximum cobalt or chromium parameter produced the highest AUC, it is acknowledged that similar AUCs and diagnostic characteristics were obtained for both cobalt and chromium alone (Table III). If clinicians wish to use cobalt alone in preference to the maximum cobalt or chromium parameter, it is important to use the respective optimal threshold, as these do differ (cobalt only, 5.7 µg/l; chromium only, 5.5 µg/l; maximum cobalt or chromium, 5.5 µg/l).

The prevalence of ARMD in patients who have undergone bilateral BHRs in this study may be considered high (16%; 30/185). Data were presented for the patient rather than the hip, because the results of blood tests are associated with patients, and not with implants. Of the 30 patients with ARMD, 27 had unilateral ARMD and three had bilateral ARMD, giving a much lower true prevalence of ARMD at the implant level of 8.9% (33/370), and a ten-year Kaplan-Meier cumulative ARMD-free survival for 370 bilateral BHRs of 92.1% (95% CI 87.5 to 95.1; 133 hips at risk). These figures are comparable with, or more favourable than, those reported by others.^{40,45} However, it is important to acknowledge that our results are based on a heterogeneous subgroup of patients at risk of ARMD, with bilateral BHRs, which is itself also considered a risk factor.^{6,14} By contrast, other studies have reported the prevalence of ARMD in the whole population of patients undergoing BHR,^{40,45} rather than in an at risk group.

In conclusion, patients with bilateral BHRs and blood metal ion levels which were below our newly devised implant specific threshold were at a low risk of having ARMD. Our implant specific threshold missed fewer patients with ARMD compared with currently recommended fixed regulatory authority thresholds. The implant specific threshold may therefore be useful when managing patients with bilateral BHRs. However, it is recommended that this newly devised threshold undergoes external validation in a number of centres prior to being implemented clinically.



Take home message:

Our implant specific threshold may be useful for managing patients with bilateral BHR implants.

Author contributions:

G. S. Matharu: Study design, Data collection, Data analysis, Manuscript draft and revision.

F. Berryman: Study design, Data collection, Data analysis, Manuscript revision and approval.

L. Brash: Data collection, Manuscript revision and approval.

P. B. Pynsent: Study design, Data analysis, Manuscript revision and approval.

D. J. Dunlop: Study design, Performed surgeries, Manuscript revision and approval.

R. B. C. Treacy: Study design, Performed surgeries, Manuscript revision and approval.

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R. B. C. Treacy reports that "I was co-owner of Midland Medical Technologies who were sold to Smith & Nephew in 2004. Subsequently I was a consultant to Smith & Nephew for five years; since 2004 I have not received any royalty or other payment in association with The Birmingham Hip Resurfacing. I travel and lecture extensively, largely at personal expense."

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