How do MRI-detected subchondral bone marrow lesions (BMLs) on two different MRI sequences correlate with clinically important outcomes?

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Abstract

Objective: To describe the association of bone marrow lesions (BMLs) present on two different MRI sequences with clinical outcomes, cartilage defect progression, cartilage volume loss over 2.7 years, and total knee replacement (TKR) over 13.3 year**s.**

Methods: 394 participants (50-80 years) were assessed at baseline and 2.7 years. BML presence at baseline was scored on T1-weighted fat-suppressed 3D gradient-recalled acquisition (T1) and T2-weighted fat-suppressed 2D fast spin-echo (T2) sequences. Knee pain, function, and stiffness were assessed using WOMAC. Cartilage volume and defects were assessed using validated methods. Incident TKR was determined by data linkage.

Results: BMLs were mostly present on both MRI sequences (86%). BMLs present on T2, T1, and both sequences were associated with greater knee pain and functional limitation (odds ratio=1.49 to 1.70; all $P<0.05$). Longitudinally, BMLs present on T2, T1, and both sequences were associated with worsening knee pain (β=1.12 to 1.37, respectively; $P<0.05$) and worsening stiffness (β=0.45 to 0.52, respectively; all $P<0.05$) but not worsening functional limitation or total WOMAC. BMLs present on T2, T1, and both sequences predicted site-specific cartilage defect progression (relative risk=1.22 to 4.63; all $P<0.05$) except at the medial tibial and inferior patellar sites. Lateral tibial and superior patellar BMLs present on T2, T1, and both sequences predicted site-specific cartilage volume loss (β= -174.77 to -140.67; $P<0.05$). BMLs present on T2, T1, and both sequences were strongly associated with incident TKR.

Conclusions: BMLs can be assessed on either T2 or T1-weighted sequences with no clinical predictive advantage of either sequence.

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INTRODUCTION

Subchondral bone marrow lesions (BMLs), visible on magnetic resonance imaging (MRI) have been shown to be an important feature in osteoarthritis (OA). BMLs are associated with pain (1-4), predict cartilage defect progression and cartilage volume loss (5-7), and total joint replacement (TKR) surgery (4, 8-10).

Conventionally, BMLs are assessed on fluid-sensitive MRI sequences such as T2-weighted fat saturation, short tau inversion recovery (STIR), intermediate weighted fat saturation (IW-FS), and proton density fat saturation (PD-FS) , although they can be detected using other MRI sequences (8, 11, 12). Previous reports indicate that gradient recalled echo (GRE)-type MRI sequences such as T1-weighted gradient echo and spoiled gradient recalled acquisition in steady state (SPGR) are insensitive to marrow abnormalities and may underestimate the lesion size, compared to fluid sensitive sequences (13-15). Although many studies have compared the performance of different MRI sequences in regard to their ability to detect BMLs (prevalence), reliability, and sensitivity to change (15-20), there are limited studies on how BMLs on different MRI sequences correlate with clinical outcomes.

In a recent study in a pain-free knee cohort, BMLs present on both T2- and T1-weighted fat saturation MRI sequences were associated with medial tibial cartilage volume loss and incident knee pain over 2 years (21). Furthermore, in separate studies, its been shown that BMLs identified on T2- and T1-weighted images predict joint replacement surgery among people with OA (8, 10). This study aimed to determine the association of BMLs detected on two different MRI sequences with pain, physical function limitation, stiffness, cartilage defect progression, and cartilage volume loss in older adults over 2.7 years, as well as knee joint replacement surgery over 13.3 years. Given that BMLs generally appear larger on T2-weighted MRI compared to T1-weighted MRI (14, 15), we hypothesised that BMLs would be easier to detect on T2-weighted MRI sequences and would be more

strongly associated with clinical outcomes compared to BMLs present on T1-weighted MRI sequences.

METHODS

Participants

This study was a part of the Tasmanian Older Adult Cohort (TASOAC) study, an ongoing prospective, population-based study aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of OA at multiple sites (hand, knee, hip, and spine). Participants between the ages of 50 and 80 years were randomly selected from the electoral roll in Southern Tasmania (population, 229,000), with an equal number of men and women. The overall response rate was 57%. Participants were excluded if they were institutionalised or reported a contraindication to having a right knee MRI scan (e.g. implanted pacemaker, metal sutures, presence of shrapnel or iron filings in the eye, claustrophobia, right knee replacement, knee too large for scanner). Figure 1 shows the study flowchart. Of all initially eligible participants, 1,100 enrolled in the study, and 1,099 attended a baseline clinic between March 2002 and September 2004. Follow-up data were collected for 875 eligible participants at a subsequent clinic approximately 2 to 3 years later. The MRI machine was decommissioned halfway through the follow-up period; therefore, MRI scans were available for approximately half of the follow-up participants.

All research conducted was in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All subjects gave informed written consent.

Anthropometrics

Weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI)

was calculated as kilograms per square meter.

Radiographic knee OA

A standing anteroposterior semi-flexed view of the right knee with 15° of fixed knee flexion was performed at baseline and scored individually for osteophytes and joint space narrowing on a scale of 0 to 3 (0=normal and 3=severe) according to the Altman atlas (22) as previously described (23). The presence of radiographic OA was defined as any score ≥1 for joint space narrowing or osteophytes.

Magnetic resonance imaging

MRI of the right knee was acquired at baseline and follow-up with a 1.5-T whole-body magnetic resonance unit (Picker, Cleveland, OH, USA) by using a commercial transmit/receive extremity coil. Image sequences included the following: (a) a T1-weighted fat saturation three-dimensional (3D) gradient-recalled acquisition (T1-w GRE MRI) in the steady state; flip angle, 30 degrees; repetition time, 31 milliseconds; echo time, 6.71 ms; field of view, 16 cm; 60 partitions, 512 × 512-pixel matrix; acquisition time, 5 minutes 58 seconds; one acquisition; sagittal images were obtained at a slice thickness of 1.5 mm without a interslice gap; and (b) a T2-weighted fat saturation two-dimensional (2D) fast spin echo (T2-w FSE MRI), flip angle, 90 degrees; repetition time, 3,067 milliseconds; echo time, 112 milliseconds; field of view, 16 cm, 15 partitions, 228 × 256-pixel matrix; sagittal images were obtained at a slice thickness of 4 mm with an interslice gap of 0.5 to 1.0 mm.

Bone marrow lesions

Subchondral BMLs were assessed on T2-w FSE and T1-w GRE fat saturation MR images by using OsiriX software at the medial and lateral sites of the femur and tibia, and the superior and inferior sites of the patella at baseline. BMLs were defined as areas of increased signal intensity on T2-w FSE and T1-w GRE, located immediately under the articular cartilage. One trained observer measured the BMLs on each sequence by measuring the maximum area of

the lesion on a single slice where the area appeared the largest in mm^2 using software cursors. If more than one lesion was present at the same site, the BML with the largest size was used. Baseline and follow-up MRI images were read paired with the chronological order known to the observer. Intra-observer reliability was assessed in 40 randomly selected subjects after a 2-week interval between the readings. The intra-class correlation coefficient (ICC) using two-way mixed-effects model (24) was 0.98 (95% CI; 0.96, 0.99) for T2 and 0.94 (95% CI; 0.90, 0.96) for T1-weighted sequences. For analysis, BMLs were categorised into three groups: 1) BMLs present on T2-weighted MRI (T2-w FSE), 2) BMLs present on T1-weighted MRI (T1-w GRE), and 3) BMLs present on both T2-weighted and T1-weighted MRI (T1 and T2).

Cartilage morphology evaluation

Cartilage defects were assessed by a trained observer at baseline and follow-up on T1-weighted MR images (score range, 0 – 4), as previously described : grade 0 = normal cartilage; grade 1 = focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and base; grade 2 = irregularities on the surface or base and loss of thickness < 50%; grade 3 = deep ulceration with loss of thickness > 50%; and grade 4 = full-thickness chondral wear with exposure of subchondral bone. A cartilage defect also had to be present on at least 2 consecutive slices. The cartilage was considered to be normal if the band of intermediate signal intensity had a uniform thickness. If more than one defect was present on the same site, the highest score was used. Medial tibial, lateral tibial, medial femoral, lateral femoral, and patellar compartments were measured. Baseline and follow-up images were read at different time points. The baseline scores were available to the reader when assessing the follow-up scores. Intraobserver repeatability was assessed in 50 subjects with at least 1-week between the 2 measurements with ICC of 0.93, 0.92, 0.95, 0.80, and 0.94 at the medial tibia, medial femur, lateral tibia, lateral femur, and patellar respectively (25). Change in cartilage defect score from baseline to follow-up was dichotomised to 0 and 1: 0 representing no

change or a decrease in cartilage defects and 1 representing an increase of 1 or more on the 0 – 4 scale.

Knee tibial and patellar cartilage volume was measured by a trained observer on T1-weighted MR images at baseline and follow-up by means of image processing on an independent workstation using Osiris software as previously described (25, 26). The volumes of individual cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312 × 312 mm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The baseline and follow-up images were read at different time points. The baseline cartilage volume value was available to the reader when assessing the follow-up scans. The coefficient of variation (CV) was 2.1% for the medial tibia, 2.2% for the lateral tibia, and 2.6% for patella.

Knee femoral cartilage volume was determined at baseline and follow-up by means of image processing on an independent workstation using Cartiscope^{TM} (ArthroLab Inc., Montreal, Quebec, Canada), as previously described (27-29). The quantitative segmentation of the cartilage- synovial interfaces was carried out with the semi-automatic method under reader supervision and with corrections when needed. Cartilage volume was evaluated directly from a standardized view of 3D cartilage geometry as the sum of elementary volumes. Baseline and follow-up images were read paired with chronological order known to the reader. The coefficient of variation percentage (CV) was approximately 2% (27). The cartilage volume assessment was done for the medial and lateral condyles delineated by the Blumensaat's line .

WOMAC scores

Knee pain, physical function limitation, and stiffness were assessed using the self-administered Western Ontario and McMaster Universities OA Index (WOMAC) (30) scale,

which was scored using a 10-point numeric rating scale from 0 (no pain, no function limitation, and no stiffness) to 9 (most severe pain, most severe physical function limitation, and most severe stiffness) (30) at baseline and follow-up. There are 5 components of pain, 17 of function limitation and two of stiffness included. Each of the subscales are summed to form a total score for pain (range 0-45), function limitation (range 0-153) and stiffness (range 0-18). The total WOMAC score was calculated by summing pain, function limitation and stiffness total scores (range 0- 216) (30). For cross-sectional analysis, we categorised the subcales into three levels (none, mild, moderate to severe). This categorisation was done due to non-normally distributed WOMAC data. These levels were based on pain cut-offs used by an OA Expert Group in the Global Burden of Disease (GBD) 2010 study (31). Total pain score was categorised as 0 (none), 1-13 (mild), and 14-45 (moderate to severe). Total function limitation score was categorised as 0 (none), 1-45 (mild), and 46-153 (moderate to severe). Total stiffness score was categorised as 0 (none), 1-4 (mild), 5-18 (moderate to severe). Total WOMAC score was categorised as 0 (none), 1-64 (mild), 65-216 (moderate to severe). For longitudinal analysis, change in WOMAC scales was calculated as follow-up minus baseline.

Total knee replacement (TKR) surgery

The incidence of TKR surgery was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) between 1 March 2002 and 21 September 2016. AOANJRR started data collection in Tasmania in September 2000 and collects data from both public and private hospitals. Data validation against State and Territory Health Department data is done using a sequential multi-level matching process (32). Identifying information such as first name, last name, sex, date of birth, current and historical addresses were provided to AOANJRR, which were used to identify participants who had a TKR. Ethical approval for data linkage was obtained from the Tasmanian Health

and Medical Human Research Ethics Committee.

Comorbidities and Pain Medication Use

Participants used a self-reported questionnaire to report whether or not they had any of the following comorbidities (yes/no); diabetes, heart attack, hypertension, thrombosis, asthma, bronchitis/emphysema, osteoporosis, hyperthrodism, hypothyroidism, rheumatoid arthritis, and other major illness. They also used a self-reported questionnaire to list the pain medications they were taking (medication name, dose and frequency).

Statistical Analysis

The exposure for all analyses were BMLs present on T2-w FSE; BMLs present on T1-w GRE; and BMLs present on both MRIs. Five outcomes were analysed and fitted into a separate model for the three exposures; baseline WOMAC scales, change in WOMAC scales, worsening or stabilising of site-specific cartilage defects, change in cartilage volume, and incident of TKR.

Adjacent category ordinal logistic regression was used to estimate the association of BMLs on T1, T2, and both MRI sequences with baseline categories of knee pain, physical function limitation, stiffness and total WOMAC. Multivariable models were adjusted for age, sex, BMI, and radiographic OA. Standard errors were adjusted to account for any correlation of observations for the same individual (i.e. BMLs present on both MRI sequences).

Linear regression was used to estimate the association of BMLs present on T1-w GRE, T2-w FSE, and both MRI sequences with change in WOMAC scales in separate models. Standard errors were adjusted to account for any correlation of observations for the same individual. Multivariable models were adjusted for age, sex, BMI in the first instance, then additionally for radiographic OA and baseline WOMAC score. The outcome variable was transformed using Box-Cox transformation to satisfy model assumptions.

Site-specific associations between BMLs and cartilage defects were defined as the

association within the same site (e.g. medial tibial BMLs predicting medial tibial cartilage defect worsening). Log binomial regression was used to estimate the risk of worsening site-specific cartilage defects over 2.7 years for baseline BMLs, adjusted for age, sex, and BMI and baseline cartilage defect score.

Multilevel mixed-effects linear regression was used to estimate the longitudinal association of baseline BMLs with cartilage volume loss over 2.7 years. Point estimates of change in cartilage volume over 2.7 years for those with BMLs at baseline compared to those without BMLs at baseline were reported. Multivariable models were adjusted for age, sex, and BMI.

Due to perfect prediction of BMLs with TKR (i.e. all those participants who underwent TKR surgery had a BML at baseline) we were unable to model this data and present it descriptively.

We conducted a sensitivity analysis to examine whether number of comorbidities and pain medication use to examine whether these factors were confounders.

All statistical analyses were performed using Stata 14 (Stata-Corp, College Station, Texas, USA). The significant p-value was set at the value of less than 0.05 (two-tailed).

RESULTS

Characteristic of participants

The study sample contained 394 participants who had MRI measures at baseline and the 2-year follow-up. There were no significant differences in participant characteristics, including age, sex, BMI, baseline cartilage defects, and cartilage volume, between the study sample (n=394) and the remainder of the cohort (n=705) who did not have MRI scans at follow-up. The characteristics of the participants stratified by BMLs on any of the MRI sequences at baseline, are shown in Table 1. There were no significant differences in terms of age, sex, BMI, radiographic OA, WOMAC scales, total cartilage volume at baseline, and absolute change in total cartilage volume between those with and without baseline BMLs. Prevalence

of any cartilage defects at baseline, an increase in cartilage defect score and incident TKR was higher in those with baseline BMLs.

BML prevalence and size

231 (59%) participants had BMLs on at least one sequence. There were 388 BMLs detected on T2-w FSE and 378 BMLs detected on T1-w GRE. 354 (86%) of BMLs were detected on both MRI sequences and very few BMLs were detected on only one of the sequence types (i.e. 34 (8%) BMLs only on T2-w FSE and 24 (6%) only on T1-w GRE) as shown in Figure 2. An example of this is presented in Figure 3. For those BMLs present on both sequences, while the size differences were not statistically significant, overall, mean area for total BMLs on T2-w FSE were slightly larger (Figure 4).

Knee pain, functional limitation, stiffness and overall disability (total WOMAC score)

Table 2 shows cross-sectional associations between BMLs present on T2-w FSE, T1-w GRE, and both MRI sequences and baseline category of knee pain, physical function limitation, stiffness, and total WOMAC score. Presence of BMLs on T2-w FSE, T1, and both MRI sequences at baseline were associated with increased odds of moving to a higher category of knee pain, physical function limitation, and total WOMAC score compared to the reference group with no BMLs. The effect sizes were similar for each sequence and remained unchanged and significant after adjustment for age, sex, BMI, and further adjustment for radiographic OA. Participants with a BML present on T2-w FSE, T1 and both MRI sequences were consistently estimated to have increased odds of moving to a higher category of stiffness but evidence for the association was weaker.

We next examined whether the presence of BMLs T2-w FSE, T1, and both MRI sequences compared to the reference group with no BMLs was associated with changes in knee pain, physical function limitation, stiffness, and total WOMAC score over 2.7 years (Table 3). BMLs present on T2-w FSE, T1, and both MRI sequences were associated with the

worsening of pain and stiffness over 2.7 years, with similar effect sizes, after adjustment for age, sex, BMI, radiographic OA, and baseline WOMAC score. There was no evidence for an association between BMLs present on T2-w FSE, T1, or both MRI sequences with changes in physical function limitation and total WOMAC score in unadjusted or adjusted analyses.

Cartilage defects

Table 4 shows the relative risks of worsening site-specific cartilage defects over 2.7 years for BMLs present on T2-w FSE, T1, and both MRI sequences. Presence of BMLs on T2 T2-w FSE T1, and both MRI sequences were associated with a higher risk of site-specific cartilage defect worsening over 2.7 years in adjusted analysis at all sites, except medial tibial and inferior patellar. The relative risk estimates for each site were of a similar magnitude for the three sequence types, with the largest effect observed for the lateral femoral site.

Cartilage volume loss

Table 5 shows estimated changes in site-specific cartilage volume over 2.7 years for site-specific BMLs present on T2-w FSE, T1, and both MRIs, compared to the reference group with no BMLs. The presence of BMLs was associated with significantly greater cartilage volume loss at the lateral tibial and superior patellar for all MRI sequences. Increased cartilage volume loss was also associated with the presence of medial femoral BMLs identified on T2-w FSE, and with lateral tibiofemoral BMLs identified on both MRI sequences and on T2-w FSE, but not for BMLs on T1-w GRE. While there was no evidence for an association between BMLs and site-specific cartilage volume loss at the medial tibial, lateral femoral, inferior patellar, medial tibiofemoral, total tibiofemoral and overall sites, the effect size estimates were consistently negative.

Total knee replacement (TKR)

6% of our study population had TKR (19 cases). 100% of TKR participants had a BML on both MRI sequences and on T1-w GRE. 95% of TKR participants had a BML on T2-w FSE.

This indicates BMLs were a very strong predictor of TKR on each sequence type. We were not able to model this data due to the perfect prediction

Further adjustment of all our presented models for number of comorbidities and use of pain medication did not change effect sizes by more than 10%, data not shown.

DISCUSSION

This study describes associations between BMLs detected on two different MRI sequences with clinical outcomes in OA including pain, function, stiffness, cartilage damage and loss, and TKR surgery. We found that subchondral BMLs were commonly seen on both T2-w FSE and T1-w GRE sequences in an older adult population. While the difference in BML size on each sequence was not statistically significant, BML area was slightly larger on the T2-w FSE sequences compared to T1-w GRE sequences. Despite this, contrary to our hypothesis, associations with clinical outcomes including symptoms, cartilage damage and loss, and TKR were similar. This suggests that either T2-w FSE or T1-w GRE MRI sequences could be used separately to assess BMLs.

Our study found that 86% of BMLs were seen on both MRI sequences in our sample of community-dwelling older adults. Prevalence assessments for BMLs in previous studies vary widely. One study reported 74% in community-dwelling adults without knee pain (21); whereas, another study reported 75% in knees with and without medial joint space narrowing (33). Our rate of BMLs detected on both MRI sequences is higher than the previous studies. A number of factors may contribute to this inconsistency including the use of different sequence types, study populations, study sizes, and different BML scoring systems and readers.

There have been limited studies evaluating how BMLs on different MRI sequences correlate with clinically important outcomes. Recently Wluka et al. (21) reported that BMLs

present on both T1- and T2-weighted MRI sequences were associated with increased cartilage loss and incident knee pain compared to BMLs seen only on T2-weighted sequences. These findings support recommendations suggesting a combination of both fluid-sensitive and GRE-type MRI sequences should be used. However, our study did not find this. We found that BMLs were typically seen on both MRI sequences, and were equivalently associated with symptoms, cartilage damage and loss, and TKR surgery. This suggests that there is no meaningful difference in prediction of clinically important outcomes using either sequence. Furthermore, in studies where both fluid-sensitive and GRE-type MRI sequences are not available, either sequence could be used for clinical research.

There is great debate about the ideal sequence to assess BMLs. Several previous studies have been conducted comparing the performance of different MRI sequences in regard to BML detection, reliability and sensitivity to change over time (15-20). This has led to mixed recommendations about what is the optimal MRI sequence to measure BMLs. As BMLs often appear larger on fluid-sensitive sequences compared to T1-weighted sequences (11, 19, 20), authors often suggest measuring them using water-sensitive sequences (11, 34). Our study also found that BMLs appeared slightly larger on the T2-weighted sequences compared to the T1-weighted sequences. However, mixed findings from other studies (17, 18) has led to the hypothesis that a combination of both fluid-sensitive and GRE-type MRI sequences would result in superior accuracy in assesssing BMLs. One other study has assessed this in addition to ours; they observed no difference between a fluid sensitive sequence (IW-TSE) compared to a DESS sequence in detecting the overall prevalence or sensitivity to change over time (33). This led the authors to conclude that either sequence could be used for assessment of BML change in a clinical trial, which is consistent with our study findings.

Studies which have used histology to characterise BMLs have offered great insight into the compositional charcteristics of BMLs. Zanetti et al were one of the first to examine

the histology of BMLs and found they consisted of oedema, fibrosis, trabecular bone changes, and necrosis (35). Combining different MRI sequences may offer new insights into the different cellular changes occurring in BMLs (36, 37). A study using a combination of fluid-sensitive and GRE-type MRI sequences showed significantly greater oedema, fibrosis and necrosis in BMLs present on both MRI sequences compared to BMLs present on only fluid-sensitive sequences (38).

This study has several potential limitations. First, this study consisted of 394 participants who had MRI scans at both time points, therefore excluding 705 from our larger cohort. However, the two groups were similar in terms of age, sex, BMI, baseline cartilage defects and volume so our findings should be generalisable. Second, in our study, the initial response rate is lower than desirable (57%), but it is similar to other Australian cohort studies (39). The relationship between outcomes and exposures is not neccesarily biased due to a lower response rate (40). The study quality and validity should be judged with other criteria and not the response rate alone (41). Third, the BMLs assessed in this study were read by one reader who measured the BMLs on both sequences at the same time. Therefore the reader may have been more likely to pick up BMLs on each sequence because they were comparing the images from each sequence to each other. This may have led to an overestimate of BML presence on each sequence. However, this method does provide assurance because the reader was able to confidently document whether or not a BML was present on each sequence, meaning that BMLs were less likely to be missed by the reader. Forth, baseline WOMAC scales were categorised into tertiles as the data was not normally distributed and had a large amount of zero's. While there is no consensus on the exact cut points to be used, we adopted cut-offs based on the expert consensus from an OA Expert Group from the GBD 2010 study.

Conclusions

BMLs were commonly seen on both T1-w GRE and T2-w FSE MRI sequences. They were

326 equivalently associated with clinical outcomes including symptoms, worsening of cartilage
327 defects, cartilage volume loss, and TKR. Our study demonstrates that BMLs can be assessed
328 on either MRI sequence alone with no clinical predictive advantage of either sequence.

LIST OF ABBREVIATIONS

2D, two-dimensions

3D, three-dimensions

AOANJRR, Australian Orthopaedic Association National Joint Replacement Registry

BML(s), bone marrow lesions

CI, confidence interval

CV, coefficient of variation percentage

GBD, Global Burden of Disease

GRE, gradient recalled echo

ICC, intra-class correlation coefficient

IW-FS, intermediate weighted fat saturation

MR, magnetic resonance

MRI, magnetic resonance imaging

OA, osteoarthritis

PD-FS, proton density fat saturation

RR, relative risk

SPGR, spoiled gradient recalled acquisition in steady state

STIR, short tau inversion recovery

T1-w GRE, T1-weighted fat-suppressed 3D gradient-recalled acquisition MRI

T2-w FSE, T2-weighted fat-suppressed 2D fast spin-echo MRI

TASOAC, Tasmanian Older Adult Cohort

TKR, total knee replacement

WOMAC, Western Ontario and McMaster Universities OA Index

DECLARATIONS

Ethics approval and consent to participate

All research conducted was in compliance with the Declaration of Helsinki and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All subjects gave informed written consent.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

JPP and JMP are shareholders in ArthroLab. The other authors declare no competing interests.

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Author's contributions

All authors were involved in drafting the article or revising it for important intellectual content. All authors have approved the final manuscript. SMM (siti.mattap@utas.edu.au) and DA (dawn.aitken@utas.edu.au) takes responsibility for the integrity of the work as a whole, from inception to finished article. KW participated in analysis and interpretation of the data,

and critically revised the manuscript. LL participated in interpretation of the data, and critically revised the manuscript. SG and MH carried out data collection and critically revised the manuscript. CD, JP, and JM-P participated in the study planning, carried out data collection, and critically revised the manuscript. FC designed and carried out the study planning, participated in interpretation of data, and critically revised the manuscript. GJ designed and carried out the study planning, participated in analysis and interpretation of the analysis, and critically revised the manuscript.

Reference

1. Felson DT, Chaisson CE, Hill CL, Totterman SMS, Gale ME, Skinner KM, et al. The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis. Ann Intern Med. 2001;134(7):541-9.
2. Davies-Tuck ML, Wluka AE, Wang Y, English DR, Giles GG, Cicuttini F. The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. Ann Rheum Dis. 2009;68(6):904-8.
3. Zhai G, Blizzard L, Srikanth V, Ding C, Cooley H, Cicuttini F, et al. Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. Arthritis Rheum. 2006;55(2):264-71.
4. Dore D, Quinn S, Ding C, Winzenberg T, Zhai G, Cicuttini F, et al. Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. Arthritis Res Ther. 2010;12(6):R223.
5. Wluka AE, Wang Y, Davies-Tuck M, English DR, Giles GG, Cicuttini FM. Bone marrow lesions predict progression of cartilage defects and loss of cartilage volume in healthy middle-aged adults without knee pain over 2 yrs. Rheumatology (Oxford). 2008;47(9):1392-6.
6. Dore D, Martens A, Quinn S, Ding C, Winzenberg T, Zhai G, et al. Bone marrow lesions predict site-specific cartilage defect development and volume loss: a prospective study in older adults. Arthritis Res Ther. 2010;12(6):R222.
7. Wildi LM, Raynauld J-P, Martel-Pelletier J, Abram F, Dorais M, Pelletier J-P. Relationship between bone marrow lesions, cartilage loss and pain in knee osteoarthritis: results from a randomised controlled clinical trial using MRI. Ann Rheum Dis. 2010;69(12):2118-24.
8. Tanamas SK, Wluka AE, Pelletier J-P, Pelletier JM, Abram F, Berry PA, et al. Bone marrow lesions in people with knee osteoarthritis predict progression of disease and joint replacement: a longitudinal study. Rheumatology. 2010;49(12):2413-9.
9. Scher C, Craig J, Nelson F. Bone marrow edema in the knee in osteoarthrosis and association with total knee arthroplasty within a three-year follow-up. Skeletal Radiol. 2008;37(7):609-17.
10. Raynauld J-P, Martel-Pelletier J, Haraoui B, Choquette D, Dorais M, Wildi LM, et al. Risk factors predictive of joint replacement in a 2-year multicentre clinical trial in knee osteoarthritis using MRI: results from over 6 years of observation. Ann Rheum Dis. 2011;70(8):1382-8.
11. Hayashi D, Guermazi A, Kwoh CK, Hannon MJ, Moore C, Jakicic JM, et al. Semiquantitative assessment of subchondral bone marrow edema-like lesions and subchondral cysts of the knee at 3T MRI: A comparison between intermediate-weighted fat-suppressed spin echo and Dual Echo Steady State sequences. BMC Musculoskelet Disord. 2011;12(1):1-9.
12. Grande FD, Farahani SJ, Carrino JA, Chhabra A. Bone marrow lesions: A systematic diagnostic approach. The Indian Journal of Radiology & Imaging. 2014;24(3):279-87.
13. Duc SR, Koch P, Schmid MR, Horger W, Hodler J, Pfirrmann CWA. Diagnosis of Articular Cartilage Abnormalities of the Knee: Prospective Clinical Evaluation of a 3D Water-Excitation True FISP Sequence. Radiology. 2007;243(2):475-82.
14. Roemer FW, Hunter DJ, Guermazi A. MRI-based semiquantitative assessment of subchondral bone marrow lesions in osteoarthritis research. Osteoarthritis Cartilage. 2009;17(3):414-5.

15. Yoshioka H, Stevens K, Hargreaves BA, Steines D, Genovese M, Dillingham MF, et al. Magnetic resonance imaging of articular cartilage of the knee: Comparison between fat-suppressed three-dimensional SPGR imaging, fat-suppressed FSE imaging, and fat-suppressed three-dimensional DEFT imaging, and correlation with arthroscopy. J Magn Reson Imaging. 2004;20(5):857-64.
16. Hilfiker P, Zanetti M, Debatin JF, McKinnon G, Hodler J. Fast spin-echo inversion-recovery imaging versus fast T2-weighted spin-echo imaging in bone marrow abnormalities. Invest Radiol. 1995;30(2):110-4.
17. d'Anjou MA, Troncy E, Moreau M, Abram F, Raynauld JP, Martel-Pelletier J, et al. Temporal assessment of bone marrow lesions on magnetic resonance imaging in a canine model of knee osteoarthritis: impact of sequence selection. Osteoarthritis Cartilage. 2008;16(11):1307-11.
18. Mirowitz SA, Apicella P, Reinus WR, Hammerman AM. MR imaging of bone marrow lesions: relative conspicuousness on T1-weighted, fat-suppressed T2-weighted, and STIR images. American Journal of Roentgenology. 1994;162(1):215-21.
19. Schmid MR, Hodler J, Vienne P, Binkert CA, Zanetti M. Bone marrow abnormalities of foot and ankle: STIR versus T1-weighted contrast-enhanced fat-suppressed spin-echo MR imaging. Radiology. 2002;224(2):463-9.
20. Raynauld J-P, Wildi LM, Abram Fo, Moser T, Pelletier J-P, Martel-Pelletier J. Reliability and sensitivity to change of IW-TSE versus DESS magnetic resonance imaging sequences in the assessment of bone marrow lesions in knee osteoarthritis patients: Longitudinal data from the Osteoarthritis Initiative (OAI) cohort. Journal of Biomedical Science and Engineering. 2013;Vol.06No.03:9.
21. Wluka AE, Teichtahl AJ, Maulana R, Liu BM, Wang Y, Giles GG, et al. Bone marrow lesions can be subtyped into groups with different clinical outcomes using two magnetic resonance imaging (MRI) sequences. Arthritis Res Ther. 2015;17:270.
22. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15(Supplement 1):A1-A56.
23. Dore D, Quinn S, Ding C, Winzenberg T, Jones G. Correlates of subchondral BMD: a cross-sectional study. J Bone Miner Res. 2009;24(12):2007-15.
24. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420-8.
25. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthritis Cartilage. 2005;13(3):198-205.
26. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum. 2000;43(11):2543-9.
27. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum. 2004;50(2):476-87.
28. Raynauld JP, Kauffmann C, Beaudoin G, Berthiaume MJ, de Guise JA, Bloch DA, et al. Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. Osteoarthritis Cartilage. 2003;11:351-60.
29. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, Labonte F, Beaudoin G, Bloch DA, et al. Meniscal tear and extrusion are strongly associated with progression of

symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis. 2005;64(4):556-63.
30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40.
31. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;7(73):1323-30.
32. Australian Orthopaedic Association National Joint Replacement Registry. Annual Report - 2016. Adelaide: 2016 1445-3657.
33. Zhang M, Driban JB, Price LL, Lo GH, McAlindon TE. Magnetic Resonance Image Sequence Influences the Relationship between Bone Marrow Lesions Volume and Pain: Data from the Osteoarthritis Initiative. BioMed Research International. 2015;2015:5.
34. Peterfy CG, Gold G, Eckstein F, Cicuttini F, Dardzinski B, Stevens R. MRI protocols for whole-organ assessment of the knee in osteoarthritis. Osteoarthritis Cartilage. 2006;14, Supplement 1:95-111.
35. Thiryayi WA, Thiryayi SA, Freemont AJ. Histopathological perspective on bone marrow oedema, reactive bone change and haemorrhage. Eur J Radiol. 2008;67(1):62-7.
36. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. Radiology. 1988;166(1):193-9.
37. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. Radiology. 2000;215(3):835-40.
38. Muratovic D, Cicuttini F, Wluka A, Findlay D, Wang Y, Otto S, et al. Bone marrow lesions detected by specific combination of MRI sequences are associated with severity of osteochondral degeneration. Arthritis Res Ther. 2015;18(1):54.
39. Hill CL, Gill TK, Menz HB, Taylor AW. Prevalence and correlates of foot pain in a population-based study: the North West Adelaide health study. Journal of foot and ankle research. 2008;1:2-.
40. Carter KN, Imlach-Gunasekara F, McKenzie SK, Blakely T. Differential loss of participants does not necessarily cause selection bias. Aust N Z J Public Health. 2012;36(3):218-22.
41. Morton SMB, Bandara DK, Robinson EM, Carr PEA. In the 21st Century, what is an acceptable response rate? Aust N Z J Public Health. 2012;36(2):106-8.

TABLES

Table 1. Characteristics of participants split by the absence and presence of BMLs on any of the MRI sequences.

	BMLs absent	BMLs present	p-value
	n=163	n=231	
Age (year)	62.8 (7.2)	63.5 (7.3)	0.345
Male sex (%)	46.6	50.6	0.433
BMI (kg/m^2)	27.4 (4.2)	27.8 (4.7)	0.297
Radiographic OA (%)	54.4	59.6	0.312
WOMAC scales			
Pain (0-45)	0 (0, 3)	1 (0, 5)	0.547
Physical function (0-153)	0 (0, 9)	1 (0, 13)	0.223
Stiffness (0-18)	0 (0, 1)	0 0, 2)	0.670
Total WOMAC (0-216)	1 (0, 14)	3 (0, 20)	0.287
Prevalent cartilage defects, baseline‡ (%)	**30**	**61**	**<0.001**
Cartilage defect score increase (%)	**55**	**73**	**<0.001**
Total cartilage volume, baseline (mm^3)	17007 (4217)	16486 (3624)	0.219
Absolute change in total cartilage volume (mm^3)	-774 (867)	-926 (867)	0.145
Incident TKR (%)	**0**	**9.9**	**<0.001**

Values expressed in mean (standard deviation) or percentages. WOMAC scales are expressed as median (25th, 75th percentile).
Bold font denotes significant p-value.
n, number of people; BMI, body mass index; OA, osteoarthritis. ‡ Defined as grade 2 or higher.

Table 2. Adjacent category logistic regression of baseline knee pain, physical function limitation, stiffness and total WOMAC on BMLs present on T2-w FSE, T1-w GRE, and both MRI sequences.

	Univariable OR (95% CI)	Multivariable 1 OR (95% CI)	Multivariable 2 OR (95% CI)
Pain			
T1 and T2	**1.68 (1.13, 2.48)**	**1.72 (1.15, 2.58)**	**1.70 (1.13, 2.56)**
T2-w FSE	**1.65 (1.15, 2.37)**	**1.69 (1.16, 2.45)**	**1.66 (1.14, 2.43)**
T1-w GRE	**1.58 (1.11, 2.25)**	**1.62 (1.13, 2.32)**	**1.60 (1.11, 2.31)**
Physical function limitation			
T1 and T2	**1.57 (1.08, 2.27)**	**1.54 (1.05, 2.27)**	**1.57 (1.06, 2.32)**
T2-w FSE	**1.65 (1.15, 2.37)**	**1.47 (1.04, 2.09)**	**1.49 (1.05, 2.14)**
T1-w GRE	**1.53 (1.07, 2.18)**	**1.50 (1.04, 2.16)**	**1.52 (1.05, 2.21)**
Stiffness			
T1 and T2	1.39 (0.99, 1.96)	1.36 (0.96, 1.93)	1.36 (0.95, 1.93)
T2-w FSE	**1.38 (1.01, 1.90)**	1.36 (0.99, 1.89)	1.34 (0.96, 1.87)
T1-w GRE	1.36 (0.99, 1.85)	1.33 (0.97, 1.83)	1.32 (0.96, 1.83)
Total WOMAC score			
T1 and T2	**1.64 (1.12, 2.39)**	**1.63 (1.10, 2.40)**	**1.63 (1.10, 2.43)**
T2-w FSE	**1.57 (1.09, 2.24)**	**1.56 (1.09, 2.24)**	**1.56 (1.08, 2.25)**
T1-w GRE	**1.56 (1.11, 2.20)**	**1.54 (1.08, 2.19)**	**1.55 (1.08, 2.22)**

ORs represent the odds of moving to a higher category of pain, function, stiffness and total WOMAC for those with a BML on each sequence type compared to no BML on that sequence type.
Multivariable 1 – adjusted for age, sex, BMI
Multivariable 2 – further adjusted for presence of radiographic OA
Bold denotes significant p-value
OR, odds ratio; CI, confidence interval

Table 3. Linear regression estimates of change in knee pain, physical function limitation, stiffness and total WOMAC after 2.7 years on presence of BMLs on T2-w FSE, T1-w GRE, and both MRI sequences at baseline.

	Univariable β coefficient (95% CI)	Multivariable 1 β coefficient (95% CI)	Multivariable 2 β coefficient (95% CI)
Change in pain			
T1 and T2	1.14 (-0.16, 2.44)	1.10 (-0.19, 2.40)	**1.34 (0.18, 2.50)**
T2-w FSE	0.96 (-0.31, 2.23)	0.91 (-0.36, 2.17)	**1.12 (0.06, 2.18)**
T1-w GRE	1.12 (-0.15, 2.39)	1.07 (-0.18, 2.33)	**1.37 (0.36, 2.39)**
Change in physical function limitation			
T1 and T2	1.53 (-1.77, 4.82)	1.37 (-1.83, 4.57)	2.42 (-0.47, 5.32)
T2-w FSE	1.12 (-1.87, 4.11)	1.00 (-1.91, 3.92)	2.09 (-0.58, 4.75)
T1-w GRE	1.57 (-1.40, 4.55)	1.40 (-1.47, 4.26)	2.25 (-0.34, 4.84)
Change in stiffness			
T1 and T2	0.45 (-0.11, 1.02)	0.42 (-0.12, 0.97)	**0.52 (0.05, 1.00)**
T2-w FSE	0.36 (-0.16, 0.87)	0.37 (-0.11, 0.86)	**0.45 (0.01, 0.89)**
T1-w GRE	0.41 (-0.10, 0.91)	0.43 (-0.10, 0.97)	**0.45 (0.03, 0.87)**
Change in total WOMAC			
T1 and T2	3.07 (-1.70, 7.84)	2.82 (-1.82, 7.46)	4.13 (-0.13, 8.39)
T2-w FSE	2.30 (-2.02, 6.62)	2.11 (-2.12, 6.34)	3.51 (-0.41, 7.42)
T1-w GRE	3.19 (-1.53, 7.48)	2.90 (-1.71, 7.03)	3.93 (0.14, 7.72)

β coefficient represent a 1 unit change of outcome score over 2.7 years for a BML present on each sequence type compared to no BML on that sequence type.
Multivariable 1 – adjusted for age, sex, and BMI
Multivariable 2 – further adjusted for presence of radiographic osteoarthritis and baseline WOMAC score
Bold denotes a statistically significant result
CI, confidence interval

Table 4. Log-binomial regression of worsening between site-specific cartilage defects over 2.7 years on site-specific presence of BMLs on T2-w FSE, T1-w GRE, and both MRI.

	Multivariable RR (95% CI)		
	T1 and T2	T2-w FSE	T1-w GRE
Medial Tibial	1.66 (0.91, 3.00)	1.40 (0.78, 2.50)	1.59 (0.88, 2.88)
Medial Femoral	**2.51 (1.66, 3.79)**	**2.38 (1.58 , 3.59)**	**2.50 (1.65 , 3.78)**
Lateral Tibial	**2.40 (1.52, 3.79)**	**2.49 (1.59, 3.89)**	**2.27 (1.44, 3.58)**
Lateral Femoral	**4.63 (3.14, 6.84)**	**4.46 (3.02 , 6.6)**	**4.37 (2.96 , 6.46)**
Superior patellar	**2.28 (1.52, 3.41)**	**2.13 (1.42, 3.21)**	**2.25 (1.53, 3.30)**
Inferior patellar	1.37 (0.82, 2.29)	1.46 (0.91, 2.34)	1.26 (0.79, 2.01)
Medial Tibiofemoral	**1.67 (1.26, 2.22)**	**1.51 (1.14, 2.00)**	**1.60 (1.21, 2.13)**
Lateral Tibiofemoral	**1.79 (1.35, 2.39)**	**1.79 (1.35, 2.39)**	**1.73 (1.30, 2.31)**
Total Tibiofemoral	**1.32 (1.08, 1.62)**	**1.26 (1.03, 1.54)**	**1.32 (1.08, 1.62)**
Total †	**1.29 (1.08, 1.54)**	**1.25 (1.05, 1.48)**	**1.22 (1.04, 1.44)**

RR represents the risk of having a site-specific cartilage defect increase in those with a BML on each sequence type compared to no BML on that sequence type.
Multivariable – adjusted for age, sex, BMI, and baseline cartilage defects score
†total of all site-specific cartilage defects
Bold denotes a statistically significant result
RR, relative risk; CI, confidence interval

Table 5. Mixed-effects model regression point estimates of mean change in site-specific cartilage volume loss over 2.7 years for site-specific BMLs present on T2-w FSE, T1-w GRE, and both T1 and T2, compared to the reference group with no BMLs.

	Multivariable β coefficient (95% CI)		
	T1 & T2	T2-w FSE	T1-w GRE
Medial tibial	-28.35 (-134.43, 77.73)	11.44 (-87.32, 110.19)	-38.55 (-142.61, 65.51)
Medial femoral	-95.90 (-192.67, 0.86)	**-106.21 (-197.34, -15.08)**	-89.58 (-186.69, 7.53)
Lateral tibial	**-148.30 (-229.72, -66.89)**	**-149.23 (-229.99, -68.47)**	**-140.67 (-221.41, -59.92)**
Lateral femoral	-23.91 (-96.98, 49.17)	-30.54 (-102.07, 40.98)	-19.97 (-91.86, 51.92)
Superior patellar	**-174.77 (-314.79, -34.75)**	**-169.69 (-306.42, -32.96)**	**-144.39 (-278.99, -9.80)**
Inferior patellar	-55.41 (-216.47, 105.65)	-42.76 (-196.66, 111.14)	-32.22 (-177.42, 112.98)
Medial tibiofemoral	-35.10 (-161.52, 91.31)	-37.33 (-156.59, 81.93)	-29.49 (-152.52, 93.54)
Lateral tibiofemoral	**-103.96 (-197.31, -10.60)**	**-110.81 (-202.86, -18.77)**	-91.19 (-183.57, 1.20)
Total tibiofemoral	-78.40 (-227.35, 70.56)	-106.93 (-251.49, 37.63)	-26.99 (-169.58, 115.59)
Total †	-131.01 (-303.72, 41.69)	-115.74 (-277.84, 46.37)	-76.22 (-236.48, 84.05)

β coefficient represents 1mm^3 change in cartilage volume over 2.7 years for a BML present on each sequence type compared to no BML on that sequence type.
Multivariable 1 – adjusted for age, sex, and BMI
† total of all site-specific cartilage volume loss
Bold denotes a statistically significant result
CI, confidence

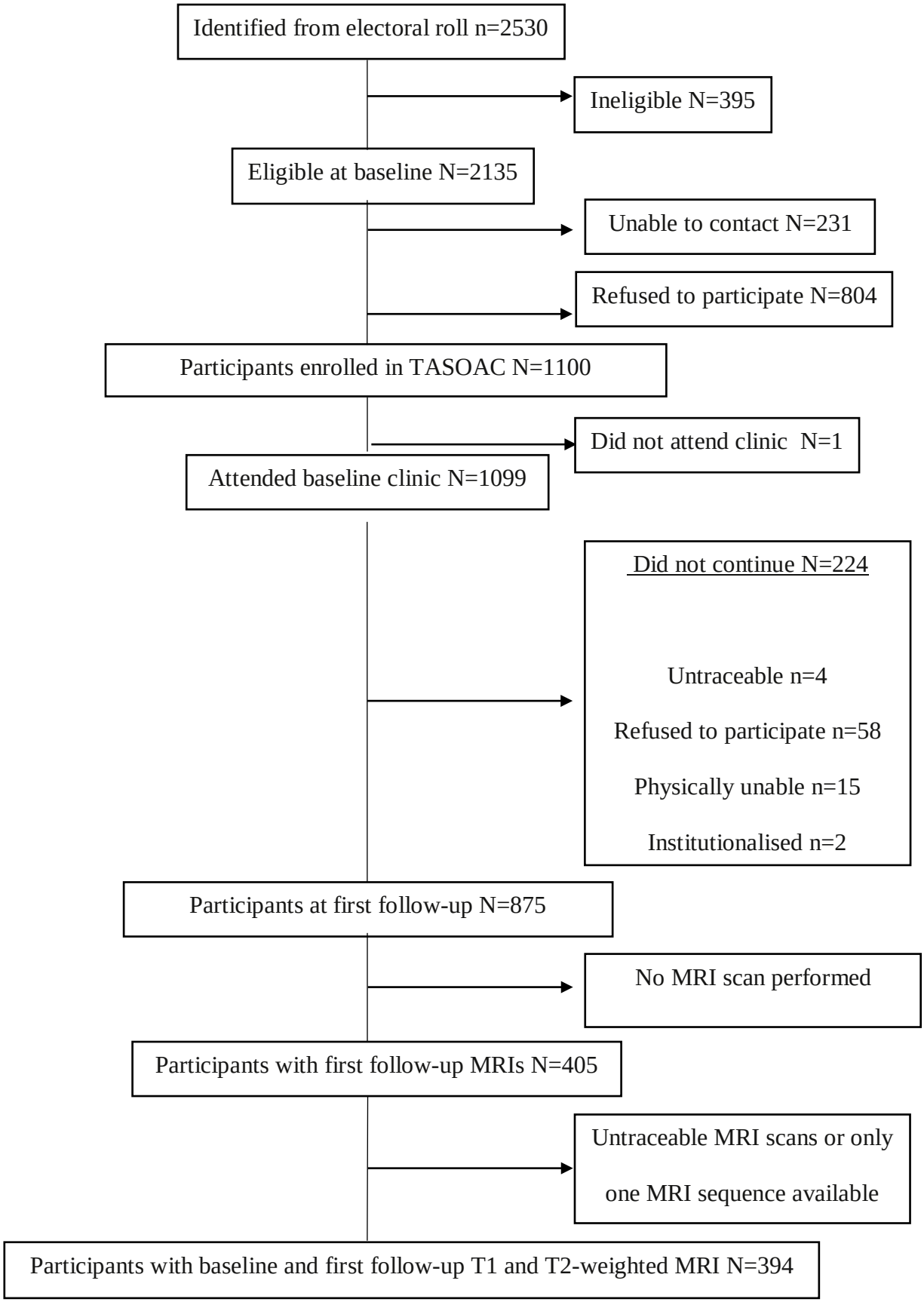

Figure 1. Flowchart of study participants

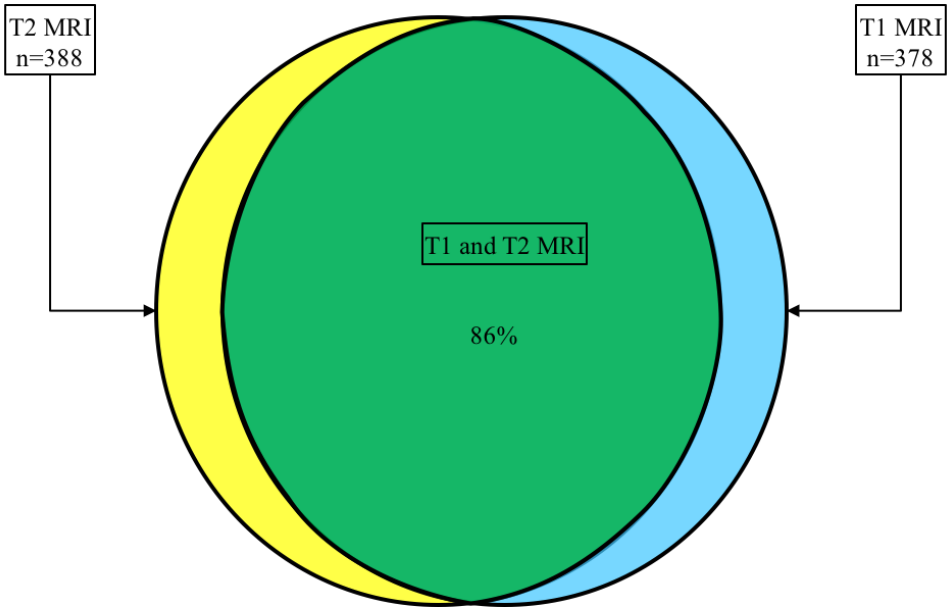

Figure 2. Venn diagram of BML distribution. Yellow circle represents the BMLs on T2-w FSE, blue circle represents the BMLs on T1-w GRE, and the green overlapping area represents the BMLs present on both sequences.

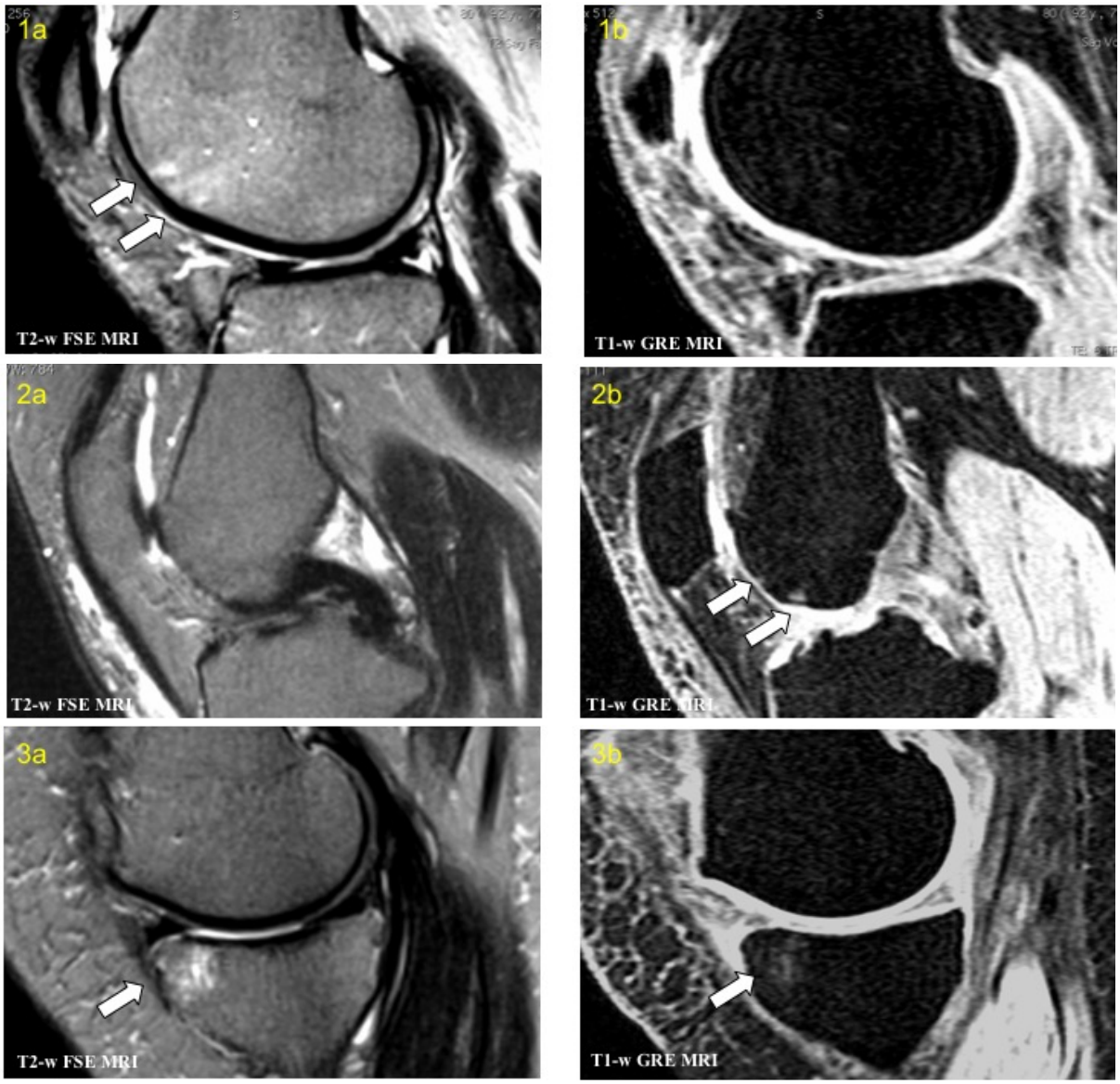

Figure 3. BMLs are indicated by white arrows. 1a and 1b: BMLs present on T2-w FSE but not on T1-w GRE. 2a and 2B: BMLs present on T1-w GRE but not on T2-w FSE. 3a and 3b: BMLs present on both MRIs sequences.

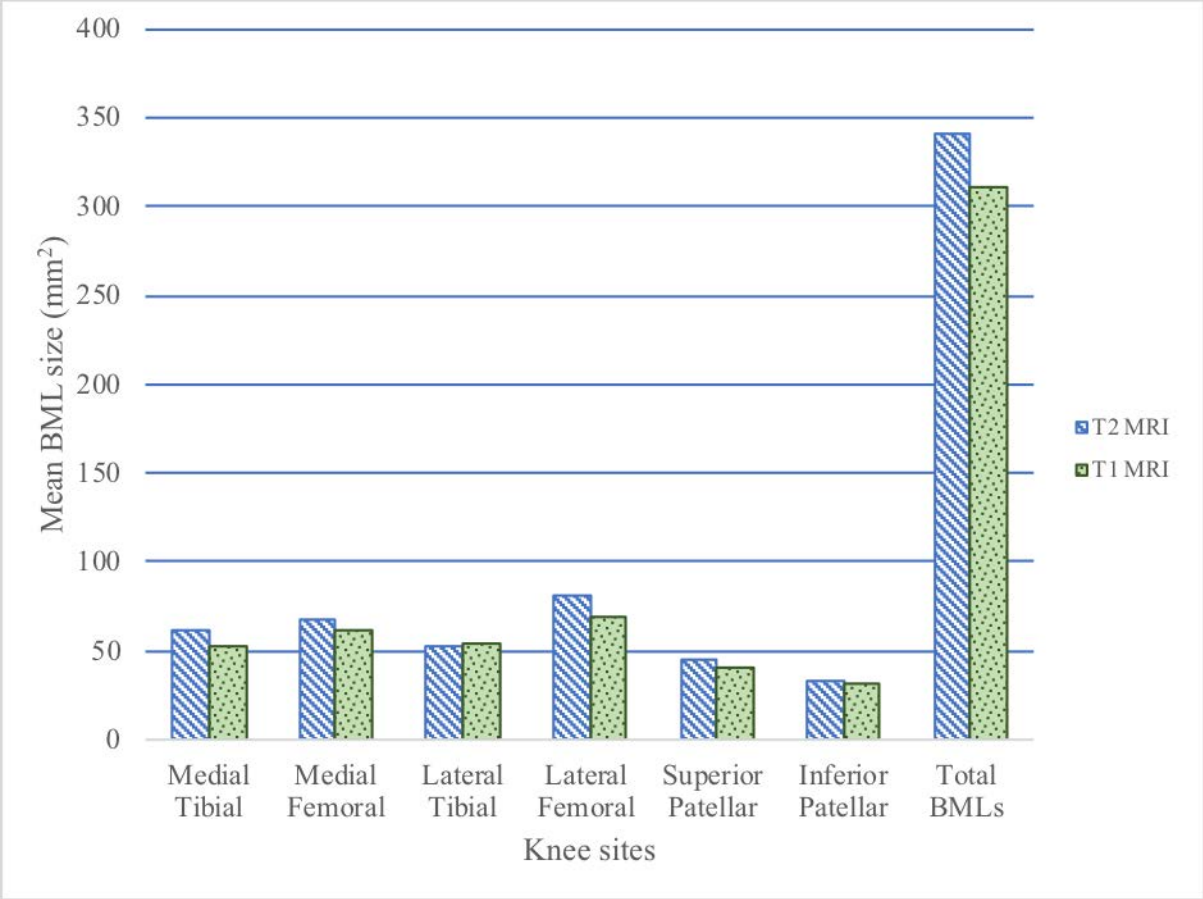

Figure 4. Mean BML size (mm^2) at each knee site on T2-w FSE and T1-w GRE.