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**The acutely ACL injured knee assessed by MRI: Are large volume traumatic bone marrow lesions a sign of severe compression injury?**

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## **Abstract**

**OBJECTIVES:** To map by MRI and qMRI concomitant fractures and meniscal injuries, and location and volume of traumatic bone marrow lesions (BML) in the acutely anterior cruciate ligament (ACL) injured knee. To relate BML location and volume to cortical depression fractures, meniscal injuries and patient characteristics.

**METHODS:** 121 subjects (26% women, mean age 26 years) with an ACL rupture to a previously un-injured knee were studied using a 1.5T MR imager within 3 weeks from trauma. Meniscal injuries and fractures were classified by type, size and location. BML location and volume was quantified using a multi-spectral image data set analyzed by computer software, edited by an expert radiologist.

**RESULTS:** Fractures were found in 73 (60%) knees. In 67 (92%) of these knees at least one cortical depression fracture was found. Uni-compartmental meniscal tears were found in 44 (36%) subjects and bi-compartmental in 24 (20%). 119 (98%) knees had at least one BML, all but 4 (97%) located in the lateral compartment. Knees with a cortical depression fracture had larger BML volumes ( $p < 0.001$ ) than knees without a cortical depression fracture, but no associations were found between meniscal tears and BML volume or fractures. Older age at injury was associated with smaller BML volumes ( $p < 0.01$ ).

**CONCLUSION:** A majority of the ACL-injured knees had a cortical depression fracture, which was associated with larger BML volumes. This indicates strong compressive forces to the articular surface and cartilage at the time of injury, which may constitute an additional risk factor for later knee OA development.

**Keywords:** Knee injuries, ACL injuries, Bone marrow lesions, Fractures, Osteoarthritis, Magnetic resonance imaging

**Running title:** ACL injury- a severe compression injury?

**Disclaimers:** Nothing to declare. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Introduction

Anterior cruciate ligament (ACL) injuries are common severe traumatic knee injuries with an annual incidence of at least 81 per 100000 persons aged between 10 and 64 years <sup>1</sup>. Rupture of the ACL, isolated or combined with meniscal or collateral ligament injury, leads to radiological changes of osteoarthritis (OA) in 50 to 70 % of the patients at 10-15 years after the injury <sup>2-6</sup>. Joint instability, altered loading patterns, presence of associated meniscal lesions and a continued high activity level after injury have been suggested to be risk factors for knee OA development. It was proposed that the acute joint trauma contributes to the development of post-traumatic knee OA, together with chronic abnormal loading following ACL injury <sup>2, 3, 7</sup>.

The injury mechanism for an ACL tear is complex. Even with a thorough video analysis of ACL injuries it was difficult to identify mechanisms of injury <sup>8</sup>. Based on patient recollection after an ACL injury, contact sports such as soccer and handball were associated with increased weight bearing (i.e. compression injury). Downhill skiing was more frequently associated with non-weight bearing injuries, (i.e. distraction injury) <sup>9</sup>. It was also suggested that increased weight-bearing at injury was associated with bi-compartmental meniscal lesions <sup>9</sup>.

The growing use of MRI has revealed traumatic bone marrow lesions (BML), also referred to as 'bone bruises', in the acute phase of a knee injury where the distribution of BML was suggested to represent a footprint of the injury mechanism <sup>10-13</sup>. A larger force is needed to displace the knee, and thereby cause an ACL injury, when an axial weight bearing load is applied to the joint <sup>8</sup>. The overlying cartilage, affected by traumatic compression, showed cell death and chondrocyte senescence <sup>14-18</sup>. Animal models showed that cell death



occurs in the impacted cartilage, spreading in depth and width with increasing stress forces<sup>18-20</sup>. Thus, it is likely that the cartilage, sub-chondral bone and bone marrow would be more severely affected by an injury involving strong compressive forces. The role of such traumatic compression forces in the ACL injured knee as a possible risk factor for knee OA development has not been previously assessed in clinical studies.

In this study we assessed subjects with a less than 5 weeks old ACL tear. Using MRI and qMRI, we mapped fractures and meniscal injuries, and the location and volume of traumatic bone marrow lesions (BML). We also related BML location and volume to cortical depression fractures, meniscal injuries and patient characteristics.

## **Subjects and methods**

### *Subjects*

In a randomized controlled trial (ISRCTN 84752559, <http://www.controlled-trials.com>) comparing surgical and non-surgical treatment of acute ACL injuries, we included 121 subjects (32 women) with an acute ACL injury in a previously uninjured knee <sup>21</sup>(Table 1). In the present report we assessed baseline data of all included subjects; the outcome of the RCT will be presented separately. The study was approved by the ethics committee of Lund University (LU-535).

An increased antero-posterior (A-P) laxity (Lachmann grade 2-3) at a clinical examination in the acute phase, confirmed by a complete ACL rupture as visualized on MRI was used to diagnose the ACL rupture. In conformity with inclusion/exclusion criteria for the RCT, subjects with an associated total rupture of the medial or lateral collateral ligament and/or an unstable meniscal tear treated with fixation using more than one Biofix® arrow were excluded <sup>21</sup>.

### *Assessment tools*

Demographic data, activity at injury and self-reported activity level according to the Tegner scale <sup>22</sup> was collected at the first clinical visit <sup>21</sup>. Activity at injury was classified into contact and non-contact sports <sup>9</sup> (Table 1).

### *MRI*

MRI was performed within a mean of 19 (SD 6.5) days after injury using a 1.5 T imager (Gyrosan Intera, Philips) with a circular polarized surface coil. The MRI scans consisted of sagittal 3D Water excitation FLASH with TR/TE/flip angle of 20ms/7.9ms/25 degree, sagittal

T2\* weighted 3D GRE with TR/TE/flip angle of 20ms/15ms/50 degree. Both series were acquired with 15 cm FOV, 1.5mm slice thickness, and 0.29mm x 0.29mm pixel size. In addition, sagittal and coronal Dual Echo Turbo Spin Echo (DETSE), both with TR/TE of 2900ms/15ms, 80ms, 15cm FOV, 3mm slice thickness with 0.6mm gap and 0.59 x 0.59mm pixel size and sagittal and coronal Short Tau Inversion Recovery (STIR) with TR/TE/TI of 2900ms/15ms/160ms, 15cm FOV, 3mm slice thickness with 0.6mm gap and 0.29mmx0.29mm pixel size were acquired.

#### *Evaluation of MR images*

MR images were re-reviewed for meniscal injuries and fractures after patient inclusion in the RCT. One radiologist (TB), with 15 years experience of knee MRI, registered and classified meniscal injuries and fractures blinded from other radiological, clinical and surgical information (Table 2).

Meniscal injuries were classified and a meniscal tear was defined as increased signal extending to at least one articular surface of the meniscal body (grade 3-4 according to this classification)<sup>23</sup>. Meniscal tears limited to either the medial or lateral meniscus were categorized as uni-compartmental and tears in both the medial and lateral menisci were categorized as bi-compartmental.

Fractures were categorized into: trabecular fracture; cortical depression fracture with or without cortical discontinuity; avulsion fracture. A trabecular fracture was defined as a line with low signal and parallel to the cortex, visualized on the DETSE sequences, and combined with a surrounding traumatic BML visualized on the STIR sequences indicating trabecular compression injury. A cortical depression fracture was defined as a trabecular fracture combined with depressed cortical bone, with or without cortical discontinuity (Figure 1). An

avulsion fracture was defined as a disruption of cortical bone without signs of depression where the avulsed fragment was dislocated. The largest depth and width of the cortical depression and/or the largest diameter of the avulsed fragment was measured and registered. The appearance of cortical depression fractures in lateral femur (Fig. 1) and lateral tibia (Fig. 2) are presented, as well as an example of a knee classified as having no fracture (Fig. 3). In the data analyses, knees affected by at least one cortical depression fracture, regardless of size and cortical continuity, were classified as knees with cortical depression fractures and considered as exposed to a strong compressive trauma.

#### *Quantitative assessment of MR images (qMRI)*

Quantification of BML was done using a combination of image analysis techniques. First, the 3D sagittal MRI data sets were fused into a dual pulse sequence MRI dataset. Secondly, the dual sequence was automatically segmented by a proprietary computer algorithm separating all individual regions with unique signal and tissue boundaries conditions (VirtualScopics Inc., 500 Linden Oaks, Rochester, NY 14625, USA)<sup>24</sup>. The automated segmentation was inspected and edited by expert technicians who identified the regions belonging to the femur, tibia and patella. Once the bone structures were identified and labeled, an unsupervised cartilage extraction algorithm was used to extract cartilage tissue which was edited and inspected for accuracy<sup>25</sup>. Segmentation of BML used a similar approach as for a previous study<sup>26</sup>. Here BML quantification was done by mapping the segmented bones and cartilage tissues into a three band composite data set composed of the two sagittal images from the dual echo and the inversion recovery MRI data set from the STIR acquisition. Furthermore, the dual echo data was used to compute the T2 values for each voxel in the image. Once the segmentation was mapped into the composite set, a computer algorithm identified all the voxels in the data set that had a large T2 value compared to bone marrow's T2, and all the

voxels that had a hyper-intense STIR signal inside the bone tissue. Highlighted voxels were presented to an expert radiologist assigning the regional tissue labels to those voxels. Any highlighted voxels not assigned to a specific BML location were considered as false positive identifications. The expert radiologist also had the ability to correct false negatives by the use of a trace tool and match filter tool. The trace tool allowed the user to freely change the voxel by voxel classification from bone tissue to BML. The match filters tools was an algorithm based approach identifying bone voxel points sharing the same signal profile as the radiologist supplied sample. Once this last step was finished by the radiologist, the classifications of bone voxels into BML entered a computer algorithm and the volume of BML inside of each ROI was aggregated and reported.

To assess reproducibility of the method 28 scans were randomly selected for a re-analysis using the procedure described above. One image pair had a more than 2.5 times larger BML volume compared to the pair of second largest BML volume and was thus removed from the analysis. Further, almost 50% of the pairs were found to have zero BML volumes at both assessments. These pairs were all removed from the analysis since they could falsely affect the reproducibility in favour of our method. After these adjustments, we found large correlations for all regions where the mean Intra Class Correlation (ICC) for all regions was 0.923.

### *Regions of interest (ROI)*

Regions of the knee were reported in conformity with a proposal for nomenclature in MRI studies of knee OA <sup>27</sup>. BML volumes were provided as described above for: lateral tibia (LT), medial tibia (MT), lateral femur, medial femur, lateral trochlea femur, medial trochlea femur, patellar crista, patella lateral facet, patella medial facet. We aggregated BML volumes for the lateral femur and the lateral trochlea femur into the lateral femoral condyle (LF), the medial

femur and medial trochlea femur into the medial femoral condyle (MF) and patella crista, lateral and medial facet into patella (P). Furthermore, BML volumes for LF and MF were summarized into femur (F) and BML volumes for LT and MT into tibia (T). BML volumes of the total knee (K) were summarized by adding BML volumes of T, F and P. Additionally, LF and LT were summarized to form the lateral compartment and MF and MT to form the medial compartment.

### *Statistics*

Descriptive data were reported as mean (SD) for all continuous variables. The Tegner scale was reported as median (range). BML volumes were not normally distributed for any region and thus data were presented as median (25<sup>th</sup>, 75<sup>th</sup> percentile). Between-group analysis was made using the Mann-Whitney U-test except for age where comparisons were made using one-way ANOVA. The Spearman coefficient of correlation ( $r_s$ ) was used for analysis of correlation between variables. To study independent associations General Linear Models were used where BML volume for separate regions of the knee joint was set as the dependent variable. Residual plots were visually analyzed to control the accuracy of assumptions of each model. Self-reported Tegner scores were related to the classification of activity at injury ( $p < 0.001$ ) and thus only the classification of activity at injury (i.e. contact vs. non-contact sports) was used in the analyses.

## Results

### *Meniscal injuries and fractures*

Eighty six fractures were found in 73 knees. Sixty one (84%) of these knees had one fracture, 11 (15%) had two separate fractures and 1 knee had three separate fractures. These fractures were mainly seen in the lateral compartment where cortical discontinuity was noted in 3/41 fractures in the lateral femoral condyle and 33/39 fractures in the lateral tibial condyle (Table 2). Sixty nine (57%) of all knees suffered from at least one cortical depression fracture, regardless of location and cortical discontinuity and were thus grouped for further analyses (Fig. 4). Furthermore, we found increased signal within at least one meniscal body in 82 (68%) of the knees. A meniscal tear, as defined in this study, was more frequent in the lateral meniscus compared to the medial meniscus (55 vs. 37), table 2. Forty four (36%) subjects had a uni-compartmental tear, 31/44 in the lateral meniscus, and 24 (20%) had bi-compartmental meniscal tears. There was no correlation between the presence of uni- or bi-compartmental meniscal tears and cortical depression fractures ( $r_s=0.02$ ,  $p=0.840$ ).

### *BML location and volume*

All but two knees (98%) had at least one BML as detected by the qMRI method. Tibia was affected in 117 (97%) knees, femur in 109 (90%) and patella in 14 (12%) knees. The patella was only affected by small BML volumes, median 0 (25<sup>th</sup>, 75<sup>th</sup> percentile 0.007-2.5) cm<sup>3</sup>, and no further analyses were made for this region. All but 4 knees (97%) had BMLs within the lateral compartment (i.e. femur and tibia laterally). The median BML volume of the total knee was 19.8 cm<sup>3</sup>, where 75% of the volume (14.8 cm<sup>3</sup>) was located within the lateral compartment (Table 3).

*BML in relation to meniscal injuries, fractures and patient characteristics*

Univariate analyses showed no associations between meniscal injury and BML volume ( $p > 0.555$  for all regions) and this variable was thus excluded from further analyses. However, knees with a cortical depression fracture had larger BML volumes, statistically significant for all regions except for patella and medial femur (Table 3).

In separate multivariate models, BML volume for each region was set as the dependent variable and age, sex, activity at injury (contact sports/non-contact sports), time between injury and MRI scan (days) and cortical depression fracture (yes/no) were set as independent variables. After adjustment for these variables, knees with cortical depression fractures were associated with larger BML volumes in all regions of the knee. In addition, age was inversely related to BML volume, especially in the femur (Table 4).



## DISCUSSION

We have shown that more than every second ACL injured knee (57%) had a cortical depression fracture, showing evidence of strong compressive forces to the cartilage and subchondral bone. These knees also had significantly larger BML volumes, suggesting that traumatic BMLs could be associated with compressive forces to the articular surface at the time of injury.

Ninety percent of all fractures were cortical depression fractures, with or without a cortical discontinuity, mainly located in the lateral femoral condyle or the lateral tibial condyle (Figure 2). Cortical discontinuity was rare in the lateral femur (7%) but frequently seen in the lateral tibia (85%), suggesting differences in compression forces or strength of cortical bone between these regions. A Segond fracture, also known as lateral tibial rim fracture, was suggested to be frequently associated with acute ACL tears<sup>28</sup>. However, we found no such fractures in this study. Possibly, a Segond fracture does not appear clearly on MR images or maybe these fractures are infrequent events. Reports on other types of fractures in the acutely ACL injured knee are rare, most likely because they do not show at arthroscopic evaluation or radiographs and rarely influence treatment. However, case-reports have presented a deep lateral notch sign, similar to a cortical depression fracture<sup>29,30</sup>. We have found no study presenting the frequency, location and size of these fractures in a population with acute ACL injuries, or their relation with BML.

Normal signal within the menisci was equally frequent medially and laterally (59 vs. 63), although meniscal tears were more frequently seen in the lateral meniscus in conformity with earlier arthroscopy reports<sup>31,32</sup>. However, using BML volume and/or cortical depression fracture as a proxy for weight bearing at injury we failed to confirm a previous suggestion that

weight bearing at injury was associated with a higher frequency of bi-compartmental meniscal injuries than non-weight bearing at injury <sup>9</sup>.

To our knowledge, this is the first report on traumatic BML using a quantitative MRI method. The occurrence of BMLs in traumatized knees is well described, and suggested to represent a footprint of the injury mechanism <sup>10-13</sup>. Assessed by radiologists, some 80% of acutely ACL injured knees have been reported to show BMLs, mainly located in the lateral compartment <sup>33, 34</sup>. Our results are in agreement with these publications, although we show that fully 98% of the knees had BML, and 97% had BML in the lateral compartment. Thus, it is likely that our method is more sensitive than those used earlier. We found large variations of BML volume, both between subjects and between locations, suggesting differences in trauma mechanisms. However, we found no relationship between BML volume and activity at injury, suggesting that activity at injury does not necessarily reflect the injury mechanism.

Our results show a strong independent relationship between the presence of a cortical depression fracture and BML volume. Micro-fractures of cancellous bone, sub-chondral lesions, edema, bleeding in the fatty marrow and osteocyte necrosis were previously observed in areas affected by traumatic BML <sup>14,35</sup>. An animal study confirmed the presence of substantial hemorrhage and edema in the marrow spaces but found no evidence of trabecular fracture or fibrosis <sup>36</sup>. Our findings support the presence of trabecular and cortical fractures in large BML volumes as visualized on MRI. We found that 10 years of older age was related to 7 cm<sup>3</sup> smaller BML volume within the knee, representing 35% of the median BML volume for all subjects in this study. However, subjects younger than 18 and older than 35 years were excluded from this study and thus we do not know if these findings are applicable outside this age range. Possibly, participation in sports becomes less violent with increasing age or there

could be age-related structural changes in the bone marrow or subchondral bone influencing the size of BML. On the basis of our results, we suggest that large BML volumes could be an indicator of strong compressive forces to the articular surface and the sub-chondral bone.

Using MRI, we have here assessed subjects with an acute ACL injury in a previously uninjured knee within a mean of 19 days after injury. The short term development of traumatic BML (i.e. within weeks from injury) is not known and some degree of restitution could have occurred within this time. However, time from injury to MRI assessment was not related to BML volume, suggesting that major restitution within 3-4 weeks was unlikely. BMLs were also found to be associated with knee osteoarthritis (OA)<sup>37-39</sup>. BMLs reported here were however unlikely to be associated with OA, as subjects in this study had a mean age of 25 years and none had OA changes or full thickness cartilage lesions as visualized on MRI.

There are some limitations to this study. First, subjects with a total collateral ligament rupture were excluded and thus we do not know if a total collateral ligament rupture would protect the articular surface from compression forces or not. Second, this is the first report of cortical depression fractures associated with ACL injury and the classification of these fractures may thus be further refined in the future. All MRI images were re-reviewed by a well experienced radiologist with regard to fractures and meniscal injuries. However, no formal assessment of intra- or interobserver reproducibility of fracture-related features was performed.

Acute knee injury was shown to be a risk factor for knee OA development and subjects with an ACL injured knee are at high risk of developing knee OA regardless of treatment<sup>2, 3, 5-7, 40</sup>. Histological analysis of cartilage taken from human knees in the area of traumatic BML after ACL injury reported degeneration of chondrocytes and loss of proteoglycans within the

impacted cartilage<sup>14</sup>. In laboratory studies, contusions or compression forces were shown to cause both cell death and cell proliferation in the cartilage<sup>17, 41</sup>. Several animal and in vitro studies of human cartilage have confirmed that compressive impact forces result in chondrocyte death and decreased levels of proteoglycan and type II collagen, increasing in depth and width with increasing stress<sup>18-20, 42-45</sup>. These findings are consistent with reports assessing human synovial fluid from traumatically injured knees<sup>46, 47</sup>, and gadolinium enhanced MRI showing joint cartilage glycosaminoglycan loss in areas corresponding to traumatic BML<sup>48</sup>. We suggest that cortical depression fractures and large BML volumes, likely to be hallmarks of strong compressive forces, indicate severe injury to the cartilage and subchondral bone after ACL injury and may represent risk factors for OA development in the ACL injured knee. Thus, the increased risk of knee OA after ACL injury might in part be dependent on the initial trauma as a contributing cause, explaining the lacking success of surgical intervention in reducing OA<sup>2, 7, 49</sup>. Continued monitoring of these patients will be needed to assess the short- and long term consequences of the observed depression fractures and BML with regard to development of OA and symptoms.

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## FIGURE LEGENDS

Figure 1. A cortical depression fracture, as visualized on MRI, located in the lateral femoral condyle in one of the knees assessed in this study (study id: KA1168). A line with low signal and parallel to a depressed cortex indicating trabecular fracture (arrow) as visualized on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left) surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right). On both images the depressed cortex without cortical discontinuity is visualized.

Figure 2. A cortical depression fracture, as visualized on MRI, located in the lateral tibial condyle in one of the knees assessed in this study (study id: KA1086). A line with low signal and parallel to a depressed cortex indicating trabecular fracture as well as a clear impression of the cortical bone (arrow) as visualized on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left) surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right). On both images the depressed cortex without cortical discontinuity is visualized.

Figure 3. A knee classified as not having any fracture as visualized on MRI (study id: KA1096). A cortical depression of the lateral femoral condyle is noted on the proton density weighted image of the dual echo turbo spin echo (DETSE) sequence (left), surrounded by BML as visualized on one image of the short tau inversion recovery (STIR) sequence (right), but not associated with any sign of trabecular fracture (black arrow). Posterior in the lateral tibial condyle, a straight cortical line without signs of depressions and/or trabecular fracture (white arrow) are noted on both the DETSE (left) and STIR (right) sequences although this area is surrounded by BML as visualized on the STIR sequence (right).

Figure 4. The distribution and frequency of cortical depression fractures presented in this study (n=78). Frontal view (left) and sagittal view (right).

Table 1. Age, activity level, activity at injury and elapsed time between injury and MRI assessment for all subjects in this study (N=121).

	Men (n=89)	Women (n=32)	p- value
Age, Mean (SD)	25.8 (4.9)	25.2 (5.0)	0.569
Tegner activity level, Median (Range)	9 (5-9)	8 (5-9)	0.001
Activity at injury			0.118
Contact Sports (%)	73 (82)	22 (69)	
Soccer	64	13	
Handball	2	6	
Floorball	6	3	
Ice hockey	1	0	
Non-contact sports (%)	16 (18)	10 (31)	
Motor sport	5	1	
Skiing	8	8	
Volleyball	2	0	
Other	1	1	
Days from injury to MRI, Mean (SD)	19 (6.6)	20 (6.4)	0.506

Table 2. Meniscal injuries and fractures as visualized by MRI for all subjects in this study (N=121).

	Number n (%)	Depth mm (range)	Width mm (range)
<b>No fracture</b>	48 (40)		
<b>Fractures*</b>			
Trabecular	4 (3)	0	10 (6-13)
LF	3		
MT	1		
Depression without cortical discontinuity	41 (34)	1.5 (1-3)	12.6 (4-25)
LF	35		
LT	6		
Depression with cortical discontinuity	38 (31)	1.9 (1-4)	12.7 (6-20)
LF	3		
LT	33		
MT	2		
Avulsion	3 (3)	-	11 (9-12)
LT	2		
MT	1		
<b>Menisci</b>			
Medial meniscus			
Normal signal	59 (50)		
(1) Increased signal – no extension to surface	14 (12)		
(2) Linear signal – no extension to surface	11 (9)		
(3) Increased signal – communicating with surface	35 (29)		
(4) Complex tear – macerated meniscus	2 (2)		
Lateral meniscus			
Normal signal	63 (52)		
(1) Increased signal – no extension to surface	2 (2)		
(2) Linear signal – no extension to surface	1 (1)		
(3) Increased signal – communicating with surface	49 (41)		
(4) Complex tear – macerated meniscus	6 (5)		

\* Twelve knees had more than one fracture

Table 3. BML volume (cm<sup>3</sup>), separated for sub-regions of the knee, as detected by qMRI (N=121). Regions and sub-regions of the knee are reported as proposed<sup>27</sup>. Univariate analysis of BML volume was performed using the Mann-Whitney U-test comparing knees with (yes) and knees without (no) depression fractures.

BML volume (cm <sup>3</sup> ), Median (25 <sup>th</sup> , 75 <sup>th</sup> percentile)				
Location	All N=121	Cortical depression fracture		p-value
		Yes n=69	No n=52	
K	19.8 (13.5, 34.3)	28.5 (16.7, 41.9)	14.6 (8.0, 24.3)	<0.001
F	4.8 (1.2, 11.7)	7.7 (2.0, 17.1)	2.9 (0.4, 7.5)	<0.001
LF	3.8 (0.5, 10.3)	6.7 (1.0, 15.7)	2.3 (0.1, 5.5)	0.001
MF	0.07 (0, 1.1)	0.3 (0, 1.7)	0 (0, 0.8)	0.076
T	14.0 (7.7, 23.0)	17.3 (10.4, 29.6)	10.3 (5.4, 17.2)	<0.001
LT	10.5 (6.0, 15.3)	12.5 (7.8, 17.6)	7.3 (3.6, 12.4)	<0.001
MT	2.6 (0.4, 9.0)	3.2 (0.9, 10.9)	1.4 (0, 5.1)	0.003
Compartment				
Medial	3.7 (0.8, 11.2)	5.2 (1.2, 12.7)	2.3 (0.1, 6.3)	0.004
Lateral	14.8 (10.4, 25.4)	20.4 (13.4, 28.4)	11.9 (7.2, 17.3)	<0.001

K= Knee, F= Femoral condyles, LF= Lateral Femoral condyle, MF= Medial Femoral condyle, T= Tibia, LT= Lateral Tibia, MT= Medial Tibia, Lateral compartment=LF+LT, Medial compartment=MF+MT



Table 4. Factors influencing BML volume (cm<sup>3</sup>) in various locations of the acutely ACL injured knee. Coefficient of determination (R<sup>2</sup>) is given for each model. Analyses were made using linear regression and all variables were adjusted for each other. Regions and sub-regions of the knee are reported as proposed <sup>27</sup>.

Dependent	Age	Cortical depression fracture	Gender	Time from injury to MRI	Activity at injury	R <sup>2</sup> %
	years	yes/no	male/female	days	contact vs. non-contact	
ROI	Regression coefficient $\beta$ (95%CI)					
K	-0.7 (-1.4, -0.02) *	15.7 (9.3, 22.1) ††	-4.4 (-11.6, 2.9)	-0.05 (-0.6, 0.5)	2.5 (-6.1, 11.1)	20
F	-0.7 (-1.0, -0.3) ††	7.9 (4.4, 11.4) ††	-0.9 (-4.9, 3.0)	-0.1 (-0.4, 0.2)	-2.9 (-7.6, 1.8)	24
LF	-0.5 (-0.9, -0.2) †	7.0 (3.8, 10.1) ††	-1.5 (-5.1, 2.0)	-0.06 (-0.3, 0.2)	-3.6 (-7.8, 0.6)	23
MF	-0.2 (-0.3, -0.05) †	0.9 (0.1, 1.9) *	0.6 (-0.4, 1.7)	-0.04 (-0.1, 0.05)	0.7 (-0.5, 2.0)	12
T	-0.05 (-0.5, 0.5)	7.8 (3.4, 12.1) ††	-3.5 (-8.4, 1.5)	0.05 (-0.3, 0.4)	5.5 (-0.3, 11.3)	15
LT	-0.04 (-0.3, 0.2)	5.0 (2.4, 7.6) ††	-0.9 (-3.9, 2.1)	0.2 (-0.03, 0.4)	2.9 (-0.6, 6.5)	18
MT	-0.01 (-0.3, 0.3)	2.8 (0.4, 5.2) *	-2.6 (-5.3, 0.2)	-0.1 (-0.3, 0.07)	2.5 (-0.7, 5.7)	10
Compartment						
Medial	-0.2 (-0.5, 0.1)	3.7 (1.0, 6.4) †	-2.0 (-5.0, 1.1)	-0.2 (-0.4, 0.05)	3.3 (-0.3, 6.8)	10
Lateral	-0.6 (-1.1, -0.05) *	11.9 (7.3, 16.6) ††	-2.4 (-7.7, 2.9)	0.1 (-0.3, 0.5)	-0.7 (-6.9, 5.6)	22

K= Knee, F= Femoral condyles, LF= Lateral Femoral condyle, MF= Medial Femoral condyle, T= Tibia, LT= Lateral Tibia, MT= Medial Tibia, Lateral compartment=LF+LT, Medial compartment=MF+MT

\* p< 0.05

† p≤ 0.01

†† p≤ 0.001







