

# BMC Medical Imaging

## Quantification of Maceration Changes using Post Mortem MRI in Fetuses

--Manuscript Draft--

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	National Institute for Health Research (Senior Research fellow award)	Prof Andrew M Taylor
<b>Abstract:</b>	<p>Background</p> <p>Post mortem imaging is playing an increasingly important role in perinatal autopsy, and correct interpretation of imaging changes is paramount. This is particularly important following intra-uterine fetal death, where there may be fetal maceration. The aim of this study was to investigate whether any changes seen on a whole body fetal post mortem magnetic resonance imaging (PMMR) correspond to maceration at conventional autopsy.</p> <p>Methods: We performed pre-autopsy PMMR in 75 fetuses using a 1.5 Tesla Siemens Avanto MR scanner (Erlangen, Germany). PMMR images were reported blinded to the clinical history and autopsy data using a numerical severity scale (0 = no maceration changes to 2 = severe maceration changes) for 6 different visceral organs (total 12). The degree of maceration at autopsy was categorized according to severity on a numerical scale (1 = no maceration to 4 = severe maceration). We also generated quantitative maps to measure the liver and lung T2.</p> <p>Results: The mean PMMR maceration score correlated well with the autopsy maceration score (<math>R^2=0.93</math>). A PMMR score of <math>\geq 4.5</math> had a sensitivity of 91%, specificity of 64%, for detecting moderate or severe maceration at autopsy. Liver and lung T2 were increased in fetuses with maceration scores of 3-4 in comparison to those with 1-2 (liver <math>p=0.03</math>, lung <math>p=0.02</math>).</p> <p>Conclusions: There was a good correlation between PMMR maceration score and the extent of maceration seen at conventional autopsy. This score may be useful in interpretation of fetal PMMR.</p>	
<b>Corresponding Author:</b>	Paolo Montaldo Imperial College London UNITED KINGDOM	
<b>Corresponding Author Secondary Information:</b>		
<b>Corresponding Author's Institution:</b>	Imperial College London	
<b>Corresponding Author's Secondary Institution:</b>		
<b>First Author:</b>	Paolo Montaldo	
<b>First Author Secondary Information:</b>		
<b>Order of Authors:</b>	Paolo Montaldo Shea Addison Vania Oliveira	

	Peter J Lally
	Andrew M Taylor
	Neil J Sebire
	Sudhin Thayyil
	Owen J Arthurs
<b>Order of Authors Secondary Information:</b>	
<b>Response to Reviewers:</b>	<p>Dear Editor,</p> <p>Thank you for reviewing our manuscript on “Quantification of Maceration Changes using Post Mortem MRI in Fetuses”. We have now revised the manuscript according to the editorial suggestions.</p> <p>Editorial Requests:</p> <p>#1 Authors Contributions:</p> <p>Please add a statement to your author contributions that all authors have read and approved the final version of the manuscript.</p> <p>We have now added the statement to our author contributions. Please see page 13, paragraph 1.</p> <p>“All authors have read and approved the final version of the manuscript”.</p> <p>#2. On uploading your revisions, please remove any tracked changes or highlighting and include only a single clean copy. We have now removed any tracked changes or highlighting and included only a single clean copy.</p>

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4 **Quantification of Maceration Changes using Post Mortem MRI in**  
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7 **Fetuses**

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10 **Running header: PMMR correlation with pathological estimates of maceration**

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12 P Montaldo<sup>1</sup>, S Addison<sup>1</sup>, V Oliveira<sup>1</sup>, P J Lally<sup>1</sup>, AM Taylor<sup>2</sup>, NJ Sebire<sup>2,3</sup>, S Thayyil<sup>1</sup>, OJ  
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14 Arthurs<sup>2,3</sup>  
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17  
18  
19 <sup>1</sup> Centre for Perinatal Neuroscience, Imperial College London, London, UK

20  
21  
22 <sup>2</sup> Institute of Child Health, University College London

23  
24 <sup>3</sup> Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 3JH,  
25  
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34 Correspondence  
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36  
37  
38  
39 Paolo Montaldo

40  
41 Centre for Perinatal Neuroscience, Level 5 Hammersmith House, Department of  
42  
43 Paediatrics, Imperial College London, Du Cane Road, London W12 0HS

44  
45  
46 E mail: p.montaldo@imperial.ac.uk , Tel: (44) 203 313 8515  
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4 **Abstract**  
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9 ***Background***  
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14 Post mortem imaging is playing an increasingly important role in perinatal autopsy, and  
15 correct interpretation of imaging changes is paramount. This is particularly important  
16 following intra-uterine fetal death, where there may be fetal maceration. The aim of this  
17 study was to investigate whether any changes seen on a whole body fetal post mortem  
18 magnetic resonance imaging (PMMR) correspond to maceration at conventional autopsy.  
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28 ***Methods:*** We performed pre-autopsy PMMR in 75 fetuses using a 1.5 Tesla Siemens  
29 Avanto MR scanner (Erlangen, Germany). PMMR images were reported blinded to the  
30 clinical history and autopsy data using a numerical severity scale (0 = no maceration  
31 changes to 2 = severe maceration changes) for 6 different visceral organs (total 12). The  
32 degree of maceration at autopsy was categorized according to severity on a numerical  
33 scale (1 = no maceration to 4 = severe maceration). We also generated quantitative maps  
34 to measure the liver and lung T<sub>2</sub>.  
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48 ***Results:*** The mean PMMR maceration score correlated well with the autopsy maceration  
49 score (R<sup>2</sup>=0.93). A PMMR score of  $\geq 4.5$  had a sensitivity of 91%, specificity of 64%, for  
50 detecting moderate or severe maceration at autopsy. Liver and lung T<sub>2</sub> were increased in  
51 fetuses with maceration scores of 3-4 in comparison to those with 1-2 (liver p=0.03, lung  
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**Conclusions:** There was a good correlation between PMMR maceration score and the extent of maceration seen at conventional autopsy. This score may be useful in interpretation of fetal PMMR.

**Key words:** MRI, Autopsy, Pathology, Fetuses, Maceration, Intrauterine death

## Background

Post mortem magnetic resonance imaging (PMMR) is increasingly used as an alternative to conventional perinatal autopsy.[1-3] PMMR along with additional minimally invasive investigations, is now considered as accurate as conventional autopsy and is particularly useful for cerebral, cardiac and abdominal imaging.[4-7] For these reasons, PMMR is now more increasingly offered worldwide to parents who refuse conventional autopsy.[8] Unlike conventional autopsy, PM MRI provides an interactive visualization and permanent archiving of three-dimensional data sets of internal organs.[9] Furthermore, internal organ volumes can be accurately estimated from the MRI data.[10]

However, there are several changes observed on PMMR that are currently interpreted as relating to decomposition of the body, although these are poorly understood.[11] This is further complicated in fetuses, where there may have been a period of maceration prior to the delivery, as well as autolysis following the delivery. Maceration is the process where skin is softened and broken down within a fluid filled cavity, which will occur following fetal death within the amniotic fluid. Autolysis occurs after delivery and is the intracellular enzymatic breakdown of body tissues, although this can be slowed by cooling, refrigeration or even freezing. Both of these processes may have different effects on tissue appearances at autopsy or at post mortem imaging, and it is important to try to differentiate these effects in order to correctly interpret imaging findings.

The criteria for quantifying post-mortem changes and estimating post-mortem interval using conventional autopsy and histopathology are well established. This includes skin slippage, skin and umbilical cord discoloration, cranial collapse, level of mummification on

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4 external examination and loss of nuclear basophilia on histological examination.[12-14]

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6 Whilst these are estimates of intrauterine retention interval, they remain the current gold  
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9 standard.

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11 Understanding such PMMR artifacts is important not only for accurate clinical reporting,  
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13 but also for the estimation of post-mortem interval, which may be of major clinical and  
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15 medicolegal significance, particularly in stillbirth and in forensic cases. As most  
16  
17 miscarriages and stillbirths occur between routine ultrasound scan appointments, which  
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19 occur months apart, pinpointing the exact date of death on a clinical basis can be  
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21 extremely difficult. In cases where PMMR is the initial investigation, information about the  
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23 extent of maceration may inform about the need and/or utility for a full conventional  
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25 autopsy and histopathological examination.  
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31 In this study, we hypothesized that some PMMR indices would correlate with pathological  
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33 estimates of maceration, in particular fluid changes across different body organs.  
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## 38 **Methods**

### 39 ***Study Participants***

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4 March 2007 and September 2011. The study had institutional approval (reference  
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6 04/Q0508/41).[16]  
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### 10 ***Demographic details***

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12 We collected data on the date of birth / delivery, fetal gestation at time of delivery, time  
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14 interval from delivery to MRI (imaging interval), and time interval from delivery to autopsy  
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16 (post mortem interval) from maternal medical records.  
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### 22 ***Imaging technique***

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24 All scans were performed on 1.5 T MR scanner (Avanto, Siemens Medical Solutions,  
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26 Erlangen, Germany) using 3D T2-weighted turbo spin echo (TSE), 3D T1-weighted  
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28 volumetric interpolated breath-hold examination (VIBE) and 3D constructive interference  
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30 in the steady state (CISS).[16] The PMMR was performed as soon as practically possible;  
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32 in most cases, this was 1–7 days after death. All fetuses were kept refrigerated at 4°C  
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34 prior to the MR imaging. In a subset of ten unselected fetuses we performed T2  
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36 relaxometry using an eight-echo turbo spin echo sequence (TR=2400ms,  
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38 TE=44,88,132,176,220,264,308,352ms), with even echo images fitted to a mono-  
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40 exponential decay function in MATLAB. T2 values were generated from the model fit in  
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42 each voxel and used to generate quantitative T2 maps, on which the lungs and liver were  
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44 delineated (Figure 1). Mean T2 values within each region were calculated.  
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### 54 ***Reporting MRI images***

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56 PMMR images were reported by an experienced Paediatric radiologist (OJA) with 7 years  
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58 of experience, using the OsiriX platform (OsiriX Foundation, Geneva, Switzerland),  
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4 masked to the age, gestation, imaging and post mortem interval of each case. Each of six  
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6 body parts was visually scored for the degree of maceration, from 0 (no maceration) to 2  
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8 (severe maceration), giving a maximum total MRI score of 12. The body parts included  
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10 brain (loss of grey/white matter differentiation), presence of subcutaneous oedema,  
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12 pleural effusion, ascites, portal venous gas, and loss of abdominal organ soft tissue  
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14 delineation. The loss of grey/white matter differentiation was based on visual evaluation  
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16 based on prior experience and no atlas was used. A second reporter (neonatologist; ST)  
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18 with 7 years of experience of PMMR also reported 42 cases, in order to give an index of  
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20 inter-observer variability in MR scores.  
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### 31 ***Reporting of autopsy data***

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33 Conventional autopsy was performed in accordance with national guidelines,[17] and  
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35 reported by one of seven experienced perinatal or Paediatric pathologists, masked to the  
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37 PMMR findings. Conventional autopsies were then retrospectively scored by a single  
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39 pathologist (NJS) who had performed some of the conventional autopsies, according to  
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41 the autopsy report and the images taken at the time of autopsy. The autopsy score was  
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43 from 1 to 4 (none, mild, moderate and severe maceration), based on the external  
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45 evaluation of the fetus including skin slippage, skin discoloration and overlapping of the  
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47 skull structures. Each of these scores suggests an approximate time of retention of the  
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49 fetus in utero after death (intrauterine interval).  
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### 57 ***Statistical analysis***

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4 We examined the correlation between PMMR score and autopsy scores of maceration.  
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6 We also correlated T2 values with gestational age using Pearson or Spearman rho test,  
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8 based on the data distribution. We also examined area under the receiver operating  
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10 characteristic curve (AUC) for PMMR scores to detect moderate-severe maceration as  
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12 reported by autopsy (gold standard), and generated diagnostic indices with 95%  
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14 confidence intervals (exact statistics) for the optimal threshold value.[18] The sample was  
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16 divided in two groups: moderate or severe maceration and no or mild maceration at  
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18 autopsy. Mann Whitney U test was used for comparison of distributions between the two  
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20 groups at a  $p < 0.05$  significance level. We used SPSS Statistics 22 (IBM Corp. - U.S.A.)  
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22 for statistical analyses.  
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## 31 **Results**

### 32 ***Demographic data***

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39 PMMR was available for assessment on seventy-five fetuses, including 15 miscarriages  
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41 (gestation <22 weeks) and 60 stillbirths (gestation >22 weeks). Mean gestation age at  
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43 delivery was  $30.5 \pm 8.2$  weeks. Nineteen (25.4%) of the 75 fetuses showed no evidence  
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45 of maceration at autopsy (autopsy score 1), 20 cases (26.6%) had mild maceration  
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47 (autopsy score 2), 24 (32%) had moderate maceration (autopsy score 3), and 12 (16%)  
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49 had severe maceration (autopsy score 4). The median time between MRI and autopsy  
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51 was 1 day (range 0-7).  
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### 58 ***Maceration/autolysis on post-mortem MRI***

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4 A good correlation was seen between the median PMMR maceration score and autopsy  
5 maceration score ( $R^2=0.93$ ). The maceration scores of all internal organs increased with  
6 increasing maceration noted at autopsy. All the fetuses who had a PMMR score 1-2  
7 (moderate-severe maceration) on assessment of brain (loss of grey/white matter  
8 differentiation), subcutaneous oedema, pleural effusion, ascites, portal venous gas or  
9 abdominal organ soft tissue delineation, showed severe maceration at autopsy (score 4).  
10  
11 Presence or absence of portal venous gas did not correlate well with the extent of  
12 maceration (Figure 2). Inter-observer reproducibility was moderate, with mean difference  
13 between repeated imaging scores of  $2.7 \pm 1.8$ .  
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16 Overall, a PMMR score of 4.5 had a sensitivity of 91% (95% Confidence Intervals (CI) –  
17 78 to 97) and a specificity of 64% (95% CI – 48 to 77) for predicting moderate or severe  
18 maceration at conventional autopsy.  
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21 The median PMMR scores for the four different levels of maceration recorded at  
22 conventional autopsy are presented in Figure 3. The median (interquartile range) PMMR  
23 score was significantly higher in cases with moderate or severe maceration at autopsy  
24 (group 3 and 4), as opposed to those who had no or mild maceration at autopsy (7 (5.8 to  
25 8.0) and 4 (2.0 to 5.0) respectively,  $P < 0.001$ ).  
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### 50 ***Postmortem Liver and Lung T<sub>2</sub>***

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52 Liver and lung T<sub>2</sub> were increased in fetuses with maceration scores of 3-4 (median  
53 (IQR): liver 110(20)ms, lung 142(24)ms) in comparison to those with 1-2 (liver 50(4)ms,  
54 lung 82(14)ms; liver  $P=0.03$ , lung  $P=0.02$ ). However, T<sub>2</sub> also correlated inversely to the  
55 gestational age at death (liver  $R^2=0.72$ , lung  $R^2=0.75$ ) (Figure 4).  
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7 **Discussion**  
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12 Our data suggest that PMMR score correlates well with the extent of maceration seen at  
13 autopsy. A PMMR score  $\geq 4.5$  had a high sensitivity for detecting moderate or severe  
14 maceration at autopsy. Furthermore, increasing maceration is associated with the  
15 prolongation of T<sub>2</sub> values in the liver and lungs. These preliminary PMMR findings are  
16 promising for establishing further imaging correlates of autopsy findings.  
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24 In particular, a reduction in the tissue contrast in the brain strongly correlated with the  
25 extent of maceration, but presence of portal venous gas did not. This is in agreement with  
26 a smaller pilot study of 11 fetuses by Victoria et al., who found that that loss of gray-white  
27 matter differentiation in the brain, the presence of pleural effusions and small lung volumes  
28 were suggestive of in utero fetal death at fetal MRI.[19] Appreciating the brain changes  
29 caused by maceration is particularly useful for accurate PMMR reporting, as PMMR has  
30 been shown to provide important clinical and diagnostic information in over 50% of fetuses  
31 where conventional brain autopsy was non-diagnostic due to maceration and autolysis.[6]  
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34 Portal venous gas instead, may better represent resuscitation related air redistribution,  
35 rather than decomposition, as has been shown on PMCT.[20]  
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44 To our knowledge, this is the first preliminary study to assess whether quantitative MR  
45 measurements can be useful to identify the degree of maceration. External features of  
46 maceration are historically better indicators of early rather than late changes of  
47 maceration.[13, 14] Pathological estimates are therefore likely to be less specific at longer  
48 intra-uterine retention intervals (higher maceration scores). Maceration likely reflects a  
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4 combination of cellular breakdown and tissue degradation, leading to changes in tissue  
5 structure and permeability and fluid redistribution throughout body compartments. Our  
6 data suggest that fluid redistribution in both lungs and liver, which occur with moderate-  
7 severe maceration, can be detected at PMMR, although gestational age changes may  
8 also contribute to the T2 signal seen.  
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11 There are limitations to this retrospective study of a small number of PMMR cases,  
12 although all had a full autopsy for comparison. Although our cases covered a broad range  
13 of maceration indices, the extent of maceration and autolysis varies depending of the  
14 exact intrauterine retention period after the fetal demise (which is rarely accurately  
15 obtainable), and storage conditions of the fetus after delivery. Although all fetuses were  
16 rapidly refrigerated after death and during transport, the period between delivery and  
17 refrigeration was not recorded. Furthermore, due to refrigeration, none of our fetuses was  
18 severely decomposed or putrefied, which may account for the low incidence of portal  
19 venous gas in this cohort. This type of imaging score may need modification where the  
20 body has been at room temperature for a prolonged period.  
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## 43 **Conclusion**

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45 The PM MRI maceration score presented in this work correlates well with the extent of  
46 maceration seen at conventional autopsy. This score may be useful in interpretation of  
47 fetal PMMR in future.  
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## 52 **Abbreviations:**

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58 PM post-mortem  
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4 PMMR post-mortem magnetic resonance imaging

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7 AUC Area under the receiver operating characteristic curve

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11 **Ethics approval and consent to participate**

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14 The study was approved by the GOSH-ICH research ethics committee (reference  
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16 04/Q0508/41). Parental consent was obtained for the MRI as stipulated by the ethics  
17  
18 committee. [21]  
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23 **Availability of Data and Materials**

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26 All relevant data supporting our findings are anonymised and stored at Great Ormond  
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28 Street Hospital for Children.  
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35 **Competing interests**

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38 None  
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43 **Authors' contributions**

44  
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48 PM undertook analysis and interpretation of data, drafting of the manuscript, critical  
49  
50 revision of the manuscript, final approval of the submitted manuscript. SA and VO assisted  
51  
52 in data analysis and contributed to writing and editing of the manuscript. PJL undertook  
53  
54 the interpretation of data, final approval of the submitted manuscript. NJS provided input  
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56 into the pathological aspects of the study, contributed to protocol development and writing  
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of the manuscript along with AMT. ST and OJA reported PMR, contributed to the design of the study and editing of the manuscript. All authors have read and approved the final version of the manuscript.

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1  
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4 **REFERENCES**  
5  
6  
7  
8

- 9  
10 1. Breeze AC, Jessop FA, Set PA, Whitehead AL, Cross JJ, Lomas DJ, Hackett GA,  
11 Joubert I, Lees CC: **Minimally-invasive fetal autopsy using magnetic**  
12 **resonance imaging and percutaneous organ biopsies: clinical value and**  
13 **comparison to conventional autopsy.** *Ultrasound in obstetrics & gynecology :*  
14 *the official journal of the International Society of Ultrasound in Obstetrics and*  
15 *Gynecology* 2011, **37**(3):317-323.  
16  
17  
18  
19  
20  
21  
22  
23 2. Thayyil S: **Less invasive autopsy: an evidenced based approach.** *Archives of*  
24 *disease in childhood* 2011, **96**(7):681-687.  
25  
26  
27  
28 3. Weustink AC, Hunink MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW:  
29 **Minimally invasive autopsy: an alternative to conventional autopsy?**  
30 *Radiology* 2009, **250**(3):897-904.  
31  
32  
33  
34  
35 4. Addison S, Arthurs OJ, Thayyil S: **Post-mortem MRI as an alternative to non-**  
36 **forensic autopsy in fetuses and children: from research into clinical**  
37 **practice.** *The British journal of radiology* 2014, **87**(1036):20130621.  
38  
39  
40  
41  
42  
43 5. Arthurs OJ, Thayyil S, Owens CM, Olsen OE, Wade A, Addison S, Jones R,  
44 Norman W, Scott RJ, Robertson NJ *et al*: **Diagnostic accuracy of post mortem**  
45 **MRI for abdominal abnormalities in fetuses and children.** *European journal*  
46 *of radiology* 2014.  
47  
48  
49  
50  
51  
52  
53 6. Arthurs OJ, Thayyil S, Pauliah SS, Jacques TS, Chong WK, Gunny R, Saunders  
54 D, Addison S, Lally P, Cady E *et al*: **Diagnostic accuracy and limitations of**  
55  
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4 **post-mortem MRI for neurological abnormalities in fetuses and children.**

5  
6  
7 *Clin Radiol* 2015, **70**(8):872-880.

- 8  
9 7. Taylor AM, Sebire NJ, Ashworth MT, Schievano S, Scott RJ, Wade A, Chitty LS,  
10 Robertson N, Thayyil S, Magnetic Resonance Imaging Autopsy Study  
11 Collaborative G: **Postmortem cardiovascular magnetic resonance imaging in**  
12 **fetuses and children: a masked comparison study with conventional**  
13 **autopsy.** *Circulation* 2014, **129**(19):1937-1944.  
14  
15  
16  
17  
18  
19  
20  
21 8. Ben-Sasi K, Chitty LS, Franck LS, Thayyil S, Judge-Kronis L, Taylor AM, Sebire  
22 NJ: **Acceptability of a minimally invasive perinatal/paediatric autopsy:**  
23 **healthcare professionals' views and implications for practice.** *Prenatal*  
24 *diagnosis* 2013, **33**(4):307-312.  
25  
26  
27  
28  
29  
30  
31 9. Persson A, Lindblom M, Jackowski C: **A state-of-the-art pipeline for**  
32 **postmortem CT and MRI visualization: from data acquisition to interactive**  
33 **image interpretation at autopsy.** *Acta radiologica (Stockholm, Sweden : 1987)*  
34 2011, **52**(5):522-536.  
35  
36  
37  
38  
39  
40  
41 10. Orasanu E, Melbourne A, Cardoso MJ, Modat M, Taylor AM, Thayyil S, Ourselin  
42 S: **Brain volume estimation from post-mortem newborn and fetal MRI.**  
43 *NeuroImage Clinical* 2014, **6**:438-444.  
44  
45  
46  
47  
48 11. Arthurs OJ, Barber JL, Taylor AM, Sebire NJ: **Normal perinatal and paediatric**  
49 **postmortem magnetic resonance imaging appearances.** *Pediatric radiology*  
50 2015, **45**(4):527-535.  
51  
52  
53  
54  
55 12. Genest DR: **Estimating the time of death in stillborn fetuses: II. Histologic**  
56 **evaluation of the placenta; a study of 71 stillborns.** *Obstetrics and gynecology*  
57 1992, **80**(4):585-592.  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 13. Genest DR, Singer DB: **Estimating the time of death in stillborn fetuses: III.**  
5  
6 **External fetal examination; a study of 86 stillborns.** *Obstetrics and*  
7  
8  
9 *gynecology* 1992, **80**(4):593-600.
- 10  
11 14. Genest DR, Williams MA, Greene MF: **Estimating the time of death in stillborn**  
12  
13 **fetuses: I. Histologic evaluation of fetal organs; an autopsy study of 150**  
14  
15 **stillborns.** *Obstetrics and gynecology* 1992, **80**(4):575-584.
- 16  
17 15. Thayyil S, Sebire NJ, Chitty LS, Wade A, Chong WK, Olsen O, Gunny RS, Offiah  
18  
19 AC, Owens CM, Saunders DE *et al*: **Post-mortem MRI versus conventional**  
20  
21 **autopsy in fetuses and children: a prospective validation study.** *The Lancet*  
22  
23 2013.
- 24  
25 16. Thayyil S, Sebire NJ, Chitty LS, Wade A, Olsen O, Gunny RS, Offiah A, Saunders  
26  
27 DE, Owens CM, Chong WK *et al*: **Post mortem magnetic resonance imaging**  
28  
29 **in the fetus, infant and child: a comparative study with conventional**  
30  
31 **autopsy (MaRIAS Protocol).** *BMC pediatrics* 2011, **11**:120.
- 32  
33 17. **The Royal College of Pathologists and The Royal College of Paediatrics and**  
34  
35 **Child Health. Sudden unexpected death in infancy: a multi-agency protocol**  
36  
37 **for care and investigation.** In.; 2004.
- 38  
39 18. Fluss R, Faraggi D, Reiser B: **Estimation of the Youden Index and its**  
40  
41 **associated cutoff point.** *Biometrical journal Biometrische Zeitschrift* 2005,  
42  
43 **47**(4):458-472.
- 44  
45 19. Victoria T, Capilla E, Chauvin NA, Johnson AM, Kramer SS, Epelman M: **MR**  
46  
47 **evaluation of fetal demise.** *Pediatric radiology* 2011, **41**(7):884-889.
- 48  
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20. Barber J.L KL, Sebire N.J., Arthurs O.J.: **Interpretation of intravascular gas on postmortem CT in children.** *Journal of Forensic Radiology and Imaging* 2015, **3**:174-179.

21. Thayyil S, Robertson NJ, Scales A, Weber MA, Jacques TS, Sebire NJ, Taylor AM, Ma RCG: **Prospective parental consent for autopsy research following sudden unexpected childhood deaths: a successful model.** *Archives of disease in childhood* 2009, **94**(5):354-358.

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4 **FIGURE LEGENDS**  
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9 **Figure 1.** Voxelwise T2 values were generated from the model fit in each voxel and  
10 used to generate quantitative T2 maps, on which the lungs and liver were delineated  
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15 **Figure 2.** Post-mortem MRI maceration scores for individual organ systems compared  
16 with autopsy maceration grade  
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22 **Figure 3.** Median (min, max, Q1 and Q3) of overall post-mortem MRI maceration score  
23 compared with maceration score at autopsy  
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29 **Figure 4.** Correlation of liver and lung T2 with maceration score and gestational age  
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Top Row: Liver T2 variation with maceration score (left) and gestational age at death  
(right).

Bottom Row: Lung T2 variation with maceration score (left) and gestational age at death  
(right).









