

Diagnostic accuracy of post-mortem MRI for thoracic abnormalities in fetuses and children

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Abstract

Objectives To compare the diagnostic accuracy of post-mortem magnetic resonance imaging (PMMR) specifically for non-cardiac thoracic pathology in fetuses and children, compared with conventional autopsy.

Methods Institutional ethics approval and parental consent was obtained. A total of 400 unselected fetuses and children underwent PMMR before conventional autopsy, reported blinded to the other dataset.

Results Of 400 non-cardiac thoracic abnormalities, 113 (28 %) were found at autopsy. Overall sensitivity and specificity (95 % confidence interval) of PMMR for any thoracic pathology was poor at 39.6 % (31.0, 48.9) and 85.5 % (80.7, 89.2) respectively, with positive predictive value (PPV)

53.7 % (42.9, 64.0) and negative predictive value (NPV) 77.0 % (71.8, 81.4). Overall agreement was 71.8 % (67.1, 76.2). PMMR was most sensitive at detecting anatomical abnormalities, including pleural effusions and lung or thoracic hypoplasia, but particularly poor at detecting infection.

Conclusions PMMR currently has relatively poor diagnostic detection rates for the commonest intra-thoracic pathologies identified at autopsy in fetuses and children, including respiratory tract infection and diffuse alveolar haemorrhage. The reasonable NPV suggests that normal thoracic appearances at PMMR exclude the majority of important thoracic lesions at autopsy, and so could be useful in the context of minimally invasive autopsy for detecting non-cardiac thoracic abnormalities.

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Key Points

- *PMMR has relatively poor diagnostic detection rates for common intrathoracic pathology*
- *The moderate NPV suggests that normal PMMR appearances exclude most important abnormalities*
- *Lung sampling at autopsy remains the “gold standard” for pulmonary pathology*

Keywords MRI · Autopsy · Pathology · Fetuses · Children

Introduction

Paediatric and perinatal autopsy rates have declined over recent decades, leading to post-mortem cross-sectional imaging being proposed as a possible alternative or adjunctive approach [1, 2]. Post-mortem magnetic resonance imaging (PMMR), when used in conjunction with other ancillary investigations (collectively known as minimally invasive autopsy [MIA]), has recently been shown to have a high diagnostic accuracy rate for cause of death or main diagnosis compared with traditional autopsy in fetuses, stillbirths and children [3]. Whilst cardiac and neurological diagnoses account for the majority of causes of death in these age groups (12 and 28 % respectively [3]), less is known about how well thoracic pathology can be diagnosed across a range of likely diagnoses, gestational age and childhood age ranges.

A systematic review of post-mortem imaging [4] identified several previous studies [5–8] which had attempted to investigate the accuracy of non-cardiac thoracic diagnosis, and reported a relatively good estimated pooled sensitivity of 82 % (95 % confidence intervals 49, 95 %) and specificity of 86 % (58, 96 %) for lung pathology. However, these studies were not fully blinded between reporting radiologists and pathologists, included highly selected small cohort groups (range, 6–37 subjects), with pooled data from only 73 fetuses and no children, giving wide confidence intervals. Breeze et al. [9] independently reported a 2.5 % sensitivity and 87 % specificity for eight lung lesions in 30 fetuses, when assessed using PMMR, with a reported diagnostic accuracy of 83 %.

The aim of the MARIAS study was specifically to establish the diagnostic utility of less invasive autopsy, using PMMR, compared with traditional autopsy, in an unselected population for the major diagnosis or cause of death. These results have already been published [3]. Here, we use the detailed MARIAS dataset for sub-analysis of the PMMR findings specifically for non-cardiac thoracic abnormalities, irrespective of whether the abnormalities contributed to the main diagnosis or cause of death.

Materials and methods

Study participants

The study design has previously been described in detail [10]. Briefly, we performed pre-autopsy PMMR in an unselected sequential cohort of fetuses and children (up to 16 years), referred for conventional autopsy between March 2007 and September 2011, to Great Ormond Street Hospital for Children and University College Hospital, London. The study had institutional approval (reference 04/Q0508/41), and parental consent was obtained as stipulated by the ethics committee [3]. All fetuses and children (≤ 16 years) undergoing conventional autopsy were eligible for recruitment. PMMR was performed as soon as practically possible. Cases were excluded if consent was not available or if PMMR could not be performed before autopsy. The bodies were stored in a mortuary at 4 °C.

Imaging technique

Post-mortem magnetic resonance imaging (MRIs) were mostly scheduled to be done out of hours (6 pm to 8 am), causing least disturbance to clinical services. All examinations were performed on a 1.5-T MRI scanner (Avanto; Siemens Medical Solutions, Erlangen, Germany) with a conventional phased-array body coil, using whole-body three-dimensional (3D) T₂-weighted turbo spin echo (TSE, TR 3,500 ms, TE 276 ms, voxel size 0.8×0.8×0.8 mm, 2 averages), 3D T₁-weighted volumetric interpolated breath-hold examination (VIBE; TR 5.9 ms, TE 2.4 ms, flip angle 25°, voxel size 0.8×0.8×0.8 mm, 8 averages) and 3D constructive interference in the steady state (CISS) sequence (TR 9.2 ms, TE 4.6 ms, flip angle 70°, voxel size 0.6×0.6×0.6 mm, 4 averages), as published previously [10]. The first 20 cases (total 423) were used for MR sequence optimisation and for imager training.

Reporting PMMR images

PMMR images were reported by one of two specialist paediatric radiologists (O.O. and C.M.O.), with 12 and 18 years' experience, using the OsiriX platform (OsiriX Foundation, Geneva, Switzerland). The radiologist was given the age and basic clinical details of the case, but was blinded to results of ancillary investigations and autopsy findings.

Reporting of autopsy data

Conventional autopsies were performed by one of several experienced specialist perinatal/paediatric pathologists (at least 8 years experience) in accordance with national guidelines, and were reported blinded to the MRI findings [3, 11].

Data and statistical analysis

Data were collected into a specific Microsoft Access database (version 2003; Microsoft, Redmond, WA, USA), which was developed as part of a study examining paediatric autopsies [12]. The radiologists and pathologists could only access their respective sections of the database until all data were reported. Prior to data unmasking, a pathologist (N.J.S.), radiologist (A.M.T.) and neonatologist (S.T.) reviewed all the PMMR and pathology reports, to define and categorise the findings according to predefined criteria [10]. The results presented here are those as recorded at the time of initial PMMR reporting, not following subsequent specialist unblinded review, so as to reflect how PMMR would be used in clinical practice.

In order to clarify the nature of the discrepancies, we then retrospectively reviewed the imaging and pathology findings. We excluded cardiac abnormalities, as they have been reported elsewhere [13] and divided specific thoracic diagnoses into one of seven categories, which were: respiratory tract infection (lung parenchymal consolidation at PMMR, pneumonia, pneumonitis and aspiration at autopsy), pulmonary haemorrhage, lung or thoracic hypoplasia/agenesis, pulmonary congestion/oedema, isolated pleural effusion, trachea-oesophageal fistula, and “other” categories.

Primary outcomes were sensitivity, specificity, positive-predictive value (PPV) and negative predictive value (NPV), where PMMR (the index test) defined the diagnosis compared with conventional autopsy (the “gold standard”), with 95 % confidence intervals (CI). Concordance was defined as the sum of true positives and true negatives divided by all cases. Exact methods were used to calculate confidence intervals [14]. SPSS (version 19 for Macintosh; SPSS IBM, New York, USA) was used for data analysis. Sub-group analysis was performed based on age (fetuses <24 weeks gestation, fetuses ≥24 gestation, and children including all newborns, infants and children ≤16 years of age).

Results

Demographic data

PMMR was performed on 403 cases, although autopsy data could not be retrieved in 3 cases. Of the remaining 400 cases, 277/400 (69 %) were fetuses (consisting of 185 at ≤24 weeks’ gestation and 92 at >24 weeks’ gestation) and 123/400 (31 %) were children (consisting of 42 newborns aged <1 month, 53 infants >1 month to ≤12 months, 28 children >12 months to ≤16 years). Hospital-requested autopsies (fetal medicine unit or in-patients) accounted for 292 cases, with HM Coroner (Medical Examiner)-requested autopsies accounting for the

remainder: 6 (2.2 %) fetuses and 102 (82.9 %) children. Mean (SD) time between death/delivery and PMMR was 4.5 (2.5) days.

Autopsy findings

Summary details of autopsy pathology in this dataset have been briefly reported previously [3]. Conventional autopsy studies revealed a total of 113/400 thoracic (28 %) abnormalities across all groups. At autopsy, in fetuses <24 weeks ($n=185$), the thorax was normal in 146/185 (78.9 %) cases, abnormal in 35/185 (19 %) and non-diagnostic in 4/185 (2.1 %). Of the 113 abnormalities, the most common abnormalities reported were infection in 15/113 (13.3 %) and pulmonary hypoplasia in 11/113 (6 %) cases. In fetuses >24 weeks ($n=92$), the thorax was abnormal in 16/92 (17 %), with infection being the commonest abnormality reported in 9/92 (10 %) cases. In newborns and children ($n=123$), the thorax was abnormal in 62/123 (50.5 %) cases, with the commonest abnormalities being infection in 24/123 (19.5 %) and aspiration/haemorrhage in 12/123 (9.7 %) cases.

Non-diagnostic cases

There were 27/400 (6.7 %) non-diagnostic thoracic PMMR scans; all of which occurred in fetuses ≤24 weeks. There were two thoracic abnormalities (lung hypoplasia) in this group. Subsequent analysis of the data has been performed on the remaining 373 cases, which had 111/373 (29.8 %) thoracic abnormalities identified by conventional autopsy.

Comparison of PMMR to conventional autopsy

The overall sensitivity, specificity, PPV, NPV, and concordance across the three subgroups with 95 % confidence intervals are given in Table 1.

Thoracic PMMR had poor sensitivity and specificity across all groups, with slightly higher sensitivity in children than smaller fetuses (45 vs 30 %), but poorer specificity (61 vs 97 %), and poor overall concordance (71.8 %). Overall sensitivity was poor at 39.6 %, although specificity was higher at 85.5 %.

PMMR was most sensitive at detecting anatomical abnormalities, including pleural effusion (100 %) and lung or thoracic hypoplasia (60 %; Table 2). PMMR was particularly poor at detecting infection with sensitivity of 12.5 % and PPV of 25.0 %. Although overall concordance, specificity and NPV were high across different pathologies, this was largely due to the majority of normal cases in this study.

Examples of concordance between PMMR and conventional autopsy findings are shown in Figs. 1, 2, and 3; examples of a lack of concordance are shown in Figs. 4 and 5.

Table 1 Diagnostic accuracy of non-cardiac thoracic PMMR imaging, according to age group

	FP/TP	FN/TN	Sensitivity %	Specificity %	PPV (%)	NPV (%)	Concordance (%)
Fetuses <24 wks (<i>n</i> =158) ^a	5/10	23/120	30.3 % [17.4, 47.3]	96.0 % [91.0, 98.3]	66.7 % [41.7, 84.8]	83.9 % [77.0, 89.0]	82.3 % [75.6, 87.4]
Fetuses >24 wks and stillbirths (<i>n</i> =92)	9/6	10/67	37.5 % [18.5, 61.4]	88.2 % [79.0, 93.6]	40.0 % [19.8, 64.3]	87.0 % [77.7, 92.8]	79.3 % [70.0, 86.4]
Newborn & children (<i>n</i> =123)	24/28	34/37	45.2 % [33.4, 57.5]	60.7 % [48.1, 71.9]	53.8 % [40.5, 66.6]	52.1 % [40.7, 63.3]	52.8 % [44.1, 61.4]
Overall (<i>n</i> =373)	38/44	67/224	39.6 % [31.0, 48.9]	85.5 % [80.7, 89.2]	53.7 % [42.9, 64.0]	77.0 % [71.8, 81.4]	71.8 % [67.1, 76.2]

Data are *n* (%), *n* or % [95 % CI]

FP false positive, TP true positive, FN false negative, TN true negative

Sensitivity calculated as TP/(TP+FN); Specificity calculated as TN/(TN+FP); PPV calculated as TP/(TP+FP); NPV calculated as TN/(TN+FN); Concordance calculated as (TP+TN)/(TP+TN+FP+FN)

^a Non-diagnostic=27, all fetuses <24 weeks

Fetuses <24 weeks

In fetuses <24 weeks, the thorax was abnormal in 33/158 cases (20.9 %). Ten correct positive thoracic diagnoses were made (10/33; sensitivity 30.3 %), of which there were six with lung or chest hypoplasia, one pleural effusion, two congenital diaphragmatic hernias and one hydrops (Table 3).

Twenty-three out of 33 (69.7 %) of diagnoses found at autopsy were not identified (apparent false negatives) on PMMR, including 15 infections, four lung hypoplasias, two trachea-oesophageal fistulae (ToFs), one abnormal lung lobation and one with absent nostrils as part of a complex facial malformation (Table 3). On unblinded review, 14 of the infection cases had normal unventilated post-mortem lung appearances; only one case had patchy lung changes,

which could have been identified prospectively. The lungs looked normal in one case of hypoplasia, but were subjectively small in the other three cases, including one with associated renal dysplasia. There were five apparent false-positive diagnoses by PMMR: three lung hypoplasias and two pleural effusions (Table 3). One case of lung hypoplasia was in a case of skeletal dysplasia, but the other two were false-positives on unblinded review. Both pleural effusions were felt to be part of normal post-mortem changes at autopsy.

Fetuses >24 weeks

In fetuses >24 weeks, the thorax was abnormal in 16/92 cases (17.4 %). Six correct thoracic pathological diagnoses were

Table 2 Diagnostic accuracy of non-cardiac thoracic PMMR imaging, according to pathology

	FP/TP	FN/TN	Sensitivity %	Specificity %	PPV (%)	NPV (%)	Concordance (%)
Pulmonary infection	18/6	42/224	12.5 % [5.9, 24.7]	92.6 % [88.6, 95.2]	25.0 % [12.0, 44.9]	84.2 % [79.3, 88.1]	79.3 % [74.3, 83.6]
Pulmonary haemorrhage	0/4	8/224	33.3 % [13.8, 60.9]	100 % [98.3, 100]	100 % [51.0, 100]	96.6 % [93.3, 98.2]	96.6 % [93.5, 98.3]
Lung or chest hypoplasia	8/9	6/224	60.0 % [35.7, 80.2]	96.6 % [93.3, 98.2]	52.9 % [31.0, 73.8]	97.4 % [94.4, 98.8]	94.3 % [90.7, 96.6]
Congestion/oedema	0/6	3/224	66.7 % [35.4, 87.9]	100 % [98.3, 100]	100 % [61.0, 100]	98.7 % [96.2, 99.5]	98.7 % [96.3, 99.6]
Pleural effusion	7/7	0/224	100 % [64.6, 100]	97.0 % [93.9, 98.5]	50.0 % [26.8, 73.2]	100 % [98.3, 100]	97.1 % [94.0, 98.6]
Other	5/12	8/224	60.0 % [38.7, 78.1]	97.8 % [95.0, 99.1]	70.6 % [46.9, 86.7]	96.6 % [93.3, 98.2]	94.8 % [91.3, 96.9]

Data are *n* (%), *n* or % [95 % CI]

FP false positive, TP true positive, FN false negative, TN true negative

Sensitivity calculated as TP/(TP+FN); Specificity calculated as TN/(TN+FP); PPV calculated as TP/(TP+FP); NPV calculated as TN/(TN+FN); Concordance calculated as (TP+TN)/(TP+TN+FP+FN)

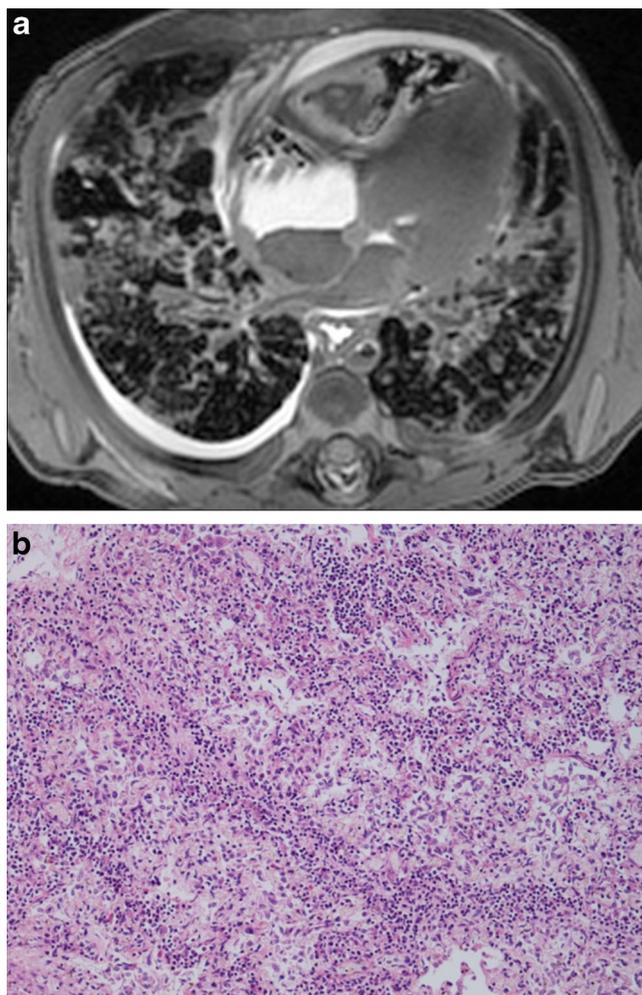


Fig. 1 Example of agreement. An 11-week-old child with atrial-septal defect who died of systemic sepsis, with patchy parenchymal consolidation on PMMR (a), confirmed as infection at autopsy (pneumonia; b)

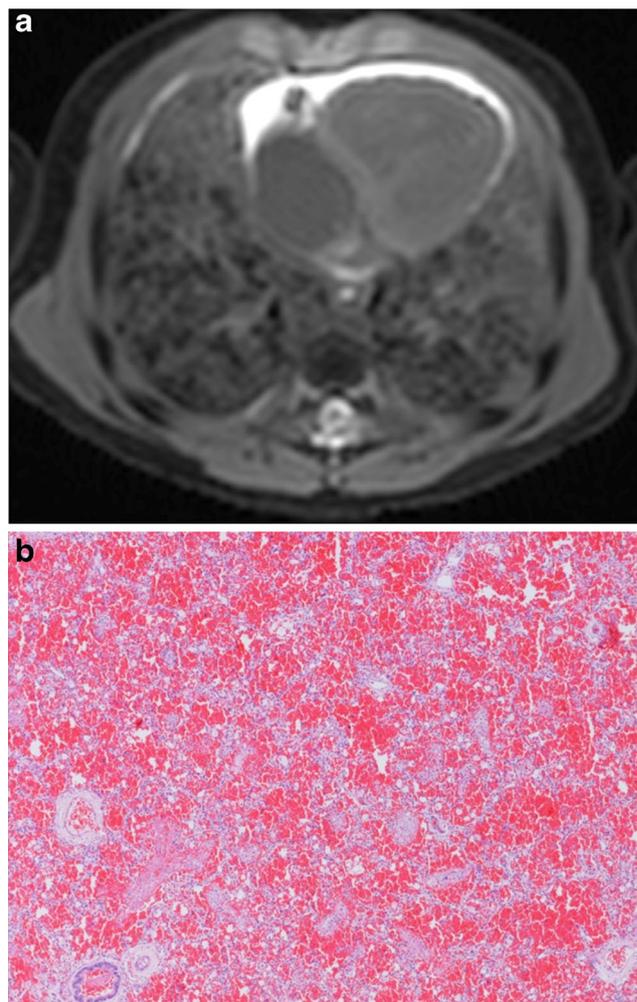


Fig. 2 Example of agreement. A 3-day-old child who died suddenly and unexpectedly with diffuse parenchymal change on PMMR (a), confirmed as diffuse alveolar haemorrhage at autopsy (b)

made (6/16; sensitivity 37.5 %; Table 3). There were ten apparent false negatives (10/16; 62.5 %), including nine infections and one lung hypoplasia (Table 3). On unblinded review, the lungs had normal unventilated post mortem appearances in all nine infections. The lung hypoplasia was missed in a severely macerated 24-week-gestation fetus.

There were nine apparent false positives by PMMR: four pleural effusions, three lung hypoplasias and two focal lung lesions (Table 3). On unblinded review, all four pleural effusions were present but interpreted as normal post-mortem change at autopsy. In one of the lung hypoplasias, the lungs looked subjectively small on PMMR in a case of massive sacrococcygeal teratoma, but were histologically normal size and weight at autopsy. Two other lung hypoplasias were over-calls. In one “lung lesion”, the lungs looked patchy on PMMR but were normal at autopsy, including histological examination, and in the other the lungs looked normal on PMMR but were distorted by large amounts of intra-pleural gas.

Newborns and children

In newborns, infants and children, the thorax was abnormal in 62/123 cases (50.4 %). Twenty-eight correct pathological diagnoses were made (28/62; sensitivity 45.2 %; Table 3). Thirty-four thoracic diagnoses were not correctly identified (34/62; 54.8 %), including 18 infections, 8 with pulmonary haemorrhage, 2 trachea-oesophageal fistulae, 3 pulmonary congestion/oedema and 1 case each of lung hypoplasia, pulmonary hypertension and hyaline membrane disease (Table 3). On unblinded review, there were patchy lung changes, which could have been interpreted as abnormal in only six of the cases in which infection was diagnosed at autopsy; in the other 12 cases, the lungs looked normal on PMMR. Equally, there were patchy lung changes in five of the cases of pulmonary haemorrhage and two cases of pulmonary congestion and oedema, but the lungs looked normal in the other three and one case respectively. The lungs looked normal on PMMR in

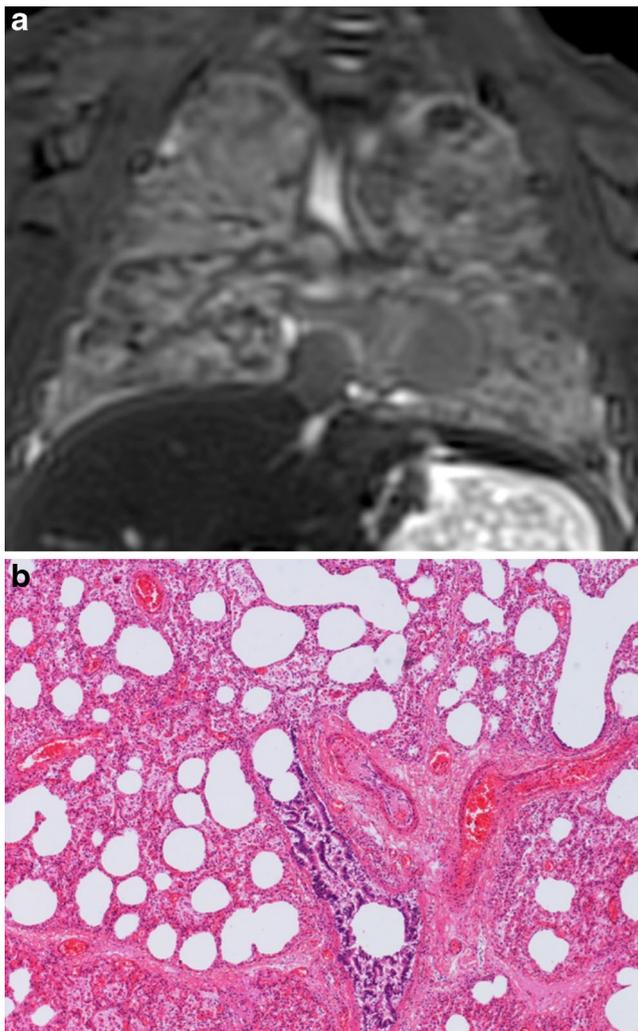


Fig. 3 Example of agreement. A 10-month-old baby who died of complications of prematurity, having been born at 28 weeks. Diffuse parenchymal change on PMMR (a) was confirmed as changes of chronic lung disease of prematurity at autopsy (b)

the cases of HMD, pulmonary hypertension and hypoplasia. The trachea-oesophageal fistulae were not identified.

There were 24 apparent false positives, including 18 infections, 2 lung hypoplasias, 2 focal lung lesions, 1 pleural effusion and 1 dilated oesophagus (Table 3). On unblinded review, there were patchy lung changes in 17 out of 18 cases of infection, and both cases of focal lung lesions, although none of these could be confirmed as abnormal at autopsy, including histology. In one case of lung hypoplasia the child had a skeletal dysplasia (osteogenesis imperfecta type IIa) with a small, dysmorphic ribcage, although the lungs were histologically normal and of normal weight at autopsy, but the other was an overcall. The case of pleural effusion was interpreted as normal post-mortem change at autopsy. The oesophagus was dilated in one case on PMMR but no abnormality was detected at autopsy.

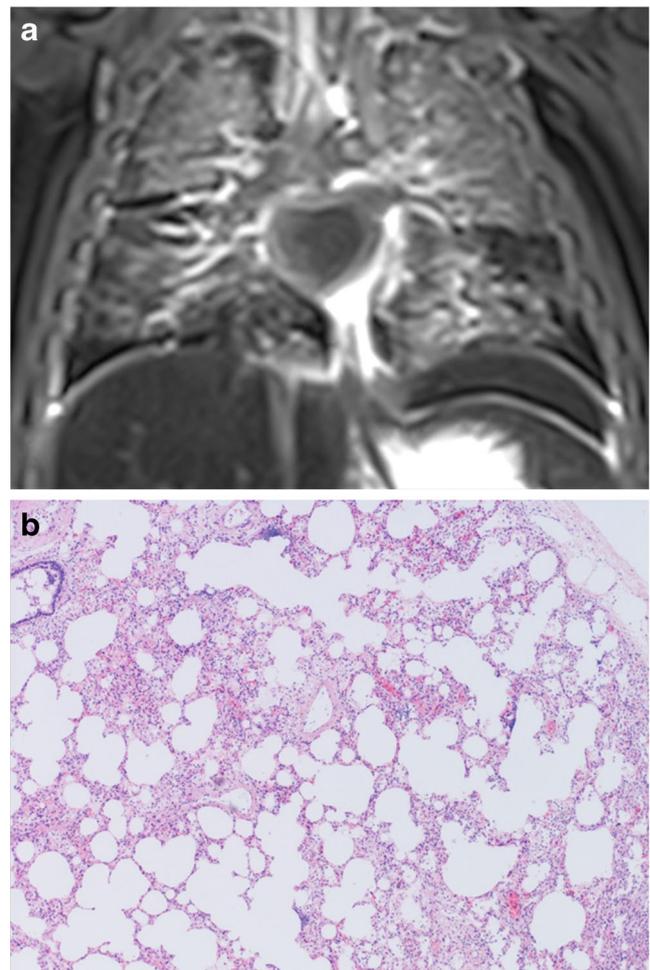


Fig. 4 Example of false-positive (overall) diagnosis on PMMR. A 1-month-old baby who died unexpectedly, where consolidation was reported on the initial PMMR (a) but the lungs were histologically normal at autopsy, i.e. showed normal post-mortem changes but no pneumonia (b)

Across all groups, the commonest abnormality was infection (consolidation on PMMR, pneumonia or pneumonitis at autopsy), accounting for 43 % of all diagnoses made, although only six correct diagnoses were made on PMMR, with 42 apparent false negatives and 18 false positives made. This gives a sensitivity of 12.5 % (5.9, 24.7) and specificity of 92.6 % (88.6, 95.2), and concordance of 79.3 % (74.3, 83.6) for infection alone (Table 2).

Discussion

In this large prospective study, PMMR demonstrated poor diagnostic utility for detection of thoracic pathology in fetuses, newborns and children. Whilst the specificity was high at 86 %, due to the large number of normal cases, the sensitivity and positive predictive value were poor at 40 and 54 %

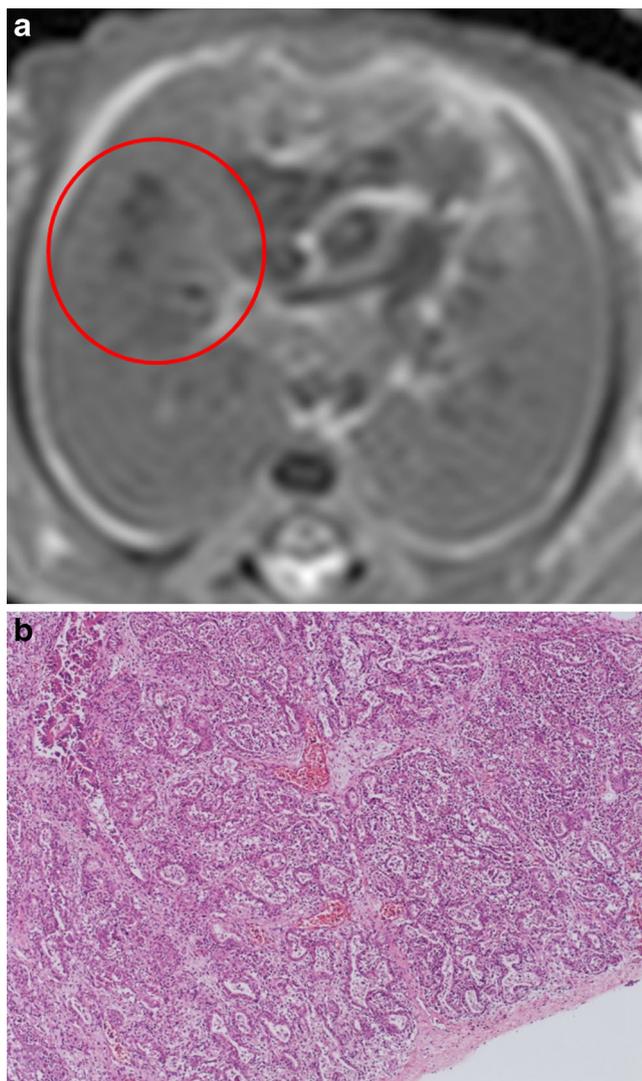


Fig. 5 Example of false negative (miss) on PMMR. A miscarriage at 24 weeks due to presumed sepsis was initially reported as having normal lungs on PMMR but retrospective review reveals focal changes in the right lung (a). This was confirmed as ascending genital tract infection with congenital pneumonia at autopsy (b)

respectively. Overall diagnostic accuracy was reasonable at 72 %. PMMR was most sensitive at detecting anatomical abnormalities such as lung or chest hypoplasia and post-mortem pleural effusions, but poor at detecting infection and pulmonary haemorrhage.

PMMR showed a 9.5 % apparent false-positive rate for thoracic imaging, which is in keeping with results from other body systems [3]. Apparent false positives do not necessarily represent a significant failure of the minimally invasive autopsy model, since the vast majority (75 %) were overcalls of possible infection (consolidation/pneumonia) in children, which would lead to additional investigations and organ sampling for histopathological confirmation. There were several false positives where normal post-mortem accumulation of fluid in bodily cavities was identified but mis-interpreted as

pathological pleural fluid, and most of the correct interpretations of lung hypoplasia were recorded in the context of skeletal dysplasia.

Our accuracy data in this large unselected population is lower than those previously published [5–8], with lower sensitivity and overall concordance, but similar specificity. This is likely to be due to the difficulty in diagnosing infection, particularly in children, where such cases were not included in the several previous studies. Breeze et al. [9] reported a reported a 62.5 % sensitivity (95 % CI=29.0, 96.0) and 87 % specificity (95 % CI=78.9, 100), for eight lung lesions over 30 fetuses. Our findings are similar, in that fetal lung hypoplasia was usually easily detected, but was also overcalled. Their series only had two false-positive lung diagnoses (2/30=6.7 %), and their PPV was 71.4 % (35.9, 91.8), NPV 87.0 % (67.9, 95.5), and overall concordance 83 % (66.4, 92.7 %), all greater than our data but with much wider confidence intervals. We postulate that lung PMMR is more difficult across a larger cohort of children when reported in a blinded fashion.

Infection (pneumonia or lung parenchymal consolidation) was by far both the commonest abnormality in our study, and also the most difficult to achieve correctly. There are several diagnostic difficulties highlighted by our study, and a small study of 44 children has previously identified similar difficulties in detecting lung parenchymal changes using whole-body post-mortem CT [15]. In unventilated fetal lungs, infection was missed in the majority of cases, and infection was equally overcalled and missed in the paediatric population, with or without patchy signal changes in the lungs at post-mortem. We conclude that infection or pneumonia is currently difficult to identify at fetal PMMR, and that lung sampling should be performed in all cases where sepsis is suspected or possible. In older children, misinterpreting consolidation as normal post-mortem change, and vice versa, represents a real challenge in PMMR, recognised by other authors [16]. Several features within the lungs may be interpreted as consolidation (as they would indicate such in life), whereas at autopsy the unequally distributed fluid accumulation within the lung parenchyma is a variant of normal post-mortem changes. We also failed to diagnose eight out of 12 cases of pulmonary haemorrhage, which were interpreted as ‘normal’ post-mortem changes. However, there are variable histological degrees of pulmonary congestion and intra-alveolar fluid in the majority of cases of infant death, regardless of cause. The high apparent false-negative rate (16.2 %; apparent pathologies present at autopsy which were not reported on PMMR) in this study also mainly relates to patchy but diffuse lung parenchymal change, i.e. pneumonia or haemorrhage. The majority of thoracic misses and overcalls in this study were in newborns and children, and mostly related to both overcalling and missing pneumonia.

A normal thoracic scan in fetuses predicts normal pathology in over 80 % of cases, probably because lung aeration does not present a confounding problem in differentiating

Table 3 Summary of all PMMR findings

	Fetuses <24 wks (<i>n</i>)		Fetuses >24 wks (<i>n</i>)		Children (<i>n</i>)		Total	
	FP/TP	FN/TN	FP/TP	FN/TN	FP/TP	FN/TN	FP/TP	FN/TN
Pulmonary infection	0/0	15/120	0/0	9/67	18/6	18/37	18/6	42/224
Pulmonary haemorrhage	0/0	0/120	0/0	0/67	0/4	8/37	0/4	8/224
Lung or chest hypoplasia	3/5	4/120	3/2	1/67	2/2	1/37	8/9	6/224
Tracheo-oesophageal fistula	0/0	2/120	0/0	0/67	0/0	2/37	0/0	4/224
Congestion/oedema	0/0	0/120	0/1	0/67	0/5	3/37	0/6	3/224
Pleural effusion	2/1	0/120	4/3	0/67	1/3	0/37	7/7	0/224
Other	0/4 ^a	2 ^b /120	2 ^c /0	0/67	3 ^d /8 ^e	2 ^f /37	5/12	4/224
Total	5/10	23/120	9/6	10/67	24/28	34/37	38/44	67/224

^a Agreement between PMMR and autopsy in fetuses <24 weeks (*n*=4) included two CDH, one hydrops and one abnormal lobation

^b False-negative PMMR imaging diagnoses (apparent misses) in fetuses <24 weeks (*n*=2) included one abnormal lung lobation and one abnormal nostril

^c False-positive PMMR imaging diagnoses (apparent overcalls) in fetuses >24 weeks (*n*=2) included two focal lung lesions

^d False-positive PMMR imaging diagnoses (apparent overcalls) in children (*n*=3) included two focal lung lesions and one oesophageal dilatation

^e Agreement between PMMR and autopsy in children (*n*=8) included two pneumothorax/HMD, two chronic lung disease, one pulmonary hypertension, one PIE, one subglottic stenosis and one trauma

^f False negative PMMR imaging diagnoses (apparent misses) in children (*n*=2) included one pulmonary hypertension and one hyaline membrane disease

between other causes of death, such as CDH or pulmonary hypoplasia, but this does not hold true for children. Our current practice is that unless a focal lung lesion is identified on PMMR, then standard lung histopathology should be performed in all childhood cases. It may be possible that in future this could be performed by percutaneous or endoscopic routes [17], but the accuracy of this approach to detect patchy lung pathology, compared with open sampling, remains undetermined.

Lung abnormalities are notoriously difficult to detect using other types of post-mortem imaging. For instance, lung opacities on post-mortem radiographs have little correlation with histologically diagnostic pneumonia [18]. Lung PMMR is unlikely to have higher diagnostic accuracy than thoracic MRI in life, and high-resolution computed tomography (CT) remains the mainstay of diagnostic imaging for parenchymal changes, including interstitial lung disease and more subtle pathology. Whilst infant and childhood lung MRI is improving, it is notoriously sequence-dependent and prone to respiratory and cardiac motion artefacts [19]. The post-mortem state negates several of these issues, but clearly brings new diagnostic challenges.

The main strength of this study is the double-blinded study design and large prospective data collection of unselected cases, which allows categorical reporting of both conventional autopsy and PMMR data, in an independent way. By identifying small pleural effusions, and lung parenchymal changes more accurately, it is likely that correct interpretation of PMMR images will be easier in the future.

A limitation of this study was that these cases were all interpreted by both specialist paediatric radiologists in a

tertiary centre and, as such, is unlikely to represent the situation in many other centres. It also highlights both the difficulty in interpreting cases correctly, as these are predominantly interpretation rather than observational errors, and therefore emphasises the need for specialist education in this field in order to maximise the diagnostic yield from both imaging and autopsy. We did not perform post-mortem CT in our cohort, the diagnostic accuracy of which in this setting remains to be evaluated. We also did not measure temperature during PMMR in this study, which may have had an impact on the reporting radiologists' ability to correctly interpret PMMR images [20]. We also did not evaluate more advanced MR techniques, such as T2 relaxometry of the lungs or diffusion-weighted imaging. Semi-quantitative measures of water redistribution may be able to differentiate pathological from non-pathological changes in the lungs, but such approaches require further investigation.

PMMR currently has relatively poor diagnostic detection rates for the commonest intra-thoracic pathologies identified at autopsy in fetuses and children, including infection and haemorrhage. The relatively high negative predictive value suggests that normal thoracic appearances at PMMR excludes the majority of important thoracic lesions at autopsy, and so could be useful in the context of minimally invasive autopsy for excluding non-cardiac thoracic abnormalities.

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Some study subjects or cohorts have been previously reported by Thayyil et al. [3]. Methodology: prospective, diagnostic study, multicentre study.

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