Predicting the risk of respiratory distress in newborns with congenital pulmonary malformations

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Shareable abstract (@ERSpublications)
The first large prospective population-based cohort of children with prenatally diagnosed congenital pulmonary malformations identified congenital pulmonary malformation volume ratio as the best predictive marker of neonatal respiratory distress, helping to guide the delivery site
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Abstract

Objectives Most children with prenatally diagnosed congenital pulmonary malformations (CPMs) are asymptomatic at birth. We aimed to develop a parsimonious prognostic model for predicting the risk of neonatal respiratory distress (NRD) in preterm and term infants with CPM, based on the prenatal attributes of the malformation.

Methods MALFPULM is a prospective population-based nationally representative cohort including 436 pregnant women. The main predictive variable was the CPM volume ratio (CVR) measured at diagnosis (CVR first) and the highest CVR measured (CVR max). Separate models were estimated for preterm and term infants and were validated by bootstrapping.

Results In total, 67 of the 383 neonates studied (17%) had NRD. For infants born at term (>37 weeks, n=351), the most parsimonious model included CVR max as the only predictive variable (receiver operating characteristic (ROC) curve area: 0.70±0.04, negative predictive value: 0.91). The probability of NRD increased linearly with increasing CVR max and remained below 10% for CVR max <0.4. In preterm infants (n=32), both CVR max and gestational age were important predictors of the risk of NRD (ROC: 0.85±0.07). Models based on CVR first had a similar predictive ability.

Conclusions Predictive models based exclusively on CVR measurements had a high negative predictive value in infants born at term. Our study results could contribute to the individualised general risk assessment to guide decisions about the need for newborns with prenatally diagnosed CPM to be delivered at specialised centres.

Introduction

Congenital pulmonary malformations (CPMs) are rare diseases mostly diagnosed in the prenatal period, during routine second-trimester ultrasound examinations, as cystic and/or hyperechoic intrathoracic lesions. Different histological entities have been described, including congenital cystic adenomatoid malformations, sequestrations, bronchial atresia, congenital lobar emphysema and bronchogenic cysts. However, the histological diagnosis of CPM cannot be predicted reliably from ultrasound findings alone [1].

Most CPMs are asymptomatic at birth. Retrospective evaluations have revealed a prevalence of neonatal symptoms of 22–25% [2–4]. The reported prevalence is lower, at about 9–17%, if the outcome is defined by the need for ventilatory support [3–8]. The true prevalence of symptomatic CPM may be even lower, as these retrospective and, often, single-centre studies may not have taken all prenatally diagnosed CPMs into account, particularly the smaller ones. However, these evaluations have highlighted that planned delivery at tertiary centres with neonatal intensive care and surgery units is frequent, but not justified for the vast majority of children with CPMs [9]. An important obstacle to preventing the overuse of tertiary services for newborns with CPMs is the lack of prognostic models for the reliable identification of those at low risk of NRD based on prenatal data.

A few retrospective studies have shown that the volume of the malformation in the fetus, estimated by the CPM volume ratio (CVR), is a significant risk factor for neonatal respiratory distress (NRD) [3, 5, 6, 10]. However, heterogeneous definitions of NRD and the inclusion of a large proportion of preterm infants with NRD are major limitations of these studies, making it impossible to assess the relationship between CVR and the risk of NRD in a consistent manner. Moreover, these studies did not consider the added value of other prenatal ultrasound parameters, such as mediastinal deviation, hydramnios, ascites or other signs of compression, for predicting the risk of NRD.

We conducted a nationally representative prospective cohort study, the MALFPULM cohort, which included more than 400 cases that were well-phenotyped from the time of prenatal diagnosis. Based on the initial results of this study, we have already been able to define the prenatal course of these malformations [11]. In the present study, our objectives were to: 1) develop a parsimonious prognostic model for predicting the risk of NRD in preterm and term infants with CPMs from the prenatal characteristics of the malformation and 2) identify term newborns at low risk of NRD, not necessarily requiring delivery at a tertiary centre.

Methods

Data source

In France, pregnant women needing a prenatal diagnosis are referred to “multidisciplinary centres for prenatal diagnosis” (MCPDs). MCPDs are accredited by the French health authorities and provide expertise in various aspects of prenatal diagnosis: clinical, laboratory and imaging studies. In particular, all MCPDs have very experienced experts in prenatal ultrasound, all of whom hold the national diploma for fetal ultrasound.

The MALFPULM study is based on a prospective, nationally representative cohort of prenatally diagnosed CPMs in France. Inclusions took place between March 2015 and June 2018, at 35 MCPDs. This study was approved by an institutional review board (Comité de Protection des Personnes Ile-de-France IV, US Department of Health and Human Services Agreement number 00003835).

The MALPULM cohort has been described in detail elsewhere [11]. Briefly, all pregnant women referred to an MCPD for the prenatal diagnosis of a CPM in the fetus were invited to participate in the study. At inclusion, and at each subsequent visit until delivery, standardised clinical and ultrasound data were collected and entered in an electronic case report form, with complete anonymisation. As this study required no change to routine clinical care, the numbers of visits and ultrasound examinations were not standardised and could differ between women seen at different centres. The identification of potentially associated malformations on ultrasound was not an exclusion criterion.

All investigators used the same definitions to describe the phenotypic appearance of the CPM, and to estimate CPM volume (supplementary material). For analysis, CPMs were classified as cystic/mixed (with at least one measurable cyst) or hyperechoic (no measurable cyst), according to phenotypic appearance on the first ultrasound examination. The CVR was obtained by dividing CPM volume by head circumference. CVR at first ultrasound examination after inclusion (CVR first) and the highest CVR value measured during pregnancy (CVR max) were analysed.

Study population

We initially included 436 pregnant women in the study, corresponding to 1742 prenatal visits and 1674 ultrasound examinations. 53 women were excluded from the final analysis because of fetal death *in utero* or pregnancy termination (n=10), missing CVR measurement data (n=42) or missing data for respiratory distress (n=1) (figure 1). The final study population therefore comprised 383 women and 1219 ultrasound examinations. The characteristics of the final study population and of the women excluded from the study population are shown in supplementary table S1.

Outcome definition

A newborn was classified as having NRD if he or she met at least one of the following criteria: persistence, 15 min after delivery, of polypnea >60 min^{-1} or signs of retraction (Silverman score greater than or equal to 2); need for oxygen therapy, non-invasive ventilatory support or invasive ventilatory support; and/or need for surgical removal of the CPM before the age of 7 days.

In France, the recommendations for newborn care in the delivery room are those currently promoted by the French Society of Neonatology, and which are regularly updated by ILCOR/ERC (International Liaison Committee on Resuscitation/European Resuscitation Council) [12], and were those used by the different teams participating in the study

Statistical analysis

Data were expressed as mean±standard deviation. We compared the characteristics of babies with and without NRD in Chi-square tests, Fisher's exact tests and t-tests. We used univariable and multivariable logistic regression models to investigate the adjusted and unadjusted associations between the CPM and patient characteristics of NRD. All analyses were conducted separately for preterm and term newborns. Our first model included CVR max as the sole predictive variable, whereas the second model included CVR together with gestational age, malformation type (cystic or non-cystic) and signs of compression (mediastinal shift, polyhydramnios, ascites, eversion of the diaphragm, hydrothorax, hydrops) during pregnancy. Caesarean section is known to be an independent risk factor for NRD, particularly in infants born at term, but we decided not to include this parameter in the models for the main analysis of the study, because our aim was to develop a predictive model for use in the prenatal period. It therefore needed to be independent of the type of delivery actually practiced at the end of the pregnancy. Nevertheless, as a complementary analysis, we also estimated a model including caesarean section as an additional predictor of NRD. Predictive ability was measured by assessing model discrimination (receiver operating characteristic, ROC), calibration (Hosmer–Lemeshow goodness-of-fit test), sensitivity, specificity, and positive and negative predictive values. Bootstrapping was then performed for model validation.

The classification thresholds for predictive models were defined with the Younden test in order to optimise the relationship between false-positive and true-positive rates. We performed the same set of analyses on CVR first and CVR max. We also looked at the changes in CVR over time (*i.e.* as a function of gestational age) for newborns with and without NRD separately for term and preterm infants. A population-average

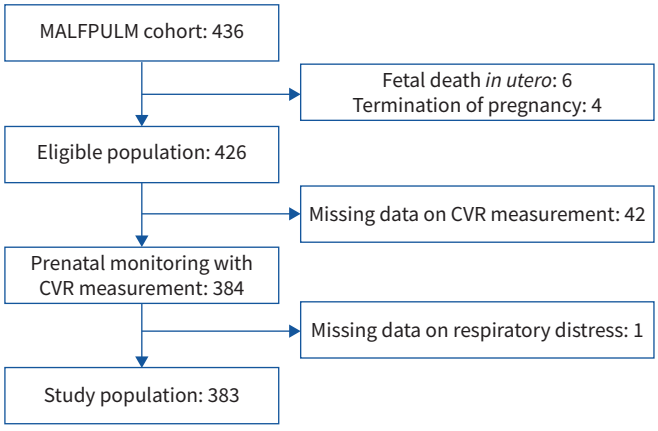

FIGURE 1 Flowchart of the study.

(generalised estimating equations) logistic regression analysis was performed. All analyses were performed with Stata v14 (StataCorp, College Station, TX, USA).

To verify that missing data did not alter our conclusions, we performed a multiple imputation by chained equations using the variables respiratory distress, CVR, type of malformation and sign of compression during pregnancy to create 10 imputed datasets; we used an augmented regression approach due to the presence of a perfect prediction.

Further, we verified the potential variance in our composite primary outcome (respiratory distress that includes O_2 administration, invasive or non-invasive ventilation, and surgery) across 35 centres by using a random intercept multilevel logistic regression model.

Results

In total, 383 women, with a mean of 4.0±1.9 ultrasound examinations each, were included in the study (supplementary table S1). Characteristics of the population are described in table 1. Most of the CPM lesions were small, with a median CVR max value of 0.41 cm^2 (supplementary figure S1). At least one sign of compression was observed during the pregnancy for 170 fetuses (supplementary table S2).

Neonatal respiratory distress

In total, 67 (17%) neonates were considered to have respiratory distress, as they met at least one of the criteria of the definition used. Polypnea or signs of retraction persisted 15 min after the delivery in 29 neonates, 45 neonates required oxygen therapy, 46 required non-invasive ventilatory support, 10 required mechanical ventilation and 15 required surgical removal of the CPM before the age of 7 days. Overall, 55 of the 67 neonates required oxygen therapy or ventilatory support.

NRD was significantly associated with preterm birth, caesarean section, higher CVR at first ultrasound examination, higher maximal CVR value, higher rate of signs of compression on ultrasound and a greater

TABLE 1 Characteristics of the study population

	No neonatal respiratory distress (n=316)	Neonatal respiratory distress (n=67)	Total (n=383)	p-value
Sex (male)	179 (57)	37 (55)	216 (56)	0.831
Gestational age at CVR first (weeks)	23.3±3.8	24.0±4.6	23.5±3.9	0.183
Gestational age at CVR max (weeks)	25.7±4.2	27.3±4.9	25.9±4.4	0.006
Gestational age at birth (weeks)	39.6±1.4	38.3± 2.7	39.4±1.8	<0.001
Preterm birth	16 (5)	16 (24)	32 (8)	<0.001
Caesarean section	40 (13)	23 (34)	63 (16)	<0.001
Birth weight (kg)	3.32±0.49	3.14±0.68	3.28±0.53	0.017
Phenotype of the CPM:				0.612
Cystic/mixed	175 (55)	38 (57)	213 (56)	
Hyperechoic	139 (45)	38 (43)	168 (44)	
Location of the malformation at inclusion:				0.577
Right	136 (43)	33 (50)	169 (44)	
Left	175 (56)	32 (48)	207 (54)	
Bilateral	4 (1)	1 (2)	5 (1)	
Systemic vascularisation during pregnancy	113 (36)	18 (27)	131 (34)	0.163
CVR first (cm^2)	0.44±0.42	0.96±0.94	0.53±0.58	<0.001
CVR max (cm^2)	0.54±0.48	1.26±1.13	0.67±0.70	<0.001
CVR max (cm^2) (median (range))	0.41 (0.00–2.60)	0.83 (0.01–4.89)	0.44 (0.00–4.89)	
Signs of compression during pregnancy:				<0.001
No	191 (60)	22 (33)	213 (56)	
Mediastinal shift only	92 (29)	18 (27)	110 (29)	
Others[#]	33 (10)	27 (40)	60 (16)	
Fetal therapy[¶]	8 (3)	14 (21)	22 (6)	<0.001

The data shown are mean±SD or n (% of the total of the column), unless otherwise indicated. [#]: includes cases with polyhydramnios, eversion of the diaphragm, ascites, hydrothorax or hydrops; [¶]: fetal therapies included amnioreduction, thoraco-amniotic shunting, or maternal corticosteroid treatment. CPM: congenital pulmonary malformation; CVR: CPM volume ratio; CVR max: highest CVR measured.

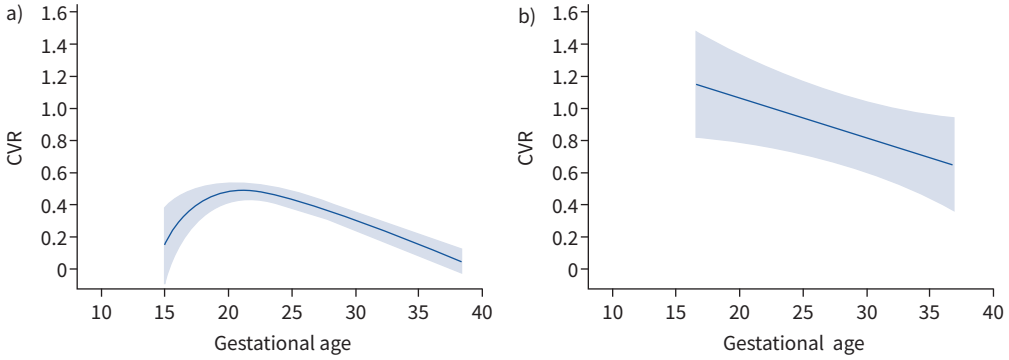

FIGURE 2 Fractional polynomial modelling of changes in congenital pulmonary malformation (CPM) volume ratio (CVR) with increasing gestational age, between CPM diagnosis and birth in term infants a) without neonatal respiratory distress (NRD) (n=943 ultrasound examinations, 300 women; p<0.001) or b) with NRD (n=172 ultrasound examinations, 51 women; p=0.029). CVR as cm^2.

need for fetal therapy (table 1). CVR max was reached significantly later in the pregnancy for the cases that went on to develop NRD. Only signs of compression other than mediastinal deviation were associated with the risk of NRD (supplementary table S2).

Estimation of models based on continuous CVR max in term infants

Fractional polynomial modelling of changes in CVR with increasing gestational age between CPM diagnosis and delivery revealed clearly different patterns between children with and without NRD (figure 2). Term infants without NRD were characterised during pregnancy by a lower CVR max and a decrease in the volume of their malformation in late pregnancy. Univariate analyses and the adjusted odds ratio for the predictors of respiratory distress in term infants are presented in table 2. CVR max and prenatal signs of compression on ultrasound were significant predictors of NRD in infants born on term in univariate analyses, whereas cystic phenotype and gestational age were not predictive in this model. The odds ratio for each one-tenth increase in CVR max was 1.14 (95% CI 1.09–1.19). The adjusted model identified CVR max as the sole independent predictor, with an adjusted odds ratio of 1.13 (95% CI 1.07–1.20).

We then compared the performance of the adjusted model to that of a simple model based exclusively on CVR max. If positive cases were classified as those with a predicted probability of NRD of 0.15 or more, according to the Youden test, the two models for infants born at term had similar performances in terms of sensitivity, specificity, positive predictive value, negative predictive value and area under the ROC curve (table 3). The rate of correctly classified cases was 79% with the adjusted model and 77% with the simple model (supplementary table S3).

Lowering the classification threshold to a probability of NRD of at least 0.10 increased sensitivity to 65%, lowered specificity to 55% and maintained the negative predictive value at 90% (supplementary table S4).

TABLE 2 Estimation of the model based on continuous CVR max for infants born at full term

Variable	uOR	95% CI	p-value	aOR	95% CI	p-value
Gestational age	0.87	0.67–1.12	0.274	0.95	0.72–1.27	0.750
Cystic/mixed CPM	1.08	0.59–1.98	0.793	0.82	0.42–1.61	0.562
CVR max[#]	1.14	1.09–1.19	<0.001	1.13	1.07–1.20	<0.001
Signs of compression during pregnancy:						
No	1 (Ref)			1 (Ref)		
Mediastinal shift only	1.63	0.79–3.38	0.189	0.75	0.32–1.75	0.504
Others	6.43	2.99–13.82	<0.001	1.64	0.58–4.65	0.352

[#]: odds ratio for an increase of 0.1 in CVR. uOR: univariate odds ratio; aOR: adjusted odds ratio; CPM: congenital pulmonary malformation; CVR: CPM volume ratio; CVR max: highest CVR measured; Ref: reference group.

TABLE 3 Performance of the simple and full adjusted models for full-term births and preterm births

	Full-term birth				Preterm birth			
	CVR max		CVR first		CVR max		CVR first	
	Simple	Full	Simple	Full	Simple	Full	Simple	Full
ROC area	0.70±0.04	0.71±0.05	0.69±0.04	0.70±0.05	0.73±0.09	0.85±0.07	0.71±0.10	0.84±0.08
Sensitivity	0.51	0.55	0.45	0.57	0.69	0.77	0.62	0.77
Specificity	0.81	0.83	0.79	0.81	0.69	0.80	0.75	0.80
Positive predictive value	0.32	0.35	0.26	0.33	0.69	0.77	0.71	0.77
Negative predictive value	0.91	0.92	0.89	0.92	0.69	0.80	0.67	0.80

Models were estimated on the basis of continuous CVR max or continuous CVR first. Cases were considered positive if the predicted probability of neonatal respiratory distress (NRD) was at least 0.15 for births at full term and at least 0.45 for preterm births. True-positive cases were those for which NRD actually occurred. ROC area is the area under the ROC curve obtained after bootstrapping. CVR: congenital pulmonary malformation volume ratio; ROC: receiver operating characteristic; CVR max: highest CVR measured; CVR first: CVR measured at diagnosis.

Fractional polynomial modelling of the risk of NRD according to CVR max revealed a gradual, almost linear rise in NRD risk with increasing CVR max, with no threshold effect (figure 3). Calibration tests and bootstrapping validated the model. The area under the ROC curve for this model after bootstrapping was 0.71 (95% CI 0.62–0.79) with a p-value for the Hosmer–Lemeshow test of 0.472 (supplementary figure S2). The addition of caesarean section to a model already including CVR max and the other prenatal predictor variables improved model discrimination, with an area under the ROC curve of 0.79 (95% CI 0.71–0.86). The negative predictive value of the model also increased slightly, from 0.90 to 0.95 (supplementary table S5).

Missing data did not influence our results. We did not find any difference between the model's estimates before and after using multiple imputation by chained equations. Further, we did not find a significant difference across the 35 centres using a likelihood-ratio test to compare the multi-level regression model with our basic logistic regression model (variance{centre}=0.26 [0.02–4.18], pr=0.187).

Estimation of the model based on continuous CVR max in preterm infants

Univariate analyses and adjusted odds ratio for the predictors for respiratory distress are presented in supplementary table S6. Due to the small number of premature neonates, the confidence intervals obtained were large and CVR max was of borderline significance in univariate analysis (p=0.054). As for term infants, polynomial modelling revealed a very gradual increase in the risk of NRD with increasing CVR max (figure 3). However, because of the inherent risk of NRD due to premature birth, the probability of developing NRD was about 0.3 for the lowest values of CVR max. The performances of the simple and

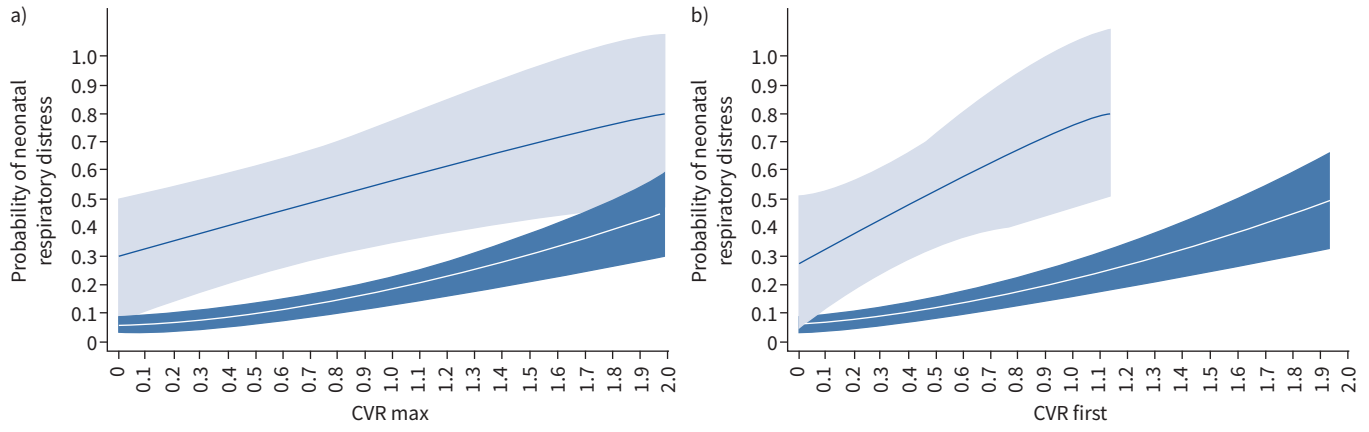

FIGURE 3 Probability of developing neonatal respiratory distress in infants born at full term (dark blue) and preterm (light blue) according to CVR max (a) simple model or CVR first (b) simple model. CVR: congenital pulmonary malformation volume ratio. CVR max: highest CVR measured; CVR first: CVR measured at diagnosis.

adjusted models for preterm neonates are shown in table 3. Overall, 79% of the cases were correctly classified with the adjusted model, and 69% with the simple model (supplementary table S7). The area under the ROC curve for the simple model after bootstrapping was 0.727±0.096 (CI 0.538–0.915) (supplementary figure S2), with p-values of 0.879 and 0.470 for the Hosmer–Lemeshow test and Pearson's test, respectively.

Estimation of the model based on continuous CVR first

We investigated whether a model based on the first CVR measurement after prenatal diagnosis could provide a predictive performance similar to that of a model based on the maximum CVR value measured during pregnancy. Fractional polynomial modelling of the risk of NRD according to CVR first gave results very similar to those obtained with CVR max (figure 3). The performances of the simple and adjusted models in preterm neonates are shown in table 3.

Discussion

Using data from a large, nationally representative, prospective cohort of children with prenatally diagnosed CPM, we aimed to develop a parsimonious predictive model that could be used for risk stratification for newborns with CPM, making it possible to identify infants with a low risk of NRD not necessarily requiring delivery at a tertiary centre.

In our study, NRD was defined by composite criteria, making it possible to include all newborns with persistent symptoms at birth, the vast majority of whom require oxygen or ventilatory support. The cutoff for surgery was arbitrarily set at day 7 of postnatal life, but was unlikely to influence our model, as the small number of children involved (n=15) also had an NRD criterion. The 15-min interval used in our study was able to accurately identify neonates with permanent respiratory distress. Indeed, the 15th postnatal minute is well after all the necessary steps for a gradual management of neonatal respiratory difficulties, as defined by the ILCOR/ERC [12], and this interval integrates the time necessary for the normalisation of pre-ductal oxygen saturation after birth [13]. This definition makes it possible to include all newborns who actually need medical supervision, while targeting only a small minority of children: 17% of our study population. As expected, this rate was lower than the 22%–25% rate reported in retrospective studies using a comparable definition of NRD [2–4]. Similarly, less than 3% of newborns in our cohort required invasive ventilation, *versus* 5–11% in previous retrospective studies [3, 4, 6, 10]. These differences are probably at least partly due to the prospective and population-based design of our study, making it possible to include all prenatally diagnosed CPMs, including the smaller ones. The robustness of the NRD definitions used in our study is reflected in the homogeneity of the results between centres, evidenced by the absence of variance in our composite primary outcome across the 35 centres, using a random intercept multilevel logistic regression model.

The volume of the CPM, as measured by the CVR, was highly significantly associated with the risk of NRD in our cohort. CVR was first developed as a tool for predicting serious prenatal complications of CPM, such as hydrops [14]. Several studies have shown prenatal CVR measurements to be predictive of the risk of NRD [3–6, 10, 15, 16]. A recent systematic review analysed 11 studies with neonatal respiratory endpoints [17]. Indirect signs of compression on ultrasound, such as polyhydramnios, eversion of the diaphragm, ascites or hydrops, were also found to be significantly associated with NRD in our population. However, given the strong causal relationship between CVR and these signs of compression, CVR alone had essentially the same predictive ability, including a negative predictive value >90%, and adding signs of compression to a model already including CVR was of no added value for prediction by the model.

Studies evaluating the predictive value of CVR have used either the maximum value of CVR during pregnancy or the initial value of CVR at diagnosis [17]. Our results are encouraging, in that models based on CVR max and CVR first had very similar predictive abilities, suggesting that CVR first is a potentially useful predictor of the pre- and postnatal prognosis of fetuses with CPM. Indeed, malformations associated with a low risk of NRD have a very low growth potential, with a lower CVR first, and a CVR max occurring early in the pregnancy and only slightly higher than CVR first.

One of the most important findings of this study was the demonstration of a linear dose-response relationship between first (or maximum) CVR values and the risk of NRD, for both term and preterm infants. Several previous studies sought to identify various thresholds for CVR values that could discriminate between cases at high and low risk of complications [17]. Only one of these studies proposed a predictive model for invasive respiratory support at birth, but its results were limited by the small number of cases with this complication (n=16), with more than two-thirds of them born prematurely [6]. This study nevertheless showed that a discriminant model performed better than simple cutoffs based on CVR max [6].

Our study has the advantage of including sufficient cases for stratification between fetuses carried to term and those born preterm. We found that the risk of NRD in term infants was below 10%, provided that CVR max remained below about 0.40 (with small differences between CVR max and CVR first). The distribution of CVR max values in the term infants in our study revealed that almost half the fetuses with CPMs had CVR max values below 0.40. Our model also provides an estimate of the probability of the CPM contributing to NRD in preterm infants. It is important for the neonatologist to assess the potential contribution of the CPM to NRD in preterm infants, and our models demonstrate that such a contribution is most likely in cases in which CVR max or CVR first is high. The comparison of our model with other retrospective studies proposing CVR thresholds to predict the risk of NRD is often difficult because of variable definitions of neonatal respiratory symptoms and/or frequent biases related to a large proportion of premature infants in the study population and/or a more limited inclusion of small malformations, as evidenced by much higher CVR mean or median values in the populations of these studies [6, 16]. This last point may notably artificially shift the CVR thresholds given by ROC curves towards higher values. Other studies with more comparable populations have proposed CVR max thresholds that may appear relatively high compared to our current results, but which are actually fully consistent with our model. For example, in our previous study, based on French referral centre recruitments, a CVR threshold of 0.84 was proposed to discriminate between children without neonatal respiratory distress and those with neonatal respiratory distress [3]. Among children with CVR <0.84, 14% had had neonatal symptoms, in full consistency with the average risk of 15% of NRD predicted by our current model for this CVR max value. The major advantage of our model is that it can assess the risk of NRD for a given CVR value, which is not possible with studies based on a single threshold. However, it must be underlined that the low prevalence (pre-test probability) of respiratory distress in term newborns with pulmonary malformation was responsible for a limited absolute difference between pre- and post-test probability of not having NRD in these neonates. By contrast, the absolute difference in the positive pre- and post-test probabilities was much higher, with a difference of 17%. Therefore, although our model allows for a better targeting of children at low risk of NRD, it cannot alone summarise the decision of the place of birth, which must take into account the specific aspects of each situation, as well as the local particularities of the health care pathway.

Caesarean section is a known risk factor for NRD in term infants, even in low-risk pregnancies [18], and can, therefore, be considered an intrinsic risk factor for NRD in infants born at term, regardless of the rest of their history. Indeed, the addition of caesarean section to the model including CVR and other predictive variables improved model discrimination and, to a lesser extent, a negative predictive value. However, we prefer to favour our parsimonious "prenatal" model (*i.e.* based on CVR max/CVR first and not including the type of delivery) for two reasons: the negative predictive value of this model exceeded 90% and the intended use of this model was primarily in risk stratification for infants with CPM born at term. The rate of caesarean section was 16% in our study, below the 20% rate reported for the general population in France [19]. We can therefore conclude that the prenatal diagnosis of CPM did not increase the frequency of elective caesarean section.

The persistence of false negatives despite the consideration of delivery by caesarean section may reflect other reasons for NRD in term infants entirely unrelated to CPM. It may also suggest that prenatal factors other than CPM volume may contribute to NRD in infants born at term. It is possible that more diffuse abnormalities of airway development are present in these children, potentially contributing to a higher frequency of neonatal respiratory morbidity, regardless of the size of the malformation. Such hypotheses have already been proposed to explain the high frequency of bronchial hyperreactivity in infants [2].

In conclusion, this study shows that, in infants born at term, predictive models based on initial or maximum values of CVR alone are of high negative predictive value. CVR max values below 0.40 were associated with a risk of NRD of less than 10% in term infants with CPM. Our study results can therefore guide decisions about the need for infants with prenatally diagnosed CPM to be delivered at specialised centres. Such decisions must however take into account not only the CPM data, but also the general risk assessment of a specific mother–infant dyad in pregnancy, including local policies and structures.

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Author contributions: C. Delacourt and B. Koshnood conceptualised and designed the study, supervised analysis, drafted the initial manuscript and reviewed and revised the manuscript. N. Bertille, L. Choupeaux and N. Lelong designed the data collection instruments, collected data, carried out the initial analyses and reviewed and revised the manuscript. M. Rahshenas carried out the analyses and reviewed and revised the manuscript. L.J. Salomon and A. Benachi conceptualised and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. A. Bonnard, J-M. Jouannic, J. Massardier, V. Fouquet, V. Goua, F. Hameury, E. Hervieux, N. Khen-Dunlop, G. Le Bouar, L. Roditis, J. Rosenblatt, A. Sartor and C. Thong-Vanh coordinated and supervised data collection, contributed to interpretation of data and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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