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Pulmonary hypertension among preterm infants born at 22 through 32 weeks gestation in France: Prevalence, survival, morbidity and management in the EPIPAGE-2 cohort study

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ABSTRACT

Objective: To determine the prevalence, short-term prognosis and pharmacologic management of pulmonary hypertension (PH) among very preterm infants born before 32 weeks gestation (WG).
Study design: In the EPIPAGE-2 French national prospective population-based cohort of preterm infants born in 2011, those presenting with PH were identified and prevalence was estimated using multiple imputation. The primary outcome was survival without severe morbidity at discharge and was compared between infants with or without PH after adjusting for confounders, using generalized estimating equations models. Subgroup analysis was performed according to gestational age (GA) groups.
Results: Among 3383 eligible infants, 3222 were analyzed. The prevalence of PH was 6.0 % (95 % CI, 5.2–6.9), 14.5 % in infants born at 22–27^{+6} WG vs 2.7 % in infants born at 28–31^{+6} WG ($P < .001$). The primary outcome (survival without severe morbidity at discharge) occurred in 30.2 % of infants with PH vs 80.2 % of infants without PH ($P < .001$). Adjusted incidence rate ratios for survival without severe morbidity among infants with PH were 0.42 (0.32–0.57) and 0.52 (0.39–0.69) in infants born at 22–27^{+6} weeks gestation and those born at 28–31^{+6} weeks, respectively. Among infants with PH, 92.2 % (95 % CI, 87.7–95.2) received sedation and/or analgesia, 63.5 % (95 % CI, 56.6–69.9) received inhaled NO and 57.6 % (95 % CI, 50.9–64.0) received hemodynamic treatments.
Conclusion: In this population-based cohort of very preterm infants, the prevalence of PH was 6 %. PH was associated with a significant decrease of survival without severe morbidity in this population.

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1. Introduction

Pulmonary hypertension (also named Persistent Pulmonary Hypertension of the Newborn, PPHN, in term babies) results from failure to transition to a normal circulation pattern at birth. The syndrome causes labile hypoxemia and hemodynamic shock, due to decreased pulmonary blood flow and right to left shunting across the ductus arteriosus and/or foramen ovale. Its prevalence among term or near-term infants has been reported to be between 0.4 and 6.8 per 1000 live-births, with the mortality rate ranging from 4 to 33 % and low morbidity [1–4]. In very preterm and extremely preterm newborns, the prevalence of PH has been much more rarely described [5,6] and seems to be higher, between 3.4 % and 8.1 % [5,6], in the few studies addressing this topic.

PH is a serious condition which is potentially completely reversible but which causes significant mortality in preterm newborns. Very preterm infants are a vulnerable population with a high risk of neonatal mortality and morbidity due to their immaturity [7]. In this context, the additional burden of PH itself and aggressive management of the condition is not known. Besides, in preterm and extremely preterm neonates PH is frequently associated with sepsis or pulmonary hypoplasia secondary to preterm premature rupture of membranes (PPROM) or oligohydramnios. Management of this condition remains controversial [8,9]. Extracorporeal oxygenation is not possible and inhaled nitric oxide (iNO) is not recommended [10,11]. The efficacy of iNO in very preterm infants with PH is uncertain and its use remains off-label. Nevertheless, even though approval of iNO by the US Food and Drug Administration (FDA) or by the European Medicine Agency was limited to infants born term and near-term at >34 weeks gestation, iNO has been used in many neonatal intensive care units, with large variations in practice [12]. Moreover, most published trials assessed the effectiveness of iNO in preventing bronchopulmonary dysplasia or severe brain injury in preterm infants [10,13] but not its effects on PH [14].

The main objectives of this study were to determine the prevalence of PH and the rate of survival without severe adverse outcome among infants with PH in a large national prospective population-based cohort of infants born preterm at 22 through 32 weeks gestation (EPIPAGE-2).

Secondary objectives were to describe treatments received by infants diagnosed with PH, to estimate the rates and causes of neonatal mortality and morbidity and to compare these with infants of the same gestational age (GA) without PH.

2. Methods

2.1. Study design

EPIPAGE-2 is a national prospective population-based cohort of children born preterm in France in 2011. Live births, stillbirths and terminations of pregnancy between 22 and 34 weeks gestation were eligible for inclusion in the study. A systematic stratified sampling design was implemented. Three strata were defined, with specific duration of recruitment period: births occurring at 22 through 26 weeks of gestational age (GA) with a duration of recruitment period of 8 months, births occurring at 27 through 31 weeks GA with a duration of recruitment period of 6 months, and births occurring at 32 through 34 weeks GA with a duration of recruitment period of 5 weeks. Maternal, obstetric and neonatal data were collected from medical records following a standardized protocol. In total, 6.7 % of the eligible livebirths at 22 through 26 w GA and 6.0 % of the eligible livebirths at 27 through 31 w GA did not participate in the study. Details of the protocol have been published elsewhere, as well as the comparison between participants and nonparticipants [15].

For the current study, livebirths occurring between 22^{+0} and 31^{+6} weeks gestation were considered. Neonates with major malformation(s) and neonatal deaths in the delivery room were excluded.

2.2. Ethics

The study was approved by the National Data 160 Protection Authority (CNIL no. 911009), by the consultative Committee on the Treatment of Data on Personal Health for Research Purposes (reference no. 10.626), and the Committee for the Protection of People Participating in Biomedical Research (reference CPP SC-2873). After being informed of the aim of the study, families who agreed to participate gave informed consent.

2.3. Data collection of maternal and obstetric characteristics

The maternal sociodemographic factors collected included maternal age at delivery, pre-conception body mass index (BMI), country of birth, level of education, socioeconomic status and social insurance coverage at delivery. The obstetric characteristics studied were number of previous deliveries, infertility treatment, multiple pregnancies, monthly examination during pregnancy (considered as adequate follow-up of pregnancy), hospitalization during pregnancy, antenatal corticosteroid use, preterm premature rupture of membranes (PPROM), chorioamnionitis (whether suspected or proven), and induced prematurity defined as induction of labor or cesarean section before onset of labor.

2.4. Neonatal characteristics

We considered the following neonatal characteristics: gestational age (GA) at delivery (defined as the best obstetric estimate combining last menstrual period and ultrasonogram assessment in completed weeks of gestation), mode of delivery, sex, Apgar score at 5 min, small for gestational age (SGA) at birth defined as birthweight <10th percentile according to EPOPé curves [16], presence of minor malformation(s), oxygenation in the delivery room, surfactant use, respiratory distress syndrome, and treatment for persistent ductus arteriosus (non-steroidal anti-inflammatory drugs, NSAIDs), surgery). Neonatal infections were classified as early-onset sepsis (before 72 h), distinguishing early-onset sepsis without blood culture or cerebrospinal fluid (CSF) from proven neonatal bacterial infection with positive cultures of CSF or blood before 72 h of life, and late-onset sepsis (after 72 h of life) among survivors after 3 days. Duration of mechanical and non-invasive ventilation (in days) and GA at hospital discharge were recorded for survivors at discharge.

2.5. Pulmonary hypertension (PH) and hemodynamic treatments

On prospectively recorded data, PH diagnosis was based on the binary item “proven persistent pulmonary hypertension” (yes/no); this item was assessed by clinician by the presence of a significant oxygen pre and post-ductal saturation gradient and/or echocardiographic criteria. Cases with a missing value on this item were (re)classified as having PH only if the items relating to inhaled nitric oxide (iNO) treatments indicated that iNO was administered and exclusively in case of refractory hypoxemia with pulmonary hypertension. Infants who clearly received iNO for an indication other than hypoxemia with pulmonary hypertension were excluded. Otherwise, the missing value for the item PH was maintained.

In the subsequent sections, PH+ and PH− denote neonates with a PH diagnosis and with no PH diagnosis, respectively. During the period of the study (2011) saturation targets were in Franc 88–96 %. Treatments of PH+ infants included the use of iNO due to hypoxemia with pulmonary hypertension. Age at start, duration of iNO and maximum administered dose of iNO were detailed. Administration of class III sedative or analgesic treatments, use of vasoactive and inotropic drugs in the first 72 h after birth and after 72 h (among day 3 survivors), with type of treatment (dobutamine, dopamine, norepinephrin) and volume expansion during the first 72 h after birth with volume of vascular filling were collected for all neonates, whatever the PH status.

2.6. Outcomes

The primary outcome was survival without severe neonatal morbidity at discharge. Severe neonatal morbidity was a composite endpoint defined as at least one adverse outcome among the following: severe bronchopulmonary dysplasia, defined as a need for oxygen for at least 28 days plus a need for oxygen concentration 30 % or greater, mechanical ventilator support, or continuous positive airway pressure at 36 weeks postmenstrual age [17]; severe cerebral lesions, defined as grade 3 or higher intraventricular hemorrhage [18]; grade 3 or higher retinopathy of prematurity according to the international classification (International Committee for the Classification of Retinopathy of Prematurity) [19]; and grade II and III necrotizing enterocolitis according to Bell staging [20].

Secondary outcomes were neonatal death before hospital discharge and severe neonatal morbidity among survivors at discharge.

2.7. Statistical analysis

Data were analyzed using STATA version 14.2 (StataCorp LLC, College Station, TX, USA). All statistical tests were two-sided and statistical significance was set at a 5 % level. In order to take the study design into account and ensure the representativeness of the sample, because of unequal probability of selection of children across GA groups due to varying recruitment durations for births occurring at 22 through 26 weeks GA and at 27 through 31 weeks GA, weighted estimations were computed. The observations weights were inversely proportional to the duration of the recruitment period in their GA group.

2.8. Descriptive statistics

Maternal, obstetrical and neonatal characteristics were described according to GA group (22–27, 28–31 weeks gestation) using bivariate analyses. Categorical variables were summarized using percentages with 95 % confidence intervals (CIs). They were compared between groups using the Pearson chi-square test with a Rao-Scott correction. Continuous variables were summarized using mean ± standard error if normally distributed, median, 1st and 3rd quartile if not normally distributed, and compared across groups using Wald tests. Variance estimates were adjusted for non-independence of observations due to multiple deliveries to the same mother, considering multiples as clustered within a pregnancy.

2.9. Multiple imputation of missing data

Maternal age, multiple pregnancy, gestational age at birth, infant's sex, birthweight and neonatal death were available for all the infants included in the study. Missing values were observed on the other variables, with around than 5 % of missing values for the majority of variables (Table 1 online). The missing-data pattern was explored (Table 1 online). Accordingly, missing data on exposure (PH), outcomes and confounders were multiply imputed by chained equations [21] among the eligible sample, assuming the missing data were missing at random (MAR) as defined in Rubin's terminology.

The imputation model included the variable related to PH diagnosis (proven PH, iNO use and timing of iNO administration before or after 7 days after birth), the potential confounders for the planned analysis model and the primary outcome. Maternal data and neonatal characteristics found to be correlated with PH diagnosis and/or with the outcome in univariate analyses performed on observed data as well as factors predicting non-response to PH treatment, and/or with missing values on the primary outcome were entered in the imputation model as auxiliary variables. As recommended in the literature, these variables were selected to make the MAR assumption more plausible and to improve the prediction models. The list and coding of these variables are reported in Table 2 online. Binary variables were imputed using logistic regression models and categorical variables using multinomial logistic models, while predictive mean matching was used for continuous variables. The imputation model accounting for the sampling weights was applied to generate a total of M = 40 independent imputed datasets, with 10 iterations each. The imputed values were explored by descriptive statistics and compared to observed data, in order to verify that the imputed data were reasonable (Table 2 online). The convergence of the procedure was visually inspected.

2.10. Analysis of the primary outcome on the imputed datasets

The prevalence of PH+ diagnosis was estimated in the total sample and by gestational age group.

The rate of survival without severe neonatal morbidity was modelled by a modified Poisson regression model with robust estimation of variances [22] and estimated by generalized estimating equations (GEE) models that accounted for the clustering effect due to multiple pregnancies [23]. The models were developed on the multiply imputed data, with estimates from each imputed dataset being pooled using Rubin's combination rules [24]. Results were expressed as adjusted incidence rate ratios (aIRR), which can be interpreted as relative risks, and their associated 95 % CIs. Significance of the regression coefficients was based on F statistics.

The primary outcome was assessed by comparing the crude rates of survival without severe morbidity, globally (Model 1) and within each GA group. Model 1 was further adjusted for GA (22–27, 28–31 weeks gestation) (Model 2). The interaction term between GA group and PH was tested at this stage. Baseline variables considered as potential confounding factors were then added to Model 2. Confounders included in the initial model were maternal age at delivery (divided into 3 categories: <25 years, 25–34 years, ≥35 years), mother's country of birth (France versus other country), maternal social insurance coverage (National Health Insurance versus state health aid, universal health insurance or none), maternal education level (higher than high school versus high school or less), antenatal corticosteroid use (no corticosteroids, one incomplete course, one complete course or more), PPROM (yes/no), suspected or proved chorioamnionitis (yes/no), sex of the neonate, Apgar score at 5 min (<7 versus ≥7), growth status at birth (small for gestational age (SGA) yes/no, <10th percentile, EPOPé curves according to Ego et al. [16], surfactant use and respiratory distress syndrome (RDS), categorized as no surfactant use or RDS, surfactant use but no RDS, and RDS), administration of catecholamines before 72 h of life (yes/no), early-onset sepsis (no versus probable or certain). These variables were selected on their clinical relevance, as they were expected to be related both to PH diagnosis and neonatal outcome, or because they were known as predicting the primary outcome [4,14]. Non-significant variables were sequentially eliminated from this initial model: the covariate with the largest *P*-value greater than the significance level was removed, unless its removal led to a relative change in the estimated regression coefficient for PH of 20 % or more.

Interactions between each adjustment variable in turn and GA, and between each maternal or pregnancy covariate in turn and PH diagnosis, were explored in the multivariate regression model. The aim was to detect subgroups of infants where the hypothesized reduction in the rate of survival without severe morbidity linked to PH was more marked. The interaction between PH status and the variable "Surfactant use and RDS" was judged as not relevant and was not tested, because we expected that there would be very few PH+ infants without surfactant administered and PH+ infants without RDS. Interactions found to be significant were removed in a sequential fashion if they did not reach the significance level in the multivariable model. The final adjusted model was named Model 3.

Finally, as we could not exclude the possibility that catecholamines were administered after PH diagnosis among PH+ infants and they could be an intermediary in the causal association between PH and the primary outcome, Model 3 was replicated excluding the covariate "use

of catecholamines before 72 hours" [25].

2.11. Analysis of secondary outcomes after on imputed datasets

Neonatal death rates were estimated and compared according to PH diagnosis and gestational age group. The incidence of neonatal death in each PH group, by gestational age, was presented using survivor functions estimated by the Kaplan-Meier product-limit estimator. Finally, the proportion of severe neonatal morbidity among survivors at discharge was described by PH diagnosis and by gestational age group. Statistical comparison tests between PH groups were performed by using a modified Poisson regression model applied on the multiply imputed datasets. We aimed to distinguish between PH profiles. The PH+ group was separated into two groups: PH+ without iNO treatment, PH+ with iNO. The regression models (Model 1, Model 2 and Model 3) were repeated using this detailed three-category PH variable as the exposition variable.

2.12. Sensitivity analyses

Two sensitivity analyses were performed on the multiply imputed datasets. Because we expected that most PH+ infants would have respiratory distress syndrome, the first sensitivity analysis consisted in applying Model 1, Model 2 and Model 3 after excluding PH+ infants without RDS in order to clarify the role of PH.

3. Results

3.1. Description of the population

Neonates were born in 276 hospitals and the PH+ neonates were hospitalized in 61 level 3 hospitals.

The eligible population for the study consisted of 3383 live-born infants, born between 22 and 31^{+6} weeks gestation, without major malformation(s) and alive at discharge from the maternity unit. Of these infants, 3103 had available data on both the exposition to PH and the survival without severe morbidity (Fig. 1).

The maternal, obstetrical and neonatal characteristics for the total population and according to gestational age groups are presented in Table 3 online. Missing values ranged between 0 % and 18 % (Table 1 online). Among eligible, 1802 observations (53 % of the eligible population) had data available for all variables planned in the analysis model, and 1026 observations had one missing value among the variables planned in the analysis model (including PH and survival without severe morbidity). Missing data were more frequent among deceased infants, and even more frequent among infants deceased before 2 days of life (data not shown). Otherwise, no specific pattern was observed. As a consequence, we assumed that the missing data were MAR. The main results are based on the imputed data.

3.2. Main objectives

The prevalence of PH was estimated at 6.0 % (95 % CI, 5.2–6.9). It differed significantly between the two gestational age groups: 14.5 % (95 % CI, 12.4–16.7) in the 22–27 weeks gestation (WG) group versus 2.7 % (95 % CI, 2.0–3.4) in the 28–31 WG group ($P < .001$). The survival rate without severe morbidity was 30.2 % (95 % CI, 23.7–36.6) in the PH+ group. It was 60 % lower (IRR = 0.39, 95 % CI, 0.32–0.48 in Model 1, $P < .001$) in the PH+ group compared with the PH− group (80.2 %, 95 % CI, 78.7–81.7, Table 1). The IRR did not significantly differ between the two GA groups. (Table 1).

Apart from the presence of chorioamnionitis and the absence of administration of antenatal corticosteroid therapy, no maternal characteristic appeared to be significantly associated with PH at the 5 % threshold in bivariate analyses (performed on the available data). Neonatal factors associated with PH were gestational age, Apgar score at 5 min, oxygenation in the delivery room, administration of surfactant, RDS, treatment of ductus arteriosus with NSAIDs and by surgery, and early onset infection within the first 72 h of life (Table 2).

After adjustment for confounding factors (Model 3), the rate of survival without severe morbidity in PH+ newborns was half that of PH- newborns (aIRR = 0.53, 95 % CI, 0.43–0.65, $P < .001$). This risk ratio did not differ significantly between the two gestational age groups. The

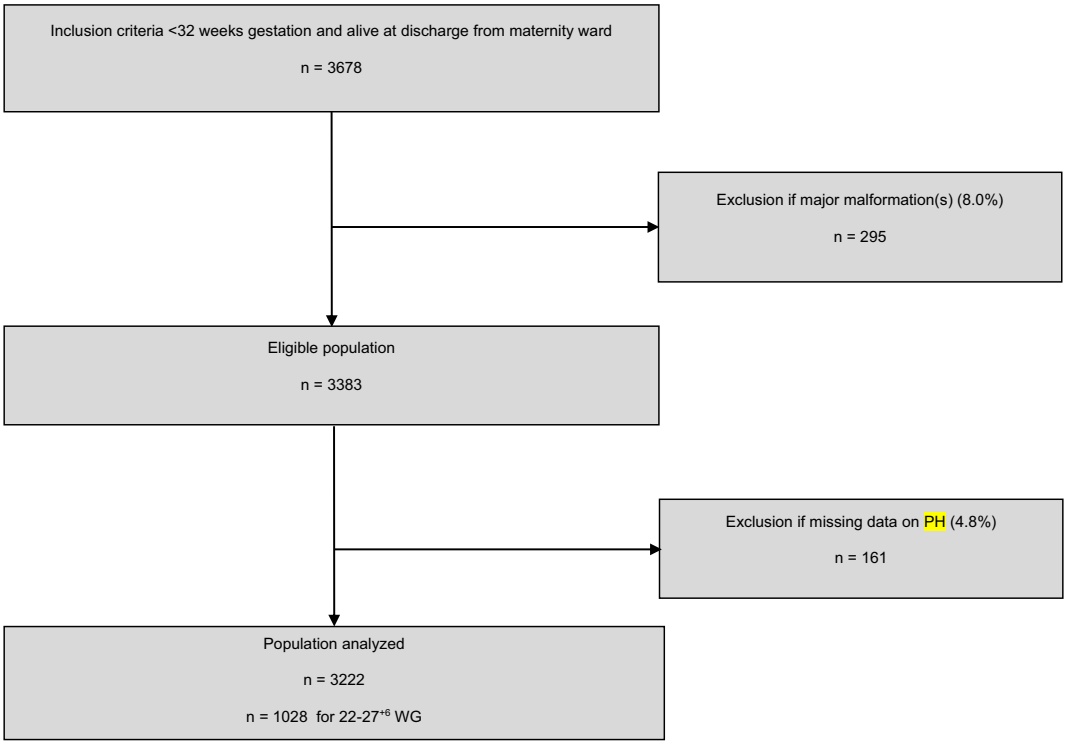

Fig. 1. Flow chart. WG: weeks gestation.

Table 1
Main outcome (survival without severe morbidity) by pulmonary hypertension, globally and by gestational age. Results from the observed data and from the pooled analysis of the imputed datasets. Data were inversely weighted according to duration of recruitment by GA groups. The variance estimation accounted for the clustering effect due to multiple pregnancies.

	22–27^{+6} weeks gestation		28–31^{+6} weeks gestation		22–31^{+6} weeks gestation		
	PH−	PH+	PH−	PH+	PH−	PH+	Total
Complete cases analysis (n = 3103)							
% (95 % CI)	56.4 (52.8–59.9)	21.7 (15.9–29.1)	89.4 (88.0–90.7)	45.9 (33.9–58.4)	81.1 (79.6–82.6)	29.7 (23.8–36.3)	77.9 (76.3–79.4)
Pooled analysis of the MI dataset (M = 40)							
% (95 % CI)	54.8 (51.4–58.2)	22.5 (15.7–29.2)	89.0 (87.6–90.3)	46.5 (33.5–59.5)	80.2 (78.7–81.7)	30.2 (23.7–36.6)	77.2 (75.7–78.7)
P-value	<0.001		<0.001		<0.001		
$IRR_{PH+ \text{ vs } PH-}$ (95 % CI)	0.42 (0.32–0.57)		0.52 (0.39–0.69)		0.39 (0.32–0.48)		

PH, pulmonary hypertension; IRR, incidence rate ratio; CI, confidence interval; MI, multiple imputations.

Model 3 included three interaction terms with gestational age at birth, which reflected that the incidence rate ratios for the variables "small for gestational age", "antenatal steroids" and "surfactant use and RDS" differed between the gestational age groups. The sensitivity analyses produced similar results, with slightly lower IRRs. The sensitivity analyses produced similar results, with slightly lower IRRs.

As we could not exclude the possibility that catecholamines were administered to PH+ infants after the diagnosis of PH and that this could intervene in the causal association between PH and the primary outcome, Model 3 was replicated excluding the covariate "use of catecholamines before 72 hours". In this model, IRR = 0.50, 95 % CI, 0.41–0.61, $P < .001$. The regression model including Model 3 and the distinction between PH treated with iNO and not treated by iNO found an aIRR = 0.37, 95 % CI, 0.27–0.52, $P < .001$, and aIRR = 0.69, 95 % CI, 0.54–0.87, $P < .002$, respectively.

3.3. Secondary objectives

3.3.1. Treatments of PH

The most frequent administered treatment was sedative treatment: 92.2 % of infants (95 % CI, 87.7–95.2), with no significant difference between gestational age groups.

Inhaled NO was administered in 63.5 % (95 % CI, 56.6–69.9) of cases, 60.8 % (95 % CI, 52.5–68.5) for 22–27^{+6} WG infants and 68.9 % (95 % CI, 56.2–79.2) for 28–31^{+6} WG infants ($P = .276$). For all the 22–31^{+6} WG infants, the median age at start of iNO treatment was 1 day of life (Q1–Q3: 0–8). Half of the infants received iNO on day 0 or day 1. Median duration of iNO administration was 2 days (Q1–Q3: 1–6). The median administered dose was 15 ppm (parts per million) (Q1–Q3: 10–15). None of these values differed significantly between the two gestational age groups. Among the PH+ neonates, 48.6 % (95 % CI, 41.9–55.3) received volume expansion within their first 72 h of life, with a median volume of 20 ml/kg (milliliter per kilogram of bodyweight). Volume expansion was more frequent (58.7 % vs 43.5 %, $P = .043$) and the amount received was greater (28 vs 20 ml/kg, $P = .043$) in infants born at 28–31^{+6} weeks gestation compared with those born at 22–27^{+6} weeks.

Lastly, 36.4 % (95 % CI, 30.3–43.1) of PH+ neonates received at least one vasoactive or inotropic drug (dopamine, dobutamine, norepinephrin) before 72 h of life, and 46.0 % (95 % CI, 39.1–53.0) after 72 h.

3.3.2. Death or severe morbidities at discharge

Neonatal death and severe comorbidities according to PH status are summarized in Table 3. Deaths before discharge were >5-fold higher in the PH+ group than in the PH− group (40.5 %, 95 % CI, 33.7–47.2 versus 7.4 %, 95 % CI, 6.5–8.3), respectively, $P < .001$), with differential estimates according to gestational age.

In the 28–31^{+6} WG group, the neonatal death rate was almost 10-fold higher in PH+ than in PH− infants, whereas in the most immature group (22–27^{+6} WG) it was only twice as high, even though the basic death rate was higher in the latter. Overall time between birth and death did not differ according to PH status or gestational age (Table 4 online). Fig. 1 online presents survival functions according to PH status and gestational age.

Respiratory causes accounted for the majority of deaths in the PH+ group. More than half the deceased neonates had severe neurologic impairment (Table 4 online) but this was not the cause of death. There was no difference between PH+ and PH− infants in relation to this factor and no difference regarding discontinuation or limitation of treatment.

Among survivors at discharge, the proportion of neonates with severe morbidity was >3-fold greater among PH+ neonates compared with PH− neonates (49.3 %, 95 % CI, 40.3–58.4 versus 13.4 %, 95 % CI, 12.1–14.7 respectively, $P < .001$), and also in the two gestational age groups (Table 3). In both gestational age groups the main morbidity was bronchopulmonary dysplasia. Intraventricular grade III or IV hemorrhage or cystic periventricular leukomalacia were significantly higher only in the 28–31^{+6} WG group (and was almost 5-fold higher in the PPHN+ group). Conversely, severe retinopathy was higher in the 22–27^{+6} WG group. No difference was observed in the incidence of necrotizing enterocolitis.

4. Discussion

In this study, the prevalence of PH among 22–31^{+6} preterm infants in a large national prospective population-based cohort (EPIPAGE-2) was estimated at 6.0 % (95 % CI, 5.2–6.9) and survival without severe morbidity was 60 % lower in the PH+ group compared with the PH− group.

This is concordant with the rare studies on this subject, with a reported prevalence ranging from 3.4 % [26] to 8.1 % [6]. This overall proportion is much higher than that reported in late preterm and term neonates (0.4 to 6.8 per 1000 live births [1–4]). By gestational age, the prevalence of PH was markedly higher in the 22–27^{+6} WG group (14.5 %) than in the 28–31^{+6} WG group (2.7 %), in agreement with the findings of Nakanishi et al. [6] In this large multicenter cohort study of 12,954 extremely preterm infants (28 WG or less), these authors found that the prevalence of PH increased with decreasing gestational age: 4.4 % for infants born at 27 WG and 18.5 % for infants born at 22 WG.

To our knowledge, our study, which highlights a significantly increased rate of neonatal death and morbidity among PH survivors, is the first to address mortality and morbidity in a large cohort of both extremely preterm and very preterm neonates. In the literature, we found no results on the short-, medium- and long-term outcome of these severely affected infants. Although the prevalence of PH was higher in the group of more immature neonates, the absolute number of very

Table 2
Maternal, obstetric and neonatal characteristics according to the newborn's PPHN status among n = 3222 eligible newborns with known PH status. The analyses are based on observed data before multiple imputation. Weighted estimations are presented; data were inversely weighted according to duration of recruitment by gestational age groups. Taylor-linearized variance estimation is used to account for the clustering effect due to multiple pregnancies.

	PH−		PH+		*P*-value
	Percent (%)	95 % CI	Percent (%)	95 % CI	
Maternal background variables					
Maternal age at infant's birth in years					0.965
Under 25 years	19.1	17.6–20.7	19.4	14.6–25.3	
25 to 34 years old	59.0	57.0–61.0	58.1	51.4–64.6	
35 years old or higher	21.8	20.2–23.6	22.5	17.4–28.5	
Mother living with partner					0.190
No	8.9	7.8–10.1	11.7	7.9–16.9	
Yes	91.1	89.9–92.2	88.3	83.1–92.1	
Mother born in France					0.657
No	24.1	22.3–25.9	22.7	17.4–29.0	
Yes	75.9	74.1–77.7	77.3	71.0–82.6	
Social insurance coverage					0.088
State health aid, universal health insurance or none	11.1	9.9–12.5	15.3	10.7–21.3	
National insurance	88.9	87.5–90.1	84.7	78.7–89.3	
Maternal education level					0.300
Under secondary level	55.4	53.2–57.6	59.8	51.5–67.6	
Higher than secondary level	44.6	42.4–46.8	40.2	32.4–48.5	
Parental socioeconomic status					
Professional or intermediate	83.1	81.5–84.5	82.1	76.0,86.9	
Manual workers	13.0	11.7–14.4	12.1	8.2,17.5	
Not employed	4.0	3.3–4.9	5.8	3.3,10.0	
Maternal body mass index before pregnancy					0.597
Underweight or normal weight	64.8	62.8–66.9	62.7	55.6–69.3	
Overweight	19.4	17.8–21.2	22.4	17.0–28.9	
Obese	15.7	14.2–17.4	14.9	10.5–20.7	
Number of previous deliveries					0.372
At least one previous delivery	64.3	62.3–66.2	61.2	54.5–67.6	
No previous delivery	35.7	33.8–37.7	38.8	32.4–45.5	
Pregnancy variables					
Infertility treatment					0.924
No	83.7	82.0–85.4	83.5	77.5–88.1	
Yes	16.3	14.6–18.0	16.5	11.9–22.5	
Multiple pregnancy					0.397
No	67.3	65.2–69.4	70.2	63.5–76.1	
Yes	32.7	30.6–34.8	29.8	23.9–36.5	
Mother hospitalized during pregnancy					0.460
No	69.3	67.3–71.2	66.8	59.8–73.1	
Yes	30.7	28.8–32.7	33.2	26.9–40.2	
Follow-up of pregnancy					0.495
Adequate	92.6	91.5–93.5	91.2	86.5–94.4	
Not adequate	7.4	6.5–8.5	8.8	5.6–13.5	
Antenatal steroids					0.006
No steroids	16.1	14.7–17.7	24.5	19.1–30.7	
One incomplete course	16.7	15.3–18.3	16.5	12.1–22.2	
At least one complete course	67.1	65.2–69.0	59.0	52.2–65.5	
Premature rupture of membranes					0.235
No	63.9	61.9–65.8	59.8	53.0–66.2	
Yes	36.1	34.2–38.1	40.2	33.8–47.0	
Chorioamnionitis					0.001
No	77.6	75.7–79.4	66.1	58.5–72.9	
Yes	22.4	20.6–24.3	33.9	27.1–41.5	
Infant's delivery and neonatal characteristics					
Cesarean section					0.573
No	34.4	32.5–36.3	36.2	30.1–42.9	
Yes	65.6	63.7–67.5	63.8	57.1–69.9	
Indicated pretermaturity					0.164
No	51.8	49.7–53.9	46.7	39.8–53.7	
Yes	48.2	46.1–50.3	53.3	46.3–60.2	
Gestational age at delivery					<0.001
22 to 27 weeks	25.3	23.6–27.0	66.8	60.0–72.9	
28 to 31 weeks	74.7	73.0–76.4	33.2	27.1–40.0	
Sex of the infant					0.514
Female	47.9	46.0–49.7	45.6	39.1–52.3	
Male	52.1	50.3–54.0	54.4	47.7–60.9	
Small for gestational age					0.163
No	65.4	63.6–67.1	70.1	63.6–75.9	
Yes	34.6	32.9–36.4	29.9	24.1–36.4	
Apgar score at 5 min					<0.001
Score of 7 to10	84.2	82.7–85.5	59.0	52.1–65.6	
Lower than 7	15.8	14.5–17.3	41.0	34.4–47.9	
Presence of minor malformation					0.302
No	96.9	96.2–97.4	95.6	92.0–97.6	
Yes	3.1	2.6–3.8	4.4	2.4–8.0	
Oxygenation of the infant in the delivery room					<0.001
No	26.7	25.0–28.5	11.9	8.1–17.1	
Yes	73.3	71.5–75.0	88.1	82.9–91.9	
Surfactant use					<0.001
No	38.0	36.1–39.9	1.4	0.5–4.4	
Yes	62.0	60.1–63.9	98.6	95.6–99.5	
Respiratory distress syndrome					<0.001
No	45.2	43.3–47.2	9.5	6.2–14.5	
Yes	54.8	52.8–56.7	90.5	85.5–93.8	
Early onset infection within the first 72 h of life					0.001
No	80.6	79.0–82.1	70.5	63.7–76.4	
Probable or sure	19.4	17.9–21.0	29.5	23.6–36.3	

(*continued on next page*)

Table 2 (*continued*)

	PH−		PH+		*P*-value
	Percent (%)	95 % CI	Percent (%)	95 % CI	
Late onset sepsis among survivors after 2 days of life					<0.001
No	80.5	79.0–81.9	65.3	58.6–71.5	
Yes	19.5	18.1–21.0	34.7	28.5–41.4	
Administration of catecholamines					<0.001
0 – no	83.1	81.7–84.5	42.4	36.0–49.1	
1 – yes	16.9	15.5–18.3	57.6	50.9–64.0	
Administration of catecholamines before 72 h of life					<0.001
No	93.8	92.8–94.6	63.6	56.9–69.7	
Yes	6.2	5.4–7.2	36.4	30.3–43.1	
Administration of catecholamines after 72 h of life					<0.001
No	91.8	90.8–92.8	54.0	47.0–60.9	
Yes	8.2	7.2–9.2	46.0	39.1–53.0	
NSAIDs for persistent ductus arteriosus					<0.001
No	77.8	76.2–79.4	51.7	44.9–58.4	
Yes	22.2	20.6–23.8	48.3	41.6–55.1	
Surgery for persistent ductus arteriosus					**<0.001**
No	96.3	95.6–96.9	83.6	78.0–88.0	
Yes	3.7	3.1–4.4	16.4	12.0–22.0	

P-values from Pearson Chi-square test with Rao-Scott correction.
PH, persistent pulmonary hypertension of the newborn; CI, confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs.
Underweight is defined as body mass index (BMI) of <18.5 kg/m^2; normal weight is defined as BMI of 18.5 to 24.9 kg/m^2; overweight is defined as BMI of 25.0 to 29.9 kg/m^2; obesity is defined as BMI higher than 30.0 kg/m^2.
Small for gestational age is defined as a birthweight <10th percentile, EPOPé curves according to Ego et al.

preterm neonate births is known to be generally higher than that of extremely preterm neonates [14]. This represents a larger number of infants requiring treatment for challenging and life-threatening PH, and there is no consensus on the limits of aggressive management of a severe condition among very vulnerable and immature neonates.

As found in a few studies [6,26], PH was associated with chorioamnionitis and with the administration of antenatal corticosteroids, but not with PROM. This result was unexpected because PROM can be responsible for infections and pulmonary hypoplasia, which are both major factors suspected of increasing pulmonary vascular resistances. Study of extremely preterm neonates with PROM at 22–25 WG (neonates also included in the EPIPAGE-2 study [27] and born between 23 and 27 WG) found a mortality rate similar to our population (48.3 % in PROM neonates versus 48.1 % in PH neonates). Survival without severe morbidity was lower in our PH population (22.5 %) than in the PROM population (38.8 %), but PROM is only one of the numerous causal factors of PH. Besides, neonatal factors associated with PH were gestational age, Apgar score at 5 min, treatment of ductus arteriosus, RDS and the onset of early infection within the first 72 h of life. Only the first three of these factors were also found to be associated with PH in a Japanese cohort consisting exclusively of preterm infants aged <28 WG [6].

Our analyses showed that survival without severe morbidity was significantly lower in the PH+ group (30.2 %) than in the PH− group (80.2 %). This is the first study to propose composite criteria for estimating the global impact of PH in preterm infants. Nakanishi et al. [6] found a significantly higher prevalence of bronchopulmonary dysplasia and severe intraventricular hemorrhage (20 % in PH+ patients versus 7 % in PH−). Unlike us, these authors also observed an increased prevalence of necrotizing enterocolitis and severe retinopathy. In our study, the occurrence of grade III or IV intraventricular hemorrhage or cystic periventricular leukomalacia was increased only in the 28–31^{+6} PH+ group. Overall, our study suggests that the impact of PH differs according to GA group. Although neonatal deaths were high in both groups, the difference tended to be more marked in the second group (28–31^{+6} WG), probably because, as could be expected, the more immature infants had a higher death rate. This was also true of overall severe morbidity, which was proportionately higher in the 28–31^{+6} WG group (4-fold higher) than in the 22–27^{+6} WG group, where it was twice as high.

Treatment of PH is quite aggressive, generally including sedative drugs, optimization of alveolar recruitment (with high frequency oscillation ventilation if required), iNO, hemodynamic support by volume expansion (if required) and vasoactive drugs. These interventions are now well established for the management of PPHN of term neonates [28–31] but they are not so common in preterm infants, particularly in extremely preterm infants [9]. The use of iNO has been widely studied in preterm infants, but not in this indication: Mercier et al. [32], Hascoet et al. [33] and more recently Greenough et al. [13] concluded that iNO for the prevention of bronchopulmonary dysplasia in very premature infants with respiratory distress did not result in long-term benefits or adverse long-term sequelae. However, the neonates studied were very different from ours, as they did not have PH. Besides, Barrington et al. [34] in 2017 in a Cochrane database review examined the effects of iNO on death, severe morbidity and neurodevelopmental outcome when this treatment was prescribed for hypoxic respiratory failure (however, hemodynamic status and the presence or absence of pulmonary hypertension were not detailed). The authors concluded that iNO does not appear to be effective as rescue therapy for very ill preterm infants. Nevertheless, some case reports and a study by Baczynski et al. [8] found that iNO was effective in 46 % of cases of PH among extremely preterm neonates, with improved oxygenation and a better survival rate without severe morbidity if immediate response to treatment was good. In the latter study [8], all neonates were treated with iNO and the prognosis of non-responders was poor. However, comparison with our data is difficult. In the EPIPAGE-2 cohort study, iNO was not administered to all neonates with a diagnosis of pulmonary hypertension, but only to 63.5 % of them, with no difference between GA groups.

One of the limitations of our study is the mode of selection of PH neonates. The diagnosis was established from database entries but the time of onset of PH after birth was not stated for neonates who were not treated with iNO (for these ones on the contrary, we could date the beginning of the disease with the beginning of administration of iNO). We cannot exclude the possibility that in a few neonates (PH not treated with iNO or with delayed treatment) the condition arose from a secondary cause of pulmonary hypertension (late sepsis or bronchopulmonary dysplasia). This is another limitation of the study. Besides, in 2011 systematic screening of PH wasn't the routine and the diagnosis of PH is hence likely to be an underestimated. Nevertheless, all the neonates included had refractory hypoxemia and we believe that the pathophysiological mechanism of PH is increased pulmonary vascular resistance. This criterion was present in all our study population.

5. Conclusion

In this nationwide population-based cohort of extremely preterm and very preterm infants, the prevalence of PH was estimated at 6 %, with higher prevalence in the more immature infants. PH was associated with significantly decreased survival without severe morbidity at discharge.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2023.105837.

Table 3
Neonatal death among the eligible sample (n = 3383 observations) and severe neonatal morbidity among survivors at hospital discharge, by pulmonary hypertension, globally and by GA. Results of complete cases analysis and pooled analysis of the multiply imputed dataset. Weighted estimations are presented; data were inversely weighted according to duration of recruitment by gestational age groups. Variance estimation accounted for the clustering effect due to multiple pregnancies.

	22–27^{+6} weeks of gestation		28–31^{+6} weeks of gestation		22–31^{+6} weeks of gestation	
	PH−	PH+	PH−	PH+	PH−	PH+
	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)	% (95 % CI)
Neonatal death						
Pooled analysis of the MI dataset (M = 40)	21.4 (18.7–24.2)	48.1 (40.0–56.1)	2.5 (1.9–3.2)	24.3 (13.2–35.5)	7.4 (6.5–8.3)	40.5 (33.7–47.2)
P-value	<0.001†		<0.001†		<0.001†	
Among survivors at hospital discharge						
Severe neonatal morbidity						
Pooled analysis of the MI dataset (M = 40)	30.2 (26.7–33.7)	56.7 (45.7–67.8)	8.7 (7.5–10.0)	38.5 (23.9–53.1)	13.4 (12.1–14.7)	49.3 (40.3–58.4)
P-value	<0.001†		<0.001†		<0.001†	
Intraventricular hemorrhage grade III or IV or cystic periventricular leukomalacia						
Complete cases analysis (n = 2877)	9.3 (7.3–11.7)	11.0 (5.8–19.8)	3.5 (2.8–4.3)	16.7 (8.6–29.9)	4.8 (4.0–5.6)	13.3 (8.5–20.4)
P-value	0.607		<0.001		<0.001	
Bronchopulmonary dysplasia						
Complete cases analysis (n = 2847)	16.7 (13.9–20.0)	41.9 (31.4–53.2)	2.2 (1.6–2.9)	21.7 (12.1–35.9)	5.3 (4.5–6.2)	33.5 (25.7–42.2)
P-value	< 0.001		< 0.001		< 0.001	
Retinopathy ≥ 3 or laser						
Complete cases analysis (n = 2897)	3.3 (2.2–5.0)	9.7 (5.1–17.7)	0.1 (0.0–0.4)	0.0 (NA)	0.8 (0.6–1.2)	5.7 (3.0–10.6)
P-value	0.004		0.790		<0.001	
Necrotizing enterocolitis Bell stage II–III						
Complete cases analysis (n = 2876)	1.7 (1.3–3.0)	1.5 (0.2–10.2)	1.7 (1.2–2.4)	4.1 (1.0–14.9)	1.7 (1.3–2.3)	2.6 (0.9–7.9)
P-value	0.937		0.209		0.448	
Mechanical ventilation duration (days)						
Complete cases analysis (n = 2902)						
Median (Q1-Q3)	8 (2–21)	28 (17–35)	1 (0–2)	9 (6–19)	1 (0–4)	20 (8–32)
Non-invasive ventilation duration (days)						
Complete cases analysis (n = 2770)						
Median (Q1–Q3)	34 (2–47)	38 (22–50)	6 (2–18)	19 (5–32)	9 (2–27)	29 (16–46)
Corrected age at discharge (weeks gestation)						
Complete cases analysis (n = 2899)						
Median (Q1–Q3)	39 (37–41)	41 (38–44)	37 (36–38)	39 (37–41)	37 (36–39)	40 (38–43)
≥43 weeks	14.5 (12.0–17.4)	38.6 (28.7–49.6)	3.3 (2.6–4.2)	18.4 (9.8 31.7)	5.7 (4.9–6.7)	30.2 (23.0–38.5)

PH, pulmonary hypertension; IRR, incidence rate ratio from GEE Poisson regression model with robust SE; CI, confidence interval; MI, multiple imputation.
† *P*-value from GEE Poisson regression model with robust SE.

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Declaration of competing interest

None of the authors have any conflict of interest.

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