|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Type 1 BPD (n=931) | Type 2 BPD (n=447) | Type 3 BPD (n=402) | p |
| Gestational age (weeks) | 27.4 (26.1-28.7) | 26.8 (25.6-28.4)\* | 26.7 (25-28.7) \* | <0.01 \* |
| Weight (g) | 935 (791.5-1114) | 850 (728-1000) \* | 815 (650-1028) \* | <0.01 \* |
| Prenatal corticosteroids | 88.5% (821) | 88.2% (389) | 89.5% (357) | 0.831 |
| Sex (male) | 52.2% (482) | 57% (254) | 61.8% (247) \* | 0.019 |
| Clinical chorioamnionitis | 15% (140) | 13.6% (61) | 13.7% (55) | 0.902 |
| Histological chorioamnionitis | 14.3% (133) | 14.5% (65) | 11.4% (46) | 0.646 |
| Intrauterine growth restriction | 16.6% (148) | 20.7% (88) | 25.1% (94) \* | 0.004 † |
| Oligohydramnios | 10.4% (95) | 15.0% (66) \* | 15.8% (62) \* | 0.013\*  |
| Maternal age | 34 (29-37) | 33 (29.2-37) | 33.5(29-37) | 0.811 |
| Mother smoked during pregnancy | 17.4% (35/201) | 14.3% (13/91) | 13.9% (11/79) | 0.845 |
| Asthmatic mother | 10.1% (20/198) | 13.6% (12/88) | 12% (9/75) | 0.724 |
| Asthmatic father | 7.8% (15/193) | 9.4% (8/85) | 5.9% (4/68) | 0.658 |
| Intubation at birth | 41.1% (383/932) | 50.3% (225/447)\* | 56.20% (226/402)\* | <0.001 |
| FiO2 > 0.30 at birth  | 68.6% (635/925) | 77.4% (340/439)\* | 80.8% (319/395)\* | <0.001 |
| FiO2 > 0.60 at birth  | 14.8% (137/925) | 24.6% (108/439)\* | 30.9% (122/395)\* | <0.001 |
| Intubation in first hour of life | 45.9% (428/931) | 58.2% (260/447)\* | 61.4% (247/402)\* | <0.001 |
| Surfactant | 71.70% (660/921) | 80% (351/439)\* | 77.5% (306/395) | 0.005  |
| Two or more surfactant doses | 27.2% (171/629) | 38.6% (128/332)\* | 47% (139/296)\* | <0.001  |
| Caffeine therapy | 98.7% (918/930) | 98.4% (435/442) | 95.5% (379/397)\*† | 0.001 |
| MV during hospitalization | 66.7% (620/929) | 82.6% (366/443)\* | 89% (356/400)\*† | <0.001 |
| Noninvasive respiratory support | 99.40% (926/932) | 99.3% (441/444) | 98% (387/395) | 0.09 |
| Nitric oxide therapy | 6.6% (61/927) | 14.4% (63/437)\* | 28% (111/396)\*† | <0.001 |
| Ectopic air | 5.10% (47/928) | 8.4% (37/443) | 13.6% (54/396)\*† | <0.001 |
| MV, days  | 6 (2-14) | 12 (5-25)\* | 27 (11-44)\*† | <0.001 |
| Positive pressure, days | 25 (14-36) | 33 (18-48)\* | 45 (31-66.2)\*† | <0.001 |
| High-flow oxygen, days | 11 (0-21) | 13 (3-24)\* | 25 (11.7-39)\*† | \*0.045 ;\*†<0.001 |
| Oxygen, days | 42 (30-54) | 67 (50-82)\* | 73 (49.5-103.5)\* | <0.001 |
| Postnatal corticosteroids for BPD | 17.8% (166) | 30.4% (136)\* | 53.2% (214)\*† | <0.001 |
| Nosocomial sepsis  | 51.7% (470/909) | 60.8% (265/436)\* | 74.6% (288/386)\*† | <0.001 |
| Nosocomial pneumonia | 6% (55/912) | 18.7% (82/438)\* | 36.2% (141/389)\*† | <0.001 |
| Patent ductus arteriosus (PDA) | 46.1% (409/887) | 57.0% (220/386)\* | 64.6% (223/345)\*† | <0.001 |
| PDA surgical closure | 4.8% (45/933) | 14.8% (66/447)\* | 22.1% (89/402)\*† | <0.001 |
| Necrotizing enterocolitis (surgical) | 4.3% (39/914) | 4.8% (21/438) | 8.4% (32/382)\* | 0.027 |
| Diagnosis of PH | 4.5% (41/914) | 12.1% (53/438)\* | 20.9% (82/392)\*† | <0.001 |
| Maximum volume of fluid in first 72 h | 110 (109.9-123.1) | 110 (110-115.1) | 116 (100-132) | 0.843 |
| Time until exclusively EN | 15 (17.5-19.7) | 18 (20.6-25.4)\* | 21 (24.3-34.4)\*† | \*<0.001; †0.013  |
| Time until exclusively EN by mouth | 65 (62. 7-66.3) | 74 (71.9-77.8)\* | 88 (85.5-98.3)\*† | <0.001 |

Table 1. Incidence of pre- and postnatal factors by severity of BPD. Data expressed in percentage (n) or median (interquartile range). Abbreviations: g (grams); FiO2 (fraction of inspired oxygen); MV (mechanical ventilation); HFO (high-flow oxygen); BPD (bronchopulmonary dysplasia); PDA (patent ductus arteriosus); PH (pulmonary hypertension); EN (enteral nutrition); h (hours); \* significant difference with type 1 BPD; † significant difference with type 2 BPD.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Type 1 BPD (n=931) | Type 2 BPD (n=447) | Type 3 BPD (n=402) | p |
| Leukomalacia (> grade 1) | 3.8% (34/895) | 4.4% (19/428) | 9.9% (37/376) \*† | <0.001 |
| IVH (grade 3 or higher) | 6.1% (55/898) | 7.7% (33/427) | 10.3% (39/377) \* | 0.032  |
| Periventricular infarction | 16.4% (131/801) | 16.8% (61/363) | 18.1% (62/341) | 0.39 |
| Ventriculoperitoneal shunt | 2.1% (13/633) | 2.6% (7/273) | 3.5% (11/313) | 0.406 |
| Retinopathy  | 33.0% (289/877) | 47.1% (181/384) \* | 51.6% (177/343) \* | <0.001  |
| Retinopathy greater than grade 2 | 19.7% (58/294) | 27.8% (52/187) | 42.9% (78/182) \*† | <0.001  |
| Respiratory support at discharge | 3.9% (36/913) | 29.1% (127/436) \* | 52.1% (177/ 372) \*† | <0.001 |
| Feeding by NGT/gastrostomy | 2.7% (25/931) | 2.9% (13/447) | 13.4% (54/402) \*† | <0.001 |
| Bronchodilators | 1.4% (13/931) | 3.6% (16/447) \* | 11.9% (48/402) \*† | <0.001 |
| Inhaled corticosteroids | 7% (65/931) | 16.3% (73/447) \* | 19.2% (77/402) \* | <0.001  |
| Diuretics  | 5% (47/931) | 8.1% (36/447) | 19.7% (79/402) \*† | <0.001 |
| Antireflux treatment | 4% (37/931) | 8.7% (39/447) \* | 18.9% (76/402) \*† | <0.001 |
| Mortality | 0.7% (6/905) | 0.7% (3/428) | 4.5% (17/377) \*† | <0.001 |

Table 2. Incidence of hospital morbidity by type of BPD. Data expressed in percentage (n). Abbreviations: IVH (intraventricular hemorrhage); NGT (nasogastric tube); \* significant difference with type 1 BPD; † significant difference with type 2 BPD.

|  |  |  |  |
| --- | --- | --- | --- |
|   | TYPE 2/3 BPD vs 1 (raw) | TYPE 2/3 BPD vs 1 (adjusted for prenatal factors: GA, sex, IUGR, oligohydramnios) | TYPE 2/3 BPD vs 1 (adjusted for prenatal factors and length of exposure to MV) |
|   | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| GA (weeks) | 0.956 | 0.918-0.995 | 0.026 | 0.876 | 0.832-0.923 | <0.001 | 1.02 | 0.96-1.084 | 0.523 |
| Weight (g) | 0.999 | 0.999-1 | <0.001 | 0.999 | 0.999-1 | <0.001 | 1 | 0.999-1 | 0.237 |
| Sex, male | 1.329 | 1.101-1.604 | 0.003 | 1.511 | 1.238-1.844 | <0.001 | **1.394** | **1.142-1.727** | **0.002** |
| Oligohydramnios | 1.567 | 1.18-2.082 | 0.002 | 1.506 | 1.12-2.025 | 0.007 | **1.568** | **1.142-2.152** | **0.005** |
| IUGR | 1.478 | 1.161-1.882 | 0.002 | 1.753 | 1.347-2.281 | <0.001 | **1.611** | **1.216-2.134** | **0.001** |
| Histological chorioamnionitis | 0.905 | 0.690-1.186 | 0.469 | 0.886 | 0.663-1.184 | 0.414 | 1.116 | 0.817-1.525 | 0.490 |
| Intubation at birth | 1.627 | 1.349-1.963 | <0.001 | 1.588 | 1.297-1.945 | <0.001 | 1.037 | 0.828-1.298 | 0.753 |
| FiO2 >. 30 at birth  | 1.72 | 1.384-2.136 | <0.001 | 1.627 | 1.294-2.046 | <0.001 | **1.303** | **1.02-1.33** | **0.034** |
| FiO2 >. 60 at birth  | 2.19 | 1.729-2.775 | <0.001 | 2.132 | 1.663-2.735 | <0.001 | **1.622** | **1.239-2.123** | **<0.001** |
| Intubation in first hour of life | 1.749 | 1.449-2.111 | <0.001 | 1.694 | 1.383-2.075 | <0.001 | 1.064 | 0.849-1.333 | 0.592 |
| Caffeine therapy | 0.426 | 0.212-0.843 | <0.016 | 0.280 | 0.136-0.580 | 0.001\* | 0.804 | 0.358-1.808 | 0.598 |
| Surfactant | 1.468 | 1.179-1.828 | 0.001 | 1.435 | 1.136-1.813 | 0.002 | 1.016 | 0.718-1.438 | 0.927 |
| Two or more surfactant doses | 1.981 | 1.564-2.509 | <0.001 | 1.752 | 1.364-2.251 | <0.001 | **1.313** | **1.003-1.717** | **0.047** |
| MV during hospitalization | 2.974 | 2.349-3.765 | <0.001 | 2.823 | 2.188-3.643 | <0.001\*\* | 1.319 | 0.994-1.751 | 0.055 |
| Duration of invasive MV, days | 1.06 | 1.051- 1.071 | <0.001 | 1.062 | 1.052-1.073 | <0.001 |   |  |  |
| Noninvasive respiratory support | 0.488 | 0.18-1.325 | 0.159 | 0.331 | 0.103-1.07 | 0.065 | 0.351 | 0.094-1.317 | 0.132 |
| Nitric oxide therapy | 3.748 | 2.753-5.106 | <0.001 | 3.863 | 2.783-5.361 | <0.001 | 1.447 | 0.987-2.123 | 0.058 |
| Ectopic air | 2.28 | 1.583-3.286 | <0.001 | 2.383 | 1.617-3.513 | <0.001 | 1.125 | 0.726-1.743 | 0.599 |
| NEC (surgical) | 1.55 | 1.014-2.371 | 0.043 | 1.435 | 0.918-2.241 | 0.113 |  **0.472 0.275-0.811 0.007** |
| PDA | 1.728 | 1.428-2.90 | <0.001 | 1.671 | 1.348-2.071 | <0.001 | 1.08 | 0.822-1.418 | 0.582 |
| Nosocomial sepsis | 1.92 | 1.579-2.334 | <0.001 | 1.721 | 1.394-2.125 | <0.001 | 1.143 | 0.87-1.501 | 0.338 |
| Nosocomial pneumonia | 5.753 | 4.207-7.867 | <0.001 | 6.719 | 4.806-9.395 | <0.001 | **1.055** | **1.043-1.063** | **<0.001** |
| Periventricular leukomalacia (> grade 1) | 1.896 |  (1.224-2.936) | 0.004 | 1.816 | 1.150-2.866 | 0.010 | 1.297 | 0.787-2.138 | 0.308 |

Table 3. Analysis of the association of pre- and postnatal factors with the development of type 2/3 BPD vs type 1. Raw and adjusted OR with 95% Cis.

Abbreviations: BPD (bronchopulmonary dysplasia); GA (gestational age); IUGR (intrauterine growth restriction); g (grams); FiO2 (fraction of inspired oxygen); MV (mechanical ventilation); PDA (patent ductus arteriosus).

\* Adjusted for GA only. \*\* Interaction between exposure to mechanical ventilation and gestational age. † All patients were exposed to MV.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|   | $<$26 wk GA (473) | 26–28 wk. GA (657) | 28–30 wk. GA (461) | $\geq $30 wk GA (189) | p |
| GA (weeks) | 25 (24.5-25.4) | 26.8 (24.4-27.4) | 28.7 (28.3-29.1) | 30.8 (30.2-32) | <0.001\* |
| Weight (g) | 711 (623-800) | 900 (780-1000) | 1055 (890-1200) | 1250 (980-1593) | <0.001\* |
| Sex, male | 49.80% (234/470) | 56.00% (366/654) | 56.80% (259/456) | 66.30% (124/187) | 0.001 |
| Corticosteroids | 92.10% (432/469) | 86.70% (568/655) | 90.10% (409/454) | 83.00% (156/188) | <0.001 |
| Intrauterine growth restriction | 5.20% (23/443) | 16.10%(101/626) | 30.10%γ ‡(133/442) | 40.00%γ‡(72/180) | <0.001 |
| Oligohydramnios | 11.00% (51/463) | 13.60% (88/646) | 12.70% (57/448) | 14.40% (27/187) | 0.54 |
| Histological chorioamnionitis | 21.60% (102/473) | 16.60% /109/657) | 6.50%γ ‡(30/461) | 1.60%γ ‡(3/189) | <0.001 |
| Intubation at birth | 68.30% (323/473) | 47.00% (309/657) | 31.50%γ ‡(145/461) | 29.60%γ ‡56/189) | <0.001 |
| FiO2 > .60 at birth | 31.00% (144/465) | 21.10% (137/650) | 12.10%γ ‡(55/456) | 16.70% (31/186) | <0.001 |
| Surfactant | 80.40% (373/464) | 76.60% (498/650) | 73.60% (335/455) | 59.20%γ ‡§(109/184) | <0.001 |
| Caffeine therapy | 99.6% (464/466) | 99.2% (647/552) | 99.3% (457/460) | 85.7% (162/189) γ ‡§ | <0.001 |
| Refractory hypoxemia | 13.50% (64/473) | 7.90% (52/657) | 6.50% (30/461) | 7.90% (15/189) | 0.001 |
| MV during hospitalization | 93.40% (437/468) | 78.30% (512/654) | 60.80%γ ‡(279/459) | 59.80%γ ‡(113/189) | <0.001 |
| Duration of MV, days | 22 (10-35) | 8 (3-20) | 5 (1-11) | 9 (3-26.2) γ § | <0.001 |
| PH | 10.8% (50/461) | 8% (52/649) | 8% (36/448) | 20.5%γ ‡§ (38/185) | <0.001 |
| Nitric oxide therapy | 18.70% (87/465) | 9.70% (63/651) | 10.30% (47/456) | 20.40%‡§ (38/186) | <0.001 |
| Postnatal corticosteroids | 50.30% (238/473) | 26.30% (173/657) | 15.80%γ‡ (73/461) | 16.90%γ‡ (32/189) | <0.001 |
| Patent ductus arteriosus | 74.70% (343/459) | 56.30% (363/645) | 37.00% (166/449) | 25.70% (47/183) | <0.001 \* |
| Nosocomial sepsis | 76.80%(351/457) | 59.90% (385/643) | 47.50%γ‡(211/444) | 40.90%γ‡ (76/186) | <0.001 |
| Necrotizing enterocolitis (surgical) | 8.30% (38/458) | 6.00% (39/647) | 2.20%γ‡(10/445) | 2.70% (5/183) | <0.001 |
| Ectopic air | 9.80% (46/468) | 5.80%(38/652) | 5.40% (25/459) | 15.60% (29/186) | <0.001 |
| Type 2/3 bronchopulmonary dysplasia | 59.80% (283/473) | 43.20% (284/657) | 37.10% (171/461) | 58.70%‡§ (111/189) | <0.001 |
| Type 3 bronchopulmonary dysplasia | 31.30% (148/473) | 18.00% (118/657) | 17.10% (79/461) | 30.20%‡§ (57/189) | <0.001 |

Table 4. Incidence of risk factors by gestational age groups. Data expressed in percentage (n) or median (interquartile range). Abbreviations: wk. (weeks); FiO2 (fraction of inspired oxygen); MV (mechanical ventilation); PH (pulmonary hypertension). \* Significant difference between all the gestational age groups.  Significant difference with the less than 26 weeks’ gestation group. ‡ Significant difference with the 26–28 weeks’ gestation group. § Significant difference with the 28–30 weeks’ gestation group.