Bronchopulmonary Dysplasia in Very Preterm Infants with Symptomatic Congenital Cytomegalovirus Infection: A Propensity Score-Matched Analysis

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Objective To assess whether symptomatic congenital cytomegalovirus infection (cCMV) is associated with bronchopulmonary dysplasia (BPD) and mortality in very preterm infants (gestational age ≤32 weeks).

Study design We performed a retrospective study using the Kids' Inpatient Database for 2003, 2006, 2009, and 2012. Diagnoses of BPD and symptomatic cCMV were determined using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. Among patients with in-hospital birth at ≤32 weeks of gestation, cases of symptomatic cCMV were matched with infants without cCMV using propensity score matching at 1:2 ratio. Outcomes of BPD and in-hospital mortality were assessed using conditional logistic regression.

Results Of 204 818 in-hospital births with gestational age ≤32 weeks, we identified 208 cases of symptomatic cCMV, 177 of which underwent matching. Symptomatic cCMV was associated with higher odds of BPD (OR, 2.34; 95% CI, 1.41-3.87), but was not significantly associated with in-hospital all-cause mortality (OR, 1.18, 95% CI, 0.64-2.17).

Conclusions Symptomatic cCMV was associated with BPD but not with in-hospital mortality among very preterm infants. Further study is needed to determine the risk of BPD among infants with cCMV to allow for evaluation of possible preventive measures. *(J Pediatr 2019;204:142-7).*

Cytomegalovirus is capable of infecting a broad range of human cells, secondary to tropisms for epithelial, endothelial, and smooth muscle cells, and fibroblasts.[1,2] Among these, the virus has a particular tropism for lung epithelium in vitro.[3,4] In the setting of congenital infection, an autopsy study of 34 fetuses with congenital cytomegalovirus infection (cCMV) diagnosed in utero has shown that the viral antigen can be detected in the lungs of 87% of subjects.[5] In human fetal cells in vitro and fetal mice, cytomegalovirus causes delayed lung maturation and decreased surfactant production.[6,7] Disruption of lung development results in distorted airways and pulmonary vasculature, causing impaired gas exchange with vulnerability to inflammatory insults from oxygen toxicity and ventilator induced volutrauma, leading to the development of bronchopulmonary dysplasia (BPD).[8] Because infection with cytomegalovirus results in substantial inflammation,[9] pulmonary infection may further facilitate the lung damage.[10] Published case reports suggest that pulmonary involvement of cCMV can manifest as severe respiratory distress with subsequent BPD.[11-14] However, pulmonary manifestation is not considered a main feature of cCMV,[15] and is more commonly implicated in perinatally or postnatally acquired cytomegalovirus infection.[10,16,17] In contrast, the risk of BPD is increased among very low birth weight infants with postnatal infection,[18,19] although such an association with congenital infection has not been extensively studied. Because BPD results in marked morbidity,[20,21] the knowledge of populations at risk would be important, possibly allowing for administration of preventive measures, such as cautious use of respiratory support or oxygen. In this study, we sought to characterize the association between cCMV and BPD, using a large sample of neonates and propensity score matching.

Methods

We performed a population-based retrospective study using the Kids' Inpatient Database (KID) for 2003, 2006, 2009, and 2012,[22] with propensity score matching. The KID is compiled by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality and released every 3 years, with the most current data from 2012. The KID is the largest publicly available all-payer pediatric inpatient care database in the US, containing a 10% sample of uncomplicated in-hospital births and an 80% sample of other pediatric discharges from all nonfederal, short-term, general, and other specialty hospitals in

BPD	Bronchopulmonary dysplasia
cCMV	Congenital cytomegalovirus infection
GA	Gestational age
ICD9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
KID	Kids' Inpatient Database

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participating states (data available at https://www.hcup-us.ahrq.gov/db/availability_public.jsp).

Discharge records from January 1 to December 31 in 2003, 2006, 2009, and 2012 were collected and analyzed. We identified discharge records with in-hospital birth using a variable provided by the database indicating whether the patient was born during the hospitalization. Among records with in-hospital births, cases with a diagnosis of cCMV were captured by searching for *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9-CM) code 771.1 (congenital cytomegalovirus infection) in any of the diagnoses listed in the database. Symptomatic disease was considered to be present when cases with cCMV were accompanied by 1 or more of the following ICD9-CM codes: thrombocytopenia (287.3, 287.4, 287.5, 776.1), requirement for platelet transfusion (procedure code 99.05), petechiae (287.2, 772.6, 782.7), hepatomegaly (789.1), splenomegaly (289.51, 789.2), intrauterine growth restriction (764), hepatitis (070.9, 571.4, 571.8, 571.9, 573.1, 573.2, 573.3, 774.4), microcephaly (742.1), other central nervous system involvement (331.3, 331.4, 742.2, 742.3, 742.4, 779.7), or chorioretinitis (363.0, 363.1, 363.20).[15,23,24]

Delivery methods were classified into cesarean delivery or vaginal delivery (ICD9-CM codes V3x.01 and V3x.00, respectively, where x can be 0, 1, 2, 3, 4, 5, 6, 7, or 9). Gestational age (GA) at birth was determined by evaluating each case for the codes 765.21-765.29. Birth weight was determined using the codes 764.01-09, 764.11-19, 764.21-29, 764.91-764.99, 765.01-09, 765.11-19, and V21.31-35. The following ICD9-CM diagnosis codes were used to further characterize each record: 772.13-4 for intraventricular hemorrhage grade 3 or 4, 777.5 for necrotizing enterocolitis, 747.0 for patent ductus arteriosus, 770.7 for BPD, and 96.70-72 and 96.04 (procedure code) for invasive respiratory support.

Statistical Analyses

The outcomes of BPD and in-hospital mortality in very preterm infants (GA ≤32 weeks) were compared between infants with symptomatic cCMV and those without cCMV. We used nearest-neighbor propensity score matching at a 1:2 with a caliper width equal to 0.25 of the SD of the logit of the propensity score.[25] We included the following variables in a logistic regression model to estimate propensity scores: GA, birth weight, cesarean birth, sex, race/ethnicity, primary payer, geographic location of the birth hospital, birth year, need for invasive respiratory support, intrauterine growth restriction, necrotizing enterocolitis, patent ductus arteriosus, and grade 3 or 4 intraventricular hemorrhage.[18] We examined the distribution of propensity scores across groups by visual inspection of quantile-quantile plots and side-by-side boxplots.[26,27] We assessed the balance of the variables included in the propensity score model between the cCMV group and the no-cCMV group using the Pearson χ^2 test.

The outcomes of BPD diagnosis at the time of discharge and in-hospital mortality were assessed at the within-sample level by fitting simple conditional logistic regression models, conditioning on the propensity score-matched data. For the cohort without matching, simple logistic regression was used. Possible temporal changes in the association between each outcome and cCMV diagnosis were assessed by developing models, including interaction terms between cCMV status and the year variable. Race data were missing in 18.0% of the entire cohort, whereas the rest of the variables had <5% missing values. Under an assumption that the values were missing completely at random, we performed complete-case analyses in this study. An additional propensity score matching was performed without including the race variable, which was missing in many cases, although we did not plan this analysis a priori.

We performed additional analyses to assess whether our conclusions would have changed had different subpopulations been used for comparison. For these analyses, we used the same procedure described above for matching and subsequent analyses, but used the following criteria for selecting cases: (1) infants with cCMV with birth GA ≤32 weeks regardless of symptomatic status; (2) infants with symptomatic cCMV with birth GA ≤28 weeks; and (3) infants with symptomatic cCMV with birth weight ≤1500 g.

Data were analyzed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). We used the MatchIt package in R to perform propensity score generation and matching. We used a 2-sided significance level of 0.05 in all analyses. The authors who had direct access to the data completed Healthcare Cost and Utilization Project data use agreement training. This study was classified as non-human subjects research based on communication with the Institutional Review Board of the University of Mississippi Medical Center.

Results

Among a total of 204 818 in-hospital births with GA of ≤32 weeks, we identified 269 infants with a diagnosis of cCMV. Of these, 208 were determined to have symptomatic disease. Infants with a diagnosis of cCMV without symptomatic disease were excluded from the analysis. Among the infants with symptomatic cCMV, 31 had missing variables used for propensity score estimation (**Figure**). Among the infants without cCMV, 40 888 had missing variables used for matching (**Figure**). A total of 177 infants with symptomatic cCMV underwent propensity score matching at a 1:2. The matched non-cCMV group comprised 354 infants. Although the cohort without matching had substantial imbalances in characteristics, propensity score matching resulted in groups with balanced characteristics (**Table I**).

In the propensity score-matched cohort, the odds of BPD were significantly higher in infants with symptomatic cCMV than in infants without cCMV (OR, 2.34; 95% CI, 1.41-3.87; $P < .001$) (**Table II**). In contrast, the odds of in-hospital all-cause mortality were not significantly different between infants with cCMV and those without cCMV (OR, 1.18; 95% CI, 0.64-2.17) (**Table II**). We found no temporal changes in the associations between symptomatic cCMV and BPD, as indicated by the lack of interaction between cCMV and the year variable. In the cohort without matching, the association of symptomatic cCMV and BPD also was observed although the magnitude of the association was greater, indicating the

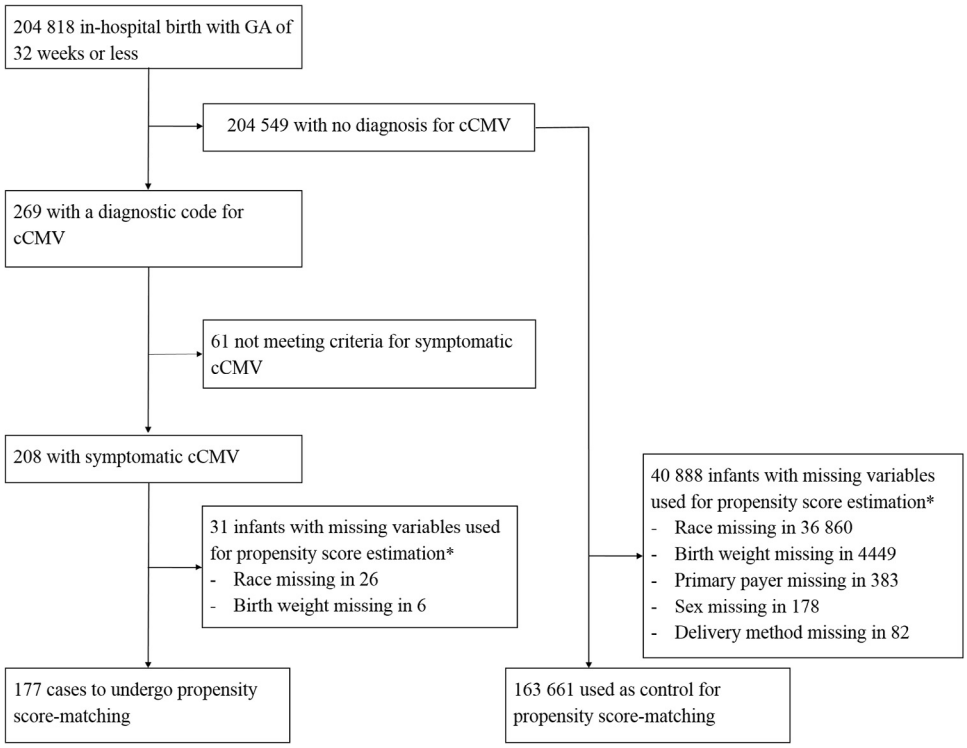

Figure. Flow chart of enrolled subjects. *Numbers do not match up because of cases with multiple missing variables.

presence of confounding factors adjusted by propensity score matching (**Table II**). Because the race variable was missing in as many as 14.9% of infants with symptomatic cCMV and 18% of those without cCMV, an additional propensity score-matched analysis was performed without including the race variable in the propensity score estimation model, the conclusion derived from which was the same (data not shown).

Analyses with propensity score matching conducted in all infants with cCMV (regardless of symptoms status), infants of GA ≤28 weeks with symptomatic cCMV, and infants with birth weight ≤1500 g with symptomatic cCMV showed similar results (**Table III**; available at www.jpeds.com).

Discussion

Using a large sample of pediatric discharges and propensity score matching, we found that the odds for BPD was 134% higher among very preterm infants (GA ≤32 weeks) with symptomatic cCMV compared with infants without cCMV with similar characteristics, although mortality was not significantly affected.

During the past several decades, the survival of preterm or low birth weight infants who are at risk for BPD has substantially increased with improvements in clinical care.[28] On the other hand, cCMV occurs at a certain rate (approximately 0.45%-0.6%) in newborns,[29-31] and symptomatic cCMV tends to be diagnosed in preterm infants.[23,24] However, information on the association of cCMV and lung disease has been scanty. Here we provide data to shed light on this association using a large database and propensity score matching, which suggest a link between cCMV and BPD.

Although no single intervention has been identified to prevent BPD with guaranteed success, some interventions may be effective in reducing the risk of BPD. These interventions include fluid restriction, caffeine therapy, and vitamin A supplementation,[32-34] in addition to protective ventilation strategies. Whether these interventions or antiviral therapy against cCMV can be effective in reducing the risk of BPD in infants with cCMV is unknown and should be a focus of future research studies.

We used propensity score matching to select a cohort of infants without cCMV who were similar to those with symptomatic cCMV in demographic and clinical characteristics, because direct comparison was expected to be heavily confounded. Low birth weight is a common feature of symptomatic cCMV, and cCMV is commonly diagnosed in preterm infants who are more likely to develop BPD and mortality.[23,24] In addition, baseline characteristics of cCMV can differ from those in the general population of neonates, because cCMV is more commonly seen in infants of minority race and low socioeconomic status.[24,35] In our study, the presence of confounding was indicated by the change in the magnitude of association, although the association remained strong even after propensity score matching.

Table I. Characteristics of the neonates included in the analysis

Characteristics	cCMV (N = 177), n (%)	No cCMV: Cohort without propensity score matching (N = 163 661) n (%)	*P* value	No cCMV: Cohort with propensity score matching (N = 354) n (%)	*P* value
Male sex	91 (51.4)	86 989 (53.2)	.70	169 (47.7)	.48
Race*			.03		.98
White	83 (46.9)	73 795 (45.1)		170 (48)	
Black	43 (24.3)	39 835 (24.3)		84 (23.7)	
Hispanic	23 (13.0)	32 534 (19.9)		42 (11.9)	
Other	28 (15.8)	17 497 (10.7)		58 (16.4)	
Birth hospital region			<.001		>.99
Northeast	17 (9.6)	30 926 (18.9)		33 (9.3)	
Midwest	26 (14.7)	26 902 (16.4)		53 (15)	
South	101 (57.1)	66 542 (40.7)		202 (57.1)	
West	33 (18.6)	39 291 (24.0)		66 (18.6)	
Birth year			<.001		.90
2003	14 (7.9)	30 142 (18.4)		23 (6.5)	
2006	35 (19.8)	38 038 (23.2)		73 (20.6)	
2009	69 (39)	46 379 (28.3)		133 (37.6)	
2012	59 (33.3)	49 102 (30.0)		125 (35.3)	
Cesarean birth	137 (77.4)	103 612 (63.3)	<.001	285 (80.5)	.47
GA, wk			<.001		.93
29-32	88 (49.7)	101 663 (62.1)		172 (48.6)	
25-28	62 (35)	40 856 (25.0)		130 (36.7)	
≤24	27 (15.3)	21 142 (12.9)		52 (14.7)	
Birth weight, g			<.001		>.99
>2500	0	1994 (1.2)		0	
2000-2499	<10† (1.1)	12 220 (7.5)		<10† (1.1)	
1500-1999	16 (9.0)	48 653 (29.7)		29 (8.2)	
1000-1499	68 (38.4)	51 705 (31.6)		136 (38.4)	
500-999	78 (44.1)	39 375 (24.1)		161 (45.5)	
<500	13 (7.3)	9714 (5.9)		24 (6.8)	
Intrauterine growth restriction	26 (14.7)	6298 (3.8)	<.001	47 (13.3)	.76
Necrotizing enterocolitis	17 (9.6)	6096 (3.7)	<.001	23 (6.5)	.27
Intraventricular hemorrhage	13 (7.3)	4785 (2.9)	.004	29 (8.2)	.86
Invasive respiratory support	131 (74)	83 899 (51.3)	<.001	250 (70.6)	.47
Patent ductus arteriosus	81 (45.8)	29 891 (18.3)	<.001	172 (48.6)	.60

*18.0% missing in the cohort without matching.
†Cells with <10 observations are omitted from presentation following the recommendation by the Healthcare Cost and Utilization Project.

This study has some limitations. First, because of the nature of retrospective research using administrative data, we needed to rely solely on accurate reporting of diagnostic codes for identification of cCMV cases and BPD. Diagnostic coding can vary among treating providers. To minimize the possibility of including postnatally acquired cytomegalovirus infection, we restricted the ICD9-CM code for identifying cCMV to 771.1 (congenital cytomegalovirus infection), and did not include 078.5 (cytomegaloviral disease) or 484.1 (pneumonia in cytomegalic inclusion disease). For diagnosing BPD, the National Institutes of Health issued a consensus statement in 2001, which likely has decreased the variation in BPD diagnosis in practice.[36,37] Nevertheless, the possibility of bias from miscoding or misdiagnosis cannot be excluded. Second, in relation to the reliance on ICD9-CM codes for identification of cases, some infants identified as "non-cCMV" actually may be cytomegalovirus-positive, because universal screening is currently not performed. If this had occurred, the 2 groups would have become more homogeneous regarding cCMV status, theoretically mitigating any differences secondary to this factor.

Table II. Clinical outcomes of symptomatic cCMV (GA ≤32 weeks)

Outcomes	cCMV (N = 177), n (%)	No cCMV: Cohort without propensity score matching (N = 163 661) n (%)	OR (95% CI)*	*P* value	No cCMV: Cohort with propensity score matching (N = 354) n (%)	OR (95% CI)†	*P* value
BPD	49 (27.7)	14 792 (9.0)	3.85 (2.75-5.32)	<.001	58 (16.4)	2.34 (1.41-3.87)	<.001
Death	21 (11.8)	18 793 (11.5)	1.04 (0.64-1.60)	.88	37 (10.5)	1.18 (0.64-2.17)	.60

*Obtained using simple logistic regression.
†Obtained using conditional logistic regression, conditioning on the propensity score-matched set.

Because we observed a significant difference, we believe this would not have altered our conclusion. Third, the database used in this study does not allow for assessing when each diagnosis code was assigned during the hospitalization. This can affect the accuracy of symptomatic status of cCMV, although we would expect the bias from this source to be minimal, given that the analysis including all cases of cCMV led to the same conclusion. Fourth, the incidence of BPD varies among institutions.[38] This variation has decreased after the aforementioned consensus on BPD diagnosis,[39] although the difference in institutional respiratory management of neonates may play a role in the variance in the incidence of BPD.[40] The KID sampling frame of virtually all acute care hospitals from a large number of the US states has likely accounted for this variance; however, the possibility of selection bias cannot be excluded. Fifth, propensity score matching does not guarantee the balance of variables not included in the model. In particular, we did not include sepsis, which is a known predisposing factor for BPD,[41] because we felt that ICD9-CM codes might not capture sepsis diagnoses accurately. Although we included many of the variables that might affect the likelihood of cCMV diagnosis and BPD development, the possibility of bias cannot be excluded.

Further study is needed to determine the risk of BPD in infants with cCMV to enable evaluation of possible preventive measures. ■

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Table III. Clinical outcomes of cCMV, additional analyses

	All cCMV*				GA ≤28 wk				Birth weight ≤1500 g			
Outcomes	cCMV (N = 229), n (%)	No cCMV (N = 458), n (%)	OR (95% CI)	*P* value	cCMV (N = 89), n (%)	No cCMV (N = 178), n (%)	OR (95% CI)	*P* value	cCMV (N = 159), n (%)	No cCMV (N = 318), n (%)	OR (95% CI)	*P* value
BPD	66 (28.8)	74 (16.2)	2.44 (1.59-3.73)	<.001	44 (49.4)	54 (30.3)	2.38 (1.37-4.15)	.002	47 (29.6)	53 (16.7)	2.43 (1.46-4.04)	<.001
Death	21 (9.2)	50 (10.9)	0.81 (0.47-1.41)	.46	14 (15.7)	33 (18.5)	0.79 (0.38-1.65)	.54	20 (12.5)	42 (13.2)	0.94 (0.52-1.70)	.84

*Matched on infants with cCMV, regardless of symptomatic status; 40 cCMV cases had missing variables used for propensity score estimation.