Peer Review File

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To Reviewer A:

We are very grateful for reviewer's supportive and constructive comments that help us improve our manuscript in many aspects. We've carefully reviewed and addressed the issues raised by the comments, which are listed below:

1. *For non-Chinese readers, please write a bit more about the "outborn" hospitals. For example, in your results include how far away they are compared to the closest perinatal center. Did any outborn center have a level 2 NICU? Or were they only hospitals with a newborn nursery? Giving a bit more detail can help the reader understand the full picture.*

   Reply: Thank you very much for comments. Definitely, these are important information. The outborn hospitals were hospitals with level I or level II NICUs or hospitals without neonatal care. At the time of this study, all transports were by land or railway without air transportation. Unfortunately, we did not collect the information on the level of neonatal care in each referral hospital or the distance of transport. We have added the information regarding the outborn hospitals in method and include the lack of detailed information in the limitation.
   Change in the text:

   Definitions

   Inborn status was defined as infants born in the eighteen perinatal centers participating in our study and subsequent admitted to the NICU of the same hospital. Outborn status was defined as infants born in level I or level II NICUs or hospitals without neonatal care, and transferred to one of the eighteen participating perinatal centers within 7 days after birth.

   Discussion

   Also, we did not collect the information on the level of neonatal care in each referral hospital or the distance of transport.

2. *In your discussion, please include more about what contributing factors led these outborn patients to be outborn. Was it distance (the mother was in active labor,*

and closest center was the outborn center?), was it education/awareness (mother did not know which center was preferred when she went inot preterm labor?), is it obstetric education (OBs are not aware of improved VPI outcomes for patients born at a perinatal center?, is it economic (OBs are reluctant to transfer mothers in preterm labor to a perinatal center due to loss of revenue from the delivery), or other factors?

Reply: Thank you very much for your professional suggestions. Understanding the contributing factors are essential for future quality improvement efforts to reduce outborn rates. We found mothers of outborn infants were less likely to receive prenatal care and antenatal steroids, and were less likely to delivery by caesarean section. These findings may indicate possible lower awareness of prenatal care of these mothers, as well as possible lower socioeconomic status which prevented them to receive appropriate care. This may also indicate the differences in medical resources and expertise between tertiary perinatal centers and lower-level perinatal centers on the management of preterm birth. However, we did not collect information regarding the socioeconomic or education status of mothers. We also did not have information on care practice and attitude of VPI delivery in referral hospitals. There is also a lack of literatures from China focusing on the topic of outborn. Therefore, we would choose not to expand the discussion regarding the contributing factors of outborn, since it will be mainly from supposition instead of objective data. We have added the lack of such information in limitation. In-depth survey is needed to investigate the contributing factors and to guide targeted quality improvement efforts. Thank you again for comments.

Change in the text:

Discussion

In addition, we also did not collect information regarding the socioeconomic or education. status of mothers.

3. *Do you have data on maternal or paternal education that you can add into Table 1? Sometimes education or socioeconomic background can be different among perinatal centers and outborn hospitals. Knowing this can help inform future interventions to increase births at the perinatal centers.*

Reply: Thank you very much for comments. Unfortunately, we didn't collect data on parental or maternal education level. We will include such information in future investigations.

Change in the text:

Discussion

In addition, we also did not collect information regarding the socioeconomic or education status of mothers.

4. *Nearly all of the poor outcomes in outborns (mortality, IVH, the trend towards NEC), save DAMA, can be explained by lower incidence of antenatal cortico steroids in ouborn alone. Have you considered including steroids in the covariates you controlled for in your multivariate analysis to show the outcomes related to outborn vs inborn?*

Reply: Thank you very much for professional comments. Antenatal steroids were not included because we considered that it might be an intermediate variable between outborn status and neonatal outcomes. We thought that the inclusion of antenatal steroids might weaken the relationship between outborn status and the prognosis.

We repeated the analysis including steroids in the covariates of the multivariate model. The results are as followed. The association between outborn status and mortality and brain injury remained significant.

	Adjusted Odds Ratio		
	Inborn	Outborn	P
DAMA	Reference	1.4 (1.2-1.6)	<0.001
In-hospital mortality	Reference	0.9 (0.7-1.1)	0.221
Overall mortality	Reference	1.1 (1.0-1.3)	0.019
Sepsis	Reference	1.0 (0.8-1.2)	0.950
BPD	Reference	0.8 (0.7-1.0)	0.105
IVH or PVL	Reference	1.3 (1.0-1.5)	0.016
NEC	Reference	0.7 (0.5-0.9)	0.018
Severe ROP	Reference	1.0 (0.6-1.8)	0.881

Change in the text:
Statistical analysis

We repeated the analysis including steroids in the covariates of the multivariate model, the. association between outborn status and mortality and brain injury remained significant.

To Reviewer B:

1. *Introduction: Introduction seems lengthy with commentary on many studies on outborns – would be good to summarize the main points from the studies presented. Also, some background on the perinatal care and outcomes in preterm infants in China would be helpful.*

   Reply: Thank you very much for your kind suggestion. We have modified the introduction.

   Change in the text:

   Introduction

   Babies born at less than 32 weeks (very preterm infants) represent about 16% of all preterm births, but account for the majority of preterm deaths (1). Many studies from various countries reported better outcomes of preterm infants born in tertiary perinatal centers (inborn) compared with those delivered in hospitals without capability to provide comprehensive care for preterm infants and transferred to tertiary centers for further treatment (outborn) (2, 3, 4, 5, 6, 7, 8, 9, 10). Outborn infants were found to have higher risks of mortality and severe brain injury compared with inborn infants (2, 3, 4, 6, 8). In 2002, the American Academy of Pediatrics and American College of Obstetricians and Gynecologists recommended that births at <32 weeks' gestational age should occur at subspecialty perinatal centers (11).

   Although there have been significant improvements of perinatal care in China, problems remain. More and more preterm infants received active care in NICUs in the recent decades, while the mortality and morbidities of very preterm infants remained high requiring quality improvement of perinatal care practices. Also, the regionalization of care for high risk mothers and the transferring systems of high-risk mothers instead of neonates has not well been established(12). Information about outborn status and outcomes of preterm infants in relation to outborn status has not been reported in China. In our study, we use the largest contemporary cohort of preterm infants born less than 32 weeks' gestation from 18 perinatal centers in China, aiming to describe the incidence of outborns in Chinese perinatal centers, and to compare neonatal outcomes of outborn and inborn infants in China. These data will provide insights to modification of current perinatal care system in China. We present the following article in accordance with the STROBE reporting checklist.

2. *Study design and settings: Line 7: change to … from May 1st, 2015 to April 30, 2018*

   Reply: Thank you sincerely for your detailed review. We have modified accordingly.

   Change in the text:
   Study design and settings

   The current study is a cohort study using data from a clinical database initially

established for a cluster randomized controlled study entitled “Reduction of Infection in Neonatal Intensive Care Units using the Evidence-based Practice for Improving Quality (EPIQ)” (REIN-EPIQ study, clinicaltrials.gov #NCT02600195). Twenty-five hospitals prospectively collected clinical data, including maternal and neonatal characteristics, treatment in the NICU and neonatal outcomes, of all admitted preterm infants using this data base from May 1st, 2015 and April 30th, 2018. All data collection followed a standard manual of operations and definitions (13).

3. *Study design and settings : It would be helpful to get a sense for the workflow for transportation of neonatal patients to the 18 perinatal centres. Specifically: Did this study specifically exclude births that may have occurred at home/outside the hospital? For perinatal centres without dedicated transport teams, do they rely on other transport systems ? Are these transports teams specific to neonatal care – ie are they specifically trained in neonatal care ?Is it possible to get an idea as to the range in distances and modes of transport for these infants?*

Reply: Thank you very much for comments. The study included all infants born outside participating tertiary hospitals including those who were born at home. For perinatal centers without dedicated transport teams, local medical emergency transport systems provided the transportation, however, staff of these general transport systems were not trained in neonatal care and the ambulances were not equipped with incubators and other necessary equipment for neonatal transport. At the time of this study, the majority of transports were by land, very few by railway and no by air. Unfortunately, we did not collect the information on the distance of transport. We have added the information regarding the outborn hospitals in method and include the lack of detailed information in the limitation.

Change in the text:
Definitions

Inborn status was defined as infants born in the eighteen perinatal centers participating in our study and subsequent admitted to the NICU of the same hospital. Outborn status was defined as infants born in level I or level II NICUs or hospitals without neonatal care, and transferred to one of the eighteen participating perinatal centers within 7 days after birth. The study included all infants born outside participating tertiary hospitals including those who were born at home.

Study design and settings

For perinatal centers without dedicated transport teams, local medical emergency transport systems provided the transportation, however, staff of these general transport systems were not trained in neonatal care and the ambulances were not

equipped with incubators and other necessary equipment for neonatal transport. At the time of this study, the majority of transports were by land, very few by railway and no by air.

Discussion:

There are some limitations of our study should be noted. We did not collect the information about the treatment received by outborn infants had in the delivery hospital, the infants who died in the delivery room and attitude of VPI delivery in referral hospitals. Also, we did not collect the information on the level of neonatal care in each referral hospital or the distance of transport. In addition, we also did not collect information regarding the socioeconomic or education status of mothers.

4. *What specific criteria were used to determine maternal diabetes and maternal hypertension in this study?*

Reply: Thank you very much for question. Maternal diabetes includes 4 types: Gestational diabetes: Diabetes which was first time diagnosed during this pregnancy; Type 1 diabetes or juvenile onset diabetes: Diabetes diagnosed at younger age; Type 2 diabetes or adult onset: Diabetes diagnosed during adulthood; Unknown type: Reported as diabetes but type is unknown.

Maternal hypertension includes 3 types: Pre-existing hypertension: Hypertension that was preexisting before current pregnancy; Gestational hypertension: Hypertension diagnosed first time during this pregnancy; Hypertension but timing unknown: Reported as hypertension but timing unknown.

We have modified our text as advised (see the part of definitions).

Change in the text:

Definitions
Maternal diabetes included gestational diabetes, Type 1 diabetes, Type 2 diabetes. or diabetes. with unknown type. Maternal hypertension included hypertension that was preexisting before current pregnancy, gestational hypertension and hypertension with unknown timing.

5. *The definition of outborn was to include infants who were transported from non-participating hospitals. It is unclear if these transferring hospitals are from other non-participating NICUs or otherwise? It would be important to state if these occurred from hospitals with lower level of care or no neonatal care or otherwise.*

Reply: Thank you very much for comments. The outborn hospitals were hospitals with level I or level II NICUs or hospitals without neonatal care. We have added the information in method.

Change in the text:
Definitions

Inborn status was defined as infants born in the eighteen perinatal centers participating in our study and subsequent admitted to the NICU of the same hospital. Outborn status was defined as infants born in level I or level II NICUs or hospitals without neonatal care, and transferred to one of the eighteen participating perinatal centers within 7 days after birth. The study included all infants born outside participating tertiary hospitals including those who were born at home.

6. *Definition of clinical sepsis: clinical manifestation needs to be clarified (are there specific signs and symptoms or as per treating physicians) and also the typical laboratory cutoff and criteria used (WBC, procalcitonin, CRP)*

Reply: Thank you very much for comments. Clinical sepsis was diagnosed when all the following criteria were fulfilled: 1) infection-related clinical manifestations; 2) abnormal white blood cell count (white blood cell $<5 \star 10^9$/L or $>20 \star 10^9$/L), CRP level (≥8mg/L), or PCT level (>0.5ng/ml); 3) antibiotics used or intended for ≥5 days; 4) negative blood culture with no or negative cerebrospinal fluid culture; 5) no evidence of concurrent focal infection, including pneumonia, urinary tract infection, and necrotizing enterocolitis.

Change in the text:

Definitions

Sepsis included both culture-proven sepsis and clinical sepsis. Culture-proven sepsis was diagnosed according to Stoll et al (19). Clinical sepsis was diagnosed when all the following criteria were fulfilled: 1) infection-related clinical manifestations; 2) abnormal white blood cell count (white blood cell $<5\times10^9$/L or $>20\times10^9$/L), CRP level (≥8mg/L), or PCT level (>0.5ng/ml); 3) antibiotics used or intended for ≥5 days; 4) negative blood culture with no or negative cerebrospinal fluid culture; 5) no evidence of concurrent focal infection, including pneumonia, urinary tract infection, and necrotizing enterocolitis.

7. *The justification of the covariates that are included in the multivariate model and analysis should be justified further. It is unclear to me how certain variables were included. The statement of the exclusion of antenatal steroids, Apgar score and*

TRIPS score in the model to be confusing and should be clarified. This is especially important as antenatal steroids significantly impacts on the risk of mortality and outcomes.

Reply: Thank you very much for professional and important comments. Antenatal steroids, Apgar score and TRIPS score were not included because we considered that they might be intermediary variable in the causal pathway of outborn and adverse outcomes. Outborn status might result in suboptimal perinatal care, including insufficient antenatal steroids use, inappropriate resuscitation which was related with lower Apgar score, as well as post-resuscitation care (e.g., temperature control) which resulted in higher illness-severity score. We think that the inclusion of these variables might weaken the relationship between outborn status and outcomes. Current model may help us to establish a relationship between outborn status and outcomes, and the differences of antenatal steroids use, Apgar score and TRIPS score may provide explanation for such relationship. The covariates of our model were similar to recent publications (e.g., Erik A Jensen, Scott A Lorch. Effects of a Birth Hospital's Neonatal Intensive Care Unit Level and Annual Volume of Very Low-Birth-Weight Infant Deliveries on Morbidity and Mortality. JAMA Pediatr 2015 Aug;169(8):e151906).

We also repeated the analysis including steroids in the covariates of the multivariate model. The results are as followed. The association between outborn status and mortality and brain injury remained significant.

	Adjusted Odds Ratio		
	Inborn	Outborn	P
DAMA	Reference	1.4 (1.2-1.6)	<0.001
In-hospital mortality	Reference	0.9 (0.7-1.1)	0.221
Overall mortality	Reference	1.1 (1.0-1.3)	0.019
Sepsis	Reference	1.0 (0.8-1.2)	0.950
BPD	Reference	0.8 (0.7-1.0)	0.105
IVH or PVL	Reference	1.3 (1.0-1.5)	0.016
NEC	Reference	0.7 (0.5-0.9)	0.018
Severe ROP	Reference	1.0 (0.6-1.8)	0.881

(Adjusted for sex, gestational age, SGA, maternal hypertension, maternal diabetes and antenatal steroids)

Change in the text:
Statistical analysis

The covariates of our model were similar to recent publications (2). We repeated the analysis including steroids in the covariates of the multivariate model, the association between outborn status and mortality and brain injury remained significant.

8. *Results: The results section can be expanded further. Were there any infants who were born of multiple gestation births? And if so, how were they handled in the analysis.*

Reply: Thank you very much for the question. The status of multiple birth was not collected in the first year of study and only available in the last two years of study. We have added the data in Table 1. We also repeat our multi-variable analysis in known singleton infants. The results are similar. We have included this in our supplemental results as sensitivity analysis (Supplemental Table 2).

Change in the text:

Table 1 Infant and maternal characteristics

	Inborn N=10023	Outborn N=1991	P
Gestational age, mean (SD)	29.9 (1.6)	29.8(1.6)	0.01
22weeks, n/8 (%)	8/8(100)	0/8(0)	
23weeks, n/14 (%)	14/14(100)	0/14(0)	
24weeks, n/71 (%)	64/71(90.1)	7/71(9.9)	
25weeks, n/175 (%)	149/175(85.1)	26/175(14.9)	
26weeks, n/436 (%)	363/436(83.3)	73/436(16.7)	
27weeks, n/781 (%)	655/781(83.9)	126/781(16.1)	
28weeks, n/1520 (%)	1221/1520(80.3)	299/1520(19.7)	
29weeks, n/2166 (%)	1795/2166(82.9)	371/2166(17.1)	
30weeks, n/2914 (%)	2441/2914(83.8)	473/2914(16.2)	
31weeks, n/3929 (%)	3313/3929(84.3)	616/3929(15.7)	
Birth weight, mean (SD)	1388.1(322.7)	1393.3(306.2)	0.5
<750g, n/194 (%)	168/194(86.6)	26/194(13.4)	
750-999g, n/1068 (%)	927/1068(86.8)	141/1068(13.2)	
1000-1249g, n/2732 (%)	2254/2732(82.5)	478/2732(17.5)	
1250-1499g, n/3517 (%)	2945/3517(83.7)	572/3517(16.3)	
1500-1999g, n/4132 (%)	3409/4132(82.5)	723/4132(17.5)	
≥2000g, n/370 (%)	319/370(86.2)	51/370(13.8)	
Male, n/N (%)	5653/10022(56.4)	1196/1991(60.1)	0.003

SGA, n/N (%)	1064/10022(10.6)	204/1991(10.3)	0.6
Multiple birth[a], n/N (%)	2244/7214 (31.1%)	335/1347 (24.9%)	<0.001
1-min Apgar≤3, n/N (%)	600/9972(6.0)	182/1744(10.4)	<0.001
5-min Apgar≤3, n/N (%)	120/9606(1.3)	56/1528(3.7)	<0.001
TRIPS score, median (IQR)	15.3(13)	16.3(1)	<0.001
Prenatal care, n/N (%)	9857/9984(98.7)	1908/1953(97.7)	<0.001
Maternal hypertension, n/N (%)	1373/9964(13.8)	265/1926(13.8)	1.0
Maternal diabetes, n/N (%)	1286/9966(12.9)	131/1924(6.8)	<0.001
Antenatal steroids, n/N (%)	7275/9895(73.5)	812/1755(46.3)	<0.001
Primigravida, n/N (%)	3556/10018(35.5)	682/1988(34.3)	0.3
Caesarean section, n/N (%)	4748/10023(47.4)	639/1988(32.1)	<0.001

[a] Data on multiple birth was only collected during the last two years of study.

Abbreviations: SD, Standard Deviation; SGA, small for gestational age infant; TRIPS, Transport Risk Index of Physiologic Stability; IQR, interquartile range.

Supplemental Table 2 Crude and adjusted risks of morality and morbidities for outborn infants compared with inborn infants among singletons

	Crude Odds Ratio			Adjusted Odds Ratio[a]		
	Inborn	Outborn	P	Inborn	Outborn	P
DAMA	Reference	1.7 (1.4-2.0)	<0.001	Reference	1.7 (1.4-2.0)	<0.001
In-hospital mortality	Reference	0.9 (0.7-1.2)	0.543	Reference	0.9 (0.7-1.2)	0.511
Overall mortality	Reference	1.4 (1.1-1.6)	<0.001	Reference	1.4 (1.1-1.6)	0.001
Sepsis	Reference	1.1 (0.8-1.4)	0.661	Reference	1.0 (0.8-1.3)	0.832
BPD	Reference	1.0 (0.8-1.2)	0.771	Reference	0.9 (0.8-1.2)	0.577
IVH or PVL	Reference	1.3 (1.1-1.7)	0.015	Reference	1.3 (1.1-1.7)	0.015
NEC	Reference	0.9 (0.7-1.3)	0.570	Reference	0.9 (0.6-1.2)	0.362
Severe ROP	Reference	0.8 (0.4-1.6)	0.456	Reference	0.8 (0.4-1.6)	0.514

[a] The covariates controlled for in this model included sex, gestational age, small for gestational age infant, maternal hypertension, maternal diabetes.

Abbreviations: DAMA, Discharge against medical advice; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorraghe; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

9. *More than 1/3 of the cohort is >1500gm – the risk of adverse outcomes would be much lower in this group. I think that additional stratification of the analysis focusing on those <1500gm would be helpful.*

Reply: Thank you very much for comments. We have repeated the analysis among infants <1500gm. The association of outborn with mortality remained significant. There was a trend of increased risk of severe brain injury among outborn infants, but not significant. We suspected that was partially because of the overall high rate of brain injury in China. We have included this in our supplemental results as sensitivity analysis (Supplemental Table 3).

Change in the text:

Supplemental Table 3 Crude and adjusted risks of morality and morbidities for outborn infants compared with inborn infants among infants <1500g

	Crude Odds Ratio			Adjusted Odds Ratio[a]		
	Inborn	Outborn	P	Inborn	Outborn	P
DAMA	Reference	1.5 (1.3-1.7)	<0.001	Reference	1.5 (1.3-1.8)	<0.001
In-hospital mortality	Reference	1.0 (0.8-1.3)	0.748	Reference	1.0 (0.8-1.3)	0.708
Overall mortality	Reference	1.3 (1.1-1.5)	<0.001	Reference	1.3 (1.1-1.5)	<0.001
Sepsis	Reference	1.0 (0.8-1.3)	0.678	Reference	1.0 (0.8-1.3)	0.838
BPD	Reference	0.9 (0.8-1.1)	0.528	Reference	0.9 (0.8-1.1)	0.278
IVH or PVL	Reference	1.1 (0.9-1.4)	0.325	Reference	1.1 (0.9-1.4)	0.231
NEC	Reference	0.8 (0.6-1.1)	0.136	Reference	0.8 (0.6-1.1)	0.121
Severe ROP	Reference	0.7 (0.4-1.2)	0.243	Reference	0.8 (0.4-1.3)	0.345

[a] The covariates controlled for in this model included sex, gestational age, small for gestational age infant, maternal hypertension, maternal diabetes.

Abbreviations: DAMA, Discharge against medical advice; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorraghe; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

10. *As clinical sepsis is ambiguous especially since it involves multiple centres with potentially different protocols, I think it might be reasonable to separate clinical and culture confirmed sepsis. Or to consider only including culture-positive cases.*

Reply: Thank you very much for comments. In our previous study, we found that because of different protocols and suboptimal culture practice, blood cultures were less frequent to be done than they were needed in some hospitals, and the positive rates of blood culture were relatively low in Chinese NICUs. Use culture-positive cases would significantly underestimate the incidence of true

infection in Chinese NICUs. Therefore, we defined sepsis as culture-proven and clinical sepsis, with relatively strict diagnostic criteria for clinical sepsis (as described in Question 6). We did the analysis separately for culture-proven sepsis and clinical sepsis, and found that there was no significant relationship between outborn status and culture-proven or clinical sepsis. Therefore, we combined these two types of sepsis in our manuscript.

Change in the text:

Definitions

Sepsis included both culture-proven sepsis and clinical sepsis. Culture-proven sepsis was diagnosed according to Stoll et al (19). Clinical sepsis was diagnosed when all the following criteria were fulfilled: 1) infection-related clinical manifestations; 2) abnormal white blood cell count (white blood cell $<5\times10^9$/L or $>20\times10^9$/L), CRP level (≥8mg/L), or PCT level (>0.5ng/ml); 3) antibiotics used or intended for ≥5 days; 4) negative blood culture with no or negative cerebrospinal fluid culture; 5) no evidence of concurrent focal infection, including pneumonia, urinary tract infection, and necrotizing enterocolitis.

11. *More information on the transfers would be helpful. What is the average age at transfers? It would be good to provide a breakdown of the types of hospitals/level of neonatal care transferring these infants. If there is significant diversity in the types or levels of care, it would be good to consider the results based on these different hospitals of initial care. Could there be an idea as to the specific reason for transfer – was these mostly due to the requirement for higher level of care, surgery, or were they born at non-NICU settings?*

Reply: Thank you very much for comments. Overall, 81.8% (1629/1991) infants were admitted to referral NICUs within 24 hours of life. Unfortunately, we did not collect the information on the level of neonatal care in each transferring hospital or the distance of transport. We have added the lack of detailed information of transferring hospital and transport in the limitation.

Change in the text:

Discussion

There are some limitations of our study should be noted. We did not collect the information about the treatment received by outborn infants had in the delivery hospital, the infants who died in the delivery room and attitude of VPI delivery in referral hospitals. Also, we did not collect the information on the level of neonatal care in each referral hospital or the distance of transport. In addition, we also did not

collect information regarding the socioeconomic or education status of mothers. Outborn infants admitted to free-standing hospitals were also not included in our study because characteristics of admitted infants as well as care practices are different between perinatal centers and children's hospitals. Therefore, our outborn rate might have been underestimated. Some of the infants in DAMA groups actually would have morbidities after discharge or did not survive to develop these morbidities, the overall risk for morbidities would be lower.

12. *I think that the group who were DAMA should be described to justify inclusion in the overall analysis of overall mortality (The inclusion of this particular group of infants in the analysis raises some questions as this may potentially bias the outcomes investigated as a function of outborn status, because withdrawal of care could be done due to a variety of reasons As such there needs to be a more extensive evaluation on this particular group of infant to justify inclusion or exclusion in the overall analysis. There should be additional analysis to justify the inclusion (or exclusion) of this group of infants in the analysis and manuscript.) In this regard, how did the authors adjust for the DAMA group with regards to the morbidities evaluated and the multivariable analysis? One would imagine that if a patient was DAMA and was not classified as mortality, that there would be no evaluation for ROP or BPD and the overall risk for morbidities would be lower.*
Reply: Thank you very much for professional comments. Yes, DAMA resulted in major problem for us to evaluate the relationship of outborn status and mortality and morbidities. However, it was a real condition currently in China, and we think it might be not appropriate to exclude these infants from analysis. We consider DAMA as an adverse outcome, because the majority of DAMA infants (75%) died after discharge. The exclusion of DAMA infants would cause significant underestimate of mortality.

As for morbidities, ROP was calculated among infant who received eye examination regardless of DAMA or non-DAMA status. BPD was defined as mechanical ventilation or oxygen dependency at 36 weeks' postmenstrual age or discharge. The majority of DAMA infants remained on respiratory support on discharge, therefore, the rate of BPD might be overestimated, instead of underestimated.

We repeated the analysis among infants with complete care (excluding DAMA) infants. We found significant association between outborn status of IVH or PVL, similar with results when including DAMA infant in the analysis. We included the result in Supplemental Table 4 as a sensitivity analysis.

Change in the text:

Supplemental Table 4 Crude and adjusted risks of morality and morbidities for outborn infants compared with inborn infants among infants received complete care

	Crude Odds Ratio			Adjusted Odds Ratio[a]		
	Inborn	Outborn	P	Inborn	Outborn	P
In-hospital mortality	Reference	0.9 (0.7-1.1)	0.384	Reference	0.9 (0.7-1.1)	0.331
Sepsis	Reference	1.1 (0.9-1.3)	0.613	Reference	1.0 (0.9-1.3)	0.692
BPD	Reference	0.9 (0.8-1.1)	0.319	Reference	0.9 (0.8-1.1)	0.181
IVH or PVL	Reference	1.2 (1.0-1.5)	0.032	Reference	1.3 (1.1-1.5)	0.013
NEC	Reference	0.7 (0.4-1.6)	0.159	Reference	0.8 (0.6-1.0)	0.072
Severe ROP	Reference	1.0 (0.8-1.2)	0.842	Reference	0.8 (0.5-1.3)	0.390

[a] The covariates controlled for in this model included sex, gestational age, small for gestational age infant, maternal hypertension, maternal diabetes.

Abbreviations: DAMA, Discharge against medical advice; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

13. *How did the authors adjust for potential centre variation with regards to the clinical practices, and also number of transports received, in evaluation of the outcome measured esp in regard to the multivariable analysis?*

Reply: Thank you very much for professional comments. Definitely, there were variations of practices in different birth hospitals as well as in referral hospitals, which would influence the outcomes of preterm infants. Unfortunately, we did not have information regarding the birth hospitals, therefore, we could not include characteristics of birth hospitals in our analysis.

We added a multilevel mixed-effects logistic regression model to further examine the association of outborn status and neonatal outcomes accounting for the intracluster correlation among the infants admitted to same hospitals. Hospitals were considered as independent clusters with random effects in the models. At the infant level, we controlled for sex, gestational age, SGA, maternal hypertension, maternal diabetes. The results were similar with our primary multivariate model. We included the result in Supplemental Table 5 as a sensitivity analysis.

Change in the text:

Supplemental Table 5 Adjusted risks of morality and morbidities for outborn. infants compared with inborn infants using multi-level logistic regression model

	Adjusted Odds Ratio		
	Inborn	Outborn	P
DAMA	Reference	1.4 (1.2-1.7)	<0.001
In-hospital mortality	Reference	1.0 (0.8-1.2)	0.842
Overall mortality	Reference	1.2 (1.0-1.4)	0.019
Sepsis	Reference	1.1 (0.9-1.3)	0.397
BPD	Reference	1.0 (0.8-1.2)	0.776
IVH or PVL	Reference	1.1 (1.0-1.4)	0.026
NEC	Reference	0.9 (0.7-1.1)	0.291
Severe ROP	Reference	1.0 (0.6-1.7)	0.940

Multilevel mixed-effects logistic regression models were used to examine the association of outborn status and neonatal outcomes accounting for the intracluster correlation among the infants within hospitals. Hospitals were considered as independent clusters with random effects in the models. At the infant level, we controlled for sex, gestational age, small for gestational age infant, maternal hypertension, maternal diabetes.

Abbreviations: DAMA, Discharge against medical advice; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

14. *Table 1: Birthweight: 1500-1999g – denominator is missing. Table 2: As the standard outcomes are already defined in the text, there is no need to include in the footnote. The variable overall mortality should be included in the methods section.*

Reply: Thank you very much for the comments. We have modified the tables. The calculation method of the incidence was not included in the text, so we keep the footnote for now, but we are totally ok if they should be deleted. We also add the method of calculation for overall mortality in the methods section.

Change in the text:

Table 1 Infant and maternal characteristics

	Inborn N=10023	Outborn N=1991	P
Gestational age, mean (SD)	29.9 (1.6)	29.8(1.6)	0.01
22weeks, n/8 (%)	8/8(100)	0/8(0)	
23weeks, n/14 (%)	14/14(100)	0/14(0)	
24weeks, n/71 (%)	64/71(90.1)	7/71(9.9)	
25weeks, n/175 (%)	149/175(85.1)	26/175(14.9)	
26weeks, n/436 (%)	363/436(83.3)	73/436(16.7)	

27weeks, n/781 (%)	655/781(83.9)	126/781(16.1)	
28weeks, n/1520 (%)	1221/1520(80.3)	299/1520(19.7)	
29weeks, n/2166 (%)	1795/2166(82.9)	371/2166(17.1)	
30weeks, n/2914 (%)	2441/2914(83.8)	473/2914(16.2)	
31weeks, n/3929 (%)	3313/3929(84.3)	616/3929(15.7)	
Birth weight, mean (SD)	1388.1(322.7)	1393.3(306.2)	0.5
<750g, n/194 (%)	168/194(86.6)	26/194(13.4)	
750-999g, n/1068 (%)	927/1068(86.8)	141/1068(13.2)	
1000-1249g, n/2732 (%)	2254/2732(82.5)	478/2732(17.5)	
1250-1499g, n/3517 (%)	2945/3517(83.7)	572/3517(16.3)	
1500-1999g, n/4132 (%)	3409/4132(82.5)	723/4132(17.5)	
≥2000g, n/370 (%)	319/370(86.2)	51/370(13.8)	
Male, n/N (%)	5653/10022(56.4)	1196/1991(60.1)	0.003
SGA, n/N (%)	1064/10022(10.6)	204/1991(10.3)	0.6
Multiple birth[a], n/N (%)	2244/7214 (31.1%)	335/1347 (24.9%)	<0.001
1-min Apgar≤3, n/N (%)	600/9972(6.0)	182/1744(10.4)	<0.001
5-min Apgar≤3, n/N (%)	120/9606(1.3)	56/1528(3.7)	<0.001
TRIPS score, median (IQR)	15.3(13)	16.3(1)	<0.001
Prenatal care, n/N (%)	9857/9984(98.7)	1908/1953(97.7)	<0.001
Maternal hypertension, n/N (%)	1373/9964(13.8)	265/1926(13.8)	1.0
Maternal diabetes, n/N (%)	1286/9966(12.9)	131/1924(6.8)	<0.001
Antenatal steroids, n/N (%)	7275/9895(73.5)	812/1755(46.3)	<0.001
Primigravida, n/N (%)	3556/10018(35.5)	682/1988(34.3)	0.3
Caesarean section, n/N (%)	4748/10023(47.4)	639/1988(32.1)	<0.001

[a] Data on multiple birth was only collected during the last two years of study.

Abbreviations: SD, Standard Deviation; SGA, small for gestational age infant; TRIPS, Transport Risk Index of Physiologic Stability; IQR, interquartile range.

Table2 Comparison of outcomes for inborn and outborn preterm infants admitted to NICUs

	Inborn N=10023	Outborn N=1991	P
DAMA, n/N (%)	1251/10023(12.5)	358/1991(18.0)	<0.001
In-hospital mortality, n/N (%)[a]	662/8772(7.6)	121/1633(7.4)	0.8
Overall mortality, n/N (%)[b]	1588/10023(15.8)	396/1991(19.9)	<0.001
Sepsis, n/N (%)[c]	741/10023(7.4)	153/1991(7.7)	0.6
BPD, n/N (%)[d]	1424/8771(16.2)	249/1633(15.3)	0.3
IVH or PVL, n/N (%)[e]	806/8832(9.1)	192/1771(10.8)	0.024
NEC, n/N (%)[f]	467/9120(5.1)	73/1795(4.1)	0.06
Severe ROP, n/N (%)[g]	116/6215(1.9)	20/1377(1.5)	0.3

[a] In-hospital mortality= number of in-hospital death/ number of infants who received active care.

[b] Overall mortality= (number of in-hospital death + number of predicted death among DAMA infants)/ total number of infants.

[c] Incidence of sepsis = number of infants with culture-proven sepsis or clinical sepsis/ number of all admissions.

[d] bronchopulmonary dysplasia. Incidence of BPD= number of infants who received active care and required mechanical ventilation or oxygen dependency at 36 weeks' postmenstrual age or discharge/ number of infants who received active care.

[e] intraventricular hemorrhage. PVL: periventricular leukomalacia. Incidence of IVH ≥grade 3 or PVL= number of infants with IVH ≥grade 3 or PVL/ number of infants with neuroimaging results.

[f] necrotizing enterocolitis. Incidence of NEC= number of infants with NEC ≥stage 2/ number of infants survived more than 72 hours.

[g] retinopathy of prematurity. Incidence of ROP= number of infants with ROP ≥stage 3/number of infants with eye examinations in NICU.

Abbreviations: DAMA, Discharge against medical advice; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

15. *Discussion: Overall, the discussion is reasonable with good points mentioned. A discussion on the potential impact of DAMA on the rates of mortality and morbidities results should be mentioned and highlighted in limitations if appropriate.*

Reply: Thank you very much for the comments. We have made the change in limitations.

Change in the text:

Discussion

There are some limitations of our study should be noted. We did not collect the information about the treatment received by outborn infants had in the delivery hospital, the infants who died in the delivery room and attitude of VPI delivery in referral hospitals. Also, we did not collect the information on the level of neonatal care in each referral hospital or the distance of transport. In addition, we also did not collect information regarding the socioeconomic or education status of mothers. Outborn infants admitted to free-standing hospitals were also not included in our study because characteristics of admitted infants as well as care practices are different between perinatal centers and children's hospitals. Therefore, our outborn rate might have been underestimated. Some of the infants in DAMA groups actually would have morbidities after discharge or did not survive to develop these morbidities, the overall risk for morbidities would be lower.

16. *Since the authors did not collect any information on pre-transfer management – I do think that the following statement is a little harsh – "Outborn infants were more likely to be delivered in an uncontrolled situation and received suboptimal initial management". Should remove or amend unless there is data to back this up.*

Reply: Thank you very much for comments. We have deleted the sentence in discussion.

Change in the text:

Discussion

The incidence of outborn VPIs was high in China, especially among infants with lower gestational ages. They were at significantly higher risk of neonatal mortality and severe brain injury compared with inborn infants. Policies and quality improvement efforts are needed to facilitate in-utero transfer of high-risk pregnancies to tertiary centers, and ultimately to improve the outcomes of VPIs in China.

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