

Peer Review File

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To Reviewer A:

Comment 1

Abstract

line 48 - need to have year that they ended. It is not stated in the abstract currently.

Reply 1:

We have modified our text as advised (see Page 3, line 50).

Changes in the text:

Data from a retrospective multi-center cohort of all complete care very preterm infants admitted to 57 neonatal intensive care units that participated in the Chinese Neonatal Network from January 1st to December 31st, 2019 were analyzed.

Comment 2

Abstract

line 55-56 - of the 19% not within the 21-35 age group what proportion were <20 and >35 this is not clear here.

Reply 2:

we added some data about the percentage of very preterm infants born to mother with different age groups (see Page 3, line 57-58).

Changes in the text:

Among 7,698 eligible newborns, 80.5% of very preterm infants were born to mothers between the ages of 21 and 35 years, with 18.0% born to mothers > 35 years and 1.5% born to mothers < 21 years.

Comment 3

Abstract

line 68-69 - Is not being younger mean you are less likely to receive appropriate antenatal care (eg steroids) and this might contribute to the higher rate of IVH?

Reply 3:

Numerous findings indicate that antenatal care can reduce the incidence of IVH in very preterm infants. In our research, we adjusted for potential confounders by including antenatal care in the regression models (eg. maternal hypertension, maternal diabetics and antenatal steroid usage), we found that young maternal age was still an independent risk factor for IVH in very preterm infants.

In addition to the perinatal factors, environmental tobacco smoke exposure and infection during pregnancy also contribute to an increased risk of IVH in preterm infants. In our study, women with young maternal age had lower rates of prenatal care, which may associate with their low education, low income and unstable marital status. At the same time, due to the lack of social support, the accessibility of prenatal care for women with young maternal age was lower. This may lead to poor prognosis and increase the risk of severe complications of VPIs. We added these points to our *Discussion* in the revised manuscript. (See Page 13, line 249-260)

Comment 4

Introduction

line 90 - I think the end of the sentence is missing an 'and'. This is a very long sentence you might consider reducing or rephrasing this sentence.

line 93 - you might consider using < 33 week rather than 'younger' it might read better

Reply 4:

We have modified our text as advised. (See Page 5, line 94-96, Line 98)

Changes in the text:

Many population studies have demonstrated an association between young or advanced maternal age and adverse birth outcomes, including increased neonatal mortality, the higher proportion of preterm birth, low birth weight, genetic anomalies or birth defects, and reduced the 5-min Apgar score.

In contrast to the birth outcomes of newborns, a few studies linking maternal age with neonatal outcomes of preterm infants indicated that advanced maternal age has improved the prognosis of less than 33 weeks' gestation at birth or extremely low birth weight infants.

Comment 5

Methods

in the study and design it would be good to know how much (ie proportion) of units in China are covered by the CHNN. this would make it easier for the reader to understand the coverage of this data.

Reply 5:

We cannot obtain the exact numbers of NICUs in China, and we didn't present the coverage of our data in the manuscript. But these 57 hospitals were from 25 provinces in China, and had the best NICUs in the local area, caring for approximately 5% of all VPIs in China. These hospitals included all government-designated neonatal centers of excellence in China. We added the reference about the introduction of CHNN. (Cao, Yun et al., 2021) (See Page 6, Line 112-114)

Cao, Yun et al. "Assessment of Neonatal Intensive Care Unit Practices, Morbidity, and Mortality Among Very Preterm Infants in China." JAMA network open vol. 4,8 e2118904. 2 Aug. 2021, doi:10.1001/jamanetworkopen.2021.18904

Changes in the text :

These 57 hospitals caring for approximately 5% of all VPIs in China,

Comment 6

Methods

study population - what is the definition of a major congenital anomaly?

136 - there is an extra space in this sentence

144 extra space

Reply 6:

The definition of *major congenital anomaly* refers to Bassil's criteria (*Bassil, Kate L et al., 2013*). A major congenital anomaly was defined as either life-threatening or if left untreated immediately would most likely lead to death or severe physical or neurodevelopmental impairments. We added the relevant reference in the manuscript and modified our text as advised. (See Page 7, Line 122)

Bassil, Kate L et al. "Association between congenital anomalies and area-level deprivation among infants in neonatal intensive care units." American journal of perinatology vol. 30,3 (2013): 225-32. doi:10.1055/s-0032-1323584

Comment 7

Methods

145 - I am not clear are we including any IVH or only IVH greater than 3 or 4? this sentence is not clear to me and I think its important that we know the extent of IVH which has been included as "brain damage" in this sentence. I am also not clear as the paragraph goes on about the secondary outcome being individual components of brain damage. I think the clarity around these definitions needs reworded.

Reply 7:

Brain damage was defined as the presence of either severe (grades III and IV) intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (cPVL). The secondary outcome was the individual components of brain damage (severe IVH and cPVL). In order to observe the effects of maternal age on severe IVH or cPVL, we set severe IVH and cPVL for secondary outcomes. We have modified our text as advised (see Page 8, line 143-147).

Changes in the text:

The primary outcome was mortality or any major morbidity, including necrotizing enterocolitis (NEC, \geq stage 2), moderate & severe bronchopulmonary dysplasia (BPD), brain damage, severe retinopathy of prematurity (ROP, \geq stage 3) and sepsis. Brain damage was defined as the presence of either severe (grades III and IV) intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (cPVL). The secondary outcome was the individual components of brain damage (severe IVH and cPVL).

Comment 8

Methods

153 - what do you mean by "intent" of antibiotics treatment. I am not clear what this means nor how reliable this would be in terms of an outcome.

168 - do you mean diabetes rather than diabetic?

170 - there is an issue with the formatting of this line. Not sure why.

Reply 8:

Newborns with positive blood or cerebrospinal fluid culture and requiring antibiotic treatment are regarded as diagnosed sepsis. Newborns with positive blood or cerebrospinal fluid culture in the data but not requiring antibiotic treatment are considered false-positive. We have modified our text as advised (see Page 8, line 152).

Changes in the text:

Sepsis was defined as positive blood or cerebrospinal fluid culture and patient treated with antibiotics for 5 or more days.

Comment 9

Methods

168 - do you mean diabetes rather than diabetic?

170 - there is an issue with the formatting of this line. Not sure why.

Reply 9:

We have modified our text as advised (see Page 9, line 166).

Changes in the text:

The independent variables including basic VPIs information (gestational age, birth weight, male, multiple birth), maternal health status (hypertension, diabetes and parity) and treatments before delivery (prenatal care, cesarean section, antenatal steroid and inborn).

Comment 10

Results

I am unclear as to why the infants who are transferred and those who discharged against medical advice are grouped together in the exclusion data. Would these infants be better separated out as this is quite different reasons.

Reply 10:

In our research, there are 344 infants were transferred to other hospitals and 1349 infants discharge against medical advice during treatment. We have modified our text as advised (see Page 9, line 178-179).

Changes in the text:

Of these, we excluded a total of 1,812 infants because of being transferred to other hospitals (n=344) or discharge against medical advice (n=1349),

Comment 11

Results

194-196 we would be better to have the percentages next to the categories to make it easier for the reader to understand the results.

197-199 I think a range of the weights for this age group would be helpful rather than just the mean. we are unable to understand the ranges in case there is a large range

which will skew the data.

Reply 11:

We have modified our text as advised (See Page 10, line 187-190).

Changes in the text:

The incidence of prenatal care (93.3%), cesarean section (28.4%), antenatal steroid usage (57.4%) and inborn (46.2%) in the mothers aged 15-20 years were significantly lower than that of other age groups. Among the infant factors, the mean birth weight was (1322.76 ± 324.67) g and the incidence of SGA was 7.8% in the VPIs born to mothers aged 36-55 years.

Comment 12

Discussion

If you found increased IVH with <20yrs here would be a good time to postulate as to why this is. Is this because of reduced antenatal care (ie less steroids and antenatal visits). In the discussion I would expect something such as this.

234 - you need to review this sentence. I think you need to replace the "found" with find to read better. This sentence is also 4 lines wrong, would you not reduce the length of this sentence?

Reply 12:

We have modified our text as advised (see Page 11, line 218-220).

Changes in the text:

In the present study, we did not find improved VPIs neonatal outcomes with advanced maternal age. Although women with advanced maternal age had higher proportion of pregnancy complications and SGA with a lower mean birth weight of infants, they are more willing to take routine prenatal care, have planned births, and have higher AN steroids use.

Comment 13

Discussion

239 - what do you mean these women have 'postpartum women' do you mean multi gravid women? I am not sure if this is what you mean.

Reply 13:

"postpartum women" means multi-gravid women. We have modified our text as advised (see Page 12, line 224).

Changes in the text:

And also, most of women with advanced maternal age are multi-gravid women, and the cesarean section rate was high, which may be related to the favorable prognosis of VPIs.

Comment 14

Discussion

250 - I think there are additional words in this sentence "may could" does not seem to make sense in this paragraph.

Reply 14:

We have modified our text as advised (see Page 12, line 234).

Changes in the text:

but the reasons for the difference in our findings from those of prior studies are unclear, lower overall survival rate and survival without major morbidity of VPIs in China could explain this difference.

Comment 15

Discussion

253 - this paragraph needs some work. While there is variation in the studies described and IVH rates I am less clear as to how they relate to your study. For example there is mention of transport yet these infants were excluded from your study. I wonder if a review would be helpful for this paragraph.

I feel strongly that we need caution to ensure we do not 'blame' younger women for the higher rates of IVH. Perhaps this is a systems issues in which health care is more difficult for them to access. there is good published data on this and perhaps you may wish to explore this.

Reply 15:

In our research, mothers aged 15-20 years had lower rates of antenatal steroid usage, cesarean section and inborn, which may increase the risk of severe IVH in VPIs. Also, in the previous studies described in the text have demonstrated that obstetrical interventions such as cesarean section, antenatal steroid usage and postnatal transport could be a vital reason for severe IVH in VPIs. These studies further validated our study findings.

In our research, definition of “inborn” is preterm infants born in tertiary perinatal centers. We excluded infants transferred to other hospitals from 57 hospitals in CHNN, but we didn’t excluded infants transferred from other hospitals to CHNN.

In our study, women with young maternal age had lower rates of prenatal care, which may associate with their low education, low income and unstable marital status. At the same time, due to the lack of social support, the accessibility of prenatal care for women with young maternal age was lower. This may lead to poor prognosis and increase the risk of severe complications of VPIs. In addition to the perinatal factors, other factors also contribute to an increased risk of severe IVH in VPIs.

We added these points to our Discussion in the revised manuscript. (See Page 13, line 249-260)

Changes in the text:

In our study, women with young maternal age had lower rates of prenatal care, which may associate with their low education, low income and unstable marital status. At the same time, due to the lack of social support, the accessibility of prenatal care for women with young maternal age was lower. This may lead to poor prognosis and

increase the risk of severe complications of VPIs. In addition to the perinatal factors, environmental tobacco smoke exposure and infection during pregnancy also contribute to an increased risk of IVH in preterm infants. Previous studies have shown that cigarette smoking was more prevalent in young women, and infection more common because of reduced blood supply to the uterus and cervix in adolescent mothers, which may increase the incidence of IVH in VPIs with young maternal age. Young mothers may involve mother-fetus competition for nutrients and reduce placental transportation, which leading to more immature of germinal matrix and caused an increase in risk of severe IVH in VPIs.

Comment 16

Discussion

269 - extra space in this sentence

270 - I think you are missing a full stop in this sentence.

260 paragraph on limitations. I think this should be extended. There is some missing data and postulating how many components of this cohort might have had an impact on the analysis of the data. You outline other characteristics, such as socioeconomic status, impact on outcomes. This is also a retrospective study and this was not mentioned. You might also want to emphasise the strengths such that a network such as yours might bring. Would you not bring this forward as a strength?

Reply 16:

We have modified our text as advised (see Page 13, line 261, Page 14, line 262-265).

Changes in the text:

Our study has several strengths. We reported the association between maternal age and neonatal outcome in VPIs in China for the first time. We conducted a large population study representative of major tertiary hospitals across the country. The definitions of outcomes were standardized and multiple measures were applied to ensure the quality of data collection. Our study also has several limitations. Our study is a retrospective investigation.

Comment 17

Figure 1 - I presume that the lower diagrams are in the years (15-20, 21-35, >35) I would suggest you state this.

*Table 1 - I am not clear why some have * for $p < 0.05$ and # for trends. How can you have both in these sections. I think perhaps this paper needs a statistical review.*

Reply 17:

We have modified Figure 1 as advised (see Figure 1) and added *P* value in Table 1 and Table 2.

Changes in the text:

Table 1. Baseline Characteristics in Each Group of Maternal Age

Outcomes	Maternal Age (years)			Overall	P-Value	P-Value for Trend
	15-20	21-35	36-55			
N	117	6199	1382	7698		
Maternal Information						
Primigravida, N (%) *#	91/117 (77.8%)	3408/6158 (55.3%)	397/1375 (28.9%)	3896/7650 (50.9%)	<0.01	<0.01
Hypertension, N (%) *#	10/111 (9.0%)	1051/6098 (17.2%)	374/1366 (27.4%)	1435/7575 (18.9%)	<0.01	<0.01
Diabetes, N (%) *#	10/111 (9.0%)	969/6092 (15.9%)	347/1358 (25.6%)	1326/7561 (17.5%)	<0.01	<0.01
Perinatal care						
Prenatal Care, N (%) *	98/105 (93.3%)	5951/6000 (99.2%)	1321/1339 (98.7%)	7370/7444 (99.0%)	<0.01	0.71
cesarean section, N (%) *#	33/116 (28.4%)	3407/6177 (55.2%)	895/1375 (65.1%)	4335/7668 (56.5%)	<0.01	<0.01
Antenatal steroid Usage, N (%) *#	54/94 (57.4%)	4404/5637 (78.1%)	1002/1266 (79.1%)	5460/6997 (78.0%)	<0.01	0.02
Inborn, N (%) *	54/117 (46.2%)	4026/6199 (64.9%)	895/1382 (64.8%)	4975/7698 (64.6%)	<0.01	0.17
Infants characteristics						
Gestational Age, Median (P25, P75) #	30.00 (28.71,31.14)	30.00 (28.71,31.00)	30.00 (28.43,31.00)	30 (28.57,31.00)	0.10	0.04
Birth Weight, Mean (Std) *#	1395.32 (301.16)	1348.99 (308.63)	1322.76 (324.67)	1344.98 (311.64)	<0.01	<0.01
SGA, N (%) * #	5/117 (4.3%)	375/6196 (6.1%)	108/1380 (7.8%)	488/7693 (6.3%)	0.03	<0.01
Multiple Birth, N (%) *#	26/117 (22.2%)	1969/6199 (31.8%)	310/1382 (22.4%)	2305/7698 (29.9%)	<0.01	<0.01
Male, N (%)	78/117 (66.7%)	3536/6196 (57.1%)	770/1380 (55.8%)	4384/7693 (57.0%)	0.07	0.11
Apgar score <7 at 5 min, N (%)	5/105 (4.8%)	362/5845 (6.2%)	90/1295 (6.9%)	457/7245 (6.3%)	0.48	0.24
TRIPS score on admission, Median (P25, P75)	13 (7,19)	12 (6,19)	13 (6,19)	12 (6,19)	0.14	0.55

Table 2. Neonatal Outcome in Each Group of Maternal Age

Outcomes	Maternal Age (years)			Overall	P-Value	P-Value for Trend
	15-20	21-35	36-55			
N	117	6199	1382	7698		
Composite Outcome ^a , N (%)	49/117 (41.9%)	2507/6199 (40.4%)	581/1382 (42.0%)	3137/7698 (40.8%)	0.53	0.35
Mortality, N (%)	7/117 (6.0%)	297/6199 (4.8%)	67/1382 (4.8%)	371/7698 (4.8%)	0.84	0.90
NEC \geq Stage II, N (%)	4/117 (3.4%)	282/6199 (4.5%)	61/1382 (4.4%)	347/7698 (4.5%)	0.83	0.99
Moderate & Severe BPD, N (%)	39/117 (33.3%)	1650/6183 (26.7%)	393/1378 (28.5%)	2082/7678 (27.1%)	0.12	0.45
Brain Damage ^b , N (%)	11/98 (11.2%)	561/5459 (10.3%)	121/1229 (9.8%)	693/6786 (10.2%)	0.85	0.59
Severe IVH ^b , N (%)	8/98 (8.2%)	350/5428 (6.4%)	84/1221 (6.9%)	442/6747 (6.6%)	0.70	0.77
PVL ^b , N (%)	4/102 (3.9%)	305/5681 (5.4%)	59/1277 (4.6%)	368/7060 (5.2%)	0.47	0.40
Severe ROP ^b , N (%)	5/105 (4.8%)	362/5845 (6.2%)	90/1295 (6.9%)	457/7245 (6.3%)	0.67	0.39
Sepsis, N (%)	6/117 (5.1%)	572/6199 (9.2%)	126/1382 (9.1%)	704/7698 (9.1%)	0.31	0.68

To Reviewer B:

Comment 1

There are some differences with the mothers of age 15-20, but the sample size of this subgroup (117) is quite small compared to the other age groups (N = 6199 for 31-35 and N = 1382 for 36-55). Thus, the claim on line 222 that findings suggest increasing maternal age was associated with higher rates of SGA and lower birth weights only holds when comparing the 15-20 year age group (N = 117) to the 20-35 year age group (N= 6199) is likely to sample size issues. Given the number of cases eliminated by exclusion rules employed, the <20 age group could be entirely considered an outlier.

There may be an opportunity find something more closely related to the authors hypothesized relationship within the model. The age groups are very broad and unevenly distributed. Partitioning maternal age into more balanced categories may reveal greater insights.

Reply 1:

As we know, there was a U-shaped relationship between maternal age and neonatal outcome. In China, the mean age of delivery was 28.4 years. We wanted to understand whether the neonatal outcome in VPIs are affected by young or advanced maternal age, so we classified the VPIs into three groups by maternal age. We also divided maternal age into six groups (15-20 years, 21-25 years, 26-30 years, 31-35 years, 36- 40 years, and 41-54 years) for regression analysis, and obtained similar results.

Comment 2

Alternatively, while not looking directly at logistic models, recent work found that, “effect estimates from [random intercept and OLS] of regression model were on average unbiased. However, deviations from the “true” value were greater when the

outcome variable was more clustered.” (1). Line 165-166 mention that the data is clustered within 57 CHNN sites. Given the sample size (particularly of the older maternal group) this many cluster variables may be obscuring the underlying relationships. I confess very little knowledge of the Chinese healthcare system, but perhaps the data could be clustered regionally by province, or through larger healthcare management systems that with site-specific effects.

Reply 2:

CHNN includes different types of hospitals in 25 provinces. There are maternal and child health centers, children's hospitals and general hospitals in each province. Apart from large differences between provinces, there are also great variations of healthcare practice and infants characteristics among different type of hospitals within each province. Therefore, it is better to use site as a cluster rather than by provinces or other systems.

Comment 3

Overall, the paper was quite clear and easy to follow. I recommend some minor edits as follows:

Line 94-95: ‘However, these studies were completed in developed countries...’

Line 250: ‘survival without major morbidity of VPI’s in China (3) could explain this difference.’

Line 269: ‘We conducted a large population study...’

Reply 3:

We have modified our text as advised (See Page 5, line 98, Page 12, line 234, Page 14, line 262).