

Association Between Blood Gas Within 1 week of Life and Bronchopulmonary Dysplasia in Preterm Infants With Less Than 32 Gestational Weeks

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Research

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Abstract

Objective: This study tested whether preterm infants of ≤ 32 gestational weeks (GWs) with a blood gas derangement within 7 days of life are at increased risk for moderate and severe bronchopulmonary dysplasia (BPD).

Method: 236 preterm infants with ≤ 32 GWs from January of 2017 to December of 2019 were included in this study. First, univariate analysis determined whether there existed associations between BPD (moderate and severe) and blood gas values, clinical characteristics, interventions, daily given liquid and energy within 7 days of life. Then multivariate regression analysis was performed to know whether there were relationships between BPD (moderate and severe) and risk factors between which and BPD (moderate and severe) univariate analysis showed that P value was less than 0.1.

Results: From univariate analysis, we found that PaO₂, PaCO₂ and HCO₃ in 7th day of life, cesarean section (OR=0.508, 95%CI:0.275-0.94), gestational age (GA, OR=0.163, 95%CI:0.077-0.344), birth weight (BW, OR=0.122, 95%CI:0.054-0.273), PDA (OR=2.839, 95%CI:1.1463-5.508), early onset infection (OR=3.00, 95%CI:1.483-6.069), and mechanical ventilation (MV, OR=4.562, 95%CI:2.405-8.653) were significantly associated with moderate and severe BPD. Because there existed close relationship between GA and BW (R=0.642, P=0.000) and BW dispersion was big in this group, we excluded BW in multivariate analysis. From multivariate analysis, besides GA (Exp (B)=0.176, 95%CI:0.08-0.389), MV (Exp (B)=3.515, 95%CI:1.746-7.076), PaO₂ (Exp (B)=0.468, 95%CI:0.226-0.969) in 7th day of life was the independent risk factor for moderate and severe BPD in the preterm infants of ≤ 32 GWs.

Conclusion: Preterm infants of ≤ 32 GWs with blood gas derangements within 7 days of life could be at risk of moderate and severe BPD.

Background

Preterm birth is rising around the world, and the incidence of preterm is different ranging from about 5% in several European countries to 18% in some African countries[1][2]. Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease in preterm infants. BPD is a common cause of death in preterm infants occupying 2.8%[3]. During clinical work, we can not change the fact of preterm delivery. We want to know what we can do to reduce and/or alleviate the development of BPD in the preterm babies, especially in first several days of life. As we know, prolonged exposure to high oxygen concentration is identified as an important contributor to retinopathy of prematurity (ROP)[4]. There exists relationships between severe ROP and blood oxygen, carbon dioxide, and pH levels during the first 3 postnatal days[5][6]. We deduced that blood gas values (PH, PaCO₂, PaO₂, HCO₃) in preterm infants be very important for mature of premature organs and systems, and changes of blood gas values in the first several days of life influence the development of premature lung and have an effect on occurrence or development of BPD in preterm infants. If that, we could control blood gas values to reduce and/or alleviate the development of BPD in the preterm babies. It is reported that BPD is associated with exposure to

antenatal and/or postnatal factors including gestational age, birth weight, gender, patent ductus arteriosus (PDA), mechanical ventilation (MV), oxygen toxicity, and infection[7][8]. In this study, we collected and analyzed such factors as gestational age (GA), birth weight (BW), cesarean section (CS), early onset infection (EOI), anemia, MV (more than 2 days) and blood gas values within 1 week of life (1st, 2nd, 3rd, and 7th day after birth). We didn't collect data of apgar score due to apgar score in very preterm infants (VPI) and extremely preterm infants (EPI) is lower than that in term babies and low apgar score in VPI and EPI is not equal to neonatal asphyxia, and antenatal corticoid therapy because of antenatal corticoid therapy being as a therapy principle of preterm delivery in the [obstetrical department](#) of the first affiliated hospital of Nanjing Medical University.

Materials And Methods

This retrospective study was conducted at neonatal department of the first affiliated hospital of Nanjing Medical University. Admitting criteria for the study: ☐The baby was admitted to the neonatal department from January of 2017 to December of 2019, ☐The preterm infant was ☐32 gestational weeks (GWs), ☐The preterm baby had no serious congenital anomalies. Exclusion criteria: ☐Infants were with congenital anomalies such as congenital lung anomaly, congenital diaphragmatic hernia, severe congenital heart diseases and primary persistent pulmonary hypertension, ☐Recorded information was incomplete, ☐An infant was dead and/or refused treatment by parents within 2 weeks of life. Excluding of 17 cases, we collected 236 cases of preterm infants, who were from 24.9 GWs to 32 GWs (median: 30.4 weeks), whose BW was from 800g to 3250g (median: 1400g). The study was approved by the ethics review committee of the first affiliated hospital of Nanjing Medical University (2014SR038).

Statistics

Categorical variables were compared using χ^2 - or Fisher's exact tests. Univariate analysis was used to determine relative risk and 95% confidence intervals. Logistic regression analysis was used to determine association between BPD and arterial blood gas values on postnatal days 1, 2, 3, and 7 of the preterm infants who were less than 32 GWs. All analyses were performed using Stata software version 19.0 (StataCorp LP, College Station, TX, USA). Significance was set at $P \leq 0.05$.

Clinical definitions

BPD was defined as required additional oxygen and/or respiratory support should be equal to or more than continuous 28 days before assessment at 36 weeks of *postmenstrual age* in preterm infants and classified as mild, moderate and severe based on the required fraction of inspired oxygen at 36 weeks' PMA: mild, no supplemental oxygen; moderate, supplemental oxygen $\leq 30\%$; and severe, respiratory support and/or oxygen $>30\%$ [9]. Here, oxygen therapy or respiratory support indicated the infant's usual therapy and for oxygen therapy, the treating time was equal to or more than 12 hours of a day in the

assessing days, not a transient or acute event; target oxygen saturation is 90-95% [09][10]. GA was established based on last menstrual period confirmed by an ultrasonographic examination prior to 20 weeks [11]. Small for gestational age (SGA) was defined as infant birth weight less than 10th percentile of BW for the same GA [12]. Early onset infection (EOI) was defined as confirmed infection (including neonatal sepsis, urine tract infection, respiratory infection, etc.) within 7 days after birth [13]. Anemia was defined as Hct <39% [14]. Patent ductus arteriosus (PDA) was diagnosed by two-dimensional color Doppler examination in 1st week of life.

Results

1. Incidence of BPD in the preterm infants

We collected 253 cases with less than 32 weeks of GA in total. After exclusion of 17 cases including incomplete recorded information, dead, refused treatment by parents and severe congenital anomalies, the left 236 preterm infants were included to be analyzed. There existed 54 cases with moderate and severe BPD. The incidence of moderate and severe BPD was 22.88% in this study.

2. Clinical characteristics and interventions(see table1)

3. Classification

We chose the extremely abnormal blood gas values each day (1st, 2nd, 3rd, and 7th day of life). When the baby's condition was stable, blood gas could just be done one time per day, and the blood gas value was included. We separated each day blood gas values, daily given liquid and energy into a low group and a high group according to each median value(see table2, table3 and table4).

4. Associations between BPD and clinical characteristics, interventions, each day blood gas values, daily given liquid and energy by univariate analysing

☒ From the univariate analysing, we found that such clinical characters as GA, BW, CS, PDA, EOI and MV were significantly associated with BPD. The less GA and lower BW, the more moderate and severe BPD. The preterm infants with PDA, EOI, MV and non CS were at high risk of moderate and severe BPD (see figure1).

☒ By univariate analysing relationships between moderate and severe BPD and daily given liquid and energy within 1st week of life, the daily given energy in the 7th day of life of preterm infants with BPD was

lower than that preterm infants with no BPD, no significant difference of daily given liquid in the 1st week of life between preterm infants with BPD and those with no BPD (see figure2 and figure3).

From the univariate analysing, we found that the blood gas values in the 7th day of life such as PCO₂, PO₂ and HCO₃ were significantly associated with BPD. Specifically, higher PCO₂, lower PO₂ and lower HCO₃ manifested in preterm infants with BPD in 7th day of life than those in preterm infants with no BPD (see figure4).

5. Relationships between moderate and severe BPD and risk factors by multivariate analysing

Although univariate analysing relationship between BW and BPD showed that P value was less than 0.01, there existed close relationship between GA and BW (R=0.642, P=0.000) and BW's dispersion was big (800-3250g), we excluded BW in multivariate analysing from the first step. From multivariate analysing relationships between BPD and the above risk factors between which and BPD univariate analysing showed that P value was less than 0.1, GA, MV and PO₂ in 7th day of life were the independent risk factors of BPD in the preterm infants of less than 32GWs (see table5).

Discussion

The United States National Institutes of Health (NIH) reported an increase of BPD in the past 20 years, more than 40% preterm infants of 22-28 GWs with BPD[15]. The incidence of BPD in preterm infants of < 32GWs was reported to be 30% in the United States[16][17]. The incidence of moderate/severe bronchopulmonary dysplasia was 22% in less than 1500g of birth weight in one study[18]. As to this study, the incidence of moderate and severe BPD was 22.9% in preterm infants with less than 32 GWs. It was similar to the previous study. Infants born at 22-25 GWs have a greater than 50% risk of BPD, and infants born at 26-27 GWs still have greater than 30% chance of developing BPD[19]. The incidence of BPD in infants with BW<1000g, 1000-1249g and 1250-1000g was 62.3%, 25.9% and 17.3% respectively[20]. In this research, not only from univariate analyzing but also from multivariate analyzing, we found that BPD was inversely associated with GA (P=0.016, OR=0.342, 95%CI: 0.143-0.819), namely, the less GA/BW in preterm infants, the higher incidence of BPD.

Mechanical ventilation is an important risk factor for the development of BPD[21] [22]. Because invasive mechanical ventilation could damage premature pulmonary, there is a high morbidity of BPD when preterm infants received long periods of invasive mechanical ventilation[23]. Watterberg reported that reducing mechanical ventilation may improve pulmonary outcomes in ELGAN infants[24]. A meta-analysis compared LISA with mechanical ventilation, LISA had a lower odds of BPD(OR, 0.53; 95% CI, 0.27-0.96)[25]. It was confirmed by this research that mechanical ventilation is associated with BPD in preterm infants of less than 32GWs (OR, 3.515, 95% CI, 1.746-7.076). PDA has also been recognized as a risk factor of BPD[26]. PDA has been linked to the development of BPD[27]. By univariate analyzing, PDA

was associated with BPD in this group preterm infants (OR=2.839, 95%CI: 1.1463-5.508). However, in multivariate regression analyzing, PDA was not associated with BPD. PDA is often present during the period that preterm infants are very susceptible to lung injury leading to BPD. There is overlapping time of PDA existing and lung injury. To day, it remains unclear whether PDA is a true causative risk factor for BPD or just a physiological marker associated with the development of BPD[27].

Neonatal sepsis could independently increase incidence of BPD[28]. A study reported that increased odds of BPD were found for SGA at 3rd percentile (OR: 3.33, 95% CI: 1.29-8.64) and neonatal sepsis: coagulase-negative staphylococcal bacteremia (OR: 3.17, 95% CI: 2.08 – 4.83), other bacteremia (aOR: 2.46, 95% CI: 1.42– 4.27); and candidemia (aOR: 8.68, 95% CI: 1.65– 45.63)[29]. A cohort study including 15839 infants reported 383 (2.4%) cases developed early onset sepsis (EOS) and EOS was associated with increased odds for BPD (OR: 1.74, 95% CI: 1.24-2.43)[30]. In this study, we found that EOI was associated with BPD by univariate analyzing (OR=3.00, 95%CI: 1.483-6.069), but from multivariate analyzing, EOI was not the independent risk factor of BPD.

Duan reported that multivariate logistic regression analysis was performed to determine the association between anemia and BPD[31]. Among 243 preterm infants, the incidence of anemia was higher in BPD patients than that in non-BPD patients ($p < 0.001$). Mean Hct in BPD patients was lower than that in non-BPD patients at different time points (1d, 7d, 14d, and 21d of life). Their results show that early anemia was associated with an increased risk of BPD. We cannot find the relationship between anemia and BPD. It may be caused by that we collected the anemia data within 4 weeks of life and did not separate into early anemia (less than 2 weeks of life) and late anemia (more than 2 weeks of life). The association between BPD and anemia and how anemia works on BPD remain to further study. Rocha reported that there existed a significant association between SGA and BPD (OR = 5.2 (CI: 1.46-18.58), $p = 0.01$) by multivariate analysis[32]. The result was different from ours, we can not find that BPD was associated with SGA. There exist differences between both in the incidence of SGA (up to 18.6% in this study) and in the study population.

Between days 7 and 27 after birth, every 10 kcal/kg/d increase in energy intake was associated with a 9% reduced risk of BPD ($p = 0.029$) in multivariable models[33]. We found that there existed inversely association between BPD and the 7th day given energy by univariate analyzing (OR=0.515, 95%CI, 0.275-0.962), but there existed no association between both by multivariate analyzing. We will continue to collect clinical data to expand the population in order to explicit the relationship between both.

The internal environment within 1st week of life such as blood gas values (PH PCO₂ PO₂ HCO₃) in preterm infants may be very important for the development of premature organs and systems. For infants of less than 32 GWs, the infants are during sacular and alveolar stages of lung. If the critical lung development is interrupted by low PH, low PO₂, high PCO₂, and low HCO₃, there would cause ineffective gas exchange in the preterm lung and the baby would need respiratory support and could suffer from BPD. This study showed that BPD was associated with higher PCO₂, lower PO₂, and lower HCO₃ in 7th day of life by univariate analyzing, and associated with lower PO₂ in 7th day of life through multivariate

recession analyzing, namely low PO₂ in 7th day of life was the independently risk factor of BPD. It suggested that the gas exchange membrane could not recover until 1 week of life and that continued low PaO₂ till 1 week after birth further hurt the premature lung and might cause BPD. The specific mechanism of low PaO₂ in 7th day of life on BPD need to further study. As we known, it is first reported that there existed association between blood gas values in the first 7 days of life and BPD.

From the above, low PaO₂ in 7th day of life, besides MV, GA/BW, was the independent risk factor of moderate and severe BPD in preterm infants of less than 32GWs. Namely, preterm infants of $\leq 32GWs$ with blood gas derangements within 7 days of life could be at risk of moderate and severe BPD.

Declarations

Ethics approval:

The study was approved by the ethics review committee of the first affiliated hospital of Nanjing Medical University (2014SR038) Consent for publication: The manuscript is approved by all authors for publication Availability of data and material: The data used or analysed during the study are included in this published article. More detailed data are available from the corresponding author if need. Code availability: N/A

Competing interests:

we declare no conflicts of interest.

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Authors' contributions

Xiaoya Han contributed writing (including drafting), data collection, formal analysis

Xiaolin Miao contributed drafting, data collection (including data curation), data analysis

Limin Guo contributed data collection and curation, methodology

Na Li contributed data curation

Cun Zhang contributed methodology and data collection.

Shudong Cui contributed design, formal analysis, writing (including review).

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Tables

Table 1

Clinical characteristics and interventions of neonates

	classification	number
Gender	male	134
	femal	102
CS	no	105
	yes	131
GA	≤median GA(30.4weeks)	120
	▯median GA	116
BW	≤median BW(1400g)	121
	▯median BW	115
SGA	no	192
	yes	44
PDA	≤ 2mm and no PDA	110
	▯2mm	126
EOI	no	90
	yes	146
anemia	no	89
	yes	147
RDS	I stage and no RDS	127
	II stage and more than II stage of RDS	109
MV	no	160
	yes	76

Table 2

1st PH	1st PaCO2	1st PaO2	1st HCO3	2nd PH	2nd PaCO2	2nd PaO2	2nd HCO3
7.30	46.25	88.5	22.3	7.39	35.45	71.00	21.30
3rd PH	3rd PaCO2	3rd PaO2	3rd HCO3	7th PH	7th PaCO2	7th PaO2	7th HCO3
7.37	37.65	67.25	21.60	7.36	39.40	71.00	22.00

Table 3

1 st fluid	2 nd fluid	3 rd fluid	4 th fluid	5 th fluid	6 th fluid	7 th fluid
71.8	84.5	96.6	105.5	115.1	123.7	131.2

Table 4

1 st energy	2 nd energy	3 rd energy	4 th energy	5 th energy	6 th energy	7 th energy
31.45	42.35	53.8	64.1	71	78.25	83.5

Table 5

Relationship between moderate and severe BPD and risk factors by the multivariate analysing

	S.E,	Wals	df	Sig.	Exp (B)	95%CI	
GA	0.404	18.476	1	0.000	0.176	0.08	0.389
PDA	0.378	3.111	1	0.078	1.949	0.928	4.09
MV	0.357	12.401	1	0.000	3.515	1.746	7.076
PO27	0.371	4.183	1	0.041	0.468	0.226	0.969

Figures

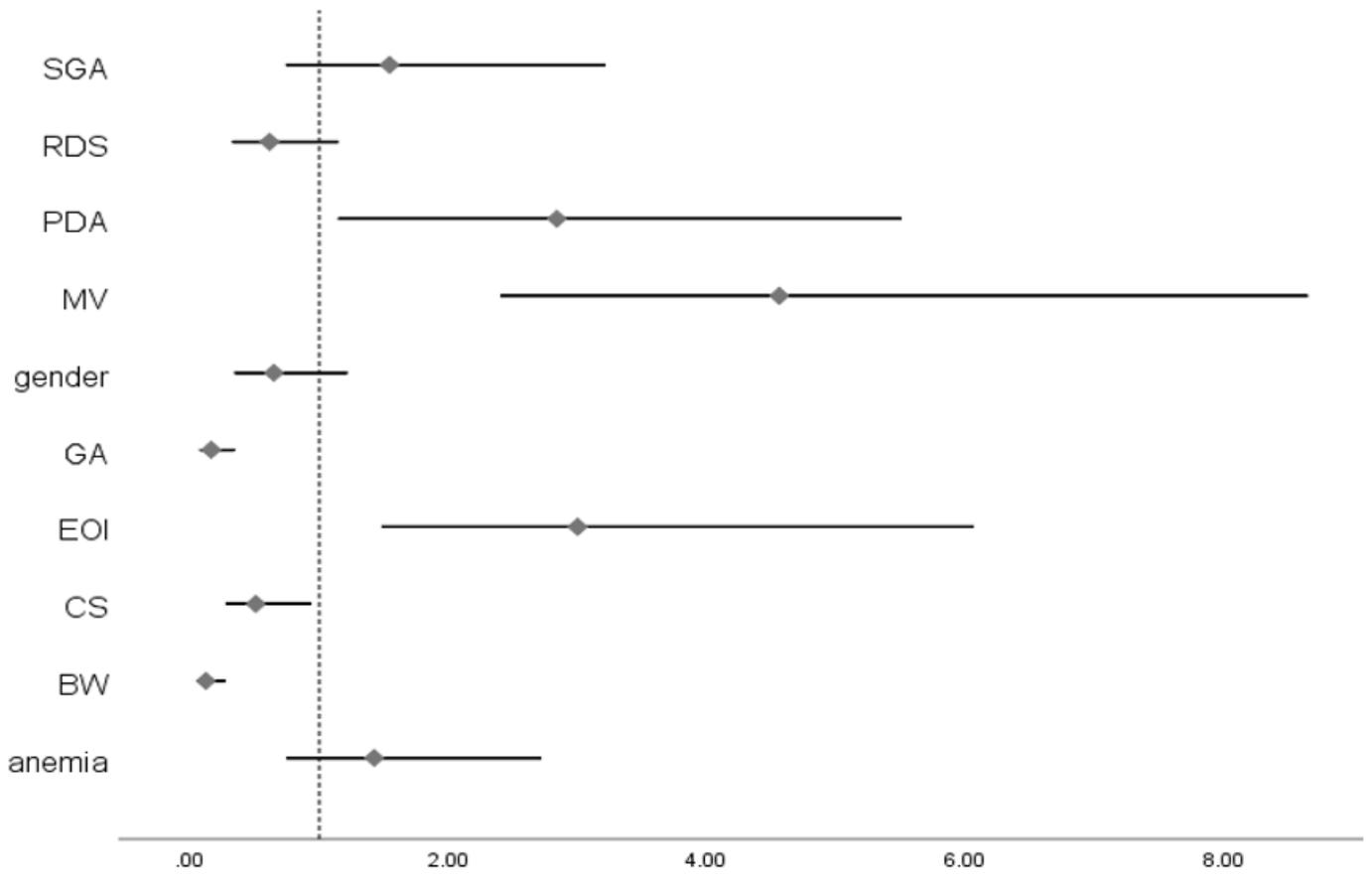


Figure 1

Relationship between moderate and severe BPD and Clinical characteristics and interventions by univariate analysing

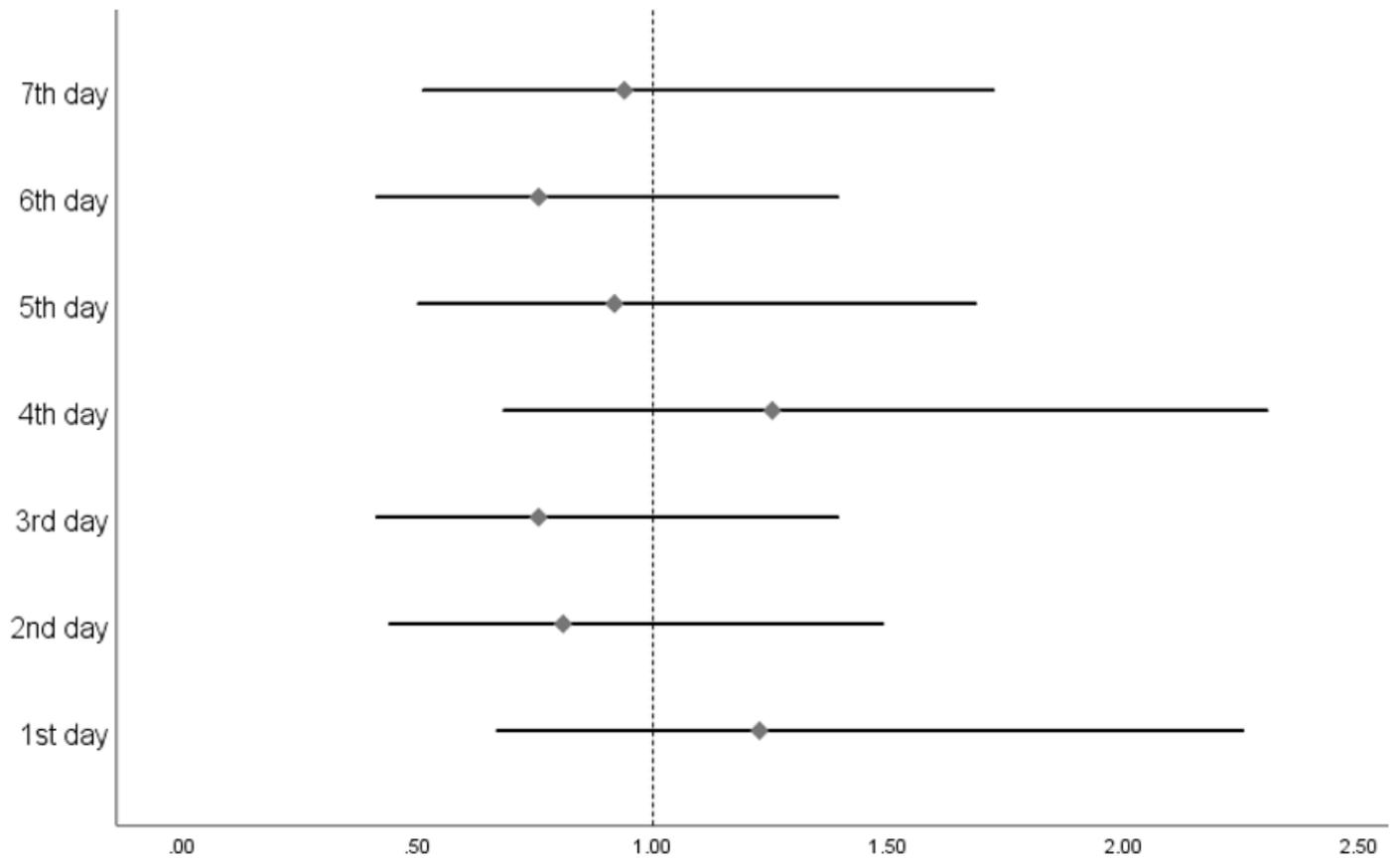


Figure 2

Relationship between BPD and daily given liquid by univariate analysing

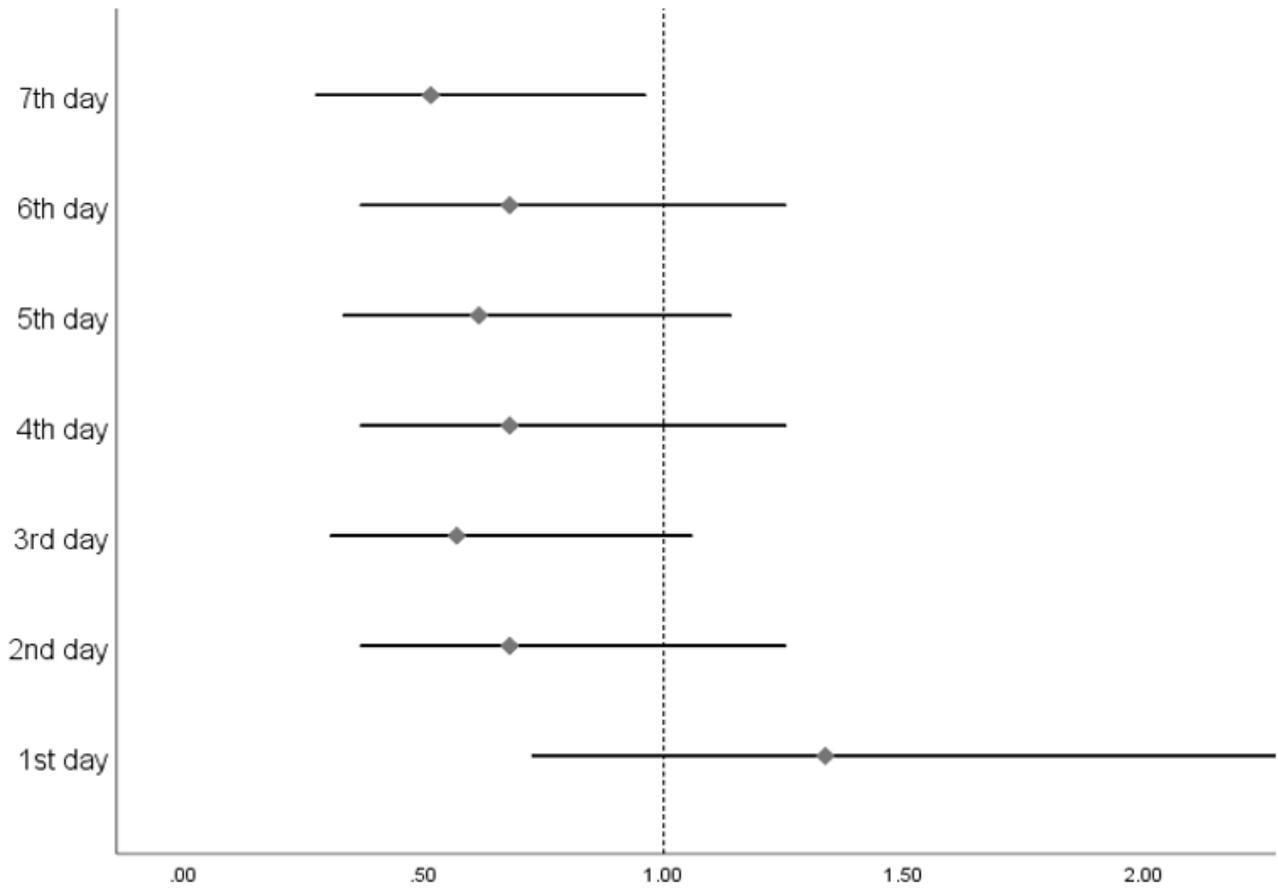


Figure 3

Relationship between moderate and severe BPD and daily given energy by univariate analysing

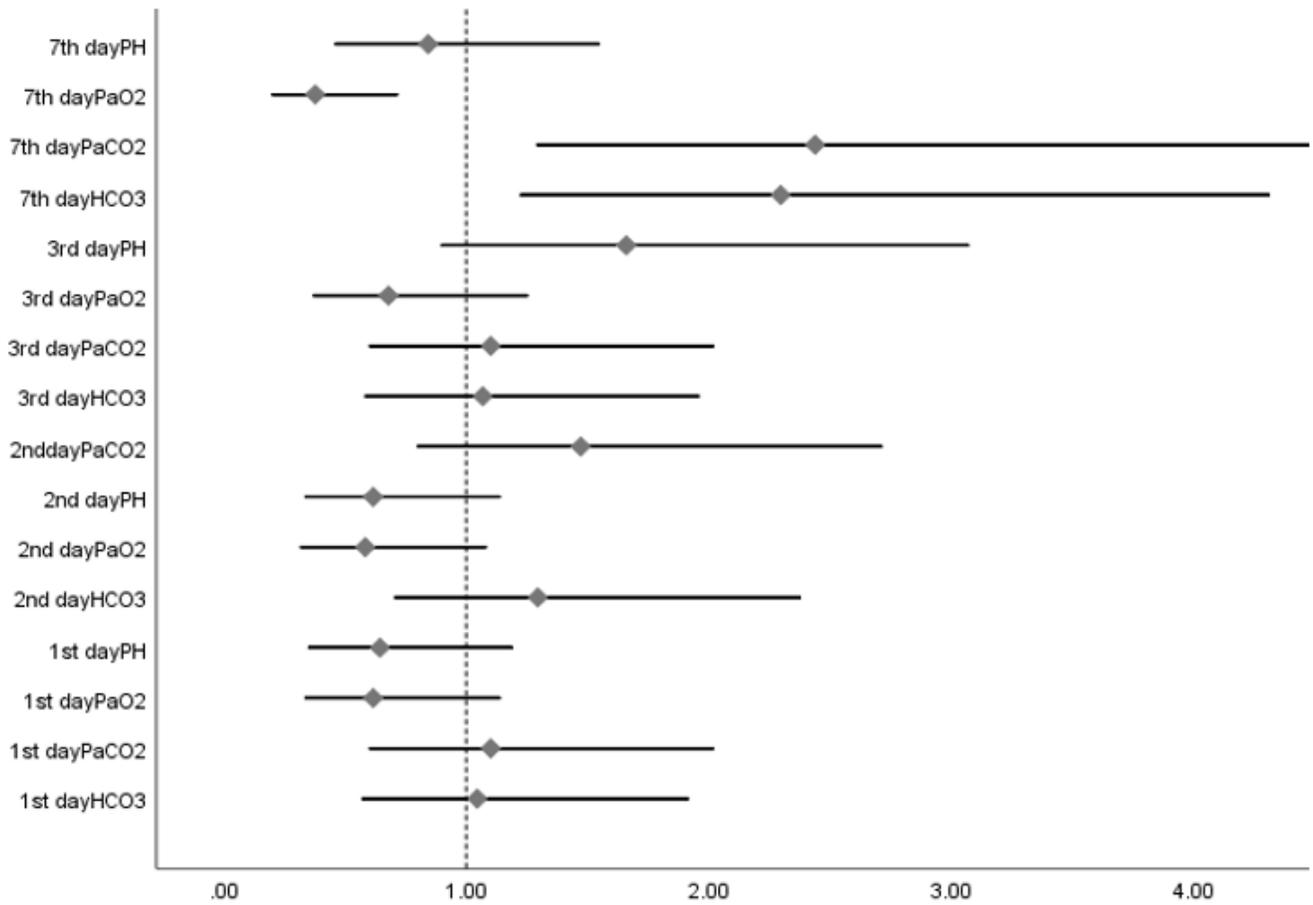


Figure 4

Relationship between moderate and severe BPD and daily blood gas values by univariate analysing