The Mantel-Haenszel Analysis to Control Confounding Variable between Birth-Weight Andearly-Onset Neonatal Sepsis at Hajj Hospital, Surabaya, Indonesia

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Abstract

The association of birth-weight and early-onset neonatal sepsis has not been consistent for decades. Classifying birth-weight as high risk group without clear evidence of a consistent association can lead to economic burdens to the health systems. Its evidence namely confounding variables. The Mantel-Haenszel test represents a simple and useful tool to obtain estimates of association adjusted for the effect of one or more confounders. This study explored the association of confounding variable between birth-weight and early-onset neonatal sepsis (EONS) using the Mantel-Haenszel Test. A cross-sectional study was undertaken at Hajj Hospital. Surabaya City. Indonesia and using retrospective documents review in NICUs. The sample size of this study was 1.461 neonates were born from January 2018 to December 2018. The confounder of this study was amniotic fluid. Bivariate analysis showed that there was a correlation between amniotic fluid and EONS (p<0.001); and there was a correlation between amniotic fluid and birth-weight (p=0.006). It means that amniotic fluid was proven as a confounding variable. Without considering amniotic fluid condition the result of binary logistic-regression shows that early-onset neonatal sepsis was influenced by birth-weight (p<0.001; cRR: 20.498; CI: 13.464-31.208). With considering amniotic fluid the result of mantel-haenszel test shows that early-onset neonatal sepsis was influenced by birth-weight (p<0.001; aRR: 24.632). It could be concluded that amniotic fluid condition can increase the chance of neonatal sepsis among neonates who had low birth-weight.

Keywords: *Mantel-haenszel test; early-onset neonatal sepsis; birth-weight; amniotic fluid*

Introduction

Confounding variable occurs when the relationship between an exposure variable and an outcome variable is distorted by the influence of a third variable between on it [1]. Confounding variable can be controlled by the study design phase and or during data analysis. There are 3 phase of study design: randomization, restriction, and matching. While the data analysis consists of stratification analysis and multivariate analysis[2]

Stratification is the simplest method to control confounding variable during the data analysis. The Mantel-Haenszel test is a one of data analysis applying stratification method. It represents a simple and useful tool to obtain estimates of association. adjusted for the effect of one or more confounders[2]. This technique was applied to explore whether the birth-weight is causally implicated in the high frequency of early-onset neonatal sepsis independently of the confounding effect of the amniotic fluid.

Neonatal sepsis is an infection occurring in neonates within 28 days of life and cause of mortality in newborns.

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It is classified into two major categories based on the time of onset: early-onset neonatal sepsis (EONS) and late onset neonatal sepsis (LONS). Early-onset neonatal sepsis appears within the first seven days of life and most cases appear within 72 hours of birth. While late onset neonatal sepsis occurs after 8 days of neonates life and is mostly acquired after delivery[3,4]

WHO showed that almost 45% child deaths under 5 years in 2016. Mostly (75%) neonatal death in the first week of life and 45% of them died at 24 hours first. That caused byneonatal sepsis[5]. Early-onset neonatal sepsis causes high morbidity and mortality in newborns. The incidence of early-onset neonatal sepsis is higher in developing countries (1.8 to 18 per 1000 live births) than in developed countries (1 to 5 per 1000 live births). The case fatality in EONS ranges from 16.7% to 19.4% [6]. The incidence rates of neonatal infection in several referral hospitals in Indonesia is approximately 8.76%–30.29% with the mortality rate is 11.56%–49.9%. The incidence rates of neonatal sepsis in several referrals hospital in Indonesia is 1.5%–3.72% with the mortality rate is 37.09%–80% [7].

In Hajj Hospital Surabaya there was an increase in cases of newborn infections in 2015-2017 to 21.50%. There are several factors that affect early-onset neonatal sepsis (EONS), including maternal factors.neonates' factors, and environmental factors. Amniotic fluid is a one of factors which affect (EONS). Romero etc. (2014) said that meconium-stained amniotic fluidwas containing a huge bacteria than clear amniotic fluid and it was affected to infection. The microorganism were Gram-negative rods, Ureaplasmaurealyticum, Gram-positive rods, and Mycoplasma hominis[8]

Other factor caused neonatal sepsis is birth-weight. The incidence and mortality of neonatal sepsis in LBW neonates was still high. In United State showed that incidence of early onset sepsis in VLBW neonates was 1.5% and that of late-onset sepsis was 25% [9]. In Dr. Soetomo General Hospital Indonesia showed that the mortality of LBW neonates with sepsis was 69%. Some condition that may contribute to the mortality of low birth weight neonates are hypothermia, hypoglycemia, overcrowding and understaffing in NICU and apneic attacks beside the sepsis condition. The LBW infant can increased the risk of sepsis by relatively immunodeficiency and may got some invasive, monitoring procedure, and longer duration of stay that may lead to nosocomial infection [10]

Meconium-stained amniotic fluid has greater bacteria than clear amniotic fluid and low-birth weight neonates had immunodeficiency. It will make the infection badly. including neonatal sepsis. This study explored the association of amniotic fluid as a confounding variable between birth-weight and early-onset neonatal sepsis (EONS) using the Mantel-Haenszel Test.

Materials and Method

This study was observational analytic with a cross-sectional design. This study using retrospective documents-medical record-review was conducted in NICUs of Hajj Hospital. The sample size of this study was1461 neonates were born from January 2018 to December 2018. The confounder of this study was amniotic fluid. A confounding variable must have two association: a confounder must be associated with the disease and a confounder must be associated with exposure. It was using Chi Square Test.

After know that amniotic fluid was proven as a confounding variable. this study used Mantel-Haenszel test for stratification between birth-weight and early-onset neonatal sepsis. This study used SPSS Statistics 17.0 for data analysis and α=0.05.

Findings: This study was received ethical approval from the Health Research Ethics Committee, Faculty of Medical, Universitas Airlangga. This study involved 1461 neonates with one hundred seventy-eight suffered of early-onset neonatal sepsis; one hundred twenty-one had low birth-weight; and one hundred eight had meconium-stained amniotic fluid. Almost half of neonates (42.7%) had low birth-weight and suffering early-onset neonatal sepsis.

Table 1. Association between Amniotic Fluid and Birth-Weight

Variables	Birth-Weight				Total		p-value
	Low (<2500 gr)		Normal (>2500 gr)				
	n	%	N	%	n	%	
Amniotic Fluid							
Meconium-Stained Amniotic Fluid	17	14.0	91	6.8	108	7.4	0.006*
Clear Amniotic Fluid	104	86.0	1249	93.2	1353	92.6	

* Significantly correlate using Chi-Square Test ($p < 0.05$)

Table 2. Association between Amniotic Fluid and Early-Onset Neonatal Sepsis

Variables	Early-Onset Neonatal Sepsis				Total		p-value
	Yes		No				
	n	%	n	%	n	%	
Amniotic Fluid							
Meconium-Stained Amniotic Fluid	53	29.8	55	4.3	108	7.4	0.001*
Clear Amniotic Fluid	125	70.2	1228	95.7	1353	92.6	

* Significantly correlate using Chi-Square Test ($p < 0.05$)

A confounding variable must have two requirements: a confounder must be associated with the disease, and a confounder must be associated with exposure. This study used Chi Square Test for correlation analysis.[11] **Table 1 and Table 2** shows that there was a correlation between amniotic fluid and early-onset neonatal sepsis (p=0.001); and there was a correlation between amniotic fluid and birth-weight (p=0.006). It means that amniotic fluid was proven as a confounding variable.

Table 3. Association between Birth-Weight and Early-Onset Neonatal Sepsis (ignoring Amniotic Fluid strata)

Variables	Early-Onset Neonatal Sepsis				Total	
	EONS		Non-Sepsis			
	n	%	N	%	N	%
Birth-weight						
Low(< 2500 gram)	76	42.7	45	3.5	121	8.3
Normal (> 2500 gram)	102	57.3	1238	96.5	1340	91.7
Result of Chi-Square Test	$\chi^2 = 316.039$ $p < 0.001$ crude RR = 20.498					
Result of Logistic-Regression Test	B = 3.020 $p < 0.001$; CI = 13.464-31.208 crude RR = 20.498					

As shown in **Table 3** there wa sa correlation between birth-weight and early-onset neonatal sepsis ($p<0.001$). Most of neonates who had normal weight (96.5%) did not suffer sepsis than neonates who had low birth-weight. In contrast almost half of participants (42.7%) who had low birth-weight were suffer early-

onset neonatalsepsis highly than neonates who had normal birth-weight. It could be concluded that the early-onset neonatal sepsis was more suffered by neonates who had low birth-weight (less than 2500 gram). The result of binary logistic-regression shows that early-onset neonatal sepsis was influenced by birth-weight without considering amniotic fluid condition (p<0.001; crude RR: 20.498; CI: 13.464-31.208). It means that the neonates who had low birth-weight were at risk for getting early-onset neonatal sepsis 20.498 times greater than neonates who had normal birth-weight.

Table 4. Association between Birth-Weight and Early-Onset Neonatal Sepsis (Amniotic Fluid strata)

Variables	Meconium-Stained Amniotic Fluid						Clear Amniotic Fluid					
	Neonatal Sepsis						Neonatal Sepsis					
	EONS		Non-Sepsis		Total		EONS		Non-Sepsis		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Birth-weight												
Low(< 2500 gram)	16	30.2	1	1.8	17	15.7	60	48.0	44	3.6	121	8.3
Normal (> 2500 gram)	37	69.8	54	98.2	91	84.3	65	52.0	1184	94.8	1340	91.7
Result of Mantel-Haenszel Test	χ^2_{MH} = 283.809 p < 0.001 adjusted RR = 24.632											
Result of Logistic-Regression Test	B = 3.212 p < 0.001; CI = 15.645-39.436 adjusted RR = 24.839						B = 3.151 p = 0.003; CI = 2.967-183.789 adjusted RR = 23.351					

Table 4 shows the association of amniotic fluid as a confounding variable between birth-weight and early-onset neonatal sepsis using the Mantel-Haenszel Test. Relative Risk (RR) for both of amniotic fluid strata increased 4 times greater than without considering amniotic fluid conditions. The result of binary logistic-regression shows that early-onset neonatal sepsis was influenced by birth-weight with considering amniotic fluid condition (p<0.001; adjusted RR: 24.632).

In meconium-stained amniotic fluid group the neonates who had low birth-weight were at risk for getting early-onset neonatal sepsis 24.839 times greater than others (p<0.001; adjusted RR: 24.839; CI: 15.645-39.436). It could be concluded that amniotic fluid condition can increase the chance of neonatal sepsis among neonates who had low birth-weight.

Discussion

Following approval from the institutional ethical committee, this study involved 1461 neonates with one hundred seventy-eight suffered of early-onset neonatal sepsis. Almost half of neonates (42.7%) had low birth-weight and suffering early-onset neonatal sepsis. Otherwise. 96.5% neonates had normal birth-weight and did not suffering early-onset neonatal sepsis. The result of binary logistic-regression shows that the neonates who had low birth-weight were at risk for getting early-onset neonatal sepsis 20.498 times greater than neonates who had normal birth-weight. This condition was similar with the previous study done by Kardana (2011) low birth-weight was significantly associated with neonatal sepsis (RR=8.4; p=0.001).Some condition that may contribute to the mortality of low birth weight neonates are hypothermia, hypoglycemia, overcrowding and understaffing in NICU and apneic attacks beside the sepsis condition. Neonates, who has low birth-weight,can increased the risk of sepsis by relatively immunodeficiency and may got some invasive, monitoring procedure, and longer duration of stay that may lead to nosocomial infection [10,12]

The result of Mantel-Haenszel analysis shows that meconium-stained amniotic fluid (MSAF) can make

the incidence of sepsis badly. Relative Risk (RR) for both of amniotic fluid strata increased 4 times greater than without considering amniotic fluid conditions. The neonates who had low birth-weight and meconium-stained amniotic fluid (MSAF) were at risk for getting early-onset neonatal sepsis 24.839 times greater than others. This condition is caused by MSAF has greater bacteria than clear amniotic fluid and low-birth weight neonates had immunodeficiency. It will make the incidence of sepsisbadly [8,10]

Conclusion

The birth-weight affected early-onset neonatal sepsis, and there was amniotic fluid as a confounding variable. It is suggested to Health Service Centre to focus on the intensive treatment for neonates who had low-birth-weight and suffered MSAF. It is also suggested to society, especially for husband, to keep supporting the pregnant-mommies for check their pregnancies regularly using USG to know baby's weight and her amniotic fluid condition.

Conflict of Interest: There was no conflict of interest in this study.

Ethical Clearance: This study was received ethical approval from the Health Research Ethics Committee, Faculty of Medical, Universitas Airlangga.

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References

1. Jager, KJ, Zoccali, C, Macleod, A, Dekker, FW Confounding: What It is and How to Deal With It, Kidney Int, 2008; p. 256–260.
2. Mantel, N,Haenszel, W.Statistical Aspects of The Analysis of Data From Retrospective Studies of Disease, J Natl Cancer Inst. 1959; p.719–748
3. Simonsen, K.A, Anderson-Berry, A.L,Delair, S.F, Davies, H.D. Early-Onset Neonatal Sepsis, Clinical Microbiology Review, Jan 2014, Vol. 25 No. 1; 2014.
4. Shehab, E.E.M, El-Sokkary, M.M, Bassiouny, M.R, Hassan, R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt; 2015.
5. WHO.Region Sepsis and Other Infectious Conditions of Newborn; 2016.
6. Chacko, B, Sohi, I. Early Onset Neonatal Sepsis, Indian J Pediatr. 2005; 72:23-6.
7. Utomo, M.Neonatal Sepsis in Low Birth Weight Neonates in Dr. Soetomo General Hospital. Indonesian Journal of Tropical and Infectious Disease, Vol. 1. No. 2; May–August 2010.
8. Roberto, Romero, Yoon, B.H, Chaemsaithong, P, Cortez, J, Park, C.W, Gonzalez, R, Behnke, E, Sonia, S, Chaiworapongsa, H.T, and Yeo, L. Bacteria and Endotoxin in Meconium-Stained Amniotic Fluid at Term: Could Intra-Amniotic Infection Cause Meconium Passage?. J Matern Fetal Neonatal Med; 2014 May. 27(8): 775–788. DOI:10.3109/14767058.2013.844124.
9. Puopolo, K. Bacterial and fungal infections, In: Cloherty J. Eichenwald EC. Stark AR. editor. Manual of neonatal care. 5th ed. Philadelphia: Lippincott William & Wilkins; 2008. p. 275–300
10. Utomo, M.T. Neonatal Sepsis in Low Birth Weight Neonates in Dr. Soetomo General Hospital. Indonesian Journal of Tropical and Infectious Disease. Vol. 1. No. 2; May-August 2010.
11. Mannocci, Alice. The Mantel-Haenszel procedure. 50 years of the statistical method for confounders control. Italian Journal of Public Health. Vol. 6. No. 4; 2009.
12. Kardana, I.M. Incidence and Factors associated with mortality of neonatal sepsis. Pediatrica Indonesiana. Vol. 51. No. 3; 2011.