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Analysis of Influencing Risk Factors of Nonsyndromic Unilateral Cleft Lip in South Sulawesi

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Abstract

Objective This study is to determine the most dominant risk factors for the potential occurrence of nonsyndromic unilateral cleft lip in South Sulawesi, Indonesia.

Materials and Methods This is a retrospective study of several hospitals in South Sulawesi, Indonesia. An analysis was performed on the medical records of patients with nonsyndromic unilateral clefts. In the period from January 2018 to December 2022, risk factors include gender, parental education, family history of cleft lip and palate, maternal history of smoking or exposure to secondhand smoke, and consumption of drugs and alcohol during gestational age. The size of the sample is determined using the cluster sampling technique. Statistics uses chi-square test analysis and logistic regression for nominal variables. It uses SPSS Statistics version 25, with a value of $p < 0.05$.

Results The highest risk factor was found in patients with parents with a history of alcohol consumption during pregnancy and in patients with family history of cleft lip and palate, history of smoking or exposure to cigarette smoke, history of drug consumption, and gender. In comparison, parents' education level does not have a significant influence.

Conclusion History of alcohol consumption during pregnancy, family history of cleft lip and palate, history of smoking or exposure to cigarette smoke, history of drug consumption, and gender are considered risk factors for nonsyndromic unilateral cleft lip in South Sulawesi, Indonesia.

Keywords
- nonsyndromic unilateral cleft lip
- cause
- risk factors

Introduction

Cleft lip and palate are the most common orofacial cleft malformation or abnormality in the head and neck region, with an estimated incidence of 1 in 500 births or 1.7 per 1,000 births worldwide, with various ethnicities and variations. The cleft lip and palate are characterized by the complete nonfuse of the right and left sides so that a gap can extend from the alveolar bone to the palate. Syndromic or nonsyndromic conditions may accompany cleft lip and palate abnormalities. Some studies reveal that cleft lip and nonsyndromic palate disorders are the most common.[1–3]

Geographical and ethnic conditions are the most significant and frequently observed. Native Asians and Americans have the highest incidence, reaching 1 in 500 births. Europeans and Africans have the lowest incidence, with 1 in 1,000 births and 1 in 2,500 births.[3–5]

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Several environmental factors have also been linked to cleft lip and palate, including the risk of smoking, diabetes before and at birth, alcohol consumption, and anticonvulsant drugs. Specific nutritional deficiencies can also increase the risk of developing cleft lip and palate, including deficiencies of folic acid, vitamins B6, B13, and B12. A systematic review suggests that consuming multivitamins in pregnant women reduces about 25% of the chances of children with cleft lips and palates.[6,7]

Genetic factors are gene variants that directly cause cleft lip and palate or can increase risk factors for cleft lip and palate. The combined effects of the environment and genetics, or a combination of both, so that it is said to be a multifactor hypothesis, cause some cases of cleft lip and palate.[8–10]

Derivatives of the multifactor theory state that risky genes interact with each other and the environment, causing defects in fetal development. Environmental factors that may cause cleft lip and palate disorders are consumption of alcohol and teratogenic drugs such as corticosteroids and anticonvulsants (phenytoin and valproic acid), smoking, and folic acid deficiency during pregnancy. Location and ethnic type can also influence the incidence rate of this lip and palate disease.[10,11]

This cleft lip and palate disorder can hurt patients if not comprehensively treated because it will have psychosocial impacts on the family and the patient himself/herself. Physiological abnormalities in patients can also occur, such as malocclusion, which will eventually interfere with the process of speech and chewing, making them susceptible to infection in the respiratory tract and ears. It requires treatment with primary measures such as preventing abnormalities by controlling their predisposing factors. Secondary procedures can be performed, such as curative procedures with surgery to unite the cleft and tertiary procedures by treating the effects caused by cleft lip and palate abnormalities.[3,12,13]

Specifically, unilateral or bilateral cleft lips have no clearly known differences in predisposing factors. In South Sulawesi, perhaps with the lives of people who still believe in some cultural traditions, the tradition of consumption of alcoholic beverages "ballo," the level of public education and economic conditions are also still below developed countries, and the health management system is still not well coordinated and evenly distributed when compared with developed countries.

Materials and Methods

The retrospective study technique is being used in this retrospective investigation, employing the cluster sampling method for sampling. This study's main goal was to ascertain the effects of gender, parental education level, family history of cleft Lip and palate (CLP), alcohol and drug use during pregnancy, smoking during pregnancy, and exposure to cigarette smoke on the incidence of nonsyndromic unilateral cleft lip in South Sulawesi.

In determining the number of samples in this study, the population in South Sulawesi was determined based on the results of the Decision of the Minister of Health of the Republic of Indonesia No. Hk.01.07/Menkes/321/2019 on the National Guidelines for Medical Services of the Administration of Cleft Lips and Palate obtained a national prevalence value of 2.4; such prevalence made the assumption of the population value of cleft lip. In determining effect size, the variable predictor used is the history of the cleft, and the response variable used is two categories of patients and one control. The large sample calculation is done with the help of the software program R studio using the package pwr function pwr.chisq.test(). However, the researchers used 0.81 for higher power. Based on the calculation, the value of *N* is 166.3933167.

Patient data for the sample were collected manually using a validated form. Interviews were conducted in two ways through the parents or representatives of the patient, even though the patient was able to communicate so that the information obtained remained through one door and the possibility of bias could be minimized. Information obtained from the form was entered into the system as data used in statistical calculations by excluding incomplete data from the start.

The age range sampled was based on the World Health Organization classification, meaning that the age range of 0 to 18 years was still included as a child. Age was not affected because interviews were conducted with parents or those accompanying the patient. Even though the patient was able to communicate, the information obtained was still obtained from one door. We did this to minimize the possibility of bias.

Inclusion criteria	Exclusion criteria
1. Patient data from January 2020 to December 2022 2. Patients with a diagnosis of nonsyndromic unilateral cleft lip 3. Data of patients who have had primary labioplasty	1. With systemic abnormalities or with other deformities 2. Incomplete nonsyndromic unilateral cleft lip cleft patient data

Data Collection

Data were collected on case groups at the Celebes Cleft Center Makassar Foundation. The data collected were obtained from the patient's medical record when the patient was anamnestic at 15 hospitals in South Sulawesi using the Patient Data Form of the Celebes Cleft Centre Makassar Foundation. From the data collected, data will be grouped based on the type of nonsyndromic unilateral cleft lip cleft disorder, age, gender, parents' last education level, family history with CBL, history of drug consumption, history of smoking or exposure to cigarette smoke, and history of alcohol consumption during pregnancy.

Statistical Analysis

The collected data are presented as percentages of numbers. In this work, logistic regression and statistical analysis of the

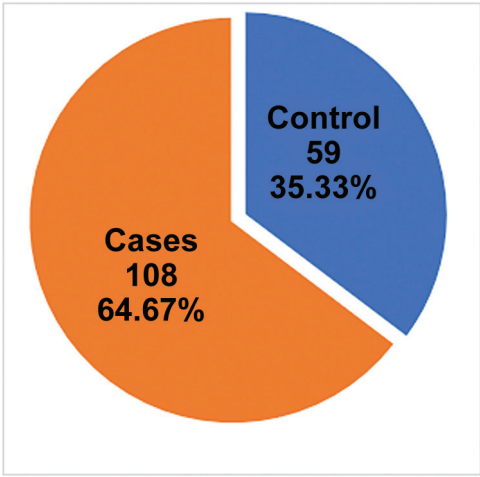

Fig. 1 Comparison between cases and control.

chi-square test were used. SPSS version 25 was used to conduct all statistical analyses. Significant data were defined as $p < 0.05$.

Results

This study had 167 respondents, 1 response variable, and 7 predictor factors. The study's response variable is the nonsyndromic unilateral cleft lip and palate occurrence in South Sulawesi. ►**Fig. 1** shows how frequently and how much these factors occur.

►**Fig. 1** shows that respondents as a control group have as many as 59 respondents (35.33%), and respondents as a patient group have as many as 108 respondents (64.67%).

The response variable in this study is a risk factor that can cause nonsyndromic unilateral cleft lip cleft in children, which includes gender, parents' recent education, family history of CBL, history of drug consumption during gestation, history of smoking or exposure to cigarette smoke during gestation, and history of alcohol consumption during gestation.

Based on gender, ►**Table 1** reveals 71 male respondents in the case group and 23 male respondents in the control group. The statistical analysis findings using chi-square test indicate a substantial correlation between the sex variable and the occurrence of nonsyndromic unilateral lip cleft, with a *p*-value of $0.001 > 0.05$.

In ►**Table 2**, based on parents' last education, 75 respondents (69.44%) were in the case group. In comparison, 35 respondents (40.68%) were in the control group.

The results of statistical analysis using chi-square test show that the last educational variable of parents does not have a significant relationship with the occurrence of nonsyndromic unilateral lip cleft, with a *p*-value of $0.187 > 0.05$.

In ►**Table 3**, based on family history with CBL, 49 respondents (45.37%) had a CBL family history in the case group. In comparison, seven respondents (11.86%) had a CBL family history in the control group.

So, statistical calculations using chi-square test show that the variable family history with CBL significantly correlates with the incidence of nonsyndromic unilateral cleft lips. The comparison of the case and control groups also showed a difference in family history with CBL between the case and control groups, with a *p*-value of $0.000 < 0.05$.

Based on the history of drug use during pregnancy, ►**Table 4** shows that 33 respondents (30.56%)

Table 1 Comparison between case and control groups by gender

Variable	Case		Control		Total	*p*-Value
	n	%	*n*	%		
Woman	37	34.26	36	61.02	73	0.001
Male	71	65.74	23	38.98	94	

Table 2 Comparison between case and control groups based on the last education of parents

Variable	Case		Control		Total	*p*-Value
	n	%	*N*	%		
Lower education	75	69.44	35	59.32	110	0.187
Higher education	33	30.56	24	40.68	57	

Table 3 Comparison between case and control groups based on family history

Variable	Case		Control		Total	*p*-Value
	n	%	*n*	%		
No family history	59	54.63	52	88.14	111	0.000
There is a family history	49	45.37	7	11.86	56	

Table 4 Comparison between case and control groups based on the history of drug consumption during pregnancy

Variable	Case		Control		Total	*p*-Value
	n	%	*n*	%		
No history of drug consumption	75	69.44	55	93.22	130	0.000
History of drug consumption	33	30.56	4	6.78	37	

Table 5 Comparison between case and control groups based on the history of smoking or exposure to smoke

Variable	Case		Control		Total	*p*-Value
	n	%	*n*	%		
Not smoking or exposure to smoke	49	45.37	42	71.19	91	0.001
Smoking or exposure to smoke	59	54.63	17	28.81	76	

Table 6 Comparison between case and control groups based on the history of consuming alcohol during pregnancy

Variable	Case		Control		Total	*p*-Value
	n	%	*n*	%		
Not consuming alcohol during pregnancy	87	80.56	55	93.22	142	0.022
Consuming alcohol during pregnancy	21	19.44	4	6.78	25	

in the case group had a history of using drugs while pregnant. In contrast, there were four responders in the control group (6.78%).

Therefore, the findings of the statistical analysis using chi-square test can be inferred from the fact that the occurrence of nonsyndromic unilateral lip cleft is related to the variable history of drug usage during gestation. With a *p*-value of $0.000<0.05$, the comparison results between the control and case groups also demonstrate variations in the history of drug intake during gestational age.

In ►**Table 5**, based on the history of smoking or exposure to secondhand smoke during pregnancy, respondents who had a history of smoking or exposure to secondhand smoke during pregnancy in the case group were 59 respondents (54.63%). In comparison, respondents in the control group were 17 respondents (28.81%).

The variable history of smoking or exposure to cigarette smoke during gestation is thus associated with the incidence of unilateral nonsyndromic cleft lip. The comparison of the control and case groups showed a difference in smoking history or exposure to cigarette smoke between the case and control groups with a *p*-value of $0.001<0.05$, according to statistical analysis using the chi-square test.

In ►**Table 6**, based on the history of alcohol consumption during pregnancy, respondents who had a history of alcohol consumption during pregnancy in the case group were 21 respondents (19.44%). In comparison, there were four respondents in the control group (6.78%).

Therefore, it can be inferred from statistical analysis using the chi-square test that the variable history of alcohol consumption during gestational age is related to the incidence of unilateral nonsyndromic cleft lip. The results of the comparison of the case and control groups also show a difference in the history of alcohol consumption during gestational age with a *p*-value of 0.001 to 0.022.

In our study, binary logistic regression analysis was used to determine the variables that affect the response status to the occurrence of nonsyndromic unilateral cleft lip cleft in children in South Sulawesi.

Discussion

Based on previous research, many risk factors can lead to cleft lip and palate, which is why it is multifactorial. Genetics and the environment, or the interaction of the two, can cause defects in fetal development.[14–19]

According to the population census data conducted by Statistics Indonesia, South Sulawesi Province, in 2018 to 2020, the population in South Sulawesi reached 8.7 million people in 2018 and increased to 9 million people in 2020, spread across various districts.

Gender can be considered a barrier or risk factor for CBL.[19,20] Several studies have identified correlations between sex and specific types of CBL. Some researchers have found that men are more at risk of suffering from cleft lips, while women are more likely to be at risk of clefts.[21–28] From the results of this study, as many as 71 respondents (65.24%) of the male sex and 37 respondents (34.26%) of the female gender experienced nonsyndromic unilateral cleft lips. Men are 2.2 times more likely to develop nonsyndromic unilateral cleft lips than women.[29–31] This is the same as Hong et al's research, Xinjiang, and Xu et al, Xuzhou, China, suggest that unilateral cleft is more common in men, with a ratio of 41 out of 66 patients and 56.8% of men experiencing

CBL.[4,32] In other studies conducted by Mbuyi-musanzayi et al in Lumbubashi, Congo, CBL occurs in 52% of men compared with 48% of women.[33,34] Although Nahas et al, Hong et al, Iran, however, suggest that men may be a factor that has less likelihood of developing CLP.[28,32] In this study, it can be caused by differences in population numbers in each region where men outnumber women. Gender can be considered a barrier or risk factor for cleft lip and palate. Several studies have identified correlations between sex and specific cleft lip and palate types.[35–37] Some researchers have found that men are more at risk of suffering from cleft lips, while women are more likely to be at risk of clefts. Then, according to Sakran et al, men can be a factor with little possibility of experiencing cleft lips and palate.[38–40]

Based on the last level of parents' education, from this study, 75 respondents (69.44%) in the case group were at a low level of education, and in the control group, as many as 35 respondents (59.32%). This is in contrast to research by Ly et al in North Africa, South Asia, and Central America, which concluded that parents' current level of education would increase risk factors for CBL. However, the results provided are still weak because they are not directly related to the increase in CBL cases.[42] Your level of education is considered the most influential and increases the risk of CBL due to a lack of knowledge about health problems.[48,52] Meanwhile, in this study, the history of parents' final education level did not become significant as a risk factor because the community actively provides education to prevent the occurrence of CBL.

Based on risk factors for family history with CBL, 49 respondents (45.37%) in the case group had a family history with CBL from this study. In the control group, only seven respondents (11.86%). This is in line with research conducted by Mbuyi-Musanzayi et al and Ly et al in Lumbubashi, Congo, which says family history has a significant influence on CBL, and it will affect the incidence rate of CBL.[2,42] Similarly, another study conducted by Maranhão et al in Damascus, Syria, and Kot and Kruk-Jeromini in Bahia, Brazil, said family history with CBL had a significant relationship with a percentage of up to 27.6%.[43]

A family history of CBL is not a risk factor for having children with CBL, according to no studies. Similarly, this study demonstrates that a family history of CBL increases a child's chance of unilateral nonsyndromic cleft lip by 5.9 times.

According to Silva et al's research in Bahia, Brazil, 40% of CBL patients may potentially be impacted by a family history of the condition. 21 and Sakran et al According to cohort research conducted in Damascus, Syria, family history significantly impacts the development of CBL in children.[43,44]

Sabbagh et al's research in Western Saudi Arabia, studies of the relationship of paternal factors to CBL, concluded that fathers strongly influence the occurrence of CBL in children.[9] This is similar to the research conducted by Noorollahian et al, which concluded that a family history of CBL would affect one-third of existing cases. The underlying mechanism for CBL influenced by family history is the possible influence of gene factors from the family. If you have a family history of CBL, then the probability of developing this disorder is about 40%, while only 18 to 20% with cleft palate.[39]

Thirty-three respondents (30.56%) in the case group and four (6.78%) in the control group had previously used drugs while pregnant, according to the history question. This study discovered that a history of drug use during pregnancy increased the likelihood of nonsyndromic unilateral lip cleft in infants by 5.6 times. This matches the study carried out by Maranhão et al, Bahia, Brazil came to the conclusion that there was a strong link between drug use and the occurrence, particularly during the first trimester of pregnancy. A shortage of vitamins during pregnancy may increase the risk of a cleft lip but not the risk of a cleft palate, according to some research. This demonstrates the genetically and embryologically distinct entities.[44]

In contrast to the research conducted by Nahas et al, The Netherlands in 2013 said that folic acid consumption at gestational age would increase the risk of CBL, especially the occurrence of cleft lips. The study is the first to report the adverse effects of folic acid on the risk of developing CBL. Folic acid is considered an inhibiting or a more significant risk factor if the mother consumes it during the periconceptional period.[28]

Another theory is that consuming folic acid may disrupt epigenetic patterns that affect gene expression.[44] This may help explain the various effects of medications that may be risk factors for CBL that have been reported in the recent literature, including anticonvulsants, retinoic acid, analgesics, benzodiazepines, antidepressants, stimulants, and antihypertensive drugs, as well as medications containing iron and folate. So, additional investigation is required.[39,43]

In this study, 59 participants (54.63%) in the case group and 17 participants (28.81%) in the control group reported a history of smoking or exposure to secondhand smoke during pregnancy. According to studies by Sabbagh et al, smoking during pregnancy or being exposed to cigarette smoke twice in the first trimester is a risk factor for CBL. It is risk If pregnant women smoke 1 to 10 cigarettes per day throughout the gestational period.[45] According to our study, there is a 2.6 times greater chance of developing unilateral nonsyndromic clefts if a woman had smoked in the past or was exposed to secondhand smoke when she was pregnant.[33,46]

The same was conveyed by Leite et al and Krapel et al, California, that mothers who smoke actively during pregnancy can cause CBL, although the exact mechanism is not yet known. The influence of existing ingredients in cigarettes is suspected to affect fetal development. Hence, hypoxia occurs due to angiogenesis and vasoconstriction disorders caused by nicotine and other cigarette ingredients.[34,47] In this study, although there were no pregnant women who smoked during pregnancy, it was found that pregnant women were exposed to cigarette smoke from husbands and families who lived in one house with a lot of frequency with an average of 10 to 20 cigarettes per day or about 1 to 2 packs per day.

Zhang et al, China, also said there was a significant increase of up to two times the occurrence of CBL in children due to exposure to cigarette smoke in pregnant women in the first trimester obtained from fathers who smoked about 20

Table 7 Odds ratio interpretation

Variable	Odds ratio	Interpretation
Gender	2.205	The male sex is 2,205 times more at risk of developing unilateral nonsyndromic cleft lips than the female sex
Family history	5.946	Patients who had a family history were 5,946 times more likely to develop nonsyndromic unilateral cleft lip than those who had no family history
History of drug consumption during the gestational age	5.579	Patients with a history of drug consumption were 5,579 times more at risk of developing nonsyndromic unilateral cleft lip than those with no history of drug consumption
History of smoking or exposure to secondhand smoke during pregnancy	2.619	Patients who had a history of smoking or exposure to secondhand smoke were 2,619 times more at risk of developing nonsyndromic unilateral cleft lip compared with those who had no history of smoking or exposure to secondhand smoke during gestation
History of alcohol consumption during pregnancy	7.220	Patients who had a history of alcohol consumption were 7,220 times more at risk of developing unilateral nonsyndromic cleft lip compared with those who had no history of alcohol consumption during gestation

cigarettes per day. Viera and Dattilo et al also evidence the same. In 2018, nicotine interfered with the fusion process in the palate carried out in animals.[34,45] In contrast, Stephanie et al's studies conducted in North Africa, South Asia, and Central America concluded that fathers who smoke are not a risk factor for CBL compared with pregnant women as active smokers during pregnancy.[33,46,48] This is thought to be due to differences in sample measurements, so further research is still needed to clarify.[41,47,49]

Another theory says that smoking at gestational age will affect the occurrence of methylation or DNA modification in the fetus, thus affecting the genes that form the lips and palate.[45] This can impact the expression of genes responsible for forming lips and palate.[28,47]

From this study, the risk factors for alcohol consumption during pregnancy were the most influential, up to 7.2 times (19.44%). This follows the research of Romitti et al and DeRoo et al in Norway in 1999 and 2008; pregnant women who consume alcohol will cause CBL in their infants. The same is true of Zhang et al's research, Norway, and Angulo-Castro et al.[50–53] Alcohol addiction or high intake, defined as five or more drinks in one night, can be harmful to fetal development.[50–53] This is brought on by an increased level of alcohol, a teratogen component, in the blood, albeit of various sorts.[7,51] Risk factors will increase by two, especially during the first trimester of pregnancy.[40]

This study has a slight obstacle for some parents and companions of patients who need to provide detailed information to provide biased information. This can be due to the fact that the population in this study generally needs a higher level of education. The advantage of this research is the large sample size, which is proportional to the large number of cleft lip and palate cases in South Sulawesi to date. While the weakness of this study is that there are still some parents and patient companions who do not provide detailed information, it can still provide biased information, even though it is conducted in relatively small numbers. This can be caused by the fact that the population conducted in this study generally has a low level of education.

Conclusion

A history of alcohol consumption during pregnancy is the highest risk factor, with up to 7.2 times its effect on the occurrence of nonsyndromic unilateral cleft lip in South Sulawesi. Gender, family history of CBL, history of drug consumption, history of smoking or exposure to cigarette smoke, and history of alcohol consumption during gestational age have an effect on the occurrence of nonsyndromic unilateral clefts in South Sulawesi (in ►**Table 7**) with a $p < 0.05$.

Consent for Participant

Inform consent was obtained from all individual participants included in the study.

Ethical Approval

Prior to starting the research, a research proposal was submitted to the Ethics Commission of the Faculty of Dentistry (FKG), Hasanuddin University (UNHAS) and the Teaching Oral and Dental Hospital (RSGMP), Hasanuddin University (UNHAS) to obtain ethical approval recommendation no. 0011/PL.09/KEPK FKG-RSGM UNHAS/2023 dated January 24, 2023. It is intended that this research can be ethically accounted for and legitimized.

Inform Consent

All participants gave written informed consent before the study began.

Conflict of Interest

None declared.

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