Comprehensive evaluation of the risk of lactational mastitis in Chinese women: Combined logistic regression analysis with receiver operating characteristic curve.

Yongshuo Yin¹ MD, Zhiyong Yu¹ MD, Min Zhao² PhD, Yuemei Wang³ MD, Xiao Guan³* MD

¹ Department of Oncology, Shandong Cancer Hospital affiliated to Shandong University, Shandong Academy of Medical Sciences, Jinan City, Shandong Province, China.
² Department of Nutrition and Food Hygiene, School of Public Health, Shandong University, Jinan City, Shandong Province, China.
³ Department of Ultrasonography, Jinan Maternity and Child Care Hospital, Jinan City, Shandong Province, China.

* Corresponding author

Full name: Xiao Guan

Institute/University/Hospital: Department of Health Management Center, Qilu Hospital of Shandong University

Tel: +86-18560083352

E-mail: gx_cindy@163.com

Address: 107# Wenhuaixi Road, Jinan City, Shandong Province, China.
Abstract:

**Objective:** To identify the potential risk factors for acute mastitis during lactation comprehensively. Subsequently, to evaluate Logistic Regression model in predicting the risk of lactational mastitis in Chinese women by applying Receiver Operating Characteristic (ROC) curve.

**Methods:** A case-control study among Chinese women enrolled 652 patients with mastitis and 581 healthy women with breastfeeding experience as control. The retrospective information was obtained by questionnaires which included medical history of pregnancy, delivery, puerperium and breastfeeding behaviors. Univariate analysis and multivariate logistic regression model were performed to investigate the relationship between these factors and the occurrence of lactational mastitis. Using ROC curve to evaluate the prognostic value of these selected indicators in the risk of acute mastitis.

**Results:** The multivariate logistic regression analysis showed that the primiparity (p<0.001), mastitis in previous breastfeeding(p<0.001), nipple’s dysplasia(p<0.001), cracked nipple(p<0.001), breast trauma(p=0.002), lateral position(p=0.007), breast pump(p=0.039), nipple sucking(p=0.007), sleep with sucking(p=0.007), and tongue-tie(p=0.013) were risk variables independently and significantly related with mastitis. While vaginal delivery(p=0.015), clean nipple before breastfeeding(p=0.015), first contact with child within one hour (p=0.027) were protective factors. The ROC analysis demonstrated that the area under the curve of model 2 was 0.8122 (95%CI=0.7885-0.8360), which stated that the model presented a high sensitivity and specificity.

**Conclusion:** By means of collecting and summarizing the risk factors associated with the occurrence of breast mastitis in Chinese women, we established risk discriminant model to identify and warn the individuals susceptible to acute mastitis early, which will allow practitioners to provide appropriate management advice and effective individual care.

**Key word:** Mastitis; Risk factors; Logistic Regression; Breastfeeding; ROC curve
Introduction:

Breastfeeding is a natural infant feeding method highly recommended by the World Health Organization (WHO)[1] and the United Nations International Children's Emergency Fund (UNICEF) to ensure the healthy growth of infants and children throughout the world[2]. Furthermore, some countries have established the breastfed infant as the norm against which to assess compliance with children's right to achieve their full genetic growth potential[3]. At present, breastfeeding is now recommended for at least 2 years[1]. The main reasons leading to failure of breastfeeding are acute mastitis and breast abscess[4]. Approximately 3-33% of breastfeeding women suffer from mastitis, particularly in the 6 months after childbirth[5,6]. The reason is that there are no interventions that have been consistently proven effective for preventing mastitis. Encouraging emptying milk from the breast, avoiding nipples damage, and taking antibiotics may reduce the risk of developing mastitis. Even so, about 3~11% of acute mastitis are still prone to develop to breast abscess in the case of rapid progression and improper treatment[7]. Mastitis and breast abscess have potential negative impacts on infant feeding. Effective managements such as education, counselling and monitoring are essential to control the discomfort and decrease the likelihood of discontinuation of breastfeeding[8].

Lactational mastitis is an acute inflammatory process of affected mammary duct and peripheral connective tissue by pathogenic bacteria, which is clinically characterized by a red, hot, swollen and wedge-shaped area of the breast with influenza-like symptoms, such as fever and malaise[5]. It can lead to stop breastfeeding and use alternative formula to feed infants, which reduce the protective effect of breastfeeding on mother and baby. Based on this, prevention of lactational acute mastitis to ensure breastfeeding rate and extend the protection of breastfeeding is extremely necessary. According to substantial epidemiologic evidence[9], lactational mastitis is a complex disease caused by sociodemographic, biophysical, and psycho-social factors[10]. More and more literatures reveal that maternal age, education, residence, physical status, breastfeeding behaviors, psychological mood,
and infant oral development defects have been widely considered as potential risk factors for the lactational mastitis[11].

In summary, lactational mastitis is the focus of renewed attention with high economic, social and public health impact. The aim of this research is to investigate and clarify the risk factors associated with the occurrence of breast mastitis in Chinese women, and to establish risk assessment model to identify and warn the individuals susceptible to lactational mastitis early. Furthermore, our aim is also to standardize propaganda and education and to formulate preventive measures, which will allow practitioners to provide appropriate management advice, scientific treatment strategies and effectively individual care.

Materials and methods:

Participants recruitment:

The patients who participated in this case-control study were recruited at breast surgery department of Shandong Cancer Hospital and Qilu Hospital of Shandong University between June 2016 and December 2017. The diagnosis was made according to the Academy of Breastfeeding Medicine(ABM) diagnostic criteria for lactational mastitis [6,12], which were defined as self-reported symptoms of tender, hot, swollen, wedge-shaped area of breast, accompanied by one or more of the following[13]: (1) an elevated temperature 38.5°C or greater, (2) one of the constitutional symptoms of fever (body aches, headaches and chills), (3) total number of white blood cells and neutrophils increased, WBC>10.0×10⁹/L and NEUT>7.0×10⁹/L. (4) axillary lymph node enlargement. Symptoms must be present for a minimum duration of 24 hours. Controls enrolled in this study were female who attended post-partum follow up clinics at Health Management Center of Qilu hospital and must meet the following criteria: (1) age ranging from 20 to 40, (2) breastfeeding experience without acute mastitis during lactation, (3) stopped breastfeeding within 2 years.

Estimate of sample size needed:

The sample size of the case-control study was estimated with PASS 11 software.
According to previous literature, the average proportion of multiple exposures in control group was about 20\%[14,15]. Meanwhile, we formulated the expected Odds Ratio(OR)=2.0, the test level \( \alpha =0.05, \beta=0.10 \), and the test performance \( 1-\beta=0.90 \). Based on the assumption above, the sample size of the case group and the control group was calculated.

Questionnaire:

Based on the previous studies and a review of the literatures[15,16], a questionnaire was developed to collect data on general sociodemographic, psychosocial, and puerperium characteristics. The questions included maternal age, residence, occupation, education, birth and breastfeeding history, family history, alcohol or smoking status and delivery mode. Psychosocial variables referred to the maternal mood, such as pleasure, happiness, depression and irritability. Puerperium characteristics concerned the time of first breastfeeding, abnormal development of nipple, frequency of nipple cleaning, sleep posture, breast trauma, maternal physical health, antibiotics use, infant feeding and sucking patterns, tongue-tie and oral thrush. Moreover, three types of papillary dysplasia including nipple retraction, flat nipple and large nipple are defined. The normal nipple is 0.8-1.5cm in diameter and 1.5-2cm in height. Nipple retraction means that the nipple is sunken in the areola and does not protrude from the outside. Nipple applananation refers to the height of the nipple <0.5cm. Large nipple refers to the diameter of the nipple >2.5cm. Poor connection between mother and baby in the questionnaire is mainly due to improper embrace position, nasal obstruction and other causes of infants that can not correctly include nipple.

In addition to considering the logic, the items listed in the questionnaire also should be arranged in order and preset as three dimensions of delivery and postpartum characteristics, breastfeeding behaviors and characteristics, infants practices and characteristics. The reliability and validity of the scale were measured by Cronbach's \( \alpha \) coefficient and exploratory factor analysis respectively. As far as possible, we selected simple and understandable questions for the respondents to simplify the
contents and ensure the accuracy of the results. Furthermore, minimized personal information related topics, and reduced the incidence of such cases which were loss of compliance due to fear of privacy leakage, so as to ensure the authenticity of the questionnaire.

**Design process and quality control:**

The procedures of research were divided into design phase, implementation phase and data analysis phase (Figure 1). (1) Design phase: on the basis literatures, we designed the research program, formulated research content and work plan, formed a unified and standardized questionnaire survey, which were revised by breast specialists and printed uniformly in the end. (2) Implementation phase: one to one surveys were conducted on the subjects who meet the inclusion criteria. Subsequently, checked the original data, stored and collated each completed questionnaire. (3) Data analysis phase: each variable in the questionnaire was assigned, and the original data were encoded and entered into the Excel table, which were imported into the SPSS software package for statistical analyses.

Strict quality control was essential to avoid measurement bias from investigators and respondents. Uniform training was provided to all investigators on the survey requirements, the definition of the contents and the methods of the investigation. In the field study, direct inquire after was adopted to make the inquiry method and time the same for each participant. Both parties established good communication to ensure that the questions in the questionnaire were fully understand by the subjects, so as to obtain objective and accurate data.

**Ethical considerations and informed consent:**

The ethical approval of the survey was obtained from the Human Ethics Committee of Shandong Cancer Hospital. Every subject signed a written consent. The original questionnaires and data were involved special person in charge, special closet for storage, special computer for registration and encryption.

**Statistical analysis:**

Participants’ baseline characteristics according to mastitis status were presented
using proportions for categorical variables. Comparisons of categorical variables in both mastitis and control groups were done using chi-square test ($\chi^2$). To analyze the association between mastitis and the potential risk factors, a multivariate logistic regression model was constructed and Odds Ratio (OR) with 95% Confidence interval (CI) were calculated. To assess abilities of combined variables with significant differences in multivariate logistic regression to predict incidence of mastitis, ROC curves, which correlated true- and false-positive rates (sensitivity and 1-specificity), were constructed. In addition, ROC curves established by risk factors from American ABM guidelines for treatment of mastitis was used as reference. Both AUCs (Area under the curve) were calculated and the statistical significance of differences between the two AUCs also was determined. All statistical analyses were performed with SAS 9.3 and a two-sided $P <0.05$ was considered as statistically significance.

**Results:**

**Calculation and collection of samples**

The sample size of case group and control group calculated by PASS 11 software is 230. Taking into account the 10% rate of lost follow-up and the 10% rate of unqualified questionnaires, at least 289 samples are required for each group. Based on the steps and procedures mentioned in the method, we approached 833 eligible patients who had acute lactational mastitis. Among them, 768 patients agreed to participate and only 691 patients completed the questionnaires, the other 77 cases were unfinished due to poor communication and cooperation during the investigation and no response/lost follow-up. Finally, 652 cases were qualified, the remaining 39 cases were excluded owing to incomplete information collection/multiple selection or mission of the options in the questionnaire. Similar to the above processes, 846 healthy women with breastfeeding experience were recruited into our study as controls and 581 females completed the investigation in the end (Figure 2). There were finally 1233 patients recruited as cases or controls, and 466 respondents left during study period due to a variety of reasons.

**Reliability and validity test of questionnaire**

Before the questionnaire was officially issued, we invited 32 patients with mastitis
and normal women with previous breastfeeding experience to conduct a small-scale test. The researchers adjusted the content and structure of the questionnaire according to the feedback and calculated the reliability and validity of the questionnaire.

The reliability of the scale measured by Cronbach’s α coefficient was 0.932. By the score with expert review, the content validity index of the scale was 0.897, and with the Bartlett test, the $\chi^2=6684.148, \ p<0.001$, and Kaiser-Meyer-Olkin(KMO)=0.858, that represented good structural validity.

**General characteristics of research objects**

The study enrolled 652 patients with lactational mastitis and 581 healthy women after completing all the questionnaires designed to collect retrospective information about different factors related to mastitis. In descriptive analyses, the average age was 29.89±3.37 for cases and 30.26±3.78 for controls. Many essential relations were also established between the age range at last delivery, residence, occupation, education, delivery number and mode, mastitis in previous breastfeeding, maternal body mass index(BMI), smoking, drinking and acute infectious mastitis.

Concerning sociodemographic characteristics, women in the case group were more likely to have Bachelor or below (p=0.010), primiparity (p=0.018), caesarean section (p=0.011), history of mastitis(p<0.001) comparing with the control. Meanwhile, there were no significant differences between case and control subjects with regard to age at last delivery(p=0.318), residence(p=0.087), occupation (p=0.163), maternal BMI (p=0.272), smoking(p=0.076), and drinking(p=0.889). Information about the main sociodemographic characteristics of the samples is shown in Table 1.

**Univariate analysis and multivariate logistic regression analyses**

Factors significantly associated with mastitis risk in a previous univariate analysis (Table 2) were included in the logistic regression and shown in Table 3. In terms of past medical history, there was no education-related significant difference, but mastitis in previous breastfeeding was obviously shown by women with mastitis compared to controls(OR=4.945, 95%CI=3.123-7.829). Between the two groups, primiparous females(OR=2.233, 95%CI=1.602-3.113) and vaginal delivery (OR=...
0.702, 95%CI= 0.527-0.934) were respectively observed to be barely significant risk factor and protective factor. Sleeping posture also revealed significant difference comparing cases with controls. Lateral position was found remarkably more frequent in the mastitis group than in the control group(OR=1.502, 95%CI=1.133-1.991).

Women in the mastitis group were more likely to have nipple’s dysplasia, such as nipple retraction(OR=9.114, 95%CI=3.629-22.884) and application nipple(OR=1.632, 95%CI=1.070-2.490). The more important concern is that cracked nipple(OR=5.807, 95%CI=4.334-7.782) would prominently lead to acute mastitis in lactating women. In contrast, cleaning nipple before breastfeeding regularly (OR=0.681, 95%CI=0.499-0.929) may effectively avoid the occurrence of infectious mastitis. Considering the breastfeeding behaviors and practices, use of breast pump(OR=1.348, 95%CI=1.015-1.790) and breast trauma(OR=1.845, 95%CI=1.256-2.711) were mastitis risk factors. Nevertheless, there was no statistically difference between cases and controls related to the non-medical staff massage.

At the same time, some associations deserving attention is variables of infants practices and characteristics. For instance, sucking manners(OR=1.664, 95%CI=1.141-2.427) and sleep with sucking(OR=1.460, 95%CI=1.110-1.921) were significantly associated with infectious mastitis. Compared with the way of areola sucking, nipple sucking(OR=1.664, 95%CI=1.141-2.427) were more administrated to children in the case group than in the control group. A higher risk of mastitis was noted when the infant suffered from tongue-tie(OR=2.026, 95%CI=1.160-3.539). In addition, connecting difficulty between mother and baby did not yield a significant difference in the case-control study.

As to the maternal physical condition and psychological mood, the factors of anemia and throat infection were illustrated without significant variation. Similarly, use of unauthorized oral antibiotics and negative emotion were not associated with mastitis which was opposite to the views reported in other literatures[16,17]. Contact with infant after birth within one hour and separation from mother longer than 24 hours had no obvious statistics difference in both case and control groups.
Evaluation discriminant model with ROC

According to the AMB treatment guidelines of mastitis[6] and common related factors, including mastitis in previous breastfeeding, abnormal nipple’s development, cracked nipple, breast trauma, poor connection of mother-infant, unauthorized oral antibiotics, tongue-tie, maternal BMI, psychologic status, and education, we have established discriminant model 1 using ROC curve, of which AUC was 0.7687, and 95%CI was 0.7424-0.7950. Additionally, screened variables with logistic regression analysis, for instance, deliver mode, deliver number, sleeping posture, breast pumps, clean nipple before breastfeeding, first contact with child within 1h, sucking manners, sleep with sucking, non-medical staff massage and tongue-tie, combined with the indicators from model 1 to perform ROC curve analysis and set up model 2, that displayed the area under the ROC curve was 0.8122 (95%CI=0.7885-0.8360). Model 1 and model 2 are statistically significant for the ability to screen and discriminate mastitis ($\chi^2=33.2405$, p<0.0001), which stated that the model 2 presented a good fit and a terrific adjustment (Figure 3).

Discussion

According to epidemiologic studies, breastfeeding has been proven to have more short-term and long-term benefits, which is highly associated with reduced risk of acute otitis media, nonspecific gastroenteritis, severe lower respiratory tract infections, childhood leukemia, and sudden infant death syndrome for babies[18,19] and type 2 diabetes, breast and ovarian cancers for mothers[18,20]. In spite of proven profits and repeated emphasis, only 42% women begin breastfeeding within an hour of birth[21], and the rate of exclusive breastfeeding(EBF) among children less than 6 months of age is only 36% globally[22-23]. WHO Member States have agreed six Global Targets, of which one target is to increase the rate of EBF in the first 6 months to at least 50% by 2025[24].

Over the years, acute infectious mastitis has still been considered to be the main cause of temporary and permanent breastfeeding weaning in lactation. Comprehensive and systematic risk factors analyses and predictive evaluations of acute mastitis have
been less reported. There is consensus in the literatures that the most common factors for mastitis depend on a large number of determinants included maternal education and employment, traditional healthcare practices, breastfeeding behaviors and characteristics[11,15,16,25]. The importance of various factors to the initiation of mastitis can be different due to socioeconomic status and cultural background[24].

The purpose of the case-control investigation is to identify the potential risk and protective factors related to mastitis. Among them, the first contact between mother-infant within 1h could reduce the risk of mastitis(OR=0.565, 95%CI=0.340-0.938). That is to say, if separation from the maternity and newborn after birth prolonged due to hypoxia, hospitalization or any other reasons may increase the risk of mastitis in lactation. The initial 1-2h after birth is the best time for sucking action and foraging reflex[26]. It is also a sensitive period to set up effective breastfeeding[27]. Early exposure and sucking can continuously stimulate the secretion of prolactin (PRL) in the anterior pituitary, which could establish breastfeeding as early as possible. For this reason, we should highlight the crucial importance of early skin-to-skin contact of mother and baby[28] to set up a powerful sucking ability, which can effectively empty milk in time and avoid mastitis.

This finding is consistent with previous evidence[29,30] that the primiparous women were found significantly more frequent in the mastitis group than in the control group(OR=2.233, 95%CI=1.602-3.113). Primipara without previous experience of childbirth lacks healthcare knowledge and preventive measures for postpartum rehabilitation, breastfeeding and lactation mastitis, but also faces the adaptation process of new roles[31]. Therefore, the primipara is in urgent need of comprehensive and meticulous guidance[32] by strengthening interactive education about the pathogenesis and prevention of lactational mastitis, so that when suffering from nipple dysplasia, cracked nipple, engorgement, plugged ducts, and galactostasis, they could take effective actions to alleviate the uncomfortable symptoms of maternal breast distention and pain. The study from Holmes demonstrates that a formal breast-feeding curriculum can improve physician’s knowledge and attitudes, change
practice around breastfeeding care, also reduce the risk of mastitis and improve clinical outcomes[33].

For the last 20 years, a few research have reported the relationship between the delivery mode and acute lactational mastitis[11,15,16]. From our study, it can be seen that the vaginal delivery is a protective factor (OR=0.702, 95% CI=0.527-0.934) for acute lactational mastitis, and the cesarean section is a risk factor in contrast. The increased morbidity of mastitis due to the mode of childbirth usually occurs during puerperium (6 weeks after childbirth). The possible reasons are as follows. Firstly, the puerpera with cesarean section are afraid of feeding the newborn because of many discomfort factors such as postpartum pain[34], infusion, indwelling catheter, and compulsive position, which lead to poor discharge of milk and galactostasis. Secondly, the women who had undergone cesarean section may result in low immunity and flora imbalance. With synergistic effect of opportunistic pathogens, the proliferation of pathogenic bacteria has happened in the damaged nipple or blocked duct, which accelerates the progress of mastitis. Moreover, the development of new strategies for mastitis management based on probiotics is particularly appealing[35].

Significantly, a previous history of lactational mastitis is also a strong mastitis predictor in our study, and this factor is associated with a nearly five-fold risk of mastitis in the multivariate analysis (OR=4.945, 95% CI=3.123-7.829). In the past, scholars used to think that lactation mastitis was a simple infectious disease, and now this view is facing a challenge. Its pathogenesis has changed from a simple infectious disease to inflammatory reaction[9]. The susceptibility and severity of mastitis are not related to the number of infectious pathogenic bacteria, but related to breast morphology, mammary duct development, the immune response of the body[36], and these factors can lead to mastitis in women time and again.

Nipple is located in the posterior part of the baby's oral cavity while sucking, which can effectively stimulate the sensory nerve on the nipple, thus promoting lactation reflex and avoiding nipple injury. As a result, the WHO, the UNICEF and Maternal and Child health Department of National Health Commission of the People’s
Republic of China have successively promulgated the breastfeeding handbook, that promote and guide breast feeding with nipple and areola, so as to better discharge milk and avoid nipple pain and breakage[37]. To conclude, our findings have supported that nipple sucking (OR= 1.664, 95%CI=1.141-2.427), nipple dysplasia such as nipple retraction (OR=9.114, 95%CI=3.629-22.884) and nipple apllanation (OR=1.632, 95%CI=1.070-2.490) were significantly more widely administered to women reporting acute mastitis. In theory, the skin of nipple retraction is delicate and the stratum corneum is not thick owing to less external stimulation at ordinary times. As a result, tender nipples are prone to chapping after sucking, where is invaded by the pathogen to the mammary lobules and their fat and fibrous tissue, and eventually cause the acute mastitis. There was a general consensus with previous studies[16] that tongue-tie (OR=2.026, 95%CI=1.160-3.539) strongly links to lactational mastitis. In conclusion, mothers need to be fully aware of and correct their nipple before giving birth, make preventive measures earlier, and better learn nipple care knowledge to compensate for potential mastitis risk caused by defects in congenital dysplasia of nipples.

In this study, the demonstrated improvement was likely a result of correlation between breast pump(OR=1.348, 95%CI=1.015-1.790), breast trauma(OR=1.845, 95%CI=1.256-2.711), sleeping lateral position(OR=1.502, 95%CI=1.133-1.991) and infectious mastitis. Because mammary gland ducts are filled with milk, the tube wall is thin, and the subcutaneous tissue of the mammary gland is rich in lymphatic vessels and capillaries, it is prone to cause local breast tissue damage and edema in the effect of external force compression, collision, inappropriate massage, and infant kicking. When sleeping on the side, the milk remains in the breast tube near the side of bed due to gravity, and the breast is compressed leading to galactostasis. Meanwhile, the frequent and improper use of breast pumps was a relevant mastitis risk factor[38], which may give rise to tissue damage, ache, and nipple trauma and if not sterilized on time they could be a source of pathogenic bacteria.

There are intimate links between bacterial invasion with occurrence and
development of acute mastitis during lactation. First of all, the bacteria on the skin surface can intrude through the cracked nipple and areola, and retrograde to interlobular mammary gland. Secondly, the microorganisms in the baby’s mouth enter the mammary duct and stay in it[39]. Finally, some studies suggest[16,40] that there is an endogenous pathway existing in the source of microbes of milk, which involve in bacterial infections in other parts of the postpartum(such as respiratory infections, acute tonsillitis, etc.) through lymphatic system and blood system to the breast. The results of this study demonstrate that long suck by babies while they sleep was significantly more widely administered to women reporting lactational mastitis (OR=1.460, 95%CI=1.110-1.921), while cleaning nipples before or after breastfeeding can reduce bacterial invasion and the incidence of mastitis (OR=0.681, 95%CI=0.499-0.929).

Previous studies[41] have confirmed that negative emotions can activate hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) axis can upregulate the levels of glucocorticoid (GCs) and catecholamines (CAs) respectively, causing raised blood pressure and vasoconstriction, which reduce the blood supply for the breast, and the secretion of milk. In addition to this, pessimism can also affect the release of prolactin, that may diminish the possibility of milk deposition. But at the same time, another research[42] displayed that negative emotions can lead to a decrease in secretory immunoglobulin A (SIgA) levels, resulting in weakening the body resistance to bacteria. The pathogenic factors of acute mastitis in lactation are milk siltation and bacterial infection. Although negative emotions decreased the former, it also enhanced the role of the latter. At present, it is still unclear which of these two factors play the dominant role. Our result revealed that no significance was found between the patients and the controls with regard to psychological mood. In any case, the mother should remain happy and optimistic during pregnancy and lactation, which is essential for strengthening immunity, reducing illness and raising babies[43,44]. As well as the family, hospital and society also need to give mothers thoughtful care and guidance.
Although unauthorized oral antibiotics was not an independent risk factor for mastitis in this analysis. Theoretically, use of large amount of antibiotics without indication can reduce maternal resistance and lead to microbial imbalance of breast bacteria, and the potential pathogens have overgrown as losing the inhibition of other bacteria[34]. Antibiotics are often used in the treatment of mastitis, but have not been popular or proven effective as a preventative agent. Increasing research indicates that specific probiotic bacteria possess significant anti-inflammatory properties and supports their potential use as immunomodulatory agents[45]. Supplementation with lactobacilli and probiotics may eliminate the risk of mastitis in women and prevent breast infection. In future, we need to pay more attention to the management of antibiotic resistant bacteria, select lactobacilli strains isolated from breast milk, evaluate the effectiveness of oral probiotics for the prevention and treatment of mastitis in breastfeeding women.

The results of our study demonstrated that relevant factors related to an increased risk of infectious mastitis in Chinese breastfeeding women, which will allow practitioners to provide appropriate management advice and professional health care. It is important to investigate preventive measures in order to maintain and increase breastfeeding exclusivity and duration, especially for high-risk individuals. There are still many questions to answer about lactational mastitis, but work is in progress to broaden our knowledge in this relevant Public Health issue.

Conflicts of interest:
The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgement:
We would like to sincerely thank Dr. Ximei Gao(Qilu Hospital of Shandong University) for providing a platform for data collection, and Dr. Yune Lu(Jinan...
Maternity and Child Care Hospital) for assistance in questionnaire collection. The study was funded by National Natural Science Foundation (Grant No. 81702565), Natural Science Foundation of Shandong Province (Grant No. ZR2017BH052), Jinan Science and Technology Development Foundation (Grant No. 201602199). They will play a role at any point in the research or publication process.

Authors' contributions:
YSY contributed to the study design and wrote the article. ZYY conducted the data collection, stratification and analyses. YMW directed the interpretation of data. MZ performed the statistical analysis. XG originated and directed the study, reviewed the manuscript. All authors read and approved the final manuscript.

Reference:
[1] Sobti J, Mathur GP, Gupta A. WHO's proposed global strategy for infant and young child feeding: a viewpoint. J Indian Med Assoc, 2002, 100(08): 502-506.
[2] Chessa KL, Ardythe LM. Protection, Promotion, and Support and Global Trends in Breastfeeding. Adv Nutr, 2013, 4(2): 213-219.
[3] Mercedes de Onis. Update on the Implementation of the WHO Child Growth Standards. World Rev Nutr Diet, 2013, 106: 75-82
[4] Kesaraju P, Jaini R, Johnson JM, et al. Experimental autoimmune breast failure: a model for lactation insufficiency, postnatal nutritional deprivation, and prophylactic breast cancer vaccination. Am J Pathol, 2012, 181(3): 775-784.
[5] Li T, Andy HL, Liqian Q, Colin WB. Mastitis in Chinese Breastfeeding Mothers: A Prospective Cohort Study. Breastfeed Med, 2014, 9(1): 35-38.
[6] Academy of Breastfeeding Medicine. ABM clinical protocol 4: mastitis. Breastfeeding Medicine, 2008, 3(3): 177-180.
[7] Cooney F, Petty NS. The Burden of Severe Lactational Mastitis in Ireland from 2006 to 2015. Ir Med J, 2019, 112(1): 855.
[8] Zekiye K, Müge S. Breastfeeding problems and interventions performed on problems: systematic review based on studies made in Turkey. Turk Pediatri Ars, 2018, 53(3): 134-148.
[9] Contreras GA, Rodríguez JM. Mastitis: comparative etiology and epidemiology. J Mammary Gland Biol Neoplasia, 2011, 16(4): 339-356.

[10] Ke S, Miaoxia C, Yuzhu Y, et al. Why Chinese mothers stop breastfeeding: Mothers’ self-reported reasons for stopping during the first six months. Journal of Child Health Care, 2017, 21(3): 353-363.

[11] Cooklin AR, Amir LH, Nguyen CD, et al. CASTLE Study Team. Physical health, breastfeeding problems and maternal mood in the early postpartum: a prospective cohort study. Arch Womens Ment Health, 2018, 21(1): 365-374.

[12] Lisa HA. ABM clinical protocol #4: Mastitis, revised March 2014. Breastfeed Med, 2014, 9(5): 239-243.

[13] Lawrence RA. The puerperium, breastfeeding, and breast milk. Curr Opin Obstet Gynecol, 1990, 2(1): 23-30.

[14] Pustotina OA. Management of mastitis and breast engorgement in breastfeeding women. J Matern Fetal Neonatal Med, 2016, 29(19): 3121-3125.

[15] Fernández L, Mediano P, García R, et al. Risk Factors Predicting Infectious Lactational Mastitis: Decision Tree Approach versus Logistic Regression Analysis. Matern Child Health J, 2016, 20(9): 1895-1903.

[16] Mediano P, Fernández L, Rodríguez JM, et al. Case-control study of risk factors for infectious mastitis in Spanish breastfeeding women. BMC Pregnancy Childbirth, 2014, 14: 195-208.

[17] Mensah KA, Acheampong E, Anokye FO, et al. Factors influencing the practice of exclusive breastfeeding among nursing mothers in a peri-urban district of Ghana. BMC Res Notes, 2017, 10: 466-471.

[18] Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet, 2016, 387(10017): 475-490.

[19] Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality: A systematic review and meta-analysis. Acta Paediatr, 2015, 104(467): 3-13.

[20] Chowdhury R, Sinha B, Sankar MJ, et al. Breastfeeding and maternal health
outcomes: A systematic review and meta-analysis. Acta Paediatr, 2015, 104(467): 96-113.

[21] Gupta A, Holla R, Dadhich JP, et al. The status of policy and programmes on infant and young child feeding in 40 countries. Health Policy Plan, 2013, 28(3): 279-298.

[22] Gupta A, Suri S, Dadhich JP, et al. The World Breastfeeding Trends Initiative: Implementation of the Global Strategy for Infant and Young Child Feeding in 84 countries. J Public Health Policy, 2019, 40(1): 35-65.

[23] Bililign N, Kumsa H, Mulugeta M, et al. Factors associated with prelacteal feeding in North Eastern Ethiopia: A community based cross-sectional study. International Breastfeeding Journal, 2016, 11(1): 13-19.

[24] Mahesh S, Alexandr P, Aileen R, et al. Comparison of national cross-sectional breast-feeding surveys by maternal education in Europe (2006-2016). Public Health Nutrition, 2019, 22(5): 848-861.

[25] Ke S, Miaoxia C, Yuzhu Y, et al. Why Chinese mothers stop breastfeeding: Mothers’ self-reported reasons for stopping during the first six months. Journal of Child Health Care, 2017; 21(3): 353-363.

[26] Moore ER, Bergman N, Anderson GC, et al. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev, 2016, 11: CD003519.

[27] Forster DA, Johns HM, McLachlan HL, et al. Feeding infants directly at the breast during the postpartum hospital stay is associated with increased breastfeeding at 6months postpartum: a prospective cohort study. BMJ Open, 2015, 5(5): e007512.

[28] Bramson L, Lee JW, Moore E, et al. Effect of early skin-to-skin mother-infant contact during the first 3 hours following birth on exclusive breastfeeding during the maternity hospital stay. J Hum Lact, 2010, 26(2): 130-137.

[29] Yu Z, Sun S, Zhang Y. High-Risk Factors for Suppurative Mastitis in Lactating Women. Med Sci Monit, 2018, 24: 4192-4197.

[30] Beltrón Vaquero DA, Crespo Garzón AE, Rodriguez Bravo TC, et al. Infectious
mastitis: a new solution for an old problem. Nutr Hosp, 2015, 31(1): 89-95.

[31] Martinez HT, Silva MA, Cabrera IP. Obstetric profile of pregnant adolescents in a public hospital: risk at beginning of labor, at delivery, postpartum, and in puerperium. Rev Lat Am Enfermagem, 2015, 23(5): 829-836.

[32] Recep A, Dilek K, Kübra G, et al. Experience and knowledge level of female health care professionals in Samsun province regarding puerperal mastitis. Ulus Cerrahi Derg, 2016; 32: 261-266.

[33] Holmes AV, McLeod AY, Thesing C, et al. Physician breastfeeding education leads to practice changes and improved clinical outcomes. Breastfeeding Medicine, 2012, 7(6): 403-408.

[34] Brown A, Rance J, Bennett P. Understanding the relationship between breastfeeding and postnatal depression: the role of pain and physical difficulties. J Adv Nurs, 2016, 72(2): 273-282.

[35] Fernandez L, Arroyo R, Espinosa I, et al. Probiotics for human lactational mastitis. Beneficial Microbes, 2014, 5(2): 169-183.

[36] Wendy IV, Danielle GJ, Mark HR. Inflammatory mediators in mastitis and lactation insufficiency. J Mammary Gland Biol Neoplasia, 2014, 19(2): 161-167.

[37] Elliman W, Golen TH, Gold HS, et al. Risk factors for Staphylococcus aureus postpartum breast abscess. Clin Infect Dis, 2012, 54(1): 71-77.

[38] Youlin Q, Yuanting Z, Sara F, et al. Maternal and breast pump factors associated with breast pump problems and injuries. Journal of Human Lactation, 2014, 30(1), 62-72.

[39] Patel SH, Vaidya YH, Patel RJ, et al. Culture independent assessment of human milk microbial community in lactational mastitis. Scientific Reports, 2017, 7(1): 7804-7814.

[40] Popova B, Mitev D, Nikolov A. The role of mother’s milk and breast feeding. Medical problems during the lactation period lactobacilus fermentum- a new approach towards the prevention and the treatment of acute and subacute mastitis. Akush Ginekol (Sofiia), 2016, 55(3): 47-52.
[41] Rui T, Gonglin H, Dan L, et al. A possible change process of inflammatory cytokines in the prolonged chronic stress and its ultimate implications for health. Scientific World Journal, 2014, 20(14): 780616.

[42] Jing L, Jianhong L, Chao W, et al. Positive or negative emotion induced by feeding success or failure can affect behaviors, heart rate and immunity of suckling calves. Physiol Behav, 2018, 196: 185-189.

[43] Borra C, Iacovou M, Sevilla A. New evidence on breastfeeding and postpartum depression: the importance of understanding women’s intentions. Matern Child Health J, 2015; 19(4): 897-907.

[44] Woolhouse H, James J, Gartland D, et al. Maternal depressive symptoms at three months postpartum and breastfeeding rates at six months postpartum: implications for primary care in a prospective cohort study of primiparous women in Australia. Women Birth, 2016, 29(4): 381-387.

[45] Bond DM, Morris JM, Nassar N. Study protocol: evaluation of the probiotic Lactobacillus Fermentum CECT5716 for the prevention of mastitis in breastfeeding women: a randomized controlled trial. BMC Pregnancy Childbirth, 2017, 17(1): 148-155.

Figure 1   Implementation Flow Chart in the Research
The procedures of research were divided into design phase, implementation phase and data analysis phase. Each variable in the questionnaire was assigned, and the original data were encoded and entered into the Excel table, which were imported into the SPSS software package for statistical analyses. Strict quality control was essential to avoid measurement bias from investigators and respondents.

Figure 2   The Flow Chart of 1679 Respondents Distribution
In the case, 768 patients agreed to participate and only 691 patients completed the questionnaires, the other 77 cases were unfinished due to poor communication and cooperation during the investigation and no response/lost follow-up. Finally, 652 cases were qualified, the remaining 39 cases were excluded owing to incomplete information collection/multiple selection or mission of the options in the
questionnaire. In the control, 846 healthy women with breastfeeding experience were recruited into our study as controls and 581 females completed the investigation in the end. There were finally 1233 patients recruited as cases or controls, and 466 respondents left during study period due to a variety of reasons.

* Cases: women with infectious mastitis in lactation

** Controls: women with breastfeeding experience

Figure 3  Receiver Operating Characteristic (ROC) Curve for Logistic Regression Model.

The model 1 was established according to the related factors including mastitis in previous breastfeeding, abnormal nipple’s development, cracked nipple, breast trauma, poor connection of mother-infant, unauthorized oral antibiotics, tongue-tie, maternal BMI, psychologic status, and education, of which AUC was 0.7687, and 95% CI was 0.7424-0.7950. The model 2 was set up based on the following factors such as deliver mode, deliver number, sleeping posture, breast pumps, clean nipple before breastfeeding, first contact with child within 1h, sucking manners, sleep with sucking, non-medical staff massage and tongue-tie, and combined with the indicators from model 1 to perform ROC curve analysis, of which AUC was 0.8122, and 95% CI was 0.7885-0.8360. Model 1 and model 2 are statistically significant for the ability to screen and discriminate mastitis ($\chi^2=33.2405$, $p<0.0001$).
Eligible participants
*Cases: 833
**Controls: 846

Reject to participate
Cases: 65
Controls: 141

Agree to participate
Cases: 768
Controls: 705

Complete the questionnaire (No)
Cases: 77
Controls: 79

Complete the questionnaire (Yes)
Cases: 691
Controls: 626

Qualified questionnaire (No)
Cases: 39
Controls: 45

Qualified questionnaire (Yes)
Cases: 652
Controls: 581

* Cases: women with infectious mastitis in lactation
** Controls: women with breastfeeding experience
| Variables                  | Case, n (%) | Control, n (%) | Crude OR  | 95% CI       | p value |
|---------------------------|-------------|----------------|-----------|-------------|---------|
| Age range at last delivery |             |                |           |             |         |
| < 25                      | 37 (5.7)    | 23 (4.0)       | 0.791     | 0.396-1.580 | 0.318   |
| 25–29                     | 411 (63.0)  | 361 (62.1)     | 1.118     | 0.694-1.802 |         |
| 30–35                     | 162 (24.8)  | 164 (28.2)     | 1.288     | 0.778-2.135 |         |
| > 35                      | 42 (6.4)    | 33 (5.7)       | Reference |             |         |
| Residence                 |             |                |           |             | 0.087   |
| Urban                     | 487 (74.7)  | 458 (78.8)     | 0.713     | 0.440-1.476 |         |
| Rural                     | 165 (25.3)  | 123 (21.2)     | Reference |             |         |
| Occupation                |             |                |           |             | 0.163   |
| Professional women        | 416 (63.8)  | 388 (66.8)     | 0.862     | 0.559-1.143 |         |
| Housewife                 | 236 (36.2)  | 193 (33.2)     | Reference |             |         |
| Education                 |             |                |           |             | 0.010*  |
| Bachelor or below         | 588 (90.2)  | 505 (86.9)     | 1.248     | 1.055-1.475 |         |
| Master or above           | 64 (9.8)    | 76 (13.1)      | Reference |             |         |
| Total                     | 652         | 581            |           |             |         |

* Significant at α ≤ 0.05
Table 2  Univariate analyses of 1233 women who participated in the case-control study

| Variables                                      | Cases, n (%) | Controls, n (%) | Crude OR | 95% CI     | p value |
|------------------------------------------------|--------------|-----------------|----------|------------|---------|
| **Delivery and postpartum characteristics**    |              |                 |          |            |         |
| Delivery number                                |              |                 |          |            |         |
| Primiparous                                    | 405 (62.1)   | 322 (55.4)      | 2.669    | 1.322-4.078| 0.018*  |
| Multiparous                                    | 247 (37.9)   | 259 (44.6)      |          | Reference  |         |
| Delivery mode                                  |              |                 |          |            |         |
| Vaginal                                        | 395 (60.6)   | 393 (67.6)      | 0.758    | 0.599-0.959| 0.011*  |
| Caesarean section                              | 257 (39.4)   | 188 (21.2)      |          | Reference  |         |
| Mastitis in previous breastfeeding**           |              |                 |          |            | <0.001* |
| Yes                                            | 132 (53.4)   | 56 (21.6)       | 1.582    | 1.258-1.988|         |
| No                                             | 115 (46.6)   | 203 (78.4)      |          | Reference  |         |
| First contact with child                       |              |                 |          |            | 0.001*  |
| ≤ 1h                                           | 577 (88.5)   | 547 (94.1)      | 0.478    | 0.314-0.729|         |
| > 1h                                           | 75 (11.5)    | 34 (5.9)        |          | Reference  |         |
| Separation of mother-infant                    |              |                 |          |            | 0.013*  |
| > 24h                                          | 61 (9.4)     | 32 (5.5)        | 3.226    | 1.887-5.525|         |
| ≤ 24h                                          | 591 (90.6)   | 549 (94.5)      |          | Reference  |         |
| Smoking / Drinking                             |              |                 |          |            | 0.869   |
| Yes                                            | 21 (3.2)     | 17 (2.9)        | 0.906    | 0.473-1.734|         |
| No                                             | 631 (96.8)   | 564 (97.1)      |          | Reference  |         |
| **Breastfeeding behaviors and characteristics** |              |                 |          |            |         |
| Feeding type                                   |              |                 |          |            | 0.002*  |
| Exclusive                                      | 463 (71.0)   | 461 (79.4)      |          | Reference  |         |
| Mixed                                          | 181 (27.8)   | 118 (20.3)      |          | Reference  |         |
| Formula                                        | 8 (1.2)      | 2 (0.3)         |          | Reference  |         |
| Nipple’s developmental malformation            |              |                 |          |            | <0.001* |
| Crater nipple                                  | 67 (10.3)    | 6 (1.0)         | 12.530   | 5.378-29.192|         |
| Applationation nipple                          | 122 (18.7)   | 52 (9.0)        | 4.617    | 1.883-11.324|         |
| Giant nipple                                   | 16 (2.5)     | 6 (1.0)         | 4.063    | 1.156-14.277|         |
| No                                             | 447 (68.6)   | 517 (89.0)      |          | Reference  |         |
| Cracked and sore nipple                        |              |                 |          |            | <0.001* |
| Yes                                            | 389 (59.7)   | 103 (17.7)      | 6.864    | 5.270-8.940|         |
| No                                             | 263 (40.3)   | 478 (82.3)      |          | Reference  |         |
| External force extrusion and collision         |              |                 |          |            | <0.001* |
| Yes                                            | 129 (19.8)   | 65 (11.2)       | 7.152    | 5.296-9.656|         |
| No                                             | 523 (80.2)   | 516 (88.8)      |          | Reference  |         |
| Variables                                      | Cases, n (%) | Controls, n (%) | Crude OR | 95% CI       | p value |
|-----------------------------------------------|--------------|----------------|----------|--------------|---------|
| **Breastfeeding behaviors and characteristics**|              |                |          |              |         |
| Sleeping posture                              |              |                |          |              |         |
| Prone position                                | 28 (4.3)     | 12 (2.1)       | 3.630    | 1.748-7.602  | 0.002*  |
| Lateral position                              | 304 (46.6)   | 233 (40.1)     | 2.650    | 1.546-3.867  |         |
| Supine position                               | 320 (49.1)   | 336 (57.8)     | Reference|             |         |
| Clean nipple before breastfeeding              |              |                |          |              |         |
| Yes                                           | 457 (70.1)   | 452 (77.8)     | 0.449    | 0.324-0.624  | 0.002*  |
| No                                            | 195 (29.9)   | 129 (22.2)     | Reference|             |         |
| Breast pump                                   |              |                |          |              |         |
| Yes                                           | 442 (67.8)   | 351 (60.4)     | 5.940    | 4.638-7.608  | 0.007*  |
| No                                            | 210 (32.2)   | 230 (39.6)     | Reference|             |         |
| Non-medical staff massage                     |              |                |          |              |         |
| Yes                                           | 305 (46.8)   | 228 (39.2)     | 7.115    | 5.506-9.194  | 0.008*  |
| No                                            | 347 (53.2)   | 353 (60.8)     | Reference|             |         |
| Maternal BMI                                  |              |                |          |              |         |
| < 18.5                                        | 35 (5.4)     | 19 (3.3)       | 1.779    | 0.961-3.292  | 0.014*  |
| 18.5-22.9                                     | 117 (17.9)   | 113 (19.4)     | 1.569    | 0.866-2.842  |         |
| 23.0-25.0                                     | 202 (31.0)   | 172 (29.6)     | 1.712    | 0.957-3.064  |         |
| > 25.0                                        | 298 (45.7)   | 277 (47.7)     | Reference|             |         |
| Throat infection                              |              |                |          |              |         |
| Yes                                           | 116 (17.8)   | 74 (12.7)      | 1.483    | 1.081-2.034  |         |
| No                                            | 536 (82.2)   | 507 (87.3)     | Reference|             |         |
| Anemia                                        |              |                |          |              |         |
| Yes                                           | 73 (11.2)    | 44 (7.6)       | 1.541    | 1.041-2.281  | 0.032*  |
| No                                            | 578 (88.8)   | 537 (92.4)     | Reference|             |         |
| Unauthorized oral antibiotics                 |              |                |          |              |         |
| Yes                                           | 122 (18.7)   | 83 (14.3)      | 1.951    | 1.456-2.615  | 0.039*  |
| No                                            | 530 (81.3)   | 498 (85.7)     | Reference|             |         |
| Psychological mood                            |              |                |          |              |         |
| Negative                                      | 498 (76.4)   | 393 (67.6)     | 3.771    | 2.806-5.068  | 0.001*  |
| Positive                                      | 154 (23.6)   | 188 (32.4)     | Reference|             |         |
Table 2  Univariate analyses of 1233 women who participated in the case-control study (continued)

| Variables                      | Cases, n (%) | Controls, n (%) | Crude OR | 95% CI          | p value   |
|--------------------------------|--------------|-----------------|----------|-----------------|-----------|
| **Infants practices and characteristics** |              |                 |          |                 |           |
| Sucking manners                |              |                 |          |                 |           |
| Nipple sucking                 | 146 (22.4)   | 72 (12.4)       | 3.734    | 2.777-5.022     | <0.001*   |
| Nipple shields                 | 32 (4.9)     | 9 (1.5)         | 1.381    | 0.602-3.169     |           |
| Areola sucking                 | 474 (72.7)   | 500 (86.1)      | Reference|                 |           |
| Sleep with sucking             |              |                 |          |                 |           |
| Yes                            | 349 (53.5)   | 255 (43.9)      | 4.159    | 3.239-5.342     | 0.001*    |
| No                             | 303 (46.5)   | 326 (56.1)      | Reference|                 |           |
| Connection difficulty          |              |                 |          |                 |           |
| Yes                            | 114 (17.5)   | 58 (10.0)       | 4.598    | 3.056-6.920     | <0.001*   |
| No                             | 538 (82.5)   | 523 (90.0)      | Reference|                 |           |
| Oral dysplasia                 |              |                 |          |                 |           |
| Yes                            | 58 (8.9)     | 29 (5.0)        | 1.571    | 1.013-2.437     | 0.008*    |
| No                             | 594 (91.1)   | 552 (95.0)      | Reference|                 |           |

* Significant at α ≤ 0.05

** Data from primiparous women were excluded for this analysis

* Significant at α ≤ 0.05
Table 3  Factors significantly associated with mastitis risk in a previous univariate analysis that were included in the multivariate logistic regression

| Variables                                  | Adjusted OR | 95%CI          | p value |
|--------------------------------------------|-------------|----------------|---------|
| Education                                  |             |                |         |
| Bachelor or below                          | 1.237       | 0.795-2.109    | 0.315   |
| Master or above                            | Reference   |                |         |
| Delivery number                            |             |                |         |
| Primiparous                                | 2.233       | 1.602-3.113    | <0.001* |
| Multiparous                                | Reference   |                |         |
| Delivery mode                              |             |                |         |
| Vaginal                                    | 0.702       | 0.527-0.934    | 0.015*  |
| Caesarean section                          | Reference   |                |         |
| Sleeping posture                           |             |                |         |
| Prone position                             | 2.105       | 0.942-4.703    | 0.007*  |
| Lateral position                           | 1.502       | 1.133-1.991    |         |
| Supine position                            | Reference   |                |         |
| Mastitis in previous breastfeeding         |             |                |         |
| Yes                                       | 4.945       | 3.123-7.829    | <0.001* |
| No                                        | Reference   |                |         |
| Nipple’s developmental malformation        |             |                |         |
| Crater nipple                              | 9.114       | 3.629-22.884   |         |
| Applanation nipple                         | 1.632       | 1.070-2.490    | <0.001* |
| Giant nipple                               | 1.853       | 0.588-5.845    |         |
| No                                        | Reference   |                |         |
| Cracked and sore nipple                    |             |                |         |
| Yes                                       | 5.807       | 4.334-7.782    | <0.001* |
| No                                        | Reference   |                |         |
| Clean nipple before breastfeeding           |             |                |         |
| Yes                                       | 0.681       | 0.499-0.929    | 0.015*  |
| No                                        | Reference   |                |         |
| Breast pump                                |             |                |         |
| Yes                                       | 1.348       | 1.015-1.790    | 0.039*  |
| No                                        | Reference   |                |         |
| Condition                          | Yes | No | Odds Ratio | 95% CI    | P-value |
|-----------------------------------|-----|----|------------|----------|---------|
| Non-medical staff message         |     |    | 1.286      | 0.975-1.695 | 0.074   |
| External force extrusion and collision | Yes | No | 1.845      | 1.256-2.711 | 0.002*  |
| Sucking manners                   | Nipple sucking | Areola sucking | 1.664 | 1.141-2.427 | 0.977-6.327 | 0.007*  |
| Sleep with sucking                | Yes | No | 1.460      | 1.110-1.921 | 0.007*  |
| Connection difficulty             | Yes | No | 1.015      | 0.662-1.555 | 0.946   |
| Oral dysplasia                    | Yes | No | 2.026      | 1.160-3.539 | 0.013*  |
| Anemia                            | Yes | No | 1.378      | 0.846-2.245 | 0.198   |
| Throat infection                  | Yes | No | 1.552      | 0.961-2.578 | 0.072   |
| Unauthorized oral antibiotics     | Yes | No | 1.057      | 0.666-1.676 | 0.814   |
| Psychological mood                | Negative | Positive | 1.328 | 0.981-1.797 | 0.066   |
| First contact with child          | ≤ 1h | > 1h | 0.565      | 0.340-0.938 | 0.027*  |

*Denotes statistically significant differences.
| Separation of mother-infant | 1.613 | Reference | 0.933-2.790 | 0.087 |
|-----------------------------|-------|-----------|-------------|-------|
| ≥ 24h                       |       |           |             |       |
| ≤ 24h                       |       |           |             |       |

* Significant at α ≤ 0.05