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Original Article

Assessment of Neonate's Congenital Hypothyroidism Pattern Using Poisson Spatio-temporal Model in Disease Mapping under the Bayesian Paradigm during 2011-18 in Guilan, Iran

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ABSTRACT

Background: Congenital Hypothyroidism (CH) is one of the reasons for mental retardation and defective growth in neonates. It can be treated if it is diagnosed early. The congenital hypothyroidism can be diagnosed using newborn screening in the first days after birth. Disease mapping helps to identify high-risk areas of the disease. This study aimed to evaluate the pattern of CH using the Poisson Spatio-temporal model in disease mapping under the Bayesian paradigm.

Methods: The recorded data of all infants diagnosed with CH between 2011 and 2018 in Guilan, Iran were used in this study. The Poisson Spatio-temporal model under the Bayesian paradigm was run using the Markov Chain Monte Carlo method in Open BUGS software. Moreover, the maps of the towns in Guilan were prepared via Arc GIS software.

Results: Out of 219800 live births in Guilan, Iran, the incidence of CH was 2:1000 in this time period. The pattern of disease mapping for the posterior mean of relative risk for CH was identical in this 7-year period. Furthermore, the pattern of disease mapping with spatial model excluding time dependence was similar to the maps of the Spatio-temporal model.

Conclusion: The incidence rate of CH was approximately constant during this time, and disease mapping revealed no rising trends in this period. This probably can be due to resolving iodine deficiency as one of the main causes of CH incidence by consuming kinds of seafood and iodized salt in Guilan province.

Keywords: Bayesian approach, Congenital Hypothyroidism, Disease mapping, Spatio-temporal model

Introduction

Congenital hypothyroidism (CH) is a lack of thyroid hormone. It will cause defective growth and mental retardations if it is not diagnosed and treated on time. However, it can be diagnosed by newborn screening in the first 3 to 5 days after birth by measuring TSH and T4 using the blood drawn from the infant's heel (1). It is categorized into transient and permanent types. The permanent CH is a resistant type that requires long-term treatment. On the other hand, transient CH is a temporary type that must be treated in the first few years of life (2). In 1974, CH screening was implemented by Dussault et al. for the first time in Quebec, Canada. Afterward, other countries performed this screening for neonates (3). In 1987, Azizi et al. introduced newborn screening in Iran (4), and it has been established as a public program in health centers from 2005 until now (3).

The estimated prevalence of CH has been changed from 1:2000 to 1:4000, and a significant increase was observed in the past decades (5). Moreover, the national screening program has shown higher CH incidence in Iran (200:100000) (6). Hazar et al. conducted a screening from March 2008 to February 2015 on 143190

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neonates in Yazd, Iran. The obtained results showed that 434 neonates had CH. Therefore, the incidence of CH was 303:100000 live births in this 7-year period (3).

The CH prevalence in Guilan was estimated at 0.0017 from 2006 to mid-2007 for a total of 9284 neonates by Mohtasham et al. (7). In a recent study, CH incidence was estimated at 1 per 542 live births. The risk factors of CH included low birth weight, postdate delivery, and macrosomia (8).

Regarding the diagnosis, treatment, and evaluation of the CH risk factors, it is necessary to detect regions with a high incidence of this disease. Disease mapping and spatial analysis help to recognize these regions. Mehrnejat et al. performed a spatial analysis of neonatal CH in Isfahan, Iran, and evaluated the effect of nitrate on CH incidence during 2010-13. Moreover, they mapped the spatial distribution of CH incidence rate and nitrate concentration in drinking water (9).

Spatial models by considering space effects, except for disease mapping, have been widely used in other sciences, such as ecology (10, 11) and environmental science (12). The effects of space and time simultaneously lead to Spatio-temporal modeling, and it can be used in disease mapping (13, 14), ecology (15), and air pollution (16). Spatial and temporal dependence is considered via space and time neighbors. Therefore, the effects of space and time, as well as their interaction are considered in this model as a random effect (17, 18).

This study aimed to assess the pattern of neonate's CH using the Poisson Spatio-temporal model in disease mapping under the Bayesian paradigm between 2011 and 2018 in Guilan, Iran.

Methods

Data Collection

This retrospective study was performed using the medical records of 219800 live births from March 21, 2011, to March 20, 2018, in Guilan, Iran. The medical records of neonates with CH were further investigated while screening all neonates aged 3-5 days for CH using the blood drawn from the heel. The CH was noted as TSH≥5 mlU/l. The neonates with transient and permanent CH in Guilan, Iran, were included in this study. The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (code: IR.SBMU.RETECH.REC.1397.1337). According to the 2016 Census of Urban Division by Statistical Center of Iran, the map of 51 towns of Guilan was provided using Arc GIS software after determining longitude and latitude. Considering the neighborhood effect of towns and time dependence, the Poisson Spatio-temporal model was fitted to data, and the relative risk of CH incidence was estimated in this study. The mapping of relative risk was created regarding a 7-year period in this study.

Statistical Analysis

Let O_{ij} represents the observed count of neonates with CH in the region (town) $i\ (i = 1, 2, \ldots, 51)$ at the time period $j\ (j = 1, 2, \ldots, 7)$ between March 21, 2011, and March 20, 2018. The O_{ij} was distributed as Poisson with mean μ_{ij}, where $\mu_{ij} = E_{ij} \times R_{ij}$. The E_{ij} was known as the expected count of CH in the *i*th town and *j*th period of time that was calculated on the basis of provincial incidence rate multiplying by the counts of at-risk neonates in town *i* and period *j*(19). The R_{ij} was an unknown relative risk of CH incidence in town *i* at period *j*. The relative risk of CH in town *i* at time *j* is estimated by the maximum likelihood method. It is equal to the Standardized Incidence Ratio (SIR),$\widehat{R_{ij}} = O_{ij}/E_{ij}$. Either the diseases are rare or the regions are small, the SIR will be indicated as a misleading estimator. Therefore, a reliable estimate was obtained for the relative risk by considering the neighboring effects of the regions that were first introduced by Besag et al. (20, 17).

The Poisson model was extended by considering space and time effect. Spatial dependence was accounted for by considering the neighborhood effects of the town. The temporal dependence was considered by neighbors for time periods j=2, 3, 4, 5, 6 as periods (j-1) and (j+1). Furthermore, the neighbors for the first and last periods of time were considered second and penultimate period, respectively. (17).

The Poisson Spatio-temporal model was performed under the Bayesian paradigm using Markov Chain Monte Carlo (MCMC) method in Open BUGS software (version 3.2.3). Accordingly, the posterior mean of relative risk was obtained in this study. The proposed model by Ugarte et al. was formulated as follow:

$$log(\mu_{ij}) = log(E_{ij}) + \alpha + \eta_i + \varphi_j + \omega_{ij} \quad (1)$$

Where $\mu_{ij}$is Poisson distribution mean and E_{ij} indicates the expected count of CH. Moreover, α

denotes the overall rate, η_i presents the random effect for spatial heterogeneity, φ_j is the random effect for the time trend, and ω_{ij} identifies the random effect for the Spatio-temporal interaction. Eventually, relative risk estimation was equal to $R_{ij} = exp(\alpha + \eta_i + \varphi_j + \omega_{ij})$ (18).

The mapping of relative risk was accomplished after recalling maps of towns in Guilan in the Open BUGS software and estimating the relative risk of CH incidence using the Poisson Spatio-temporal model.

Results

Out of 219800 live births in Guilan, Iran, during the study period, 492 neonates were diagnosed with CH. The incidence of CH was 2:1000 live births in a 7-year period. According to Table 1, the spectrum of incidence rate during 7 years was changed from 0.002 to 0.003. The count of neonates with CH was separately specified in 51 towns of Guilan for 7 years. Figure 1 (a) shows the bar charts of the observed count of CH in this period. In the majority of the time periods, the frequency of zero, one, or two was higher than the other counts. The Poisson Spatio-temporal model under the Bayesian paradigm was fitted to this data and the predicted count of CH can be observed for 7 years in Figure 1 (b). The bar

Table1. Incidence of congenital hypothyroidism per 10000 live births by time periods from 2011 to 2018

Time	Between March 21, 2011, and March 20, 2012	Between March 21, 2012, and March 20, 2013	Between March 21, 2013, and March 20, 2014	Between March 21,2014, and March 20, 2015	Between March 21, 2015, and March 20, 2016	Between March 21, 2016, and March 20, 2017	Between March 21, 2017, and March 20, 2018	Between March 21, 2011, and March 20, 2018
Incidence	19	21	29	17	24	19	27	22

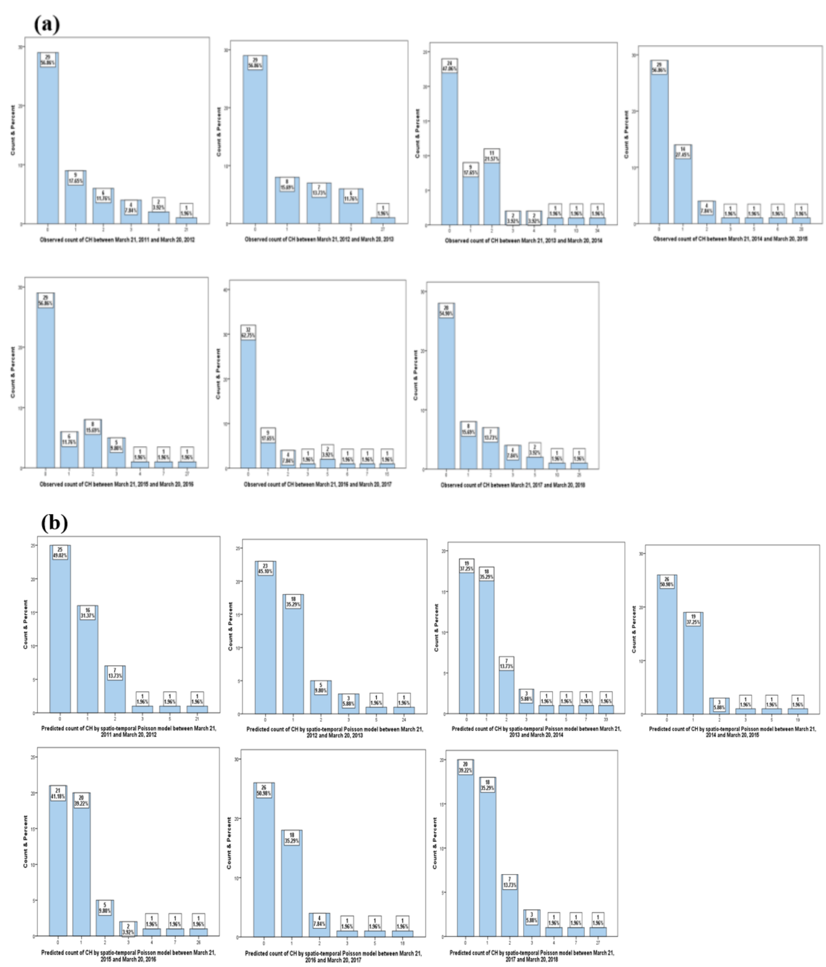

Figure 1. (a) Observed count of congenital hypothyroidism during 7 years from 2011 to 2018, (b) Predicted count of congenital hypothyroidism by Poisson Spatio-temporal model during 7 years from 2011 to 2018 separately

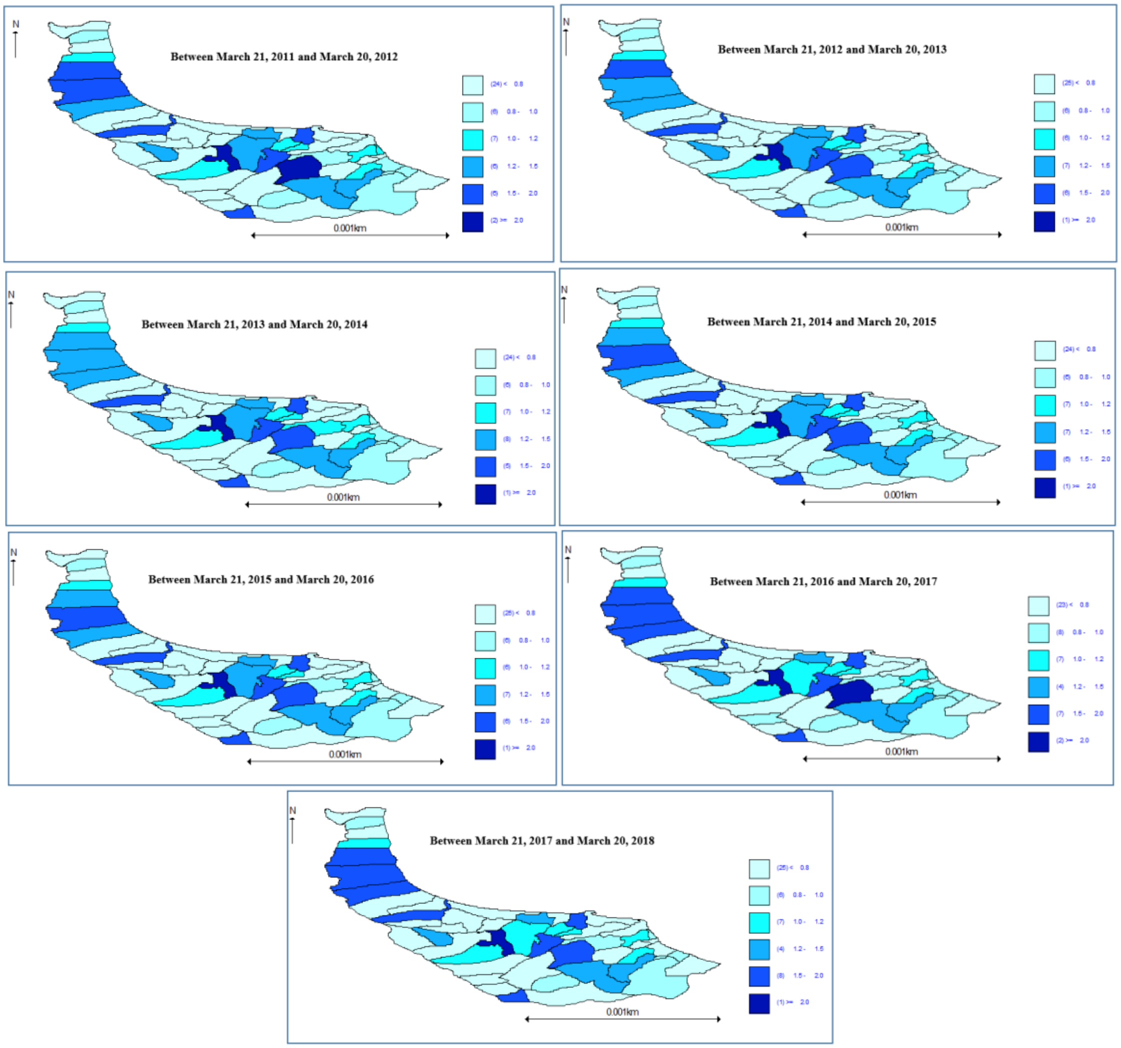

Figure 2. Separate maps of the posterior relative risk of congenital hypothyroidism incidence in Guilan during 7 years from 2011 to 2018

charts display that in the majority of the towns, the predicted frequencies of CH are equal to zero, one, or two for each period.

Figure 2 illustrates the maps of the posterior relative risk of CH incidence based on 51 towns in Guilan, Iran. Only one or sometimes two central towns in all periods of time had a relative risk of >2. The relative risk was between 1.2 and 2 for some western towns in all periods of time. In addition, the relative risk was between 1.2 and 2 in a few eastern and central towns and one of the southern towns. Approximately, in more than half of the towns, the relative risk was lower than one. The trend of disease mapping for the relative risk of CH incidence was identical for periods of time. Eventually, investigators ran a Poisson spatial model on the count of CH excluding the effect of time.

Figure 3 illustrates the observed and predicted count of CH for the mentioned model. In both charts, the frequencies of CH incidence for half of the towns were zero, one, two, or three. The map of the posterior relative risk of CH incidence based on the Poisson spatial model is displayed in Figure 4. As it is shown, this map is nearly similar to maps in Figure 2.

Discussion

The incidence assessment of CH (2:1000 live births) in this study showed no impressively change during a 7-year period. According to the observed and predicted count of CH, the frequencies of CH were equal to zero, one, or two for most of the towns in each period. Except for small changes in the mapping of relative risk among time periods, the overall pattern of mapping of relative risk in towns of Guilan was invariant during the time periods. The mapping

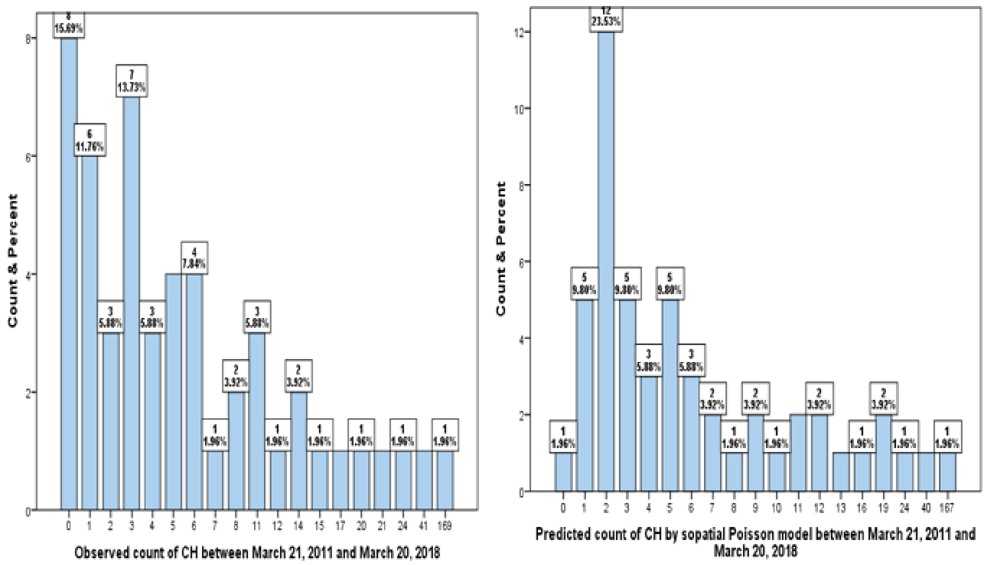

Figure 3. Observed and predicted count of congenital hypothyroidism from 2011 to 2018

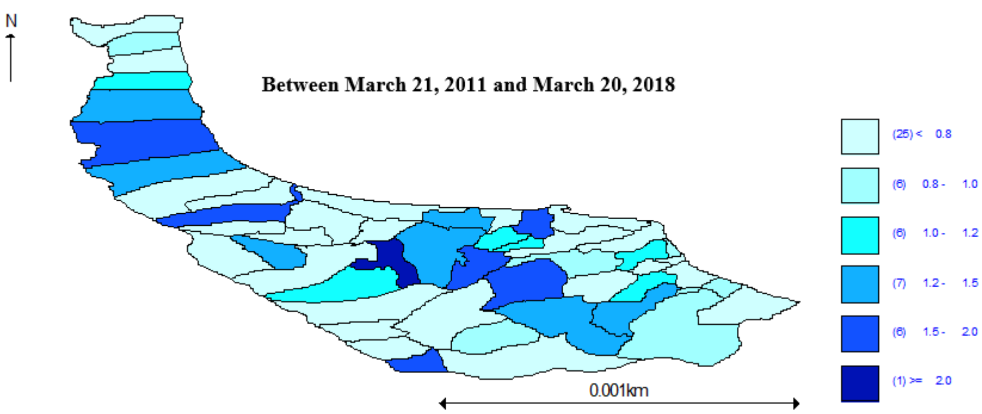

Figure 4. Map of the posterior relative risk of congenital hypothyroidism incidence in Guilan from 2011 to 2018

pattern of relative risk regardless of time dependence between 2011 and 2018 was almost similar to that in 7 separate time periods.

Various studies have been performed so far on CH. These studies aimed to gain proportion and risk factors associated with this condition. Birth season, maternal age, birth weight, and height, as well as multiple pregnancies, were reported as the birth risk factors of CH (8, 21-23). Osuli et al. investigated the geographic dispersion of the CH incidence rate in Iran in 2008. They revealed that provinces, such as Sistan and Baluchestan, Yazd, Qom, Chaharmahal and Bakhtiari, and Western Azerbaijan had higher incidence rates than other provinces (24).

In another study, Mehrnejat et al. determined the spatial distribution of CH and nitrate concentration in drinking water and investigated the impact of nitrate on CH incidence. No significant association was found between nitrate and CH incidence in this study (9). In the same line, Dalili et al. conducted previous studies on CH in Guilan province, and they screened 119701 neonates in a 5-year period. According to the results, the CH was found in 221 of them, and the incidence rate of CH was reported as 0.0018. This finding was consistent with the results of Table 1 in the current study. They mentioned low birth weight, postdate delivery, and macrosomia as the risk factors of CH (8).

Although the CH may induce growth and developmental failure, the investigation showed that neonates with CH who were diagnosed and treated early had normal growth (25). Moreover, iodine deficiency during pregnancy may damage mental and growth development in neonates.

However, the assessment of iodine deficiency in school-aged children and neonates between 2006 and 2010 in Guilan showed that this province was not only an iodine-deficient area but also an iodine-excess one (26).

A large number of studies have been accomplished in the field of Spatio-temporal disease mapping in the world. Manda et al. investigated the similarities of Spatio-temporal features in the epidemiology of diabetes and leukemia in childhood. They presented maps to show the posterior probability, and the standard incidence rate exceeded 1. Both diseases displayed a steadily increasing incidence rate over the study period. They claimed that combining a time-dependent component in the model disclosed a rising risk of disease during the time for both diseases, especially for type 1 diabetes (17).

In a similar vein, Ugarte et al. evaluated the performance of 6 various Bayesian Spatio-temporal models in disease mapping. They analyzed the mortality data of colorectal cancer in males for four time periods in Spain. The maps of the posterior mean of relative risk estimations showed a rising trend from the middle to the east of the regions during the time (18).

In a study performed by Ugarte et al., approximate Bayesian inference was used for fitting Spatio-temporal disease mapping models on Spanish male brain cancer mortality. They exhibited a pattern of spatial mortality risk for each region while keeping the time constant. This map showed that the Northern provinces had a higher risk of male brain cancer than the whole country. They also depicted the maps of relative mortality risk of male brain cancer for each province during the time period using the Spatio-temporal model. The maps displayed an increase in risk. Similar to the spatial model, the provinces located in the north showed a considerable high risk, compared to the whole country (14).

The findings of the aforementioned Spatio-temporal studies showed that the incidence of diseases or mortality risk increased during the time. Therefore, the consideration of the time dependence may disclose the risk increase. In this study, no increasing trend was observed for the relative risk of CH during the time, and there was just a constant trend during the time period. This trend was similar to the map of the spatial pattern of the CH incidence relative risk in towns regardless of time dependence.

Limitations of the Study

One of the limitations of this study was that no Spatio-temporal model was found in disease mapping for the CH in previous studies.

Conclusion

The incidence rate of CH was approximately constant in a 7-year period, and disease mapping revealed no rising trend during this time. This probability can be due to resolving iodine deficiency as one of the main causes of CH incidence by consuming kinds of seafood and iodized salt in Guilan, Iran. Since there are few cities in Guilan that include higher relative risks than others, further studies are needed to investigate the causes of high-risk CH in these towns.

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Conflicts of interest

The authors declare no conflict of interest.

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