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Investigating the factors affecting the transition rates between states of neonatal hypothermia using markov model

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ABSTRACT

Background: At birth, the wet neonate is suddenly confronted with a cold and dry weather and reacts to this new situation by increasing heat production. Hypothermia is an important determinant of the survival of newborns, especially among low-birth-weight babies. Prolonged hypothermia leads to edema, general hemorrhage, jaundice and death. **Aims and Objectives:** The aim of this observational longitudinal study is to examine effective factors on passing the hypothermia state. **Materials and Methods:** In this study rectal temperature was measured immediately after birth and every half hour after that for 439 neonates, until they passed hypothermia stage. The rate of transition between states of neonatal hypothermia and effect of covariates, newborn baby birth weight, Apgar score and environmental temperature on it is estimated by multi state Markov model. **Results:** Newborn baby weight and environmental temperature were significant effect on transition rate from mild to normal hypothermia, too, but the Apgar score effect was not significant. Mean sojourn times in mild hypothermia state for three birth weight levels, very light, light and normal are 38, 29 and 22 min respectively. In addition, in the environmental temperature over 28°C, the average time in which the neonate remained in mild hypothermia state was shorter than that in the environmental temperature below 28°C (29 vs. 38 min). **Conclusions:** Since the birth weight is not under the control of the health personnel, keeping a suitable thermal environment for the newborns results in a faster change from hypothermia to a normal state. Therefore, training in this area is of enormous importance.

Key words: Neonatal care, Neonatal weight, Environmental temperature, Multi state Markov models, Transition rate

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INTRODUCTION

Neonatal hypothermia can be defined as an abnormal condition in which neonate's body temperature drops below 36.5°C.[1] Prolonged body temperature reduction may lead to some undesirable effects from metabolic problems to death.

At birth, the wet neonate is suddenly confronted with a cold and dry weather and reacts to this situation by increasing heat production and trying to maintain the existing heat by contracting dermal vessels. The reaction is happening in a moment but can continue for hours.[2] In the lack of heat protection, the newborn may lose a considerable amount of body heat. Sometimes at the first moments of birth, skin temperature falls by 2-4°C.[3,4] In fact, a naked baby exposed to an environmental temperature of 23°C suffers the same heat loss as does an adult at 0°C.[5] Some acts such as leaving the baby without thermal protection, postponing drying and wrapping the baby, and bathing immediately after the birth may increase the likelihood of developing hypothermia.[1]

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In developing countries, hypothermia in the first hours after birth is one of the main reasons of neonatal illness and death.[6] The high prevalence of hypothermia has been reported from the countries with the most burden of neonatal mortality. World Health Organization (WHO) has included thermal control principles among neonatal care principles for developing countries.[5]

Hypothermia is common even in tropical climates. For instance, in Nepal, 85% of newborns have body temperature below 36ºC in the first two hours of life.[7] In Ethiopia,[8] Zambia[9] and Zimbabwe[10] 1/2 - 2/3 of neonates develop hypothermia after birth. A survey conducting in Iran, including 940 newborns, revealed the prevalence of hypothermia among them to be 53.3%.[11]

In medical studies, people's health status or the response to a special cure or stimulus is often recorded as discrete states, sometimes this state observation is repeated through time. Continuous-time multi-state models are widely applied in modelling the classified and collected variables through time. In medical applications, the response variable can be related to the disease stages and these stages might have been observed at irregular intervals. Such an observation scheme is called panel observation.[12] In such a situation, transition times are often accompanied by interval censoring, it means that the exact transition times from one stage of disease to the other is not definite. In general, this type of censoring makes it difficult to estimate the model parameters. Therefore, multi-state processes are sometimes assumed to have Markov property.[13] This assumption makes it easier to calculate likelihood function and in consequence, to estimate model parameters.[14] These types of models have been used in a wide range of medical applications such as HIV/AIDS,[15,16] breast cancer[17] and diabetic retinopathy.[18,19]

In the previous studies, hypothermia prevalence has been estimated and the risk factors have been tested and specified using descriptive methods and logistic regression.[20,21] However, transition rate between hypothermia stages and also transition from hypothermia state and the factors of this transition have not been studied so far. Therefore, using Markov model, this study tries to estimate the transition rate between discrete states of neonatal hypothermia and determine the effects of baby birth weight and environmental temperature on this rate.

MATERIALS AND METHODS

The sample used in this study is a part of a wider observational longitudinal research conducting by Nayeri and Nili in 2006 on neonates hospitalized in NICU, at Vali-Asr Hospital of Tehran.[11] Entry criteria included developing hypothermia at birth and remaining in this state at least until the second temperature measuring and exit criterion was infant's getting to a normal state. Considering these criteria, 439 neonates were examined in this study.

In this dataset, firstly, neonates' rectal temperature were measured immediately after birth, in case the rectal temperature was below 36.5ºC, the measurements were repeated every 30 minutes until the infant passed the hypothermia state. The response was considered hypothermia severity graded as normal temperature (rectal temperature of 36.5ºC-38ºC), mild hypothermia (rectal temperature of 35ºC-36.5 ºC), moderate hypothermia (rectal temperature of 32ºC-35ºC) and severe hypothermia (rectal temperature below 32ºC). In this study the two last groups were combined and considered as severe hypothermia. According to the recommendation of WHO, infants' body temperature were measured until getting to a normal state,[22] thus each baby was examined at its particular times.

In multi-state models, data are considered as series of observations $x_{i0}, x_{i1}, ..., x_{in}$ at times $t_{i0}, ..., t_{in}$ which is the product of $X(t)$ process. In this process the amount of $1, ..., R$ states is $i = 1, ..., N$ for each patient. Therefore, the log-likelihood can be expressed as:[23]

$$l(\theta) = \sum_{i=1}^{N} \sum_{j=1}^{ni} \log(p_{x_{i(j-1)}x_{ij}}(t_{i(j-1)}, t_{ij}; \theta))$$

Where

$$p_{rs}(t_0, t_1, \theta) = p(x(t_1) = s \mid x(t_0) = r; \theta)$$

(r, s) Entry of $R \times R$ matrix is the transition probability which can be found by solving following Kolmogrov Forward equation:[24]

$$\frac{dP(t_0, t)}{dt} = p(t_0, t)Q(t)$$

In this equation, Q is the matrix of transition intensities whose entries are defined as follows under condition $q_{rr} = -\sum_{r \neq s} q_{rs}$ for $r = 1, ..., R$. Obtaining the matrix of transition intensities in this model, we are able to compute mean sojourn time for each disease state; this scale is equal to the inverse of main diagonal entries of transition intensity matrix. Numerical algorithm was offered in 1985 in order to compute the maximum likelihood estimate for above model.[25] Fitting this model, we will be also able to estimate the hazard ratio for both states of disease in independent variable states.

In this study, multi-state Markov model was fitted to the data with two covariates, newborn baby birth weight and environmental temperature. The effects of these variables were examined as the effective factors on transition rate from severe to mild hypothermia and from mild hypothermia to normal state. Newborn weight in three classes of very low weight (<1500g), low weight (1500-2500g) and normal (>2500g), and environmental temperature in two classes of below 28°C and over 28°C were entered into the model as covariates. Moreover, another model with three covariates; newborn baby weight, environmental temperature and Apgar score, was fitted to the data.

RESULTS

All 439 newborns entered into the study were hypothermic at birth. From among them, 11 infants (2.5%) have moderate to severe hypothermia and 428 infants (97.5%) have mild hypothermia. Table 1 shows the frequency distribution of newborns' hypothermia states in the studied times.

Fitting multi-state Markov model with two covariates, the transition rates from severe to mild hypothermia and from mild hypothermia to normal state were estimated 0.1192 and 0.0549 per minute, respectively. It means that transition from severe to mild hypothermia occurs faster than transition from mild hypothermia to a normal state. Weight did not have a significant effect on the transition rate from severe to mild hypothermia. Ninety-five percent confidence interval was found for the effect of newborn baby weight on the transition rate (2.276, -1.619), but this effect on the transition rate from mild hypothermia to normal state was significant (p-value<0.001) and 95% confidence interval was estimated for this parameter (0.4165, 0.1364). Table 2 presents the effect of weight on the transition rate from mild hypothermia to a normal state separately for each weight group in the form of estimating the mean sojourn time in mild hypothermia state. Moreover, the effect of environmental temperature on the transition rate from mild hypothermia to normal state was significant (p-value<0.001) and 95% confidence interval was found for this parameter (0.4963, 0.0439). The effect of this variable on the transition from severe to mild hypothermia was not significant, 95% confidence interval was found for this parameter (2.448, -1.915). Sojourn times in mild hypothermia state for two temperature levels are separately shown in Table 2.

According to this table, it took almost 38 minutes for very low weight neonates to get a normal state from mild hypothermia, while low weight neonates remained almost 29 minutes in mild hypothermia state. In addition, in the environmental temperature over 28°C, the average time in which the neonate remained in mild hypothermia state was shorter than that in the environmental temperature below 28°C (29 vs. 38 min).

The hazard ratio in different levels of weight was estimated 1.388 for mild in proportion to severe hypothermia state with 95% interval confidence (9.740, 0.1980) and 1.318 for normal state in proportion to mild hypothermia with 95% interval confidence (1.1461, 1.5167). The hazard ratio in different levels of environmental temperature was estimated 1.3058 for mild in proportion to severe hypothermia state with 95% interval confidence (0.147, 11.5692) and 1.3101 for normal state in proportion to mild hypothermia with 95% interval confidence (1.6426, 1.0448).

The model with three covariates produced the following results: newborn baby weight and environmental temperature were significant in this model, too, but the Apgar score was not significant, therefore we follow the discussion based on the model with two covariates.

Table 1: Frequency distributions of newborns and their percentages in the observed times in these times, frequency distributions of hypothermia states have been offered only for the newborns that have been in mild hypothermia state in the previous time

Hypothermia states	Time (minute)				
	1	30	60[a]	90[a]	120[a]
Severe hypothermia					
Frequency	11	0	0	0	0
Percent	2.5	0.0	0.0	0.0	0.0
Mild hypothermia					
Frequency	428	100	16	2	0
Percent	97.5	22.8	16.0	12.5	0.0
Normal					
Frequency	0	339	84	14	2
Percent	0.0	77.2	84.0	87.5	100.0
Sum					
Frequency	439	439	100	16	2
Percent	100.0	100.0	100.0	100.0	100.0

Table 2: The estimate of mean sojourn time in mild hypothermia state in the studied hypothermic neonates separately for each weight group and environmental temperature at birth

Covariate name	Covariate levels	Mean sojourn time in mild hypothermia state (minute)
Birth weight	Very lightweight <1500 gr	38.049
	Lightweight 1500-2500 gr	28.858
	Normal >2500 gr	21.887
Environmental Temperature	<28°C	38.292
	>28°C	29.228

DISCUSSION

Neonatal hypothermia is an important determinant of the survival of neonates especially among low-birth-weight ones. Lack of attention by health care providers to some simple primary steps such as providing a warm, clean and without air current environment at birth is a main cause of this condition.[1]

As it was mentioned in the introduction, according to the results of researches, remaining in hypothermia state leads to some clinical irreparable damages from metabolic problems to neonatal death, thus a quick transition of newborn from hypothermia state is absolutely vital, and learning the factors which accelerate this transition can be a positive step in preventing the post-hypothermia problems. Therefore, this study aimed at estimating the temporary sojourn time in hypothermia state and determining the effective factors in transition from hypothermia state to a normal state for newborns.

In this study, three states were considered for newborn weight, very low weight (<1500g), low weight (1500-2500g) and normal (>2500g). The effect of newborn weight on transition from hypothermia to normal state was significant as the very low weight neonates passed the hypothermia with a lower rate in comparison to the normal-weight neonates.[2,11] This result proves the findings of other studies investigated the outbreak of neonatal hypothermia. Most of the conducted studies in this area have identified weight as a risk factor in developing neonatal hypothermia. Considering the results of this study, it can be remarked that not only weight is a key factor in developing hypothermia but also it is an important factor in transition from hypothermia state. Moreover, the effect of environmental temperature at birth on the transition from hypothermia states was investigated. Environmental temperature was entered into the model in two states of below 28ºC and above 28ºC. The results revealed that the neonates born in temperature above 28ºC stay in hypothermia state for a shorter time. This point also supports the recommendations of international organizations to keep the baby warm at birth.[5]

Previous studies have often been cross-sectional studies on the prevalence and the risk factors of neonatal hypothermia; and a longitudinal study investigating the trend of transitions from hypothermia state is scarce.

As already mentioned, infant's remaining in hypothermia state may lead to many clinical damages. Using multi-state Markov models, this study investigated the transition rate and particularly the factors affecting this rate. From this perspective, the advantage of this study over previous studies is the investigating of transition rate and the factors affecting it that can be a great help to decrease the harm of neonatal hypothermia.

Multi-state Markov models have been normally used in the study of chronic diseases in which the patient's condition changes between discrete states of disease through time. For instance, in order to study the post-transplant problems in heart diseases, a model with four states was fitted and the effects of patient and donor's age and patient's sex on the success of transplant in different levels and a combination of covariates were investigated; in that study, using four-state models, the authors showed that in some of the covariate combinations patients get to the fourth state of disease with a higher rate.[26] Estimating the transition rate between disease states, studying the effect of risk factors on these transitions and investigating the effect of medical interventions, if any, are the considerable subjects in fitting these models. In medical studies, data often include a series of diagnosis of disease states in the times unique to each patient. While changes in patient's condition occur in continuous time intervals, observations of the conditions are carried out in discrete time points, therefore it is likely to miss the exact time of change. In order to be fitted to medical longitudinal data and analyze them, lots of models are available, multi-state models, among them, have the ability to provide the estimate of transition rates considering this interval censoring.[27] Since the data of this study possessed this quality, this model was applied to estimate the transition rates. It is worth mentioning that most studies on neonatal hypothermia have investigated the factors affecting its prevalence, for example Bhatt et al. have studied the prevalence of hypothermia in preterm newborns of different weights; and there are few studies on the effective factors in the transition to a normal state.[28]

In this study, the effects of birth weight and environmental temperature on the transition from severe to mild hypothermia were not statistically significant, however, it may result from a small sample size for sever hypothermia group, and this subject can be examined by means of larger sample sizes. In addition, study of transition rate considering the babies' Apgar score may offer a more complete result.

CONCLUSION

Since the birth weight is not under the control of the health personnel, keeping a suitable thermal environment for the newborns results in a faster change from hypothermia to a normal state. Therefore, training in this area is of enormous importance.

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Authors Contribution:
SJ and AAB- Fit statistical models, analysis data set and interpret results; **FN**- Provides data set in Imam Khomeini Hospital, Maternal, fetal & Neonatal Research Center; **VT**- Translates the manuscript to English.

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