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Brief Report

Modeling the Recurrent Failure to Thrive in Less than Two-year Children: Recurrent Events Survival Analysis

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ABSTRACT

Background: This study aimed to evaluate the failure to thrive (FTT) recurrent event over time.

Methods: This longitudinal study was conducted during February 2007 to July 2009. The primary outcome was growth failure. The analysis was done using 1283 children who had experienced FTT several times, based on recurrent events analysis.

Results: Fifty-nine percent of the children had experienced the FTT at least one time and 5.3% of them had experienced it up to four times. The Prentice–Williams–Peterson (PWP) model revealed significant relationship between diarrhea (HR=1.26), respiratory infections (HR=1.25), urinary tract infections (HR=1.51), discontinuation of breast-feeding (HR=1.96), teething (HR=1.18), initiation age of complementary feeding (HR=1.11) and hazard rate of the first FTT event.

Conclusions: Recurrence nature of the FTT is a main problem, which taking it into account increases the accuracy in analysis of FTT event process and can lead to identify different risk factors for each FTT recurrences.

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Introduction

Failure to thrive (FTT) is considered for infants or children when their weight or rate of weight gain is significantly lower than expected of similar children of the same sex and age. FTT has long been a major focus of attention and critical thought for pediatricians; because it is an excellent sign of their well-begin and under nutrition for children [1]. Over many years, consensus has evolved about its causes, outcomes, diagnosis, and management [1, 2]. It was estimated that FTT and intrauterine growth restriction together were responsible for 2.2 million deaths as well as 21% of disability-adjusted life-years and is an underlying cause in a third of deaths in children younger than 5 years worldwide [3, 4]. In Iran, the relatively high prevalence of growth failure among children makes it one of the main health problems in pediatrics and health care policy [5, 6]. Accordingly, health policies applied the continuum monitoring in most health centers for children less than 8 years old. Most research studies were about the prevalence and risk factors of growth failure and dealt with the FTT as a single event, while it is a recurrent event phenomenon and each child may have experienced the FTT more than one time.

Prentice–Williams–Peterson (PWP) model an extension of the Cox model to recurrent event data is an event-specific regression model and is appropriate model to find the event-specific risk factors [7, 8]. Therefore in this study the PWP model was used as an analytical method for revealing the significant associated factors with the FTT.

The aim of the present study was to consider the recurrence nature of the FTT and identify the risk factors for each FTT events separately. The recurrence nature of FTT as a main problem was not regarded in primary studies. But accounting it can lead to determine the separate risk factors for each FTT recurrence.

Methods

This longitudinal study was performed on children less than 2 years old referred to health centers related to Shahid Beheshti University of Medical Science in Tehran (SBUMS) from February 2007 to July 2009. Based on a cluster sampling technique, eight health centers were selected from total 64 centers related to SBUMS. All children who were term labor, uniparous labor, with no genetic or congenital disease were included. After a preliminary assessment, a total of 2,182 children were engaged in the study. They attended every month regularly. The primary outcome of the study was growth failure and secondary outcomes of the study were the incidence of diarrhea, respiratory infections, urinary tract

infections (UTI) and teething. The required data were recorded every month in the first year and bimestrial in the second year. In addition, information about discontinuation of breast-feeding and time of initiation of complementary food, vitamins A and D and iron drops, were also collected in a checklist.

Recurrent event data can be represented in different ways depending on the timescale that is used. Gap time between successive recurrent events indicate disease free survival is one of the timescales. In this study, a gap time between successive FTT events was selected as an analytical timescale. Gap times measured monthly and computed as $W_{ij}= T_{ij} - T_{ij-1}$ which T_{ij} is the occurrence time for ith child and jth FTT recurrence. Children were observed over the time interval [0, 24], that $T_{i0}=0$ was considered as the birth time and corresponds to the start of the event process of the FTT.

First of all, to reveal an autocorrelation between gap times, Kaplan Meier survival curves were plotted. Then PWP model is used for assessing risk factors' effect. It is given by

$$h(t|\beta_j)=h_{0j}\left(t-t_{j-1}\right)\exp(\beta_j x_{ij}) \quad i=1,2,\cdots,n \quad j=1,2,\cdots,n_i \qquad (1)$$

Where h_{0j} is an event-specific baseline hazard for jth event and regression parameter, β_j, is an event specific effect[8, 9]. Since the PWP model has event-specific baseline hazards, so it can has either overall (common) estimates or event-specific (uncommon) estimates for each covariate [8]. In the PWP model with common effects assume that a covariate has a shared effect on all of event times but with uncommon effects assume that a covariate has a different effect on any of event times.

Statistical analysis was performed using the Statistical Analysis System (SAS) software, version 9.1 and Minitab version 15.0. *P*-values less than 0.05 were considered as statistically significant.

Results

As referred to before, children evaluated in 17 points of time and the FTT occurrence time registered for them. Overall 1283 (59%) [708(55.2%) girls and 575 (44.8%) boys] of total 2182 cases experienced the FTT at least one time and 68 cases experienced FTT up to four times.

Table 1 shows the median of the FTT recurrence events times during the two years, and mean of the gap times between the FTT recurrences. Gap times between successive recurrent events indicate disease (FTT) free survivals have decreasing trend over the time (Table 1).

Table 1: Descriptive of time distribution of the failure to thrive (FTT) event and gap times between recurrent FTT (Q1-Q3)

	Number of children	Median (SD) of occurrence time of FTT (month)	Mean (SD) survival Gap times (month)
1st event	687	9 (7,11)	9.53 (4.4)
2nd event	376	11 (9,15)	4.14 (3.6)
3rd event	152	15 (10,19)	4.12 (3.4)
4th event	68	17 (13,21)	3.62 (2.6)

First gap time tend to be clearly longer than subsequent gap times, which appear to have similar length distribution (Figure 1). This result indicates that the first FTT event influenced subsequent growth failures, but other FTT events did not affect each other. So in general, the gap times are approximately dependent and there was indication of little trend or autocorrelation within children each.

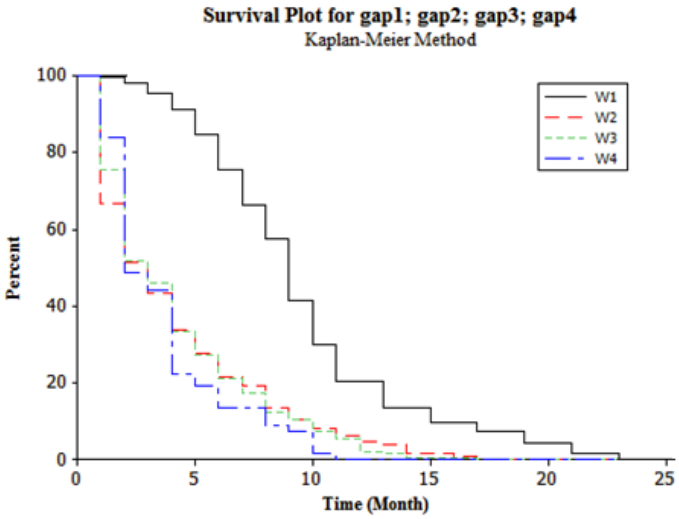

Figure 1: Kaplan-Meier Survival plot for gap times between the sequential failure to thrive FTT evens

In the next step, to assess the effect of different risk facators on hazard rate of the FTT the PWP gap times model with event-specific estimates was used. Regard this process, firstly the univariate model was fitted with all the explanatory variables. Based on the univariate findings, time discontinuation of breast-feeding, teething, initial age of feeding of complementary food, iron, vitamin A and D drops, and presence of diarrhea, UTI, respiratory infection, were significantly related with hazard rate of recurrent FTT ($P<0.05$). Furthermore, to assess the simultaneous impact of different risk indicators on the hazard of recurrent FTT of children, multiple PWP gap times model was fitted using all significant factors in prior step.

Presence of diarrhea, respiratory infections and UTI as well as discontinuation of breast-feeding, teething and initiation age of complementary feeding, vitamin A+D drops indicated a strong effect on hazard rate of the first FTT event (Table 2). Whereas just some of these factors were statistically significant risk factors for subsequent FTT events. However presence of diarrhea, respiratory infections and teething are significant causes for all subsequent FTT events, except teething for last FTT event that it did not happen for any children at that time.

Discussion

Although various studies in different areas of various aspects of growth failure have been conducted in Iran, but none of them have considered the recurrence nature of it [5, 6]. The recurrence nature of FTT is a main problem that its taking into account can identify different risk factors for each FTT recurrent events. Risk factors that interfere with growth failure function are especially important during infancy because the first 2 years of life are an essential period of rapid growth and development. So identification and evaluation these factors on hazard rate of FTT recurrent events is a main problem in pediatric issues and can promote the knowledge level of mothers and healthcare providers to control this health problem in Iran. This study aimed to evaluate the main causes underlying FTT recurrent events during first two years of children's life.

Our data showed that 59% of children under study experienced growth failure in this period of their life. In addition, about 3.2% of these infants had at least 5 experiences of growth failure, while they are less than two years old.

In Iran result of two latest studies on less than 5 and 6 years age children from Karaj and South Khorasan show almost considerable underweight prevalence. In the first study the prevalence of underweight, stunting and wasting was estimated 13.9%, 20.3%, and 4.9%. The next study estimated weight index as 34.4% lightly underweight, 11.7% moderately underweight and 1.2% severely underweight [5, 6].

Table 2: Prentice–Williams–Peterson (PWP) model results for concurrent effect of different risk indicators on recurrent failure to thrive **(**FTT)

Variable	FTT	Estimate	SE	*P* value	HR	HR (95%CI)
Urinary tract infections	1st	0.41	0.13	0.002	1.51	(1.16, 1.96)
Respiratory infections	1st	0.23	0.04	<0.001	1.25	(1.16, 1.35)
Diarrhea	1st	0.23	0.04	<0.001	1.26	(1.16, 1.37)
Discontinuation of breast-feeding	1st	0.67	0.12	<0.001	1.96	(1.55, 2.47)
Initiation Complementary feeding	1st	0.10	0.02	<0.001	1.11	(1.07, 1.14)
Initiation vitamin A+D	1st	0.02	0.01	0.019	1.02	(1.00, 1.04)
Teething	1st	0.16	0.04	0.002	1.18	(1.08, 1.28)
Urinary tract infections	2nd	0.27	0.18	0.126	1.31	(0.93, 1.86)
Respiratory infections	2nd	0.21	0.06	0.001	1.23	(1.09, 1.39)
Diarrhea	2nd	0.26	0.07	0.006	1.29	(1.12, 1.49)
Discontinuation of breast-feeding	2nd	0.07	0.12	0.562	1.07	(0.85, 1.36)
Complementary feeding	2nd	0.02	0.02	0.365	1.02	(0.98, 1.06)
Initiation vitamin A+D	2nd	0.02	0.01	0.357	1.01	(0.99, 1.03)
Teething	2nd	0.63	0.07	<0.001	1.87	(1.63, 2.16)
Urinary tract infections	3rd	0.13	0.25	0.615	1.14	(0.69, 1.86)
Respiratory infections	3rd	0.33	0.11	0.002	1.38	(1.13, 1.70)
Diarrhea	2nd	0.53	0.10	<0.001	1.70	(1.40, 2.07)
Discontinuation of breast-feeding	2nd	0.19	0.16	0.238	1.20	(0.88, 1.64)
Complementary feeding	2nd	0.02	0.02	0.520	1.02	(0.97, 1.06)
Initiation vitamin A+D	2nd	0.50	0.01	<0.001	1.64	(1.63, 1.66)
Teething	2nd	0.89	0.29	0.002	2.42	(1.37, 4.26)
Urinary tract infections	4th	1.4	0.32	<0.001	4.06	(2.17, 7.62)
Respiratory infections	4th	0.60	0.15	<0.001	1.83	(1.35, 2.47)
Diarrhea	4th	0.67	0.12	<0.001	1.96	(1.55, 2.47)
Discontinuation of breast-feeding	4th	0.17	0.17	0.324	1.19	(0.85, 1.66)
Complementary feeding	4th	0.06	0.05	0.217	1.06	(0.97, 1.16)
Initiation vitamin A+D	4th	0.10	0.03	0.008	1.11	(1.04, 1.17)
Teething	4th	-	-	-		

Based on our findings it seems that first few months of infant's life are a crucial period, because all evaluated factors had a significant effect on the first FTT when the median of its occurrence was 9 month.

Moreover our result showed that presence of infectious diseases including diarrhea and respiratory infections were statistically significant risk factors for all hazard rate of FTT recurrent events ($P<0.05$). Thus children with infectious disease in first months period were at higher risk of developing recurrent FTT. Previous studies have been limited by use of the FTT as an single event, but they confirmed that infectious diseases are important determinants of the FTT. Infectious disease through suppressing appetite directly affect nutrient metabolism and leading to poor nutrient utilization and growth failure[10]. Some studies have reported the diarrhoea as the main infectious diseases adversely affect growth and nutritional status, especially during infancy [5, 11, 12]. Some other studies revealed that faltering of growth often coincides with the onset of respiratory infection and the growth failure may be a consequence of repeated respiratory infections [10].

Furthermore our result revealed that UTI (HR:1.51) as well as discontinuation of breast-feeding (HR:1.96), teething (HR:1.18) and complementary feeding (HR:1.11) were the statistically significant risk factors for the first FTT ($P<0.05$).

UTI is one of the most common bacterial infections in children, and it has the highest incidence during the first year of life. Some studies which conducted regarding UTI in children confirmed our result about the association of the UTI and FTT [13, 14].

Numerous studies has consensus about initiating time of complementary feeding, that either too early or too late starting complementary diet is cause to malnutrition and the FTT [3, 15]. Our finding concurred with this result from studies, because it was significant factor only for the hazard of the first FTT event that occurred on average 9th month.

As already mentioned, discontinuation breast-feeding was significant factor for the hazard of the first FTT. This is a proved consequence in several studies and it is known as the principal factor for decreasing weight in children [4, 16]. The reason for this conclusion may be is the immunoprotective effect of breast-feeding against infectious disease. It is most important aspect in the first 2 to 3 months of life [3, 16-18]. Lack of exclusive breast-feeding or discontinuation it for the first six months of life lead to growth failure [5, 19]. Teething is another influential factor in our study, but there are restricted studies about this relation. Eruption of primary teeth usually begins around 4-8 months of age and teething has troubles such as the FTT [20].

We did not find any published article about the relationship between initiation time vitamin A and D supplementation and growth failure, but numerous studies have discussed the association between the vitamin D deficiency and FTT. Vitamin D deficiency cause to rickets and it leads to growth failure due to progressive bowing of the legs and loss of height as compared to arm span [3, 4, 16].

In this study we considered the recurrence nature of growth failure in children and applied the PWP model with event-specific baseline hazards. However in future studies one can consider multistate models for the FTT event process in children. Actually deal with each event as a state and estimate the transition probability between the growth failures. It is an interesting question in medical research to know the transition probability between the events.

Conclusions

Identification the risk factors that interfere with growth failure function are main issues in pediatric so it should carry out truly. The recurrence nature of the FTT is an influential problem, which taking it into account increases the accuracy in analysis of the FTT event process and can lead us to identify different risk factors for each FTT recurrences.

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Conflict of interest statement

There is no conflict of interest.

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