In the name of God

Shiraz E-Medical Journal
Vol. 9, No. 3, July 2008

http://semj.sums.ac.ir/vol9/jul2008/86036.htm

Evolution of the pH Level over Time in Patients Suffering from Reflux.

Ohidullah M*, Jamaluddin M**.

*Assistant Professor, **Lecturer, Department of Statistics, Shahjalal University of Science and Technology (SUST), Sylhet-3114, Bangladesh.

Correspondence: M. Jamal Uddin, Department of Statistics Shahjalal University of Science and Technology (SUST) Post Office: Shahjalal University Sylhet-3114, Bangladesh, PABX: 880-821-713491, 714479, Ext-257, Fax: 880-821-715257 Mobile: +8801716972846 E-mail: mjamalu@yahoo.com

Received for Publication: August 13, 2007, Accepted for Publication: July 15, 2008.

Abstract:

The esophagus carries food from the mouth to the stomach. Continuous exposure to the refluxed stomach acid on the esophageal lining causes a burning sensation in the chest or throat known as heartburn. In this study an attempt has been made to investigate the evolution of the pH level over time. In this study we used the Linear Mixed Model to handling the simulated longitudinal data. We built our model considering random intercept and random slope with cubic trend of time reflected by the mean profile and variance structure. We found that all the components of cubic trend of time (hour, hour2 and hour3) are significant at 5% significance level. This also coincide the mean profile in exploratory data analysis, that is, cubic evolution of the pH level over time exists. The study revealed that there is significant evolution of the pH level over cubic time effect exists in the patients.

Keywords: Acid Reflux, Linear Mixed Model, simulation, pH level.

Introduction:

The body is largely made up of water, a medium which is biologically useful in allowing nutrients, oxygen and other bio-chemical components to be transported from place to place. This water-based medium can have either acid or alkaline properties which are measured by a graduated scale called pH (for "potential hydrogen"), where in 1.0 to 6.9 is considered acidic, 7.0 is neutral, and 7.1 to 14.0 is alkaline. The lower the pH number, the greater the acidity, and the higher the pH number, the greater the alkalinity [(1)]. Gastro esophageal reflux disease, commonly referred to as GERD, or acid reflux, is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. Acid Reflux is a condition in which the lower esophageal sphincter does not properly close and acid from the stomach leaks back into the esophagus. The esophagus carries food from the mouth to the stomach. Continuous exposure to the refluxed stomach acid on the esophageal lining causes a burning sensation in the chest or throat known as heartburn. Gastro esophageal reflux disease should not be mistaken with occasional heartburn. If the heartburn occurs more than twice a week, it may be GERD. This disease affects an estimated 5% - 7% of the global population [(2)]. Dr. Allan Spreen states that about 66 % of patients suffering from heartburn, indigestion and reflux have responded well to the use of frequent acidophilus powder which relieves the pain without altering acid production by the stomach [(3)].

Stomach emptying only starts when the content has been sufficiently crushed and mixed to the gastric secretions, to be transformed into an assimilable mash for the intestine, called chyme. Stomach's emptying starts 15 to 60 mn after ingestion. It works very slowly, and it is not at all like a "flushing effect". Total emptying lasts between 5 and 10 hours for a solid meal, but more than half of the content is evacuated around 3 hours after ingestion. This is not the initial volume of the meal that induces the speed of the stomach emptying. Evolution of the gastric emptying percentage according to the time, after ingestion of a solid meal. Gastric emptying is a disorder in which the stomach takes too long to empty its contents. Normally, the stomach contracts to move food down into the small intestine for digestion. Food then moves slowly or stops moving through the digestive tract. Gastro esophageal reflux disease (GERD) is one of the most common diseases of the alimentary system of the Western adult population. Indirect evidence has been presented to indicate that the disease is affecting an expanding proportion of the population [(4-8)]. Moreover, it seems as if the disease is expressed in increasing numbers also in other parts of the world as well, where traditionally very few patients have been affected [(9-13)]. During the last decades, it was noted that GERD manifested itself in different ways, with a dominant proportion of patients presenting without macroscopically recognizable lesions at the time of diagnostic endoscopy. It is a challenging possibility, related to the many enigmas surrounding the disease, that an increasing number of patients suffering from the

disease will not have esophagitis and hypothetically will not even develop it, even though they report the same duration and intensity of symptoms. Despite these many uncertainties, it is obvious that GERD is a chronic disease that requires sustained and maintained therapy in order to control the symptoms and thereby normalize patients' quality of life. Traditionally, chronic GERD patients were seldom seen by the general practitioner but rather by the gastroenterologist [4, 14-17]. The objectives of the study are to investigate the evolution of the pH level over time on the basis simulated data.

Materials and Methods:

The data set considered from a simulated longitudinal data, assuming 100 patients suffering from reflux problems. We assume that patients have been followed during approximately two and half hours after intake of a standardized meal. Each time a reflux occurs, the pH level of the reflux is measured in the esophagus in every half an hour, a burning sensation in the chest or throat, indigestion criteria were used to diagnose an episode of reflux. On the basis of literature [1, 20], we simulated the pH level taking sample size 100 for 5 time points (0.5 hour, 1 hour, 1.5 hour, 2 hour, 2.5 hours) and assume that pH level follows Normal distribution with mean(variance) : {4.5(3.2), 3.06(2.15), 3.18(2.9), 3.0(3.3), 3.5(4.8)} respectively. We simulated data using R statistical package. Ultrasonography is non-invasive, cheap, widely available, and can be repeatedly performed because of its safety in this kind of study. Two- dimensional ultrasound has, for many years, been widely used to assess gastric emptying rates [18]. In this kind of study gastric emptying could be measured by Ultrasonography. Gastroesophageal reflux disease (GERD) is usually diagnosed by clinical history and endoscopy, and is treated empirically with a trial of medical management.

The Esophageal pH monitoring can be done through the using the instrument of a Tube with a pH (anti-log of hydrogen ion concentration) electrode attached to its tip, which is then passed to 5 cm above the upper margin of the lower esophageal sphincter (LES). The electrode is attached to a data logger worn on a waist belt or shoulder strap. Every instance of acid reflux as well as its duration and pH is recorded, indicating gastric acid reflux.

We try to study the evolution of the pH level over time on the basis of simulated or generating data. Variables, to be used in this study: pH: acidity (pH level) of the reflux (the lower the pH, the more acidic the reflux is), HOUR: point in time at which the reflux occurs (hours).

We are dealing with longitudinal data since for each subject the pH level was measured at several different time points and since this evolution of pH over time is of primary interest. The aim of any longitudinal analysis is to study how subject change over time, and what characteristics influence such changes. When our interest is in describing the evolution of each subject separately, or predicting subject specific evolution, then in the likelihood framework, one can use linear mixed models to analyze continuous longitudinal data. The measurements on the

same subject are not independent but clustered within subjects. In our dataset, we have therefore as many clusters as there are subjects. For these reasons, Linear Mixed Model rather than linear regression model is preferable.

The general linear mixed model (19) is given by:

$$Y_i = \mathrm{X_i}\beta + \mathrm{Z_i b_i} + \varepsilon_i$$

Where Yi is the ni-dimensional response vector for subject i, Xi and Zi are (ni x p) and (ni x q) dimensional matrices for the fixed effects and the random effects respectively. The β represents fixed effects that describe the average trend in the population and b contains all subject-specific parameters which describes how a subject deviates from the average trend. The model assumptions are given as:

$b_i \sim N(\mathbf{0}, D)$; D is (q x q) covariance matrix with (i, j) elements dij = dji

$\varepsilon_i \sim N(\mathbf{0}, \sum_i)$; here we can assume $\sum_i = \sigma^2$ I ni is (ni x ni) covariance matrix

$\varepsilon_1, \varepsilon_{2,} \ldots \varepsilon_N$ and $b_1, b_2 \ldots, b_N$ are independent.

This model can be written as

$Y_i \mid b_i \sim N(X_i\beta + Z_i b_{i,}$ Σi),

$b_i \sim N(\mathbf{0}, D)$

and it is called hierarchical models. To apply linear mixed model in our simulated data, we used Procedure 'mixed' in SAS program.

Results:

This study based on 100 sample size (patients) suffering from reflux problems and the acidity or the pH level of these patients ranged from ~0 to ~8. We start presenting the evolution of the pH level for each patient suffering from reflux. Figure 1 shows Individual profiles of pH level. Individual profile show very dissimilar evolution for all subjects. Here we see that starting point of pH level of each patient is different and we also observed that the pH level of different patients does not look the same over time. So we found that the above individual profile suggest random intercept and random slope.

Figure 2 below shows the mean profile of pH level. The mean profile indicate that the response is having a cubic trend. Figure 3 below reflects the overall smoothed variance function of the OLS residual over time. From the variance function, it can be observed that in the beginning variability was high and it sharply dropped and after one and half hour it took an upward trend until the third hour. If variance function shows constant variability over time, we assume stationarity and we do not include random effects other than intercepts [19]. This figure indicate the variance is not constant over time, we can assume non stationarity. It means that there is some remaining systematic structure in the residual profile. So we may use to select one or more random effects additional to the random intercept to build our model.

To describe how measurements within a subject correlate, we plot a scatter matrix of residual (Res) OLS. In this simulation study, we assumed that the time is

fixed. Res1, Res2, Res3, Res4, and Res5 indicate the residual from 0.5, 1, 1.5, 2, and 2.5 hour respectively. Figure 4 shows a scatter plot matrix of residual and the correlation between time points. From Figure 5, we can see that correlation between different times points are not very high. We have seen that the correlation pattern of each residual is not well defined; therefore we may conclude that our covariance is unstructured.

From the Table 1, we can see that all the components of cubic trend of time (hour, $hour^2$ and $hour^3$) are significant at 5% significance level. This also coincide the mean profile of Figure 3 that is cubic evolution of pH level over time exists.

Table 1: Parameter estimates for fixed effects in cubic trend time

Parameter	Estimate	Standard Error	P-value
Intercept	7.6567	0.8384	<.0001
Hour	-8.1584	2.1449	0.0002
$Hour^2$	4.3950	1.5805	0.0065
$Hour^3$	-0.6993	0.3494	0.0481

Discussion:

In this simulated data analysis we try to investigate the evolution of the pH level over time. First we carried out exploratory data analysis which include plot of the individual profile, mean structure, variance structure and correlation structure to investigate the pattern or characteristics of the data. We observed that the initial pH level vary from individual to individual also their pH level change heterogeneously as well.

Since the data were generated assuming Normal distribution repeatedly over time at each subject, so this data set is longitudinal data set. Therefore the linear mixed model is preferable. After carrying out exploratory data analysis we decided to use random intercept and random slope since our profiles were originating from different pH levels and differing in time. Therefore we built our model considering random intercept and random slope with cubic trend of time reflected by the mean profile and variance structure.

Conclusion:

We found that there is significant evolution of the pH level over cubic time effect, exists of the patients on this simulated study.

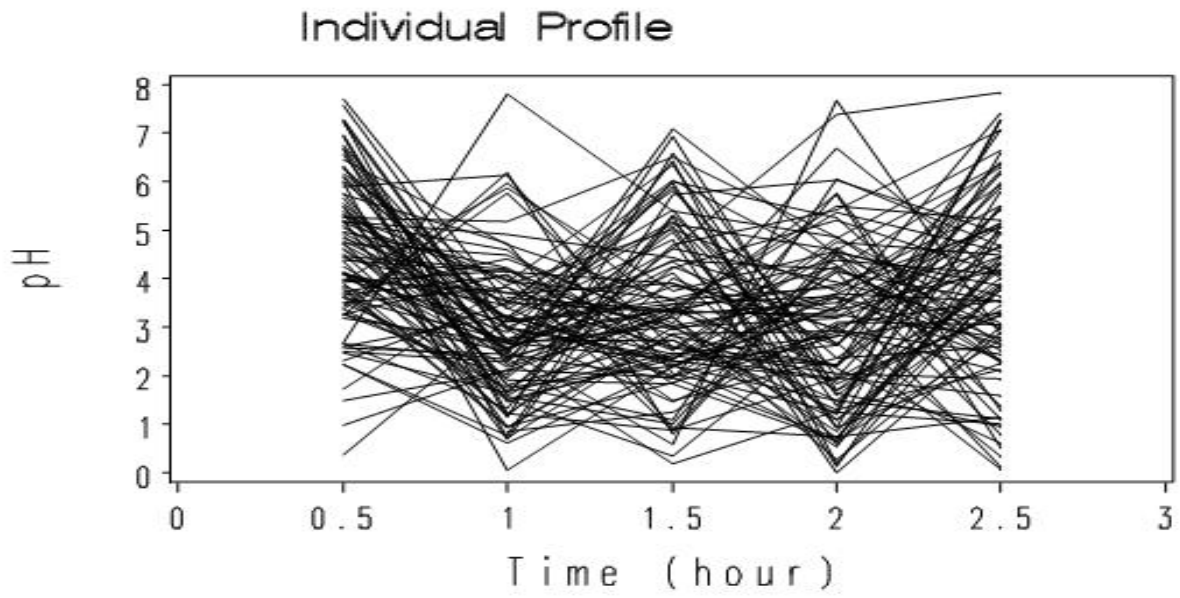

Figure 1, Individual profiles of pH level over time.

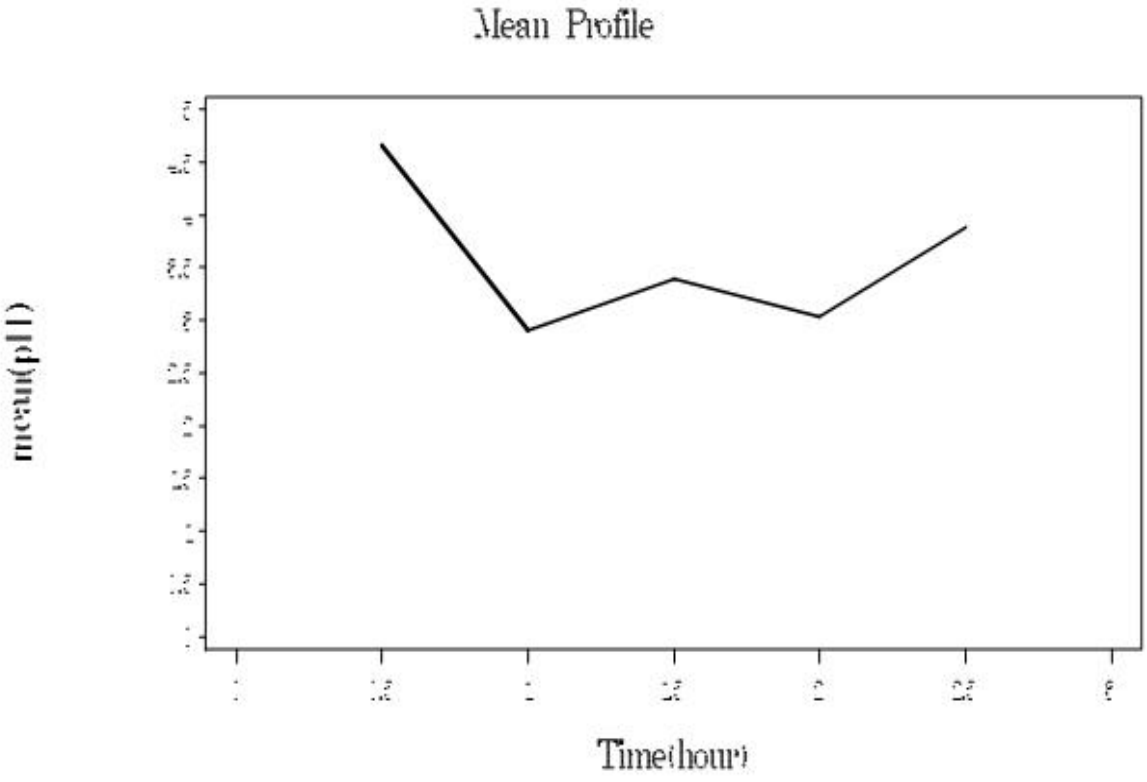

Figure 2: Mean profile of pH level over time

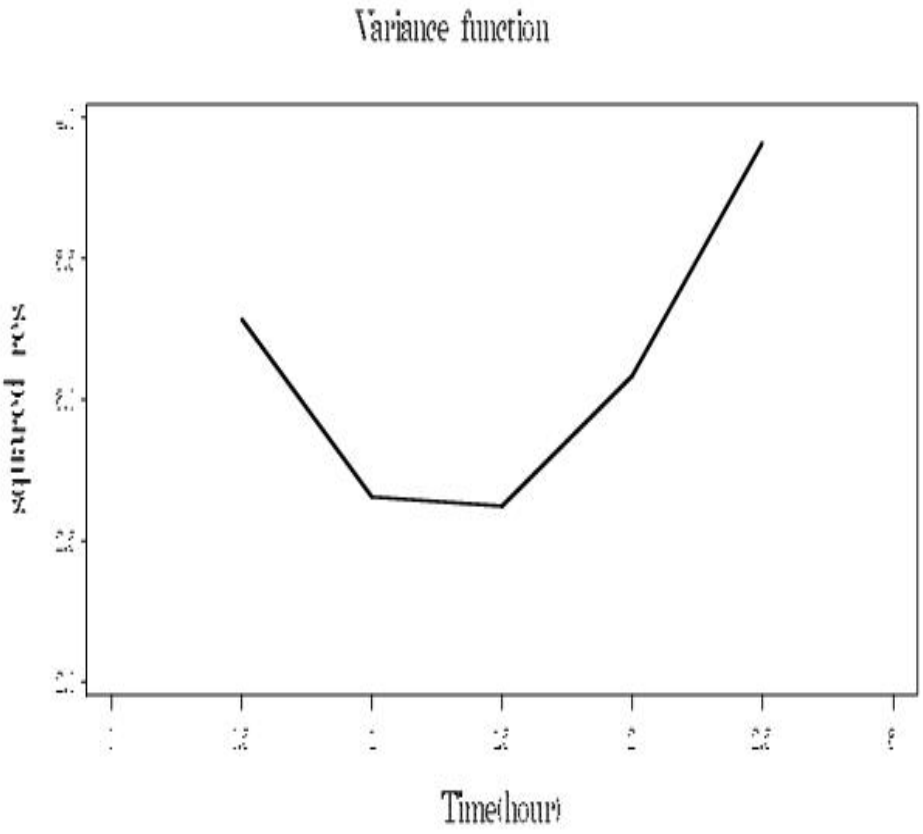

Figure 3: Variance profile of pH level over time.

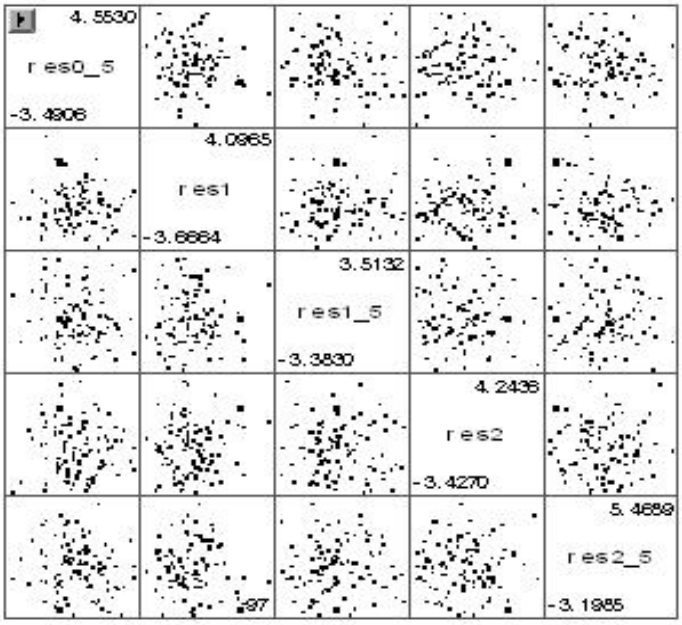

Figure 4: Correlation structure of OLS residual over time

References:

1. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1999; 94:1434-42.

2. http://www.medicinenet.com/gastroesophageal_reflux_disease_gerd/page5.htm. 9 March 2007.

3. HSIResearch@healthnews.com Nov. 11, 2004 pg 1-2, website: http://www.newswithviews.com/Howenstine/james21.htm, 28 April 2007.

4. Ollyo JB, Monnier P, Fontolliet C, et al. The natural history, prevalence and incidence of reflux oesophagitis. Gullet 1993; 3(suppl):3–10.

5. Locke GRIII, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997; 112:1448–1456.

6. Todd JA, Johnston DA, Dillon JF. The changing spectrum of gastroesophageal reflux disease. Eur J Cancer Prev 2002; 11:215–219.

7. Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. Ann Med 1995; 27:67–70.

8. Mäntynen T, Färkkilä M, Kunnamo I, et al. The impact of upper GI endoscopy referral volume on the diagnosis of gastroesophageal reflux disease and its complications: a 1–year cross-sectional study in a referral area with 260000 inhabitants. Am J of Gastroenterol 2002; 97:2524–2527.

9. Kang JY. Systematic review: geographical and ethnic differences in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2004; 20:705–717.

10. Fock KM, Talley N, Hunt R. et al. Report of the Asia-Pacific consensus on the management of gastroesophageal reflux disease. J Gastroenterol Hepatol 2004; 19:357–367.

11. Segal I. The gastro-oesophageal reflux disease complex in sub-Saharan Africa. Eur J Cancer Prev 2001; 10:209–212.

12. Wong WM, Lai KC, Lam KF, et al. Prevalence, clinical spectrum and health care utilization of gastro-oesophageal reflux disease in a Chinese population: a population-based study. Aliment Pharmacol Ther 2003; 18:595–604.

13. Yeh C, Hsu CT, Ho AS, et al. Erosive esophagitis and Barrett's esophagus in Taiwan: a higher frequency than expected. Dig Dis Sci 1997; 42:702–706.

14. Richter JE. Peptic strictures of the esophagus. Gastroesophageal Reflux Dis 1999; 28:875–891.

15. Lundell L. Acid suppression in the long-term treatment of peptic stricture and Barrett's oesophagus. Digestion 1992; 51:49–58

16. Hands LJ, Papavramidis S, Bishop H, et al. The natural history of peptic esophageal strictures treated by dilation and antireflux therapy alone. Ann R Coll Surg Engl 1989; 71:360–370.

17. Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. Risk factors for erosive reflux esophagitis: a case-control study. Am J Gastroenterol 2001; 96:41–46.

18. Odd Helge Gilja, Trygve Hausken, Svein Ødegaard and Arnold Berstad. Gastric emptying measured by ultrasonography. World Journal of Gastroenterology 1999; 5(2):93-94.

19. Verbeke G and Molenbergs.G. Linear Mixed Model for Longitudinal Data. Springer Series in statistics. New –York:Springer – Verlag. 2000.

20. John H Walsh, Charles T Richardson, and John S Fordtran. pH Dependence of Acid Secretion and Gastrin Release in Normal and Ulcer Subjects. The Journal of Clinical Investigation 1975; 55:462-468.