Quantitative Analysis of Reflux Episodes in Gastroesophageal Reflux Disease (GERD)

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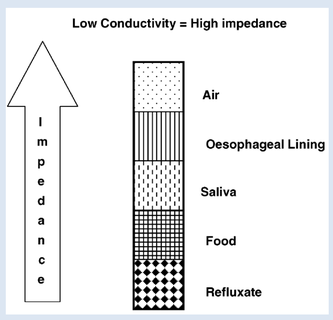
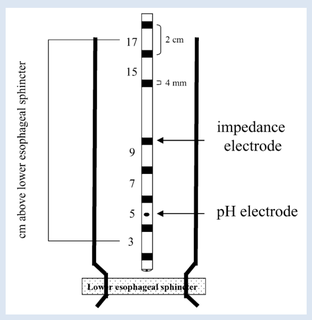
OBJECTIVES

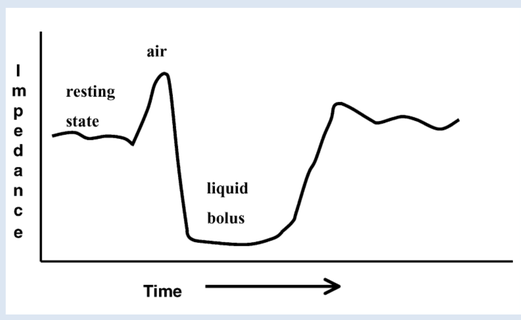
The purposes of this study was (i) to develop a time-to-event model to characterize the reflux patterns in PPI-resistant and PPI-reactive groups among GERD patients and examine the associated influencing factors, (ii) to assess the feasibility of applying the model-based drug treatment approach in the area of GERD, and (iii) to find diagnosis criteria for PPI-resistant versus PPI-reactive GERD patients.

METHODS

A repeated time to events (RTTE) model was developed within the mixed effect model framework using a dataset composed of a series of reflux event times collected through a 24hr combined pH/MII monitoring device from 34 patients who were diagnosed with GERD at Severance hospital, Seoul, Korea and took a PPI once daily in the morning from 2008 to 2010. The PPI was administered with one of the following agents: esomeprazole, rabeprazole, pantoprazole, lansoprazole, esomeprazole, omeprazole, rameprazole.







Exact times of events were assumed and the likelihood at each event time L(t) was formulated as L(t) = S(s,t)·h(t) where S(s,t) and h(t) denote the survival function and the hazard function, respectively, s denotes the previous event time (or start of observation), and t denotes the current event time.

$$h(\tau)d\tau = \Pr(\tau \le T < \tau + d\tau \mid T \ge \tau) = f(\tau)d\tau / S(\tau) = -S'(\tau)dt / S(\tau)$$

$$H(s,t) = \int_s^t h(\tau)d\tau = -\log(S(s,t))$$

$$S(s,t) = \exp(-H(s,t))$$

$$\ell(t) = S(s,t)h(t)$$

Three hazard functions tested were as follows: Constant, h(t) = λ ; Gompertz, h(t) = exp(λ + γ·t) ; Weibull hazard, h(t) = λ + γ(λ·t)$^{\gamma-1}$. Inter-individual random effect was allowed for each hazard parameter. The drug effects among different PPIs were assumed similar.

$$h(t) = \lambda \quad : \text{Constant hazard}$$
$$h(t) = \lambda \cdot \gamma\,(\lambda\ t)^{\gamma-1} \quad : \text{Weibull hazard}$$
$$h(t) = \exp(\lambda + \gamma\ t) \quad : \text{Gompertz hazard}$$

The covariate effects were tested with stepwise covariate modeling (SCM) using NM-NM method and the significance levels for selecting or deleting the covariate were $p < 0.05$ for forward selection and $p < 0.001$ for backward elimination, respectively. The following covariates were tested: age, sex, disease duration and characteristics of symptom (typical versus atypical) where typical symptom was defined as the one among regurgitation, heartburn, and chest pain. The baseline (no-covariate) hazard was also allowed to vary between acidic and non-acidic refluxes. This covariate analysis was performed separately for responder and non-responder groups to formally assess the differences in patient characteristics between the two groups. In addition, in an effort to find a potential marker that could distinguish non-responders from responders, differences between the two groups in the number of acidic refluxes and the ratio of non-acidic to acidic refluxes were further examined.

The goodness of fit of the finally developed model was visually examined by comparing the predictions and the observations for both the population and the individual levels on the basis of the number refluxes per hour over the entire 24-hr period, for acidic and non-acidic refluxes for each of non-responder and responder groups. Finally, visual predictive check (VPC) was performed on the basis of 100 simulations.

RESULTS

The median age (range) of the patients (male 12, female 22) was 53 (19-75) years. The median disease duration (range) was 56 (28-400) months. 16 patients had typical symptoms, while 18 had not. The numbers of the PPI responders and Non-responders were 13 and 21, respectively.

Sex	Men 12 / Women 22
Age	53 (19-75) years
Disease period	56 (28-400) months
Typical Sx	Yes 16 / No 18

The acidic and non-acidic refluxes were best explained by the constant hazard model in both the PPI responder and the non-responder groups. The baseline values of the log hazard in responders were 1.36 and 0.534 for acidic and non-acidic refluxes, respectively, and those in non-responders were 1.24 and 0.853 for acidic and non-acidic refluxes, respectively, indicating the hazard of non-acid refluxes lower than that of acid refluxes in both groups.
The disease duration (P) was found to have a significant effect for the non-responder group, resulting in a decrease in the log hazard by 0.2 per 56 months of disease duration. No other covariate was found significant.

$$\ln\lambda = \theta_1 + \theta_2\,(P/56)$$
$$\lambda = \exp(\ln\lambda)\ \exp(\eta)$$
$$h(t) = \lambda$$

Non-responder Group

θ_{1_acid}	$\theta_{1\_nonacid}$	θ_2	ω^2
1.24	0.853	-0.208	0.0767

Responder Group

θ_{1_acid}	$\theta_{1\_nonacid}$	θ_2	ω^2
1.36	0.534	-	0.19

Figure 1. Number of refluxes per 0.5 hr : Population (Line: Prediction, Histogram: Data)

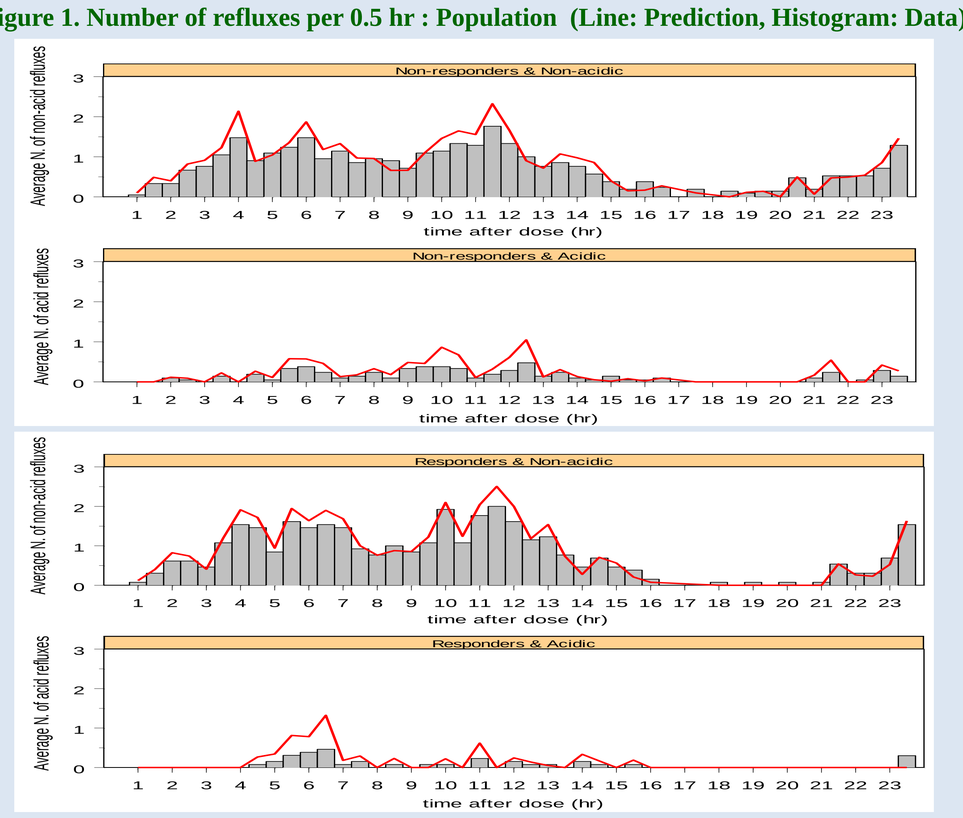
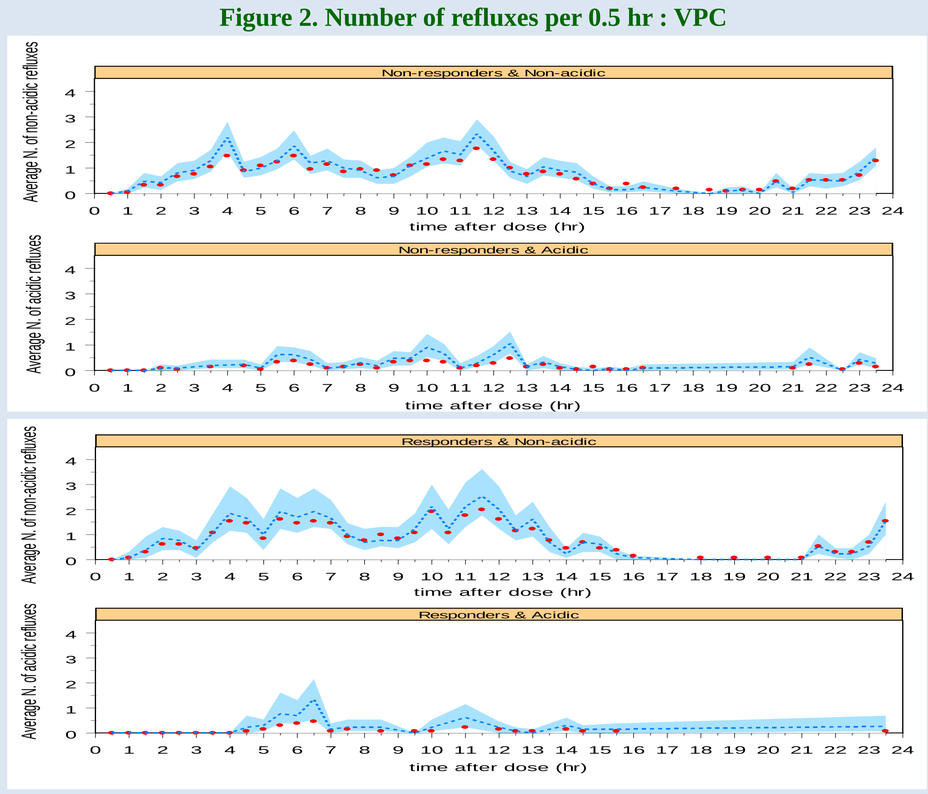
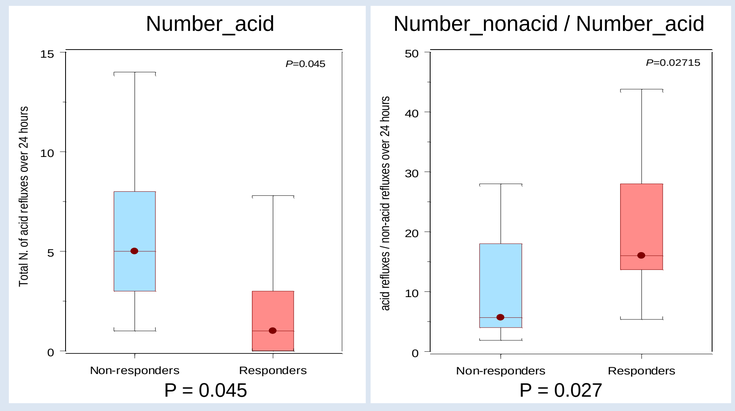


Figure 2. Number of refluxes per 0.5 hr : VPC



The data showed that in the responder group the number of acidic refluxes and the ratio of acidic to non-acidic refluxes were significantly suppressed compared to the non-responder group as a result of the treatment effect (p = 0.045 and 0.027, respectively).
Evaluated by the goodness of fit plot and VPC, in general, the observed trends of the refluxes were well explained by the final model for acidic and non-acidic refluxes for both non-responder and responder groups although over-predictions were found for some data points.

Figure 3. Comparison between non-responders & responders



CONCLUSIONS

This work represented the feasibility of applying a model-based approach in characterizing reflux patterns in GERD which can be used as a supportive tool for an optimal treatment. This preliminary modeling result showed that the hazard rate is lower in non-acidic refluxes and decreases with the disease duration in non-responders. The model developed has several limitations: no placebo group, a few covariates tested, and a small number of subjects, which will be reinforced in future studies. In addition, model validation will be needed with more subjects in a prospective study.
Nevertheless, it is meaningful that the method developed here analyzed routine clinical data from the perspective of a model-based drug treatment and thus can similarly be applied in various kinds of clinical situations.

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