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EDITORIAL

Mean-Variance Serum Sodium Associations with Diabetes Patients

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Serum sodium (SNa) is a critically significant component of hyponatremia and bones, has firmly been established as a risk factor correlated with many diseases such as diabetes, heart, anaemia, etc and the incidence of fragility fractures. Note that the fragility fractures are a general complication in type 2 diabetes (T2D) patients, contributing to high rates of mortality and morbidity together with mounting public health costs [1]. SNa is a fundamental component for normal physiological processes, and T2D patients may experience osmotic diuresis as a consequence of disease-related hyperglycemia, contributing to the excess excretion of sodium in the urine and resulting in hyponatremia [2]. Dysnatremias [hyponatremia (<136 mmol/L) and hypernatremia (>145 mmol/L)] can severely affect several physiologic organ systems and functions [3-5]. Note that the low serum osmolality is less than 275 mosm/L that usually accompany low serum Na [6]. Diabetes is correlated with many important electrolyte disorders, predominantly affecting magnesium, SNa, and potassium [7]. The relation between serum Na and outcomes such as new-onset diabetes and all cause mortality is discussed in the recent article by Peng *et al*. [8]. In addition, the mechanisms of low serum Na such as activation of renin-angiotensin aldosterone systemic and its consequences are discussed by Ames, Atkins, Pitt [9]. However, the correlation/ association of SNa with diabetes patients is not clear. This can be confirmed based on the proper probabilistic model of SNa with diabetes status along with the other explanatory factors of the disease. On the other hand, this type of association can be obtained based on the models of fasting glucose/post glucose/random glucose/HbA1c level with SNa and other explanatory factors of the diabetes disease.

The current editorial note examines the following research queries.

- Is there any association of SNa with diabetes patients? If it is affirmative, what is the most probable SNa association model?
- How do we derive the most probable SNa association model?
- What are the mean-variance associations of SNa with the diabetes patients?

These above research queries are examined herein based on a real data set of 299 subjects

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with 13 covariates, and the data set is clearly illustrated in the two articles [10,11], which is available in the site [12].

The 13 covariates are:

- Age,
- Anaemia status (ANS) of subjects (0=no anaemia, 1=anaemia),
- Creatinine phosphokinase (CRP),
- Diabetes status (DIS) of subjects (0=no diabetes, 1=diabetes),
- Ejection fraction (EJF),
- High blood pressure (HBP) of subjects (0=normal BP, 1=high BP),
- Serum creatinine (SEC),
- Serum sodium (SNa),
- Sex (0=female, 1=male),
- Smoking habit (SMH) (0=no smoking, 1=smoking),
- Time up to the end of the follow-up period (TTF),
- Death event (DEE) (0=alive, 1=death).

The above data set is multivariate, heteroscedastic, non-normal physiological. The response in this study is SNa, which is a non-constant variance response variable. The variance of the response SNa is not stabilized by any suitable transformation, so it should be modeled by joint generalized linear models (JGLMs), which is clearly illustrated in the book by Lee, Nelder and Pawitan [13].

The derived mean and variance SNa gamma fitted models are as follows.

Gamma fitted SNa mean (μ) model is,

μ=exp.(4.90 –0.02 DIS +0.02 EJF +0.03 EJF*HBP +0.01 PLC –0.02 HBP +0.01 ANS –0.01 PLC*ANS +0.01 SMH –0.01 CRP*SMH +0.01 CRP –0.01 CRP*HBP –0.01 DEE +0.02 ANS*DEE –0.02 TTF +0.01 AGE*TTF –0.01 AGE*PLC +0.02 AGE –0.03 SEC +0.02 AGE*SEC +0.04 SEX –0.01 AGE*CRP –0.0001 EJF*PLC –0.07 AGE*SEX +0.03 EJF*SEC +0.01 CRP*TTF),

and the fitted SNa variance $(\hat{\sigma}^2)$ model is,

$\hat{\sigma}^2$= exp.(-4.27 –0.89 DIS +0.01 CRP*DIS –0.01 CRP +0.07 EJF*DEE –0.08 EJF +1.14 SEC*DIS +0.02 AGE +1.83 DEE –0.06AGE*DEE -1.94 ANS –0.41 SEX +0.03 EJF*SEX –0.01 PLC –0.18 SEC –0.53 SEC*SEX -1.31 SMH +0.03 AGE*ANS +1.04 SEC*SMH –0.02 TTF +0.01 EJF*TTF).

The above two SNa gamma fitted equations represent the mean $(\hat{\mu})$ and the variance $(\hat{\sigma}^2)$ models, which are very complex. In the mean model there is only one term with diabetes status of the subjects. The mean SNa model reveals that mean SNa is inversely associated with the diabetes status (DIS) (0=no diabetes, 1=diabetes) (P=0.01) of the subjects, indicating that SNa level is higher for non-diabetic subjects than diabetic. It is generally observed in practice. In addition, it confirms the previous published results [2, 13]. So, diabetes patients should always be cared for SNa level.

From the variance $(\hat{\sigma}^2)$ model, it has been derived that SNa variance is directly related with the joint interaction effects of serum creatinine (SEC) and DIS i.e. SEC*DIS (P<0.01), while it is inversely related with the marginal effect DIS (P=0.05) and indifferent to SEC. It indicates that SNa levels are highly dispersed (or scattered) for the diabetic subjects with higher SEC levels than non-diabetic subjects with low SEC levels. Also, it is inversely related with the marginal effect DIS (P=0.05), showing that SNa levels are highly dispersed for the non-diabetic subjects than diabetic, without considering SEC effect.

Also, SNa variance is directly related with the joint interaction effects of creatinine phosphokinase (CRP) and DIS i.e., CRP*DIS (P=0.01), while it is inversely related with both

the marginal effects of CRP (P<0.01) and DIS (P=0.05). It implies that SNa levels are highly dispersed for the diabetic subjects with higher CRP levels than non-diabetic subjects with lower CRP levels.

The considered data set does not contain the fasting glucose/post glucose/random glucose/ HbA1c levels, so it is not possible to examine the associations of SNa with these diabetes markers. The full report will be submitted soon. The findings of the variance model are completely new in the diabetes literature. SNa has many complex functional effects on diabetes subjects, so the medical treatment/ research process should care on the SNa levels of the subjects.

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