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Original Research

Inter-Relationship between Creatinine Phosphokinase and Ejection Fraction

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ABSTRACT

Objectives

It is interesting to examine the associations between serum creatinine phosphokinase (CPK) level and some of the cardiac risk factors such as blood pressure, heart rate, ejection fraction (EFT), etc. in heart patients. The article aims to examine the interrelationship between CPK level and EFT in heart patients.

Methods

The inter-relationship between CPK level and EFT in heart patients is examined herein using the probabilistic model of CPK on EFT along with the other explanatory variables and factors, and conversely. The CPK level or EFT model is derived by applying joint generalized linear models (JGLMs).

Results

The CPK level mean model shows that mean CPK is directly related to EFT (p=0.04) and AGE (p=0.03), while it is inversely related to their joint interaction effect of AGE and EFT, i.e., AGE*EFT (p=0.01). The mean CPK is inversely related to serum creatinine (SCT) (p<0.01), while it is directly related to the EFT (p=0.04), and their joint interaction effect is EFT*SCT (p<0.01). From the EFT mean model, it is derived that EFT is directly related to CPK (p=0.01) and AGE (p<0.01), while it is inversely partially related to their joint interaction effect, AGE*CPK (p=0.12). Mean EFT is indifferent to SCT (p=0.39), while it is directly related to the joint interaction effect of CPK (p=0.01) and SCT, i.e., CPK*SCT (p<0.01). Mean EFT is directly related to serum sodium (SNa) (p<0.01) and CPK (p=0.01), while it is inversely related to the joint interaction effect of CPK*SNa (p=0.01). From the variance model of EFT, the variance of EFT is inversely related to CPK (p=0.04).

Conclusion

Based on the derived CPK level and EFT models, it is derived that CPK and EFT are interrelated with each other through AGE, SCT, SNa, and some interaction effects. Heart patients and practitioners should care about the interrelationship of CPK levels and EFT for better treatment.

Keywords

Blood pressure status (BPS); Cardiac risk factors; Ejection fraction (EFT); Joint generalized linear models (JGLMs); Serum creatinine phosphokinase (CPK).

INTRODUCTION

The serum creatinine phosphokinase (CPK) level for an individual is very high, which generally shows that there are some injuries to muscle tissue or stress to the heart or brain. A higher CPK level most likely indicates a muscle tissue injury. When a muscle is injured, serum CPK transmits into the bloodstream.

For the past few decades, excessive lifestyle changes such as lack of physical activity, obesity, and stress have led to life-threatening circumstances such as acute myocardial infarction (AMI) as a principal cause of death in developed and developing countries as well as in industrialized races.[1,2] Myocardial necrosis, or AMI, is connected with the release of structural proteins and other intracellular macromolecules. When the integrity of the cellular membranes is compromised, a few biomarkers, such as creatine kinase (CK), MB, CPK, cardiac-specific troponin T (cTnT), and cardiac-specific troponin I (cTnI), transmit into the bloodstream, which are measured

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in serum, aiding in the detection of myocardial infarction (MI).[3,4] In practice, these biomarkers are examined using advanced biochemistry approaches for collecting primary observations of AMI.[4-6] The reports[3,4] have examined the relationship between serum and saliva levels of CPK, and they have further compared salivary CPK as a biomarker between healthy subjects and AMI patients. Based on advanced probabilistic modeling of the above biomarkers, many interesting outcomes can be derived for AMI patients, which are very little examined. The basic myocardial energy maintains the reaction for developing adenosine triphosphate (ATP), which is the CK reaction that reversibly changes high-energy phosphate between phosphocreatine (PCr) and adenosine diphosphate (ADP).[7,8] It has been reported that serum CPK levels have some effects on heart patients, but the outcomes are mostly obtained using simple correlation or regression analysis, which are not appropriate statistical methods for identifying these associations.[1-8]

The association between serum CPK level and heart patients is not clear in most of the previously published articles, as these associations are not derived by suitable probabilistic modeling of CPK level with heart patients (or cardiac risk factors) along with other explanatory factors. Reversely, this association can be studied using probabilistic models of heart rate, blood pressure (diastolic and systolic), and ejection fraction with CPK levels along with other heart disease explanatory factors or variables. The present study is based on a probabilistic model of CPK level based on high blood pressure status, ejection fraction (cardiac factors), and other explanatory factors. It also contains a probabilistic model of EFT on CPK levels, along with the other explanatory variables. The current article examines the following research problems:

- Is there any correlation or association between CPK and heart disease-related factors such as high blood pressure, ejection fraction, or heart patients? If it is affirmative, what is the appropriate CPK association or relationship model with high blood pressure, ejection fraction, or heart disease patients?
- Conversely, is there any correlation or association between EFT, CPK level, and other explanatory variables or factors? If it is affirmative, what is the appropriate EFT association or relationship model with the other factors or variables?
- How do we obtain the most probable CPK or EFT association model with the other explanatory factors?
- What are the effects of CPK levels on high blood pressure, ejection fraction, or heart disease subjects? Similarly, what are the effects of EFT on CPK levels?

The present article examines the interrelationship between CPK level and EFT using the above four research queries and a real data set. The data set (CPK, EFT, and other factors) is well-described in the materials section, and the data analysis methods (CPK and EFT analysis) are discussed in the methods section. Data analysis outcomes only related to CPK level with EFT and EFT with CPK level are displayed in the result section. The outcomes of CPK and EFT analysis are discussed in the discussion section, which is followed by a conclusion section.

MATERIALS AND METHODS

Materials

The above research problems are examined herein using a real data set of 299 heart disease subjects with 13 covariates or factors, which are well-described in the articles,[9] and the data set can be found on the site https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+records.[10] The report considers 13 factors, or covariates, which are:

- Age
- Sex/Gender (0=female, 1=male),
- Creatinine phosphokinase (CPK),
- Diabetes mellitus status (DMS) of subjects (0=no diabetes, 1=diabetes),
- Platelet count (PLC)
- Anaemia disease status (ADS) of subjects (0=no anemia, 1=anemia),
- Ejection fraction (EFT),
- Smoking status (SMS) (0=no smoking, 1=smoking),
- Serum creatinine (SCT),
- Blood pressure status (BPS) of subjects (0=normal BP, 1=high BP)
- Serum sodium (SNa),
- Total time to follow-up period (TTP),
- Death event (DEE) (0=alive, 1=death).

The data set was recently reproduced in the articles by Das et al[11] and Das et al[12]. Interested readers about the data set are requested to go through the articles.[9-12]

Statistical Methods

There are two responses, such as CPK level and EFT, in the present article, according to the aims of the report. It is identified herein that both the responses (CPK level and EFT) are heteroscedastic, continuous, and non-normal. Both the responses (CPK level and EFT) are analyzed herein using joint generalized linear models (JGLMs) following the log-normal and gamma distributions, which are clearly given in Lee et al,[13] Das et al,[14] Qu et al,[15] Lesperance et al,[16] Das et al.[17] Interested readers may go through JGLMs from the book by Lee et al[13]. Note that CPK level analysis is better in the log-normal model, while EFT analysis is better in the gamma JGLMs, which are shortly reported herein.

Log-normal distributed JGLMs: For the positive response Y_i (=EFT or CPK) with $E(Y_i$=EFT or CPK$)=\mu_i$ (mean) and $Var(Y_i$=EFT or CPK$)=\sigma_i^2\mu_i^2=\sigma_i^2 V(\mu_i)$ say, where σ_i^2's are dispersion parameters and $V(\cdot)$ presents the variance function. Specially, log transformation Z_i=log (Y_i=EFT or CPK) is applied to stabilize the variance Var $(Z_i)\approx\sigma_i^2$, but the variance may not always be stabilized.[13] For developing an improved model of EFT or CPK, JGLMs for the mean and dispersion are considered. For the response EFT or CPK, assuming log-normal distribution, JGL mean and dispersion models (with Z_i=log (Y_i=EFT or CPK)) are as follows:

$$E(Z_i)=\mu_{zi} \text{ and } Var(Z_i)=\sigma_{zi}^2,$$
$$\mu_{zi}=x_i^t\beta \text{ and } \log(\sigma_{zi}^2)=g_{it}\gamma$$

where x_i^t and g_{it} are the explanatory factors/variables vectors of EFT or CPK associated with the mean regression coefficients β

and dispersion regression coefficients γ, respectively.

Gamma distributed JGLMs: As above stated Y_i's (=EFT or CPK), the variance has two parts such as (function on the mean parameters μ_i's) and (independent of μ_i's). The GLM family distribution is represented by the variance function V(·), and if V(μ)=1, it is normal, Poisson if V(μ)=μ, and gamma if $V(\mu)=\mu^2$ etc. For the responses EFT or CPK, gamma JGLMs mean and dispersion models are as follows:

$$\eta_{zi}=g(\mu_i)=x_i^t\beta \text{ and } \varepsilon_i=h(\sigma_i^2)=\omega_i^t\gamma$$

where g(·) and h(·) are the GLM link functions attached with the mean and dispersion linear predictors respectively, and x_i^t, ω_i^t are the explanatory factor vectors of EFT or CPK attached with the mean and dispersion parameters respectively. Estimation method is clearly given in Lee et al.[13]

STATISTICAL ANALYSIS AND RESULTS

Results of CPK level Statistical Analysis

It is aimed at examining the interrelationship between CPK level and EFT in the report. So, two models (one for CPK level and the other for EFT) are to be derived herein. The dependent variable CPK is modeled on the other 12 explanatory factors and variables herein by JGLMs with both the log-normal and gamma distributions. It is found that the log-normal model gives better results based on the smallest Akaike information criterion (AIC) value.[18] Herein only the log-normal fitted CPK level analysis outcomes, which are only related to EFT, are presented (Table 1). CPK-level analysis has many outcomes except for the EFT-related outcomes. These are not presented herein, as they may confuse the aims of the article.

Table 1. *Joint Log-Normal Fitted CPK Level Analysis Outcomes Only Related with EFT*

Model	Associated with	Nature of Association	*p*-value
Mean	AGE	Positive	0.03
	EFT	Positive	0.04
	AGE* EFT	Negative	0.01
	SCT	Negative	<0.01
	EFT* SCT	Positive	<0.01

The CPK level mean model shows that mean CPK is directly related to EFT (p=0.04) and AGE (p=0.03), while it is inversely related to their joint interaction effect of AGE and EFT, i.e., AGE*EFT (p=0.01). The mean CPK is inversely related to serum creatinine (SCT) (p<0.01), while it is directly related to the EFT (p=0.04), and their joint interaction effect is EFT*SCT (p<0.01).

Log-normal fitted CPK level mean ($\hat{\mu}_z$) model is

$\hat{\mu}_z$=9.78–0.35SMS+0.01TTP+0.01 SMS*TTP+0.97SEX–0.01 SEX*TTP-7.14 DEE-0.04 SNa+0.05 SNa*DEE–0.47DMS–0.62 SCT+0.40DMS*SCT+0.01PLC+0.01PLC*DEE+0.03AGE-0.20 ADS -0.01 ADS*PLC+0.04 EFT -0.01 AGE*EFT -0.01 SCT*TTP +0.01 EFT*SCT,

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

$\hat{\sigma}^2_z$=exp.(-7.08 +0.01TTP+0.01AGE+1.72SEX–0.01SEX*TTP +0.06SCT-0.01SCT*TTP+0.27SMS +0.18 DMS –1.25 DMS*SMS +1.57ADS–0.93ADS*SEX+0.03SNa+0.01PLC–0.01 ADS*PLC).

Results of EFT Statistical Analysis

The dependent variable EFT is modeled on the other 12 explanatory factors and variables herein by JGLMs with both log-normal and gamma distributions. It has been found that the gamma model gives better results based on the smallest AIC value. Herein, only the gamma-fitted EFT analysis outcomes, which are only related to the CPK level, are presented (Table 2). EFT analysis has many outcomes except the CPK-level-related outcomes, which are not shown herein to avoid confusion about the aims of the article.

Table 2. *Joint Gamma Fitted EFT Analysis Outcomes only Related with CPK Level*

Model	Associated with	Nature of Association	*p*-value
Mean	AGE	Positive	<0.01
	CPK	Positive	0.01
	AGE*CPK	Negative	0.12
	SCT	No association	0.39
	CPK*SCT	Positive	<0.01
	SNa	Positive	<0.01
	CPK*SNa	Negative	0.01
	CPK	Negative	0.04
Variance	SCT	Negative	<0.01

From the EFT mean model, it is derived that EFT is directly related to CPK (p=0.01) and AGE (p<0.01), while it is inversely partially related to their joint interaction effect, AGE*CPK (p=0.12). Mean EFT is indifferent to SCT (p=0.39), while it is directly related to the joint interaction effect of CPK (p=0.01) and SCT, i.e., CPK*SCT (p<0.01). Mean EFT is directly related to serum sodium (SNa) (p<0.01) and CPK (p=0.01), while it is inversely related to the joint interaction effect of CPK*SNa (p=0.01). From the variance model of EFT, the variance of EFT is inversely related to CPK (p=0.04).

The Gamma-fitted EFT mean ($\hat{\mu}$) model is

$\hat{\mu}$ = exp.(0.74+0.01CPK+0.01AGE–0.01SCT–0.01AGE*CPK+0.01 CPK*SCT+0.01TTP+0.02SNa–0.01CPK*SNa–0.13SEX–0.01 AGE*TTP–0.09DDE–0.19SEX*DEE–0.11BPS–0.13 BPS*DEE+0.22BPS*SEX–0.14DMS*SMS+0.03DMS+0.05 SMS), and the fitted EFT variance ($\hat{\sigma}^2$ model is

$\hat{\sigma}^2$=exp.(-0.76+0.01AGE–0.01 CPK+1.72 ADS–0.03 AGE*ADS –1.47 BPS–0.02 TTP–0.01 PLC+0.01 PLC*TTP–0.30 SCT+0.01 SCT*TTP–0.35SEX+0.66BPS*SEX+0.29BPS*S

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CT+0.01 BPS*TTP).

DISCUSSION

The above log-normal fitted (for the response CPK level) equations show, respectively, the CPK's mean ($\hat{\mu}_z$) and the variance ($\hat{\sigma}^2_z$) models. In the considered data set, there are two cardiac factors, such as ejection fraction (EFT) and the subject's blood pressure status (BPS) (0=normal BP, 1=high BP), while BPS is an attribute character and the EFT is a continuous variable.

From the above CPK's mean model, it is derived that mean CPK is directly related to EFT (p=0.04) and AGE (p=0.03), while it is inversely related to their joint interaction effect, AGE* EFT (p=0.01). This indicates that even for higher EFT levels at older ages, CPK levels may not be higher. It shows that CPK levels rise as the joint effect of EFT and AGE, i.e., AGE*EFT, decreases. The marginal effects of EFT and AGE are directly related to CPK levels, but these marginal effects are unimportant as their joint effect is statistically significant. It implies that CPK is related to the ejection fraction (EFT), along with AGE and AGE*EFT.

Again, the mean CPK level is inversely related to SCT (p<0.01), while it is directly related to the EFT (p=0.04), and their joint interaction effect EFT* SCT (p<0.01). This shows that CPK levels rise as the joint effect of SCT and EFT, i.e., EFT*SCT, rises. The marginal effects of EFT and SCT are not important, as their joint effect, EFT*SCT, is statistically significant. It shows that CPK level is related to the ejection fraction (EFT), along with SCT and EFT*SCT.

Note that the mean CPK level is not connected with the subject's blood pressure status (BPS) (0=normal BP, 1=high BP). In addition, CPK's variance is not associated with the ejection fraction or the subject's blood pressure status. Here, BPS is an attribute character in the original data source article,[9] but it is actually a continuous variable. If the original BP levels are given in the data set, they may be associated with the CPK level.

Conversely, one can consider the relationship between ejection fraction, treating it as the response variable, and creatinine phosphokinase level, along with the other 12 factors and covariates. Based on the above EFT gamma-fitted JGL mean ($\hat{\mu}_z$) model, it is derived that EFT is directly related to CPK (p=0.01) and AGE (p<0.01), while it is inversely partially related to their joint interaction effect AGE*CPK (p=0.12). This implies that EFT increases as the joint effect of AGE*CPK decreases. Both the marginal effects of AGE and CPK are significant with EFT, but they are not important as the joint effect AGE*CPK is significant. This scenario is the same as the CPK model with EFT and others.

Also, mean EFT is indifferent to serum creatinine (SCT) (p=0.39), while it is directly related to the joint interaction effect of CPK (p=0.01) and SCT, i.e., CPK*SCT (p<0.01). This indicates that EFT increases as the joint effect CPK*SCT increases. In addition, mean EFT is directly related to serum sodium (SNa) (p<0.01) and CPK (p=0.01), while it is inversely related to the joint interaction effect of CPK and SNa, i.e., CPK*SNa (p=0.01). This indicates that EFT rises as the joint effect of CPK*SNa decreases. From the above EFT gamma fitted variance ($\hat{\sigma}^2$) model, it is found that the variance of EFT is inversely related to CPK level (p=0.04). This implies that EFT is highly scattered for heart patients with lower CPK levels.

Similarly, the relationship of blood pressure (BP) with CPK can be examined along with the other 12 variables. But herein BP is recorded as an attribute character, which is originally a continuous variable. Therefore, the relationship between BP and CPK is not reported herein.

CONCLUSION

It is developed herein that the mean CPK level is connected with EFT, AGE, SCT, AGE*EFT, and EFT*SCT, while it is indifferent to BPS. Conversely, mean EFT is connected with CPK, AGE, SCT, SNa, AGE*CPK, CPK*SCT, and CPK*SNa. The variance of EFT is connected with CPK. The relationship between CPK and heart disease risk factors such as blood pressure, ejection fraction, heart rate, maximum blood pressure, etc. is little studied in the cardiology literature. All these above findings from the JGLMs of CPK level and EFT are completely new inputs in the cardiac disease literature. It is noted herein that CPK level has a very complex relationship with EFT along with other factors, and conversely, EFT has a similar complex association with CPK along with other factors. These reported findings will be helpful to medical practitioners, researchers, and the general public.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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