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Research Article

Impacts of Serum Creatinine Phosphokinase on Heart, Diabetes and Anaemia Patients

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Abstract

The report searches the impacts of serum creatinine phosphokinase (CPK) on diabetes, heart, and anaemia patients using a real data set of 299 subjects and a derived statistical modeling. It is shown that mean CPK is positively associated with AGE (P=0.0335) and ejection fraction (EFT) (P=0.0417), while it is negatively associated with their joint interaction effect (JIE) of AGE* EFT (P=0.0058). Mean CPK is negatively associated with serum creatinine (SCT) (P<0.0001), while it is positively associated with EFT (P=0.0417), and their JIE of EFT* SCT (P<0.0001). Mean CPK is indifferent to both the marginal effects of the subject's anaemia disease status (ADS) and platelets count (PLC), while it is negatively associated with their JIE of ADS*PLC (P=0.0184). Mean CPK is negatively associated with SCT (P< 0.0001) and the subject's diabetes mellitus status (DMS) (P=0.0103), while it is positively associated with their JIE of DMS*SCT (P<0.0001). Variance of CPK is indifferent to DMS and the subject's smoking status (SMS), while it is negatively associated with their JIE of DMS*SMS (P=0.0023). Variance of CPK is positively associated with ADS (P=0.0229) and SEX (P= 0.0005), while it is negatively associated with their JIE of ADS*SEX (P=0.0212). CPK's variance is indifferent to PLC, and positively associated with ADS (P=0.0229), while it is negatively associated with their JIE of ADS*PLC (P=0.0400). It is observed that CPK is associated with diabetes, anaemia patients, cardiac factor EFT along with many other risk factors. These research outcomes may give much information for better treatment and research process.

Keywords: Creatininephosphokinase (CPK); Diabetes mellitus status (DMS); Ejection fraction (EFT); Joint generalized linear models (JGLMs); Subject's Anaemia disease status (ADS)

Abbreviations: ADP: Adenosine Diphosphate; ADS: Anaemia Disease Status; AMI: Acute Myocardial Infarction; ATP: Adenosine Triphosphate; BPS: Blood Pressure Status; CK MB: Creatine Kinase; CPK: Creatinine Phosphokinase; cTnI: Cardiac Specific Troponin I; cTnT: Cardiac Specific Troponin T; DEE: Death Event; DMS; Diabetes Mellitus Status; EFT: Ejection Fraction; JIE: Joint Interaction Effect; PCr: Phosphocreatine; PLC: Platelets Count; MI: Myocardial Infarction; SCT: Serum Creatinine; SNa: Serum Sodium; SMS: Smoking Status; TTP: Total Time to Follow-up Period; T2DM: Type 2 Diabetes Mellitus

Introduction

For an individual, if the total serum creatinine phosphokinase (CPK) levels are very high, it often indicates that there has been stress or injury to muscle tissue, or the brain, or the heart. Higher CPK levels most likely present muscle tissue injury. If a muscle is injured, CPK leaks into the bloodstream.

During the last few decades, extreme lifestyle changes such as obesity, stress, and lack of physical activity have led to life threatening situations such as acute myocardial infarction (AMI) as a fundamental cause of death in the developing world as well as in industrialized nations [1]. Myocardial necrosis is associated with the release of structural proteins and other intracellular macromolecules. If the unity of the cellular membranes is endanger, then some biomarkers such as CPK, creatine kinase (CK) MB, cardiac specific troponin I (cTnI), and cardiac specific troponin T (cTnT) leaks into the bloodstream and are measured in serum aiding in the detection of MI [2,3]. Generally, these biomarkers are analyzed by advanced biochemistry approaches for obtaining primary observation of AMI [4-6]. The article [3] has studied the association between serum and saliva levels of CPK, and it has compared salivary CPK as a biomarker between AMI patients and healthy individuals. Using advanced statistical modeling of these biomarkers, many interesting observations can be obtained regarding AMI, which are little studied. The basic myocardial energy holds reaction for generating adenosine triphosphate (ATP) is the CK reaction that reversibly transfers high-energy phosphate between adenosine diphosphate (ADP) and phosphocreatine (PCr) [7, 8].

The key enzyme serum CPK is considered in regulating energy metabolism. It is considered as associated with insulin resistance Type 2 diabetes mellitus (T2DM), and as a risk factor for growing low muscle mass [9-11]. The article [9] has investigated the association of CPK with low muscle mass in T2DM patients. The correlation between CPK level and plasma glucose level for T2DM patients is studied in some articles [12-15]. Pierro, et al. [16] presented a retrospective analysis of the effects of a standard mixture of some components in dyslipidemia patients. There are very few articles focused on the effects of CPK on anaemic patients [17-20].

Many earlier published articles [1-20] have studied the effects of CPK on diabetes, heart and anaemia patients, using correlation, regression, meta-analysis approaches. The earlier findings related to the effects of CPK on the different patients such as diabetes, cardiac, and anaemia invite many doubts and debates, as the outcomes are not accepted based on statistical diagnostic tests. Moreover, earlier models are not accepted based on model fitting diagnostics tests. The effects of CPK are little searched using appropriate probabilistic modeling. The current report enquires the following research hypotheses.

- Is there any association of CPK with anaemia, diabetes and heart patients along with other anatomical/ biochemical variables? For the affirmative response, what is the most suitable CPK association model?
- How do we develop the most probable CPK relationship model?
- What are the effects of CPK on the anaemia, diabetes and heart patients and the other explanatory factors?

The article searches the above research hypotheses using the following paragraphs such as materials & methods, statistical analysis & results, discussions, and conclusions. The developed CPK probabilistic model is displayed using the data set stated in the materials section. The statistical CPK mean and dispersion models are derived using joint generalized linear models (JGLMs), which is illustrated in the methods section. The developed outcomes are presented in the results paragraph, while the outcomes of the analysis are illustrated in the discussion section. On the basis of the derived CPK mean and variance models, the report has obtained some new information that are presented in the conclusions section.

Material & Statistical Methods

Materials

The CPK probabilistic model is obtained herein from a data set of 299 heart failure subjects collected from Faisalabad Cardiology Institute (under an Allied Hospital), Faisalabad, Punjab province, Pakistan. The observations were collected for nine months i.e., April, 2025 to December 2015, and the data set was clearly described in the articles [21, 22]. The data set can be found in the site (https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+records). The considered research study [21] contained 194 male and 105 female study subjects, who had left ventricular systolic dysfunction. The study individuals had earlier

heart failures, and they were classed in III or IV heart failure stages of New York Heart Association (NYHA) classification [23]. The subject consents and the study ethics approval are neatly illustrated in the main article [21]. The study characters such as attributes and variables in the current research are separately illustrated in the article by Chicco and Jurman [24]. Recently an article by Das et al. [25] has shortly described the data set. For more information on the data set, interested authors are requested to go through the articles [21, 22, 24, 25].

The current study considers 13 interested characters out of which 7 are continuous variables, and the rest 6 are attributes. The 7 continuous variables are age (c1), creatinine phosphokinase (CPK) (c3), ejection fraction (EFT) (c5), platelets count (PLC) (c7), serum creatinine (SCT) (c8), serum sodium (SNa) (c9), total time to follow-up period (TTP) (c12), while the 6 attribute characters are the subject's anaemia disease status (ADS) (0= no anaemia, 1= anaemia) (Fa2), diabetes mellitus status (DMS) (0= no diabetes, 1= diabetes) (Fa4), blood pressure status (BPS) (0= normal BP, 1=high BP) (Fa6), sex (0=female, 1=male) (Fa10), smoking status (SMS) (0=no smoking, 1= smoking) (Fa11), death event (DEE) (0=alive, 1=death) (Fa13). A study individual was classed as anaemia subject (Fa2) if her/his haematocrit level was lower than 36% [21]. The main article [21] of this data source does not give any information regarding the grouping of high BPS (Fa6) of the subjects. The death event (Fa13) presents that the patient survived (=0), or died (=1) up to the study termination time of 130 days on average [21].

Serum CPK levels gradually rise up early in the process of an acute myocardial infarction. Generally, CPK levels show its enzyme levels in blood. Enzyme elevations are encountered in the presence of brain damage and skeletal muscle. CPK flows into the blood, if a muscle tissue gets damaged. In contrast, individuals with diseases of the lung and liver consistently have normal CPK levels. Therefore, high blood's CPK enzyme levels of an individual might show an injury or a heart failure [26]. A waste product serum creatinine (SCT) is produced by creatine if a muscle breaks down. Higher SCT blood levels may show renal dysfunction [27]. Therefore, kidney failure function is examined based on blood SCT levels. The original data source article [21] does not give any information regarding the subject's kidney disease status/. The ejection fraction (EFT) represents the percentage blood amount the left ventricle pumps out per contraction. A mineral element, serum sodium (SNa) that is responsible for the accurate functioning of muscles and nerves. An abnormally very low SNa blood levels might be caused by heart failure [28]. More information about the data set is available in the original data source article [21].

Statistical Methods

The article considers CPK is the aimed continuous response random variable that is to be modeled with the left diabetes/cardiac/ anaemia status, physiological and biochemical factors. It is found that the response CPK is continuous, heteroscedastic, and non-normally distributed random variable. The variance of CPK can't be stabilized using any suitable transformation, so it is modeled in the article adopting joint generalized linear models (JGLMs) under both the log-normal and gamma distribution, which is clearly illustrated in [29-32]. Interested readers may go through JGLMs from the book by Lee, Nelder and Pawitan [29]. Log-normal and gamma JGLMs are shortly presented herein.

JGLMs for log-normal distribution

For the positive response Yi (=CPK) with E (Y_i=CPK) = μ_i (mean) and Var (Y_i=CPK) = $\sigma_i^2 \mu_i^2 = \sigma_i^2 V(\mu_i)$ say, where, σ_i^2 are dispersion parameters and V() reveals the variance function. Generally, log transformation Z_i = log (Y_i=CPK) is adopted to stabilize the variance Var (Z_i) $\approx \sigma_i^2$, but the variance may not always be stabilized [33]. For developing a CPK improved model, JGLMs for the mean and dispersion are considered. For the response CPK, assuming log-normal distribution, JGL mean and dispersion models (with Z_i = log(Y_i=CPK)) are as follows:

$E(Z_i)= \mu_{zi}$ and $Var(Z_i) = \sigma_{zi}^2$,

$\mu_{zi}=x_i^t \beta$ and $\log(\sigma_{zi}^2)= g_i^t \gamma$,

Where x_i^t and g_i^t are the explanatory factors/variables vectors of CPK associated with the mean regression coefficients β and dispersion regression coefficients γ, respectively.

JGLMs for gamma distribution

In the above stated Y_i's (=CPK), the variancehas twoportions such as $V(\mu_i)$ (based on the mean parametersμ_i's) and σ_i^2 (free of μ_i's). The variance function$V(\cdot)$shows the GLM family distributions. For example, if $V(\mu)$= 1 , it is normal, Poisson if $V(\mu) = \mu$, and gamma if $V(\mu) = \mu^2$ etc. Gamma JGLMs mean and dispersion models of CPK are as follows:

$$\eta_i = g(\mu_i) = x_i^t \beta \text{ and } \varepsilon_i = h(\sigma_i^2) = w_i^t \gamma ,$$

Where $g(\cdot)$ and $h(\cdot)$ are the GLM link functions attached with the mean and dispersion linear predictors respectively, and x_i^t , w_i^t , are the explanatory factor vectors of CPK attached with the mean and dispersion parameters respectively. Maximum likelihood (ML) method is used for estimating the mean parameters, while

the restricted ML (REML) method is applied for estimating the dispersion parameters, which are explicitly stated in the book by Lee, Nelder and Pawitan [29].

Statistical Analysis & Results

Statistical Analysis

The response CPK is modeled herein by JGLMs with both the log-normal and gamma distributions. In the present statistical analysis, CPK is considered as the dependent variable, and the other 12 factors/ variables are considered as the CPK's explanatory variables. Final CPK model has been taken based on the smallest Akaike information criterion (AIC) value (within each class), that reduces both the squared error loss and predicted additive errors [33, p. 203--204]. Based on the AIC rule, JGLMs Log-normal fit (AIC= 4197) is better than gamma fit (AIC=4249.731).

In the selected Log-normal mean model, three effects such as SMS*TTP (P=0.1590) (for gamma fit P=0.0298), PLC*DEE (P=0.1319) (for gamma fit P=0.0103), ADS*PLC (0.5516) (for gamma fit P=0.0184) show partially significant, while they are significant in the gamma model (Table 1). In addition, ADS*PLC (P=0.5516) is insignificant in the mean Log-normal fitted model, while it is highly significant (ADS*PLC; P=0.0184) in the gamma fitted mean model. Without ADS*PLC, the Log-normal model can't be fitted. In the Log-normal dispersion model, three effects such as SEX*TTP (P=0.0773), SCT*TTP (P=0.1509) and SNa (P=0.1437) are partially significant. In Epidemiology, the partially significant effects (<16%) are called confounders, which are important in Epidemiology study. Also some partial or insignificant effects are sometimes very important for better model fitting [33].

Due to the marginality rule by Nelder [34], that isif an interaction effect (as an example in Table 1, SMS*TTP) is significant, or partially significant, all its associated lower-order effects (as an example in Table 1, SMS and TTP) should be included in the model even insignificant. Based on the marginality rule, some partially significant, or insignificant effects such as SMS (P=0.1350), PLC (P=0.9045) and ADS (P=0.5456) are included in the mean model. Similarly, in the dispersion model, some partially significant, or insignificant effects such as AGE (P=0.2182), SCT (=0.6924), DMS (P=0.3861), SMS (P=0.2815) and PLC (P=0.8043) are included based on the marginality rule by Nelder [34].

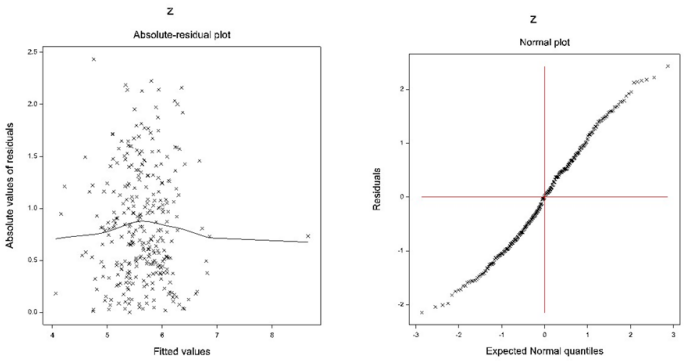

Figure 1 (a) Figure 1 (b)

Figure 1: For the joint Log-normal fitted models of Creatinine Phosphokinase (Table 1), the (a) absolute residuals plot with the fitted values, and (b) the normal probability plot for the mean model

The derived CPK Log-normal fitted probabilistic JGLM (Table 1) is a data derived model that is to be examined by model checking diagnostic plots. The valid conclusions regarding CPK are considered from the data derived Log-normal fitted CPK probabilistic model (Table 1) that should be admitted using model diagnostic checking plots, which are revealed in Figure 1. Figure 1(a) presents the absolute residuals for the Log-normal fitted CPK model (Table 1) with respect to the fitted values that is approximately a flat line, implying that the variance is constant with the running means. The normal probability plot for the Log-normal fitted CPK mean model (Table 1) is presented by Figure 1(b), which does not show any lack of fit. These two figures 1(a) and 1(b) show that the Log-normal CPK model fit is appropriate, which can be accepted as an approximate model of the unknown CPK model.

Results

Based on the AIC criterion, the Log-normal fitted model is better than the gamma fit. Here the outcomes of the Log-normal CPK fitted model are presented based on the comparison of the gamma CPK fitted outcomes.

The derived CPK mean model shows that mean CPK is positively associated with the AGE (P=0.0335) and EFT (P=0.0417), while it is negatively associated with their joint

interaction effect (JIE) of AGE* EFT (P=0.0058). Mean CPK is negatively associated with the SCT (P<0.0001), while it is positively associated with the EFT (P=0.0417), and their JIE of EFT*SCT (P<0.0001). Mean CPK is indifferent to both the marginal effects of the subject's ADS (P=0.5456) and PLC (P=0.9045), while it is negatively associated with their JIE of ADS*PLC (P=0.0184, from gamma fit) (or P=0.5516, from Log-normal fit). Mean CPK is negatively associated with SCT (P< 0.0001) and the subject's DMS (P=0.0103), while it is positively associated with their JIE of DMS*SCT (P<0.0001).

Mean CPK is partially negatively associated with SMS (P=0.1350), while it is positively associated with TTP (P<0.0001), and the JIE of SMS*TTP (P=0.1590) (partially). It is positively associated with SEX (P<0.0001) and TTP (P<0.0001), while it is negatively associated with their JIE of SEX*TTP (P=0.0003). Mean CPK is negatively associated with SNa (P=0.0022) and DEE (P=0.0092), while it is positively associated with their JIE of SNa*DEE (P=0.0121). Mean CPK is negatively associated with DEE (P=0.0092), and it is indifferent to PLC (P=0.9045), while it is positively associated with their JIE of PLC*DEE (P=0.1319) (partially). Mean CPK is positively associated with TTP (P<0.0001), while it is negatively associated with SCT (P<0.0001) and the JIE of SCT*TTP (P=0.0125).

Variance of CPK is indifferent to DMS (P=0.3861) and SMS (P=0.2815), while it is negatively associated with their JIE of DMS*SMS (P=0.0023). Variance of CPK is positively associated with ADS (P=0.0229) and SEX (P= 0.0005), while it is negatively associated with their JIE of ADS*SEX (P=0.0212). CPK's variance is indifferent to PLC (P=0.8043) and positively associated with ADS (P=0.0229), while it is negatively associated with their JIE of ADS*PLC (P=0.0400).

Variance of CPK is partially positively associated with SNa (P=0.1437) and AGE (P=0.2182). CPK's variance is positively associated with SEX (P=0.0005) and TTP (P=0.0205), while it is negatively associated with their JIE of SEX*TTP (P=0.0773). Variance of CPK is indifferent to SCT (P=0.6924), and positively associated with TTP (P=0.0205), while it is negatively associated with their JIE of SCT*TTP (P=0.1509) (partially).

Log-normal fitted CPK mean ($\hat{\mu}_z$) model (Table 1) is $\hat{\mu}_z$ = 9.7874 + 0.0063 TTP – 0.3558 SMS + 0.0024 SMS*TTP + 0.9725 SEX – 0.0060 SEX*TTP - 0.0439 SNa -7.1459DEE + 0.0512 SNa*DEE – 0.6232 SCT – 0.4787 DMS + 0.4091 DMS*SCT + 0.0001 PLC+ 0.0001 PLC*DEE – 0.2058 ADS – 0.0001 ADS*PLC + 0.0332 AGE + 0.0474 EFT – 0.0010 AGE*EFT + 0.0131 EFT*SCT – 0.0015 SCT*TTP, and the fitted CPK variance ($\hat{\sigma}^2_z$) model is

$\hat{\sigma}^2_z$ = exp.(-7.0836 + 0.0098 AGE + 0.0068TTP + 1.7261 SEX – 0.0050 SEX*TTP+ 0.0698 SCT - 0.0023 SCT*TTP+ 0.1872 DMS + 0.2753SMS –1.2557 DMS*SMS + 1.5743 ADS – 0.9375 ADS*SEX + 0.0001 PLC – 0.0001 ADS*PLC + 0.0373 SNa).

From the above CPK mean ($\hat{\mu}_z$) and variance ($\hat{\sigma}^2_z$) models, it is noted that mean CPK is expressed by TTP, SMS, SMS*TTP, SEX, SEX*TTP, SNa, DEE, SNa*DEE, SCT, DMS, DMS*SCT, PLC, PLC*DEE, ADS, ADS*PLC, AGE, EFT, AGE*EFT, EFT*SCT, and SCT*TTP, while the CPK's variance is expressed by AGE, TTP, SEX, SEX*TTP, SCT, SCT*TTP, DMS, SMS, DMS*SMS, ADS, ADS*SEX, PLC, ADS*PLC, and SNa.

Discussion

The CPK analysis outcomes for Log-normal and gamma fitted models are displayed in Table 1. The Log-normal fitted CPK mean and variance models are displayed above. There are some discrepancies between the fitted Log-normal and gamma models, which are well discussed in [35]. Note that the considered data set contains two cardiac disease factors/parameters such as ejection fraction (c5) and high blood pressure status (0= normal BP, 1=high BP) (Fa6). It contains only one diabetes disease factor, namely the subject's diabetes mellitus status (0= no diabetes, 1= diabetes) (Fa4), and one anaemia disease factors, namely the subject's anaemia disease status (0= no anaemia, 1= anaemia) (Fa2). The given data set is a multivariate form. So, simple correlation study is not a proper method of finding the relationship. Again, multiple regression analysis is not a suitable method as the data set is heteroscedastic. Herein, appropriate data analysis models (Log-normal and gamma) are derived. Based on the derived models, the effects of CPK on heart, anaemia and diabetes patients are discussed.

Model	Covariates	LOG-NORMAL FIT				GAMMA FIT			
		estimate	s.e.	t(278)	P-value	estimate	s.e.	t(278)	P-value
Mean	Constant	9.7874	2.1991	4.45	<0.0001	8.0575	2.2497	3.582	0.0004
	TTP (c12)	0.0063	0.0014	4.44	<0.0001	0.0072	0.0014	5.043	<0.0001
	SMS (Fa11)	-0.3558	0.2374	-1.50	0.1350	-0.5374	0.2607	-2.061	0.0402
	SMS*TTP (Fa11.c12)	0.0024	0.0017	1.41	0.1590	0.0038	0.0018	2.184	0.0298
	SEX (Fa10)	0.9527	0.2253	4.23	<0.0001	1.4279	0.2384	5.989	<0.0001
	SEX*TTP (Fa10.c12)	-0.0060	0.0017	-3.62	0.0003	-0.0079	0.0017	-4.750	<0.0001
	SNa (c9)	-0.0439	0.0142	-3.09	0.0022	-0.0237	0.0146	-1.620	0.1063
	DEE (Fa13)	-7.1459	2.7262	-2.62	0.0092	-6.6743	2.8469	-2.344	0.0197
	SNa*DEE (c9.Fa13)	0.0512	0.0203	2.53	0.0121	0.0452	0.0212	2.129	0.0341
	SCT (c8)	-0.6232	0.1351	-4.61	<0.0001	-0.6771	0.1336	-5.066	<0.0001
	DMS (Fa4)	-0.4787	0.1855	-2.58	0.0103	-0.4701	0.1894	-2.482	0.0136
	DMS*SCT (Fa4.c8)	0.4091	0.1019	4.02	<0.0001	0.3508	0.1022	3.433	0.0007
	PLC (c7)	0.0000	0.0000	0.12	0.9045	0.0000	0.0000	-0.091	0.9275
	PLC*DEE (c7.Fa13)	0.0000	0.0000	1.51	0.1319	0.0000	0.0000	2.583	0.0103
	ADS (Fa2)	-0.2058	0.3405	-0.61	0.5456	0.3372	0.3555	0.949	0.3434
	ADS*PLC (Fa2.c7)	0.0000	0.0000	-0.60	0.5516	0.0000	0.0000	-2.370	0.0184
	AGE (c1)	0.0332	0.0155	2.14	0.0335	0.0245	0.0159	1.540	0.1247
	EFT (c5)	0.0474	0.0232	2.05	0.0417	0.0250	0.0236	1.058	0.2909
	AGE*EFT (c1.c5)	-0.0010	0.0004	-2.78	0.0058	-0.0007	0.0004	-1.858	0.0642
	EFT*SCT (c5.c8)	0.0131	0.0022	6.03	<0.0001	0.0143	0.0021	6.937	<0.0001
	SCT*TTP (c8.c12)	-0.0015	0.0006	2.51	0.0125	-0.0019	0.0006	-3.229	0.0014

Dispersion	Constant	-7.0836	3.7126	-1.91	0.0574	-7.6725	4.2714	-1.796	0.0736
	AGE (c1)	0.0098	0.0079	1.23	0.2182	0.0099	0.0080	1.233	0.2186
	TTP (c12)	0.0068	0.0030	2.27	0.0205	0.0052	0.0030	1.739	0.0831
	SEX (Fa10)	1.7261	0.4939	3.50	0.0005	1.4334	0.5096	2.813	0.0052
	SEX*TTP (Fx10.c12)	-0.0050	0.0028	-1.77	0.0773	-0.0037	0.0029	-1.290	0.1981
	SCT (c8)	0.0698	0.1763	0.40	0.6924	0.0447	0.1739	0.257	0.7974
	SCT*TTP (c8.c12)	-0.0023	0.0016	-1.44	0.1509	-0.0023	0.0015	-1.525	0.1283
	DMS (Fa4)	0.1872	0.2156	0.87	0.3861	0.1981	0.2180	0.909	0.3641
	SMS (Fa11)	0.2753	0.2552	1.08	0.2815	0.3907	0.2583	1.513	0.1314
	DMS*SMS (Fa4.Fa11)	-1.2557	0.4087	-3.07	0.0023	-0.9784	0.4357	-2.246	0.0254
	ADS (Fa2)	1.5743	0.6883	2.29	0.0229	1.5999	0.7272	2.200	0.0286
	ADS*SEX (Fa2.Fa10)	-0.9375	0.4046	-2.32	0.0212	-0.8240	0.4118	-2.001	0.0463
	PLC (c7)	0.0000	0.0000	0.25	0.8043	0.0000	0.0000	0.381	0.7034
	ADS*PLC (Fa2.c7)	0.0000	0.0000	-2.06	0.0400	0.0000	0.0000	-1.812	0.0711
	SNa (c9)	0.037	0.0254	1.47	0.1437	0.0417	0.0289	1.441	0.1507
	AIC	**4197**				**4249.731**			

Table 1: Results for mean and dispersion models for serum Phosphokinase from Log-normal & Gamma fit.

For heart patients, it is observed from the derived CPK mean model (Table 1) that mean CPK is positively associated with AGE (P=0.0335) and EFT (P=0.0417), while it is negatively associated with their joint interaction effect of AGE* EFT (P=0.0058).This implies that even for older ages with higher EFT levels, CPK levels may not be higher. This indicates that CPK levels increase as the joint effect of AGE and EFT i.e., AGE* EFT decreases. The marginal effects AGE and EFT are positively associated with CPK, but their marginal effects are not important as their joint effect is present. It shows that CPK is associated with EFT along with AGE and AGE* EFT. Also, mean CPK is negatively associated with SCT (P<0.0001), while it is positively associated with the EFT (P=0.0417), and their JIE of EFT*SCT (P<0.0001). This implies that CPK levels increase as the joint effect of EFT and SCT i.e., EFT*SCT increases. The marginal effects SCT and EFT are unimportant as their joint effect EFT*SCT is significant. It implies that CPK is associated with EFT along with SCT and EFT*SCT.

For diabetes patients, it is observed from the derived CPK mean model (Table 1) that mean CPK is negatively associated with SCT (P< 0.0001) and the subject's DMS(0= no diabetes, 1= diabetes) (P=0.0103), while it is positively associated with their JIE of DMS*SCT (P<0.0001). This implies that CPK increases as the joint effect of DMS and SCT i.e., DMS*SCT increases. It indicates that diabetes patients with higher SCT levels should have higher CPK levels than normal patients with lower SCT levels. From the derived CPK variance model (Table 1), it is observed that variance of CPK is indifferent to DMS (0.3861) and SMS (0=no smoking, 1=smoking) (P=0.2815), while it is negatively associated with their JIE of DMS*SMS (P=0.0023). This shows that CPK levels are highly scattered for normal and non-smoker patients than smoker subjects with diabetes mellitus. This shows that CPK level's mean is associated with DMS, SCT and DMS*SCT, while its variance is associated with DMS*SMS.

For anaemia patients, it is observed from the derived CPK mean model (Table 1) that mean CPK is indifferent to both the marginal effects of the subject's ADS (0= no anaemia, 1= anaemia) (P=0.5456) and PLC (P=0.9045), while it is negatively associated with their JIE of ADS*PLC (P=0.0184, from gamma fit) (or P=0.5516, from Log-normal fit). From the fitted Log-normal model, the JIE of ADS*PLC (P=0.5516) is insignificant, but it is highly significant in the gamma fitted model (P=0.0184). Note that the Log-normal model is not fitted without ADS*PLC, so it is highly important for the model. This indicates that CPK levels increase as the joint effect of ADS*PLC decreases. This implies that CPK levels are higher for non-anaemic subjects with lower PLC levels. From the CPK's variance model, it is observed that the variance

of CPK is positively associated with ADS (P=0.0229) and SEX (0=female, 1=male) (P= 0.0005), while it is negatively associated with their JIE of ADS*SEX (P=0.0212). This indicates that CPK levels are highly scattered for non-anaemic female subjects. Also, CPK's variance is indifferent to PLC (P=0.8043) and positively associated with ADS (P=0.0229), while it is negatively associated with their JIE of ADS*PLC (P=0.0400). This shows that CPK levels are highly scattered for non-anemic subjects with lower PLC levels than anaemic subjects with higher PLC levels.

There are some factors other than heart, anaemia and diabetes mellitus related factors, which are also connected with the mean CPK levels. From the fitted mean Log-normal model, it is derived that mean CPK is negatively partially associated with SMS (0=no smoking, 1= smoking) (P=0.1350), while it is positively associated with TTP (P<0.0001), and their JIE of SMS*TTP (P=0.1590) (partially). It shows that CPK levels rise up as the joint effect SMS*TTP increases. This indicates that CPK levels are higher for smoker subjects with longer follow up time. Mean CPK is positively associated with SEX (0=female, 1=male) (P<0.0001) and TTP (P<0.0001), while it is negatively associated with their JIE of SEX*TTP (P=0.0003). It indicates that CPK levels increase as the joint effect SEX*TTP decreases. This implies that CPK levels are higher for females with shorter follow up time than male with longer follow up time.

From the fitted mean Log-normal model, it is derived that mean CPK level is negatively associated with SNa (P=0.0022) and DEE (P=0.0092), while it is positively associated with their JIE of SNa*DEE (P=0.0121). This indicates that CPK levels increase as the joint effect SNa*DEE increases. Note that the associations of the marginal effects of SNa and DEE are of opposite nature than their joint effect. Mean CPK is negatively associated with DEE (P=0.0092), and it is indifferent to PLC (P=0.9045), while it is positively associated with their JIE of PLC*DEE (P=0.1319) (partially). This indicates that CPK levels increase as the joint effect PLC*DEE rises. Also, mean CPK is positively associated with TTP (P<0.0001), while it is negatively associated with SCT (P<0.0001) and their JIE of SCT*TTP (P=0.0125). This shows that CPK levels increase as the joint effect SCT*TTP decreases.

There are some factors other than heart, anaemia and diabetes mellitus related factors, which are also connected with the variance of CPK levels. From the fitted variance Log-normal model, it is derived that variance of CPK is partially positively associated with SNa (P=0.1437) and AGE (P=0.2182). It shows that CPK levels are highly scattered for the subjects with higher SNa levels, and at older ages. It is also derived that CPK's variance is positively associated with SEX (0=female, 1=male) (P=0.0005) and TTP (P=0.0205), while it is negatively associated with their JIE of SEX*TTP (P=0.0773). It indicates that scatteredness of CPK levels increases as the joint effect of SEX*TTP decreases. This implies that CPK levels are highly scattered for the female subjects with shorter follow up time. Finally, the variance of CPK levels is indifferent to SCT (P=0.6924), and positively associated with TTP (P=0.0205), while it is negatively associated with their JIE of SCT*TTP (P=0.1509) (partially). It indicates that scatteredness of CPK levels increases as the joint effect of SCT*TTP decreases.

The above discussion is presented herein based on the present CPK data analysis outcomes (Table 1). It is noted herein that most of the above outcomes, specially variance model related outcomes are completely new findings in the CPK study literature, therefore, these are not pointed out in the earlier articles. So, the present above outcomes are not compared with the earlier published results.

Conclusions

The report has derived the impacts of serum creatinine phosphokinase on diabetes, heart, and anaemia patients along with some factors such as sex, age, smoking habit, serum sodium, ejection fraction, serum creatinine, platelets count, follow-up time, and death event, using a real data set of 299 subjects and a derived statistical joint modeling. The fitted CPK probabilistic model has been accepted based on the AIC criterion, on comparison of joint gamma and log-normal models, estimates standard error, and model diagnostic graphical plots (in Figure 1). It is found herein that the fitted Log-normal model is better than the gamma model fit based on AIC rule, but the interpretations are almost similar. The above interpretations are presented herein using the appropriate Log-normal fitted CPK probabilistic model. The above outcomes focus on the real facts, which are commonly observed in practice. The report basically contains two aims such as the derivation of appropriate CPK's probabilistic models, and based on these models, the impacts of CPK are obtained. The obtained findings regarding CPK's associations with different patients and factors though not fully conclusive, are revealing. Advanced appropriatealong with proper model diagnostic scientific research methods are used to derive the above findings, so they should be believed by all the scientific community.

The fitted CPK models (Table 1) are derived using the data set as noted in the article [21]. It is expected that for the similar data sets, the present findings of CPK analysis will be reproduced, which is not examined herein as the similar data sets for CPK are not available. These findings will be very helpful for common people, medical scientists and practitioners. It is shown that CPK has several complex functional effects on heart, anaemia and diabetes patients along with other factors. Medical treatment management and process should be improved by following the derived CPK's associations with different patients and factors.

Declarations

The article is an original research report that has been prepared based on joint statistical modeling, and it has not been submitted in any journal for publication.

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Author CONTRIBUTIONS

Conceptualization, R.D. and M.D.; methodology, R.D., S.B. and A. A.; software, R.D. and O.N.B.; validation, R.D. and S.B.; formal analysis, R.D. and GB; investigation, R.D. R.S.D. and M.D..; resources, M.D.; data curation, S.B.; writing—original draft preparation, R.D.; writing—review and editing, R.D. and S.B.; visualization, R.D. A. A., O.N.B and M. D.; supervision, M.D.; project administration, R.D.; funding acquisition, S.B.; All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

Data Availability Statement

The data set is available in the site https://archive.ics.uci.edu/ml/datasets/Heart+failure+clinical+records.

Institutional Review Board Statement

Note that the current study has been performed based on a secondary data set, which was first collected by Ahmad T, Munir A, Bhatti SH, Aftab M, Ali Raza M. The study ethics approval and the subject consents are clearly described in the original article [21], which are not reproduced herein.

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