

Relationship of Alanine Aminotransferase (SGPT) with other Liver Biomarkers

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Abstract

Objectives: The report focuses the relationship of Alanine Aminotransferase (SGPT) with other liver biomarkers along with age, sex and types of the patients.

Background: Very few research articles have considered the relationship of SGPT with many liver biomarkers along with age, sex and types of the patients.

Materials and Methods: A real data set of 583 (416 liver & 167 non-liver) patients with 11 (2 attribute & 9 continuous) study characters are considered in the report. Probabilistic joint generalized linear models (JGLMs) are adopted, considering both Gamma & Log-normal distributions.

Results: The mean SGPT is negatively associated with sex ($P=0.0007$), patients type (P-Type) ($P=0.0032$), age ($P=0.0045$), and the interaction effect of Total Bilirubin (TB) & Aspartate Aminotransferase (SGOT) ($TB*SGOT$) ($P<0.0001$), and it is positively associated with Alkaline Phosphatase (ALP) ($P<0.0001$), TB ($P=0.0003$), (SGOT) ($P=0.0235$), and the interaction effect of SGOT & Total Proteins (TP) ($SGOT*TP$) ($P=0.0298$). The variance of SGPT is negatively associated with age ($P=0.0098$) and positively associated with SGOT ($P<0.0001$).

Conclusions: The mean relationship of SGPT with other liver biomarkers is complicated (containing two interaction effects), while its variance relationship is quite simple. SGPT is higher for male, or younger, or liver patients, and it is explained by many factors, which are little reported in earlier reports.

Keywords: Alanine Aminotransferase (SGPT); Alkaline Phosphatase (ALP); Biomarkers; Joint generalized linear models (JGLMs); Total Bilirubin (TB).

Introduction

Liver, an important organ of human being performs different kind of functions such a synthetic and excretory, therefore, no single pathological test can identify the global liver function. Several forms (more than 100) of known liver disease are caused by many risk factors [1-3]. The role of liver functions, several forms of liver diseases, and their risk factors are given in many research articles, which are not discussed herein [4-8].

Liver can perform its normal functions even its some parts are damaged. Therefore, it is difficult to identify a patient with liver disease by a single biochemical test. The early diagnosis of the liver disease is the main step in liver cancer treatment. For identifying liver disease, many biochemical liver disease biomarkers such as Total Bilirubin (TB) (normal range (NR):0.22–1 mg/dl), Direct Bilirubin (DB) (NR: 0.0 – 0.02 mg/dl), Alkaline Phosphatase (ALP) (NR:110–310 U/L), Alanine Aminotransferase (SGPT) (NR:5–45 U/L), Aspartate Aminotransferase (SGOT) (NR:5–40 U/L), Total Proteins (TP) (NR:5.5–8 gm/dl), Albumin (ALB) (NR:3.5–5 gm/dl), Albumin and Globulin Ratio (A/G Ratio) (NR: ≥ 1), Gamma-Glutamyl Transpeptidase (GGT) (NR:5–45U/L), Mean Corpuscular Volume (MCV) (NR: 80-96 fL/red cell in adult) etc, are generally used [9, 10]. Many research articles have pointed that there is correlation between any two liver disease biomarkers [11-13]. Note that the data set obtained from some patients with these markers along with some physical and interested characters is a multivariate data. So, simple correlation between any two markers is meaningless, while partial correlation is more appropriate. It is better to examine the association of any biomarker with the remaining markers by appropriate modeling. Most of the earlier studies used only simple or multiple regression analysis, which are not appropriate for the present considered data set, as the interested response variables are non-normal, heteroscedastic & positive [11-15].

The present reports search the following queries. What is the relationship of SGPT with other biomarkers? What are the associations of SGPT with other liver biomarkers? What are the effects of other liver biomarkers on SGPT? What is the approximately true model of SGPT? How do we control SGPT with the help of other liver biomarkers & physical parameters? These queries are inquired in the report with the help of a real data set of 583 individuals with 11 study characters.

Materials & Statistical Methodology

Materials

The report takes into account a real data set of 583 individuals

with 11 explanatory factors, which was obtained from the North-East of Andhra Pradesh, India. The data set is available in the site from UCI Machine Learning Repository .The study population, covariates and data collection method are well described in [16, 17]. These are not reappeared herein. For ready use in the report, the 11 study covariates are restated as Age, Sex (Male = 1; Female = 2), Total Bilirubin (TB), Direct Bilirubin (DB), Alkaline Phosphatase (ALP), Alanine Aminotransferase (SGPT), Aspartate Aminotransferase (SGOT), Total Proteins (TP), Albumin (ALB), Albumin and Globulin Ratio (A/G Ratio), Patient type (PTYTP) (liver patient=1 ; non-liver patient=2).

Statistical Methods

The report examines the association of SGPT with the remaining other liver biomarkers based on appropriate modeling. The response SGPT is positive, continuous, with non-constant variance & non-normally distributed random variable. It may be appropriately modeled by JGLMs with Log-normal and Gamma distribution, and these are bluntly explained in [9, 18-20]. These are not restated herein. Interested readers may visit [9, 18-20]. The response SGPT has been modeled using both the distributions, and it is noted that Log-normal JGLMs are more appropriate for it. Very shortly JGLMs with Log-normal distribution is restated herein.

JGLMs with Log-normal distribution

For the positive random dependent variable Y_i 's (here SGPT= Y_i) with heteroscedastic variance σ_i^2 (dispersion parameter), if $E(Y_i) = \mu_i$ (mean parameter) and $Var(Y_i) = \sigma_i^2 \mu_i^2 = \sigma_i^2 V(\mu_i)$ say, the log transformation $Z_i = \log(Y_i) = (\log SGPT)$ is adopted to stabilize the variance $Var(Z_i) \approx \sigma_i^2$, but the variance may not be stabilized always. For advanced model, JGLMs for mean & variance are adopted. For the log-normal distribution, JGLM of mean & variance (for the random response $SGPT=Y_i$, with $Z_i = \log Y_i$) are displayed by

$$E(Z_i) = \mu + z_i^t \beta$$

$$\log(\sigma_i^2) = \gamma + z_i^t \gamma$$

where z_i^t and γ are the independent variable vectors

attached with the regression coefficients β (mean model) and γ (variance model), respectively. The maximum likelihood (ML) and the restricted ML (REML) method are adopted for estimating the mean and dispersion parameters, respectively [18, 19].

Statistical & Graphical Analysis

The random variable SGPT (=Y) is considered as the interested response variable, and the rest others are treated as the explanatory variables. It has been identified that SGPT is heteroscedastic, so log transformation ($Z_i = \log Y_i$) is adopted, but the variance is not stabilized. So, JGLMs using both the distributions such as Log-normal & Gamma are adopted. The final model is obtained depending on the lowest Akaike information criterion (AIC) value (within each class) which minimizes both the squared error loss and predicted additive errors [21, p. 203--204]. Final analysis outputs are shown in Table 1. One insignificant effect (here TP) is retained in the mean model due to the marginality rule, namely that if an interaction effect (here SGOT*TP) is significant all its related lower-order interactions (here nil) & main effects (here SGOT & TP) should be included in the model [22]. In the variance model, one partially significant effect (PTYTP) is included for better fitting [20, 21]. In epidemiology, partially significant effects included in the model are recognized as confounder. AIC value shows that JGLMs Log-normal fit (AIC=5199) is improver than Gamma fit (AIC=5268.567) (Table 1).

All valid interpretations are drawn from the data generated model assumed to be true. So it should be verified by model checking tools. For the response SGPT, Log-normal fit is better than Gamma fit, so the graphical analysis of Log-normal fit (Table 1) is displayed in Figure 1. For Log-normal fit (Table 1), absolute residuals are plotted with respect to fitted values, which are displayed in Figure 1(a). This is approximately linear except the right tail, indicating that the variance is constant with the running means. The right tail is decreasing as one of the smaller absolute residual is located at the right boundary. The normal probability plot for the fitted Log-normal mean model (Table 1) is presented in Figure 1(b), which does not show any sign of lack of fit. Therefore, both the figures show that the data generated fitted Log-normal models are approximately true models.

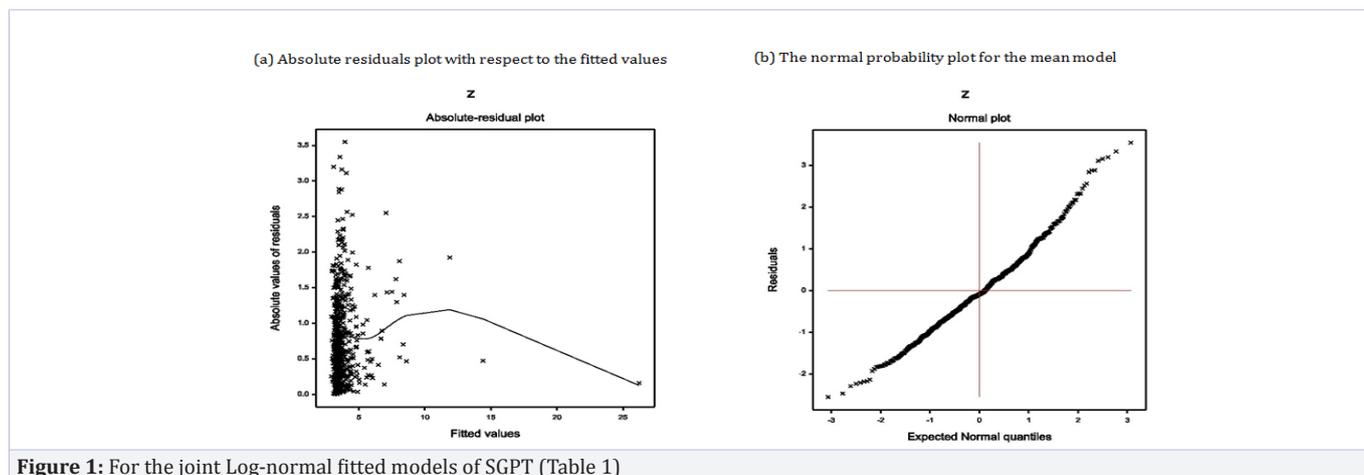


Figure 1: For the joint Log-normal fitted models of SGPT (Table 1)

Results

The response SGPT has been modeled adopting JGLMs, and the outputs (for both the distributions) are presented in Table 1. Log-normal fitted models for SGPT is better, so the following results are related to the Log-normal fitted model (Table 1). The mean SGPT is negatively associated with sex (P=0.0007), patients type (PTYP) (P=0.0032), age (P=0.0045), and the interaction effect of Total Bilirubin (TB) & Aspartate Aminotransferase (SGOT) (TB*SGOT) (P<0.0001), and it is positively associated with Alkaline Phosphatase (ALP) (P<0.0001), TB (P=0.0003), (SGOT) (P=0.0235), and the interaction effect of SGOT & Total Proteins (TP) (SGOT*TP) (P=0.0298). The variance of SGPT is negatively associated with age (P=0.0098), patients type (PTYP) (P=0.1396) (partially), and positively associated with SGOT (P<0.0001).

The Log-normal fitted mean (\hat{Z}) model of SGPT (from Table 1) is

$$\hat{Z} = 3.3314 - 0.1592 \text{ Sex} - 0.1328 \text{ P-TYP} - 0.0037 \text{ AGE} + 0.0005 \text{ ALP} + 0.0194 \text{ TB} + 0.0031 \text{ SGOT} - 0.0002 \text{ TB*SGOT} - 0.0041 \text{ TP} + 0.0005 \text{ SGOT*TP},$$

and the Log-normal fitted variance ($\hat{\sigma}^2$) model is

$$\hat{\sigma}^2 = \exp. (-1.0938 - 0.2015 \text{ P-TYP} - 0.0102 \text{ AGE} + 0.0023 \text{ SGOT}).$$

These above two equations present the relationship of mean & variance of (Z=log SGPT). It is noted that sex, age, PTYP, ALP, TB, SGOT, TB*SGOT, TP and SGOT*TP are associated with mean, while age, PTYP, SGOT are associated with the variance of Z=log SGPT.

Table 1: Results for mean and dispersion models of SGPT from Log-normal and Gamma fit

Model	Covariates	Log-normal				Gamma			
		Estimate	s.e.	t-value	P-Value	Estimate	s.e.	t-value	P-Value
Mean	Constant	3.3314	0.1781	18.706	<0.0001	3.4848	0.18321	19.021	<0.0001
	Sex	-0.1592	0.04702	-3.386	0.0007	-0.1698	0.04935	-3.44	0.0006
	PTYP	-0.1328	0.04489	-2.958	0.0032	-0.1579	0.04683	-3.372	0.0007
	Age	-0.0037	0.00128	-2.852	0.0045	-0.0052	0.00135	-3.882	0.0001
	ALP	0.0005	0.00009	5.638	<0.0001	0.0006	0.00009	5.919	<0.0001
	TB	0.0194	0.00533	3.642	0.0003	0.0212	0.00528	4.025	<0.0001
	SGOT	0.0031	0.00138	2.271	0.0235	0.0025	0.00117	2.173	0.0302
	TB*SGOT	-0.0002	0.00004	-4.79	<0.0001	-0.0002	0.00003	-5.878	<0.0001
	TP	-0.0041	0.02319	-0.177	0.8595	0.0001	0.02364	0.001	0.9992
Dispersion	Constant	-1.0938	0.20459	-5.346	<0.0001	-0.8684	0.20252	-4.288	<0.0001
	PTYP	-0.2015	0.13623	-1.479	0.1396	-0.2996	0.13685	-2.189	0.029
	Age	-0.0102	0.00394	-2.589	0.0098	-0.0122	0.00397	-3.07	0.0022
	SGOT	0.0023	0.00042	5.448	<0.0001	0.0015	0.00033	4.428	<0.0001
AIC=5199					AIC=5268.567				

Discussion

The derived fitted mean and variance models of SGPT are shown above, and their summarized forms are given in Table 1. From the above mean & variance models of SGPT the following conclusions can be drawn.

1. The mean SGPT (MSGPT) is negatively associated with sex (Male = 1; Female = 2) (P=0.0007), indicating that SGPT is higher for male than female.
2. MSGPT is negatively associated with patients type (PTYP) (liver patient=1; non-liver patient=2) (P=0.0032), concluding that SGPT is higher for liver patients than non-liver.
3. MSGPT is negatively associated with age (P=0.0045), interpreting that SGPT is higher at younger patients than older.
4. MSGPT is positively associated with ALP (P<0.0001), concluding that SGPT rises, as ALP increases.
5. MSGPT is positively associated with TB (P=0.0003), indicating that SGPT rises, as TB rises.
6. MSGPT is positively associated with (SGOT) (P=0.0235), implying that SGPT increases, as SGOT increases.
7. MSGPT is negatively associated with the interaction effect (TB*SGOT) (P<0.0001), interpreting that SGPT rises, as TB*SGOT decreases. Note that both the marginal effects TB & SGOT are positively associated, while their interaction effect (TB*SGOT) is negatively associated with mean SGPT.
8. MSGPT is positively associated with the interaction effect (SGOT*TP) (P=0.0298), interpreting that SGPT rises, as TB*SGOT increases. Here SGOT is positively associated, while

- TP is insignificant, and their interaction effect (SGOT*TP) is also positively associated with mean SGPT. So, both the effects SGOT & SGOT*TP have the same association with mean SGPT.
- Variance of SGPT (VSGPT) is negatively partially associated with PTYP (liver patient=1; non-liver patient=2) ($P=0.1396$), concluding that SGPT variance is higher for liver patients than non-liver.
 - VSGPT is negatively associated with age ($P=0.0098$), interpreting that SGPT variance is higher at younger patients than older.
 - VSGPT is positively associated with SGOT ($P<0.0001$), indicating that SGPT variance rises as SGOT increases.

Interpretations of the derived outputs of SGPT analysis have been presented above point wise. The effect of each explanatory variable on SGPT is clearly explained above. The report shows that SGPT is higher for liver, or younger, or male patients which are observed in practice. Moreover, the report supports the earlier results of the association between SGPT & ALP [9] and SGPT & SGOT [10]. Best of our knowledge, there are a few research articles examine the association of SGPT with the remaining other liver biomarkers based on joint mean & dispersion modeling. Therefore, it is more difficult to compare all the present findings with many earlier reports.

Conclusion

The relationship (or models) of SGPT with other liver biomarkers has been derived through mean & variance models of SGPT. The associations & effects of other liver biomarkers on SGPT have been clearly explained above. The relationship of SGPT has been developed based on the smallest AIC value (Table 1), small standard error of the estimates (Table 1), and model checking plots (Figure 1), and comparing the appropriate distribution of SGPT (Table 1). The derived estimates of the explanatory factors of SGPT are stable as their standard errors are very small (Table 1) [18]. Moreover, the derived results show some practical situations such as SGPT is higher for liver, or younger, or male patients, and they also support some similar results in [9, 10]. Mean SGPT is explained by sex, age, PTYP, ALP, TB, SGOT, TB*SGOT, TP and SGOT*TP, while variance of SGPT is expressed by age, PTYP, SGOT. Mean model is more complicated as it contains two interaction effects. Note that the natures of marginal effects of TB & SGOT (positive) are different from their interaction effect TB*SGOT (negative) on SGPT. On the other hand, both marginal effect SGOT and interaction effect SGOT*TP have identical (positive) role on SGPT, while TP is insignificant.

The developed relationship of SGPT is based on the considered data set in [16, 17]. It may be little different (in respect of regression coefficient magnitudes) from the other data set, but the association of SGPT with other liver biomarkers will be identical. It has been partly examined with the data set in [10]. Note that the data set in [10] is partially similar to the considered data set [16, 17]. For parallel data set it has not been verified, as we have not parallel data set. The considered data set does not

include the liver biomarkers Gamma-Glutamyl Transpeptidase & Mean Corpuscular Volume. Future researchers may consider all possible liver biomarkers, lifestyle characters & food habits for deriving the models of SGPT and other liver biomarkers. The present derived results are little compared with the earlier results, as there are very few earlier similar studies.

Medical practitioners can examine the consistency of any pathological report about the liver biomarkers based on the results of the present report. The similar relationship of all the liver biomarkers will give more concrete knowledge to the medical practitioners about the behaviors of the biomarkers. The other relationships will be focused in our future research. Care should be taken for male, younger liver patients as SGPT is higher for them. Medical practitioners may be familiar with the role of SGPT based on the report.

Conflict of interest

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

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