ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Complex Association of Albumin with Other Liver Biomarkers

Rabindra Nath Das[1,2]*, Youngjo Lee[2], Sourav Sengupta[1], Ranjan Kumar Sahoo[3] and Sabyasachi Mukherjee[4]

[1]*Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India*

[2]*Department of Statistics, College of Natural Science, Seoul National University, Seoul, Korea*

[3]*Department of Statistics, Utkal University, Bhubaneswar, Odisha, India*

[4]*Department of Mathematics, NSHM Knowledge Campus, Durgapur, West Bengal, India*

***Corresponding Author:** Rabindra Nath Das, Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India.

Received: November 29, 2018; **Published:** January 31, 2019

Abstract

Liver performs synthetic and excretory complicated functions with many biomarkers. Serum albumin (ALB) is one human liver disease biomarker, which is a critical plasma protein formed by the liver. It has very complex association with other liver disease biomarkers. Mean ALB is positively associated with Total Proteins (TP) ($P < 0.001$), Albumin and Globulin Ratio (A/G) ($P < 0.001$), Alanine Aminotransferase (SGPT) ($P = 0.015$), Types of patients (TPT) ($P = 0.012$), interaction effects AGE*A/G ($P < 0.001$), and Alkaline Phosphatase (ALP)*A/G ($P < 0.001$), while it is negatively associated with Aspartate Aminotransferase (SGOT) ($P = 0.009$), AGE ($P < 0.001$), ALP ($P < 0.001$), Direct Bilirubin (DB) ($P = 0.014$), and interaction effect TP*A/G ($P < 0.001$). Variance of ALB is positively associated with Total Bilirubin (TB) ($P < 0.001$), AGE*ALP ($P = 0.010$), while it is negatively associated with ALP ($P = 0.002$), TP ($P < 0.001$), AGE*TB ($P = 0.001$), TB*SGOT ($P = 0.054$). Therefore, the association of ALB with other liver biomarkers is very complex. So, the functional role of ALB is very complicated.

Keywords: *Alanine Aminotransferase; Albumin; Albumin and Globulin Ratio; Total Bilirubin; Total Proteins; Non-Constant Variance*

Introduction

Liver performs mainly two complex functions such as synthetic and excretory. Albumin (ALB), an important plasma protein (also a liver biomarker), which is used frequently to manage liver cirrhosis and acute-on-chronic liver failure patients [1,2]. Initially ALB is used in liver and other diseases as a plasma expander depending on its oncotic function [2,3]. Presently, it is clear that ALB has multiple other biologic properties such as immunomodulatory, antioxidant and endothelial regulatory functions. Liver cirrhosis is correlated with reduced albumin synthesis, specific alterations to its structure and function such as oxidative damage, and posttranscriptional changes, which have been correlated with impaired function and clinical outcomes [1,3,4]. It has led to the idea of 'effective albumin concentration' which gives insights into the contribution of ALB to clinical complications of liver cirrhosis [5,6]. Improved pathobiology understanding of ALB also helps to present its role in an established range and proposed therapeutic indications in liver disease. Review articles [6,7] have discussed functional and structural changes of ALB in liver cirrhosis with a view to interpreting the important clinical implications of ALB in liver disease.

Many research articles have focused that liver cirrhosis is associated with reduced albumin synthesis, specific alterations to its structure and function [6-9]. It has been pointed that the functional role of ALB is very complicated [6,7,9-11]. Naturally, the following queries arise. Why does ALB show complicated functional role? Does it affect other liver disease biomarkers? Do the other liver disease biomarkers influence on ALB? Is there any association of ALB with other liver disease biomarkers? What are the effects of other liver disease biomarkers on ALB? Best of our knowledge, very few articles have focused the associations of ALB with other liver disease biomarkers. The report aims to evaluate the above queries based on the association of ALB with other liver disease biomarkers with the help of a real data set.

Materials and Statistical Methodology

Materials

A real data set of 583 (167 non-liver and 416 liver) individuals with 11 (9 continuous and 2 attribute) study variables are considered in the report. The data set has been collected from the North-East of Andhra Pradesh, India, and it may be obtained from the site archive. ics.uci.edu/ml/machine-learningdatabases/00225/. The data set, along with its collection method and covariate descriptions are clearly given in [12,13]. These are not redisplayed herein. For the ready use of the factors/covariates, they are reproduced as Sex (Male = 1; Female = 2), Age, Direct Bilirubin (DB), Total Bilirubin (TB), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (SGOT), Alanine Aminotransferase (SGPT), Albumin (ALB), Total Proteins (TP), Albumin and Globulin Ratio (A/G Ratio), Types of Patient (TPT) (liver patient = 1; non-liver patient = 2).

Statistical Methods

The associations of ALB with the other liver disease biomarkers along with age and sex have been examined in the report with the help of modeling. It is identified herein that the response ALB is with non-constant variance, positive continuous random variable. It may be generally modeled by stabilizing variance with suitable transformation. Note that ALB may not be stabilized by any suitable transformation. Therefore, it may be modeled by joint generalized linear models (JGLMs) with Log-normal and Gamma distributions, which have been explicitly presented in [14-17]. These have not been redisplayed herein. Interested readers may go through [14,16].

Statistical and graphical analysis

Albumin (ALB) is treated as the response variable herein, and it has been modeled with the help of the remaining other variables. Both the Log-normal and Gamma JGLMs have been fitted for the response ALB, and it has been found that Gamma JGLMs give better results (Table 1). The final Gamma fitted model is obtained based on the lowest Akaike information criterion (AIC = -259.615) value (within each class) which minimizes both the squared error loss and predicted additive errors [18, p. 203-204]. In the mean model all marginal and interaction effects are significant, while in the variance model marginal insignificant effects AGE and SGOT have been included in the model according to marginality rule by Nelder [19].

Valid conclusions can be drawn from the data generated probabilistic model assumed to be approximately correct to the true unknown model. Therefore, the derived model to be verified by model diagnostic tools. For the Gamma fitted models of ALB (Table 1), model diagnostic plots are displayed in figure 1. The absolute residuals (For gamma fitted models in table 1) are plotted against the fitted values, which is presented in Figure 1a. It is almost a straight line except the right tail, concluding that variance is constant with the running means. Right tail is increasing as one of the larger absolute residual is located at the right boundary. Figure 1b shows the normal probability plot for the fitted mean model in Table 1. It does not show any discrepancy in the fitted models. So, both the figures reveal that data generated Gamma fitted models in Table 1 are closely to the true models of ALB.

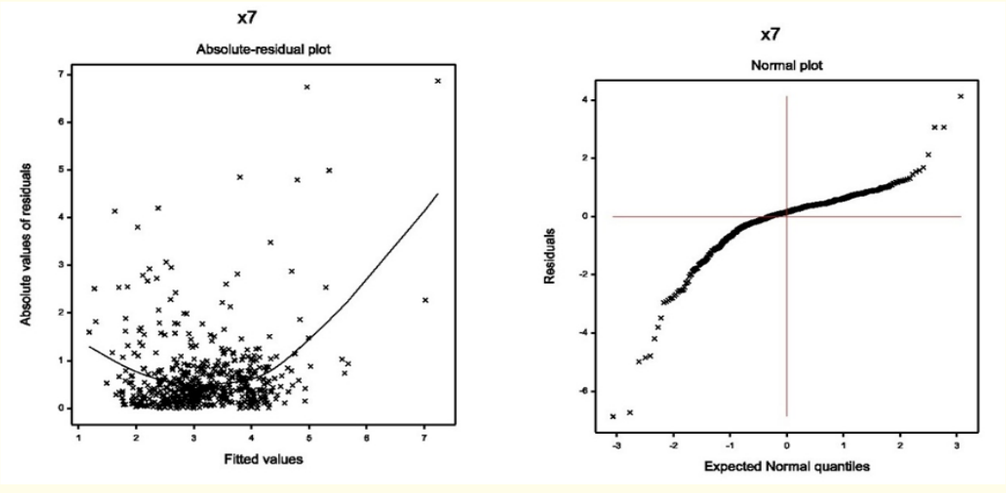

Figure 1: *For the joint Gamma fitted models of ALB (Table 1), the (a) absolute residuals plot with respect to the fitted values, and (b) the normal probability plot for the mean model.*

Results

Final Gamma fitted summarized analysis results are presented in table 1. It is noted that mean ALB is positively associated with Total Proteins (TP) (P < 0.001), Albumin and Globulin Ratio (A/G) (P < 0.001), Alanine Aminotransferase (SGPT) (P = 0.015), Types of Patient (TPT) (P = 0.012), interaction effects AGE*A/G (P < 0.001), and Alkaline Phosphatase (ALP)*A/G (P < 0.001), while it is negatively associated with AGE (P < 0.001), Aspartate Aminotransferase (SGOT) (P = 0.009), ALP (P < 0.001), Direct Bilirubin (DB) (P = 0.014), and interaction effect TP*A/G (P < 0.001). Variance of ALB is positively associated with Total Bilirubin (TB) (P < 0.001), AGE*ALP (P = 0.010), while it is negatively associated with ALP (P = 0.002), TP (P < 0.001), AGE*TB (P = 0.001), TB*SGOT (P = 0.054) and (TPT) (P = 0.060).

The Gamma fitted mean ($\hat{\mu}$) model of ALB (from table 1) is

$\hat{\mu}$ = exp. (-0.6360 + 0.2219 TP + 0.8116 A/G - 0.0709 TP*A/G - 0.0002 ALP + 0.0002 ALP*A/G - 0.0001 SGOT - 0.0020 AGE + 0.0018 AGE*A/G - 0.0055 DB + 0.0001 SGPT + 0.0119 TPT),

The Gamma fitted mean ($\hat{\sigma}^2$) model of ALB (from table 1) is

$\hat{\sigma}^2$ = exp. (-3.5085 + 0.0084 AGE + 0.3342 TB - 0.0035 AGE*TB - 0.0032 ALP + 0.0001 AGE*ALP - 0.0001 SGOT - 0.0001 TB*SGOT - 0.3866 TP -0.2695 TPT).

The above two equations display the mean and variance relationship of ALB. It is observed that age, TP, A/G, ALP, SGOT, DB, SGPT, TPT, TP*A/G, ALP*A/G, AGE*A/G are associated with mean ALB, while age, TB, ALP, SGOT, TP, TPT, AGE*TB, AGE*ALP, TB*SGOT are associated with the variance of ALB.

Model	Cofactors	Estimate	St. Error	t- value	P-value
Mean	Constant	-0.6360	0.06603	-9.632	< 0.001
	TP	0.2219	0.00840	26.432	< 0.001
	A/G	0.8116	0.06565	12.362	< 0.001
	TP*AG	-0.0709	0.00832	-8.525	< 0.001
	ALP	-0.0002	0.00004	-4.804	< 0.001
	ALP*A/G	0.0002	0.00004	5.344	< 0.001
	SGOT	-0.0001	0.00001	-2.598	0.009
	AGE	-0.0020	0.00052	-3.726	< 0.001
	AGE*A/G	0.0018	0.00051	3.476	< 0.001
	DB	-0.0055	0.00224	-2.447	0.014
	SGPT	0.0001	0.00002	2.412	0.015
	Patient type (TPT)	0.0119	0.00478	2.487	0.012
Dispersion	Constant	-3.5085	0.51794	-6.774	< 0.001
	AGE	0.0084	0.00735	1.146	0.252
	TB	0.3342	0.05174	6.459	< 0.001
	AGE*TB	-0.0035	0.00112	-3.117	0.001
	ALP	-0.0032	0.00103	-3.106	0.002
	AGE*ALP	0.0001	0.00002	2.569	0.010
	SGOT	-0.0001	0.00062	-0.199	0.842
	TB*SGOT	-0.0001	0.00005	-1.962	0.054
	TP	-0.3866	0.05267	-7.341	< 0.001
	Patient type (TPT)	-0.2695	0.14319	-1.882	0.060

Table 1: *Results for mean and dispersion models of albumin from gamma fit.*

Discussion

The derived Gamma fitted mean and variance models of ALB are given above, and their summarized forms are displayed in table 1. These above Gamma fitted mean and variance models of ALB conclude the following:

- A1) The mean ALB (MALB) is positively (highly significant as t-value is very large) associated with TP ($P < 0.001$), concluding that ALB increases as TP increases. Note that ALB is a critical plasma protein, so it increases if TP increases. It is the natural phenomena. The derived results show the real situation.

- A2) MALB is positively (highly significant) associated with A/G ($P < 0.001$), interpreting that ALB increases as A/G increases. Note that ALB is directly proportional to A/G (from its definition). So, ALB should be positively associated with A/G. The derived results show the real mathematical relationship.

- A3) MALB is negatively (highly significant) associated with the interaction effect (TP*A/G) ($P < 0.001$), indicating that ALB increases as (TP*A/G) decreases. Note that marginal effects TP and A/G are positively associated with mean ALB, while their interaction effect is negatively associated with ALB. This implies that TP and A/G increase ALB, but their joint effect deceases ALB. This is the real fact. Biological explanations are unknown to us.

- A4) MALB is negatively associated with ALP ($P < 0.001$), implying that ALB increases as ALP decreases.

- A5) MALB is positively (highly significant) associated with interaction effect (ALP*A/G) ($P < 0.001$), interpreting that ALB increases as (ALP*A/G) increases. Note that the marginal effect ALP (if it increases) decreases ALB, but both A/G (if it increases) and (ALP*A/G) (if it increases) increases ALB.

- A6) MALB is negatively associated with SGOT ($P = 0.009$), indicating that ALB increases as SGOT decreases.

- A7) MALB is negatively associated with AGE ($P < 0.001$), concluding that ALB is higher at younger ages.

- A8) MALB is positively associated with interaction effect (AGE*A/G) ($P < 0.001$), interpreting that ALB increases as (AGE*A/G) increases. Note that the marginal effect AGE (if it increases) decreases ALB, but both A/G (if it increases) and (AGE*A/G) (if it increases) increases ALB.

- A9) MALB is negatively associated with DB ($P = 0.014$), concluding that ALB increases as DB decreases.

- A10) MALB is positively associated with SGPT ($P = 0.015$), interpreting that ALB increases as SGPT increases.

- A11) MALB is positively associated with Types of Patient (TPT) (liver patient = 1; non-liver patient = 2) ($P = 0.012$), interpreting that ALB is higher for non-liver patients than liver patients. The derived results show the practical situation.

- A12) Variance of ALB (VALB) is positively associated with TB ($P < 0.001$), interpreting that ALB variance increases as TB increases.

- A13) VALB is negatively associated with (AGE*TB) ($P = 0.001$), concluding that ALB variance increases as (AGE*TB) decreases. Note that the marginal effect AGE is insignificant, while TB is positively associated but their interaction effect (AGE*TB) is negatively associated.

- A14) VALB is negatively associated with ALP ($P = 0.002$), indicating that ALB variance increases as ALP decreases.

- A15) VALB is positively associated with (AGE*ALP) ($P = 0.010$), implying that ALB variance increases as (AGE*ALP) increases. Note that the marginal effect AGE is insignificant, while ALP is negatively associated but their interaction effect (AGE*ALP) is positively associated.

- A16) VALB is negatively associated with (TB*SGOT) ($P = 0.054$), implying that ALB variance increases as (TB*SGOT) decreases. Note that the marginal effect SGOT is insignificant, while TB is positively associated but their interaction effect (TB*SGOT) is negatively associated.

- A17) VALB is negatively associated with TP (P < 0.001), indicating that ALB variance increases as TP decreases.
- A18) VALB is negatively associated with Types of Patient (TPT) (liver patient = 1; non-liver patient = 2) (P = 0.060), indicating that ALB variance higher for liver patients than non-liver.

Conclusions of the present derived findings of ALB analysis have been discussed above point wise. The role of each explanatory variable on ALB is clearly expressed above. It is shown herein that relationship of ALB is very complicated with other liver diseases markers. Each of the mean and variance model of ALB contains three interaction effects. The derived results show that ALB is higher for younger and for non-liver individuals which are observed in practice. In addition, the results support the real (conclusion A1) and mathematical relationship (conclusion A2). Best of our knowledge, a few research articles have derived the association of ALB with the other liver disease biomarkers. Therefore, it is really difficult to compare the present findings with earlier reports. This report may be the first probabilistic relationship of ALB with the other liver disease biomarkers in medical literature.

Conclusion

The Gamma fitted mean and variance models of ALB have been derived (Table 1). Each model (mean or variance) of ALB contains three interaction effects. The effects and associations of other liver disease biomarkers on ALB have been clearly presented above. The relationship of ALB has been derived herein based on small standard error of the estimates (Table 1), the smallest AIC value, model diagnostic plots (Figure 1), and comparing the two distributions Log-normal and Gamma. The estimates of regression coefficients of the independent variables of ALB are stable as their standard errors are small (Table 1) [14]. In addition, the derived outputs reveals some real, mathematical and practical incidents such as ALB is higher for younger and non-liver patients. Mean ALB is explained by AGE, TP, A/G, ALP, DB, SGOT, SGPT, TPT, TP*A/G, ALP*A/G, AGE*A/G, while variance of ALB is expressed by AGE, TB, ALP, SGOT, TP, TPT, AGE*TB, AGE*ALP, TB*SGOT.

The derived relationship of ALB is valid for the considered data set in [12,13]. The estimates of the regression coefficient of explanatory variables of ALB may be little different for other similar data set, but the association of ALB with other liver biomarkers may be identical. It has not been examined in the report, as we have not similar data sets. The present data set does not contain the liver biomarkers Mean Corpuscular Volume and Gamma-Glutamyl Transpeptidase. Future investigators may include all possible liver biomarkers, food habits and lifestyle characters for deriving the ALB models, and other liver biomarkers. The present developed results may not be compared with the previous findings, as there are a few previous similar studies.

Medical practitioners may have a clear idea about the functional role of ALB from the report. The similar relationship of all the liver biomarkers will present 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 about ALB at older ages.

Conflict of Interest

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

Acknowledgement

This research was supported by the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (2014M3C7A1062896).

Bibliography

1. Domenicali M., *et al*. "Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis". *Hepatology* 60 (2014): 1851-1860.
2. Gines P and Cardenas A. "The management of ascites and hyponatremiain cirrhosis". *Seminars in Liver Disease* 28 (2008): 43-58.
3. Oettl K., *et al*. "Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival". *Journal of Hepatology* 59 (2013): 978-983.

4. Jalan R., *et al*. "Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality". *Hepatology* 50 (2009): 555-564.

5. Spinella R., *et al*. "Albumin in chronic liver disease: structure, functions and therapeutic implications". *Hepatology International* 10 (2016): 124-132.

6. Jalan R and Bernardi M. "Effective albumin concentration and cirrhosis mortality: from concept to reality". *Journal of Hepatology* 59 (2013): 918-920.

7. Evans TW. "Review article: albumin as a drug-biological effects of albumin unrelated to oncotic pressure". *Aliment Pharmacology Theraphy* 16.5 (2002): 6-11.

8. Fanali G., *et al*. "Human serum albumin: from bench to bedside". *Molecular Aspects of Medicine* 33 (2012): 209-290.

9. He XM and Carter DC. "Atomic structure and chemistry of human serum albumin". *Nature* 358 (1992): 209-215.

10. Arroyo V., *et al*. "Human serum albumin, systemic inflammation, and cirrhosis". *Journal of Hepatology* 61.2 (2014): 396-407.

11. Quinlan GJ., *et al*. "Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion". *Clinical Science* 95.4 (1998): 459-465.

12. Ramana BV., *et al*. "A Critical Study of Selected Classification Algorithms for Liver Disease Diagnosis". *International Journal of Database Management Systems* 3.2 (2011): 101-114.

13. Ramana BV and Babu MSP. "Liver Classification Using Modified Rotation Forest". *International Journal of Engineering Research and Development* 1 (2012): 17-24.

14. Lee Y., *et al*. "Generalized Linear Models with Random Effects (Unified Analysis via H-likelihood)". London: Chapman and Hall (2006).

15. Qu Y., *et al*. "A unified approach to estimating association measures via a joint generalized linear model for paired binary data". *Communications in Statistics - Theory and Methods* 29.1 (2000): 143-156.

16. Lesperance ML and Park S. "GLMs for the analysis of robust designs with dynamic characteristics". *Journal Quality Technology* 35.3 (2003): 253-263.

17. Das RN., *et al*. "Alkaline Phosphatase Determinants of Liver Patients". *Journal of the Pancreas* 19.1 (2018): 18-23.

18. Hastie T., *et al*. "The Elements of Statistical Learning". Springer-Verlag (2001).

19. Nelder JA. "The statistics of linear models: back to basics". *Statistics and Computing* 4.4 (1994): 221-234.

Volume 6 Issue 2 February 2019