

Association of Serum Adiponectin with Age, BMI and Other Breast Cancer Biomarkers

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Abstract

Throughout the world, the most commonly observed cancer in women is breast cancer. Low serum adiponectin levels are positively associated with breast cancer, so it is treated as a breast cancer biomarker. The report focuses the association of adiponectin with age, body mass index, and other breast cancer biomarkers. It is derived herein that mean adiponectin is negatively associated with Age ($P=0.0006$), Body mass index (BMI) ($P<0.0001$), Resistin ($P=0.0237$), while it is positively associated with interaction effects Age*BMI ($P=0.0017$) and BMI*Resistin ($P=0.0615$). Some partially significant effects such as Leptin (mean model) and Age (variance model) are also included in the model as confounder (known in Epidemiology). Adiponectin is higher for younger women with low body mass index and low resistin levels, and it is not associated with serum glucose and insulin levels.

Keywords: Adiponectin; Breast cancer; Leptin; Resistin; Non-constant variance

Introduction

Serum adiponectin is a protein hormone which modulates many metabolic processes, along with fatty acid oxidation and glucose regulation [1,2]. It is secreted from adipose tissue (and also from placenta in pregnancy) into the bloodstream, and it is very abundant in plasma relative to many hormones [2]. Due to high obesity, serum adiponectin levels are reduced, and it is increased after severe weight loss [3,4]. Low levels of adiponectin are associated with insulin resistance, hyperinsulinaemia, and breast cancer risk [5-7]. Obesity is positively associated with the mortality, incidence and prevalence of breast cancer [3]. Obese breast cancer patients have a higher risk of larger tumors, lymph node metastasis, and higher mortality rates than non-obese patients [4]. The relationship between BMI and risk of breast cancer has been well established [8-10]. Some research articles have shown that adiponectin and leptin have significant correlation with insulin and HOMA-IR [11-13]. Most of the earlier results are based on simple correlation, simple, multiple, Logistic regression analysis which are not appropriate for examining the association of any two variables for a multivariate non-normal heteroscedastic positive continuous data set.

The earlier findings related to the association of adiponectin with age, BMI, glucose, insulin, and other breast cancer biomarkers invite many doubts and debates. The association of adiponectin can only be identified through appropriate modeling of it with age, BMI, glucose, insulin, and other breast cancer biomarkers, which has been little studied in medical literature, considering the original nature of the data set. The present report tries to focus the real associations of adiponectin with age, BMI, glucose, insulin and many breast cancer biomarkers through probabilistic modeling.

Material and Statistical Methods

Materials

The report examines the association of adiponectin with age, BMI, glucose, insulin, and other breast cancer biomarkers based on 116 (64 patients and 52 healthy controls) subjects including 10 (1 attribute and 9 continuous) study variables, and the data set is available in the UCI Machine Learning Repository. The study population, data collection

process and covariates have been clearly expressed [14]. These are not redisplayed herein. Some research articles are related with the Wisconsin Breast Cancer Dataset (WBCD), Wisconsin Prognosis Breast Cancer (WPBC), and Wisconsin Diagnosis Breast Cancer (WDBC) data sets [15-17]. For ready presenting the covariates in the article, they are reproduced as Age (AGE) (years), Glucose (GCS) (mg/ dL), BMI (kg/m²), Insulin (ISL) (μ U/mL), Leptin (LPT) (ng/mL), HOMA, Adiponectin (ANT) (μ g /mL), MCP-1 (MCP) (pg/dL), Resistin (RST) (ng/mL), Types of subjects (TOS) (1=Healthy controls; 2=Patients).

Statistical methods

The report aims to derive the relationship of adiponectin with age, BMI, glucose, insulin, and other breast cancer biomarkers using appropriate probabilistic modeling. The aimed response adiponectin is positive heteroscedastic continuous and non-normally distributed random variable. It can be modeled by adopting suitable transformation when the variance is stabilized with the transformation. If the transformation fails, it can be modeled by joint generalized linear models (JGLMs) with Gamma and Log-normal distributions [18-22]. These have not been reproduced in the report. For elaborate ideas about JGLMs, readers may go through [18,21]. The response adiponectin has been modeled using both the Log-normal and Gamma JGLMs, and they give identical results. Therefore, these two models are shortly reproduced herein.

Log-normal JGLMs: Let us consider a positive continuous dependent random variable y_i 's with $E(y_i) = \mu_i$ (mean parameters), and non-constant variance σ_i^2 (dispersion parameters), with $\text{Var}(Y_i) = \sigma_i^2 \mu_i^2 = \sigma_i^2 V(\mu_i)$ say. Generally, the log transformation $Z_i = \log(Y_i)$ is

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Received December 04, 2018; **Accepted** December 14, 2018; **Published** December 22, 2018

Citation: Das RN, Lee Y (2018) Association of Serum Adiponectin with Age, BMI and Other Breast Cancer Biomarkers. J Blood Lymph 8: 233. doi: [10.4172/2165-7831.1000233](https://doi.org/10.4172/2165-7831.1000233)

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used to stabilize the variance $\text{Var}(Z_i) \approx \sigma_i^2$, but the variance may not be stabilized always. For determining improved model, JGLMs for the mean and variance are adopted. For Log-normal distributed positive random variable Y_i , with $Z_i = \log Y_i$, JGLM of the mean and variance are given by

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

Where x_i' and g_i' are the vectors of explanatory variables associated respectively, along with the regression coefficients β (mean model parameters) and γ (variance model parameters).

Gamma JGLMs: For a continuous positive random response y_i if $E(y_i) = \mu_i$ and $\text{Var}(y_i) = \sigma_i^2 V(\mu_i)$, where μ_i 's and σ_i^2 's are respectively, mean and dispersion parameters, and $V(\cdot)$ reveals the variance function with two parts (in GLM) such as σ_i^2 (free of mean changes) and $V(\mu_i)$ (depends on the mean changes). It is noted that the GLM family distribution is located by $V(\mu_i)$, as it is Poisson if $V(\mu) = \mu$, Gamma if $V(\mu) = \mu^2$, and Normal if $V(\mu) = 1$, etc. So, the Gamma JGLMs of mean and dispersion (when $V(\mu) = \mu^2$) are

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

where $g(\cdot)$ and $h(\cdot)$ are GLM link functions related to the mean and variance linear predictors respectively, and x_i' , w_i' are the vectors of explanatory factors/variables, connected to the mean and dispersion parameters respectively. Practically, the maximum likelihood (ML) and the restricted ML (REML) method are used respectively, for estimating the mean and dispersion parameters [17].

Statistical and Graphical Analysis

The response adiponectin is identified as heteroscedastic which is not stabilized by any suitable transformation. It is considered as the response variable, and the remaining other 9 factors are adopted as the explanatory variables. Adiponectin has been modeled by JGLMs considering both Log-normal and Gamma distributions. The best fitted models have been selected based on the smallest value of Akaike information criterion (AIC) (within each class) which minimizes both the squared error loss and predicted additive errors [23]. Three partially significant factors such as Leptin and interaction effect BMI*Leptin (in mean model) and age (in variance model) are adopted in the final models as confounder. It is known that partially significant factors adopted in the model are called confounder in Epidemiology. Both

the Log-normal and Gamma model analyses outcomes are presented in Table 1. Log-normal (AIC=673.8) and Gamma (AIC=673.368) fits show similar results (Table 1) based on AIC rule.

All possible valid interpretations are obtained from the data generated probabilistic model considering it as the approximately correct model of the true unknown model. So, the developed model is to be examined using model diagnostic tools. From Table 1, AIC of Gamma fitted models is little smaller than Log-normal, so model checking is adopted to the Gamma fitted models (Table 1), which is displayed in Figure 1. The absolute residuals are plotted against the Gamma fitted values (Table 1) in Figure 1a, which is approximately linear, indicating that variance is constant with the running means. Figure 1b displays the normal probability plot for the Gamma fitted mean model (Table 1), which presents no lack of fit. Hence, both the figures support that the fitted Gamma models (Table 1) are approximately same to the unknown true models.

Results

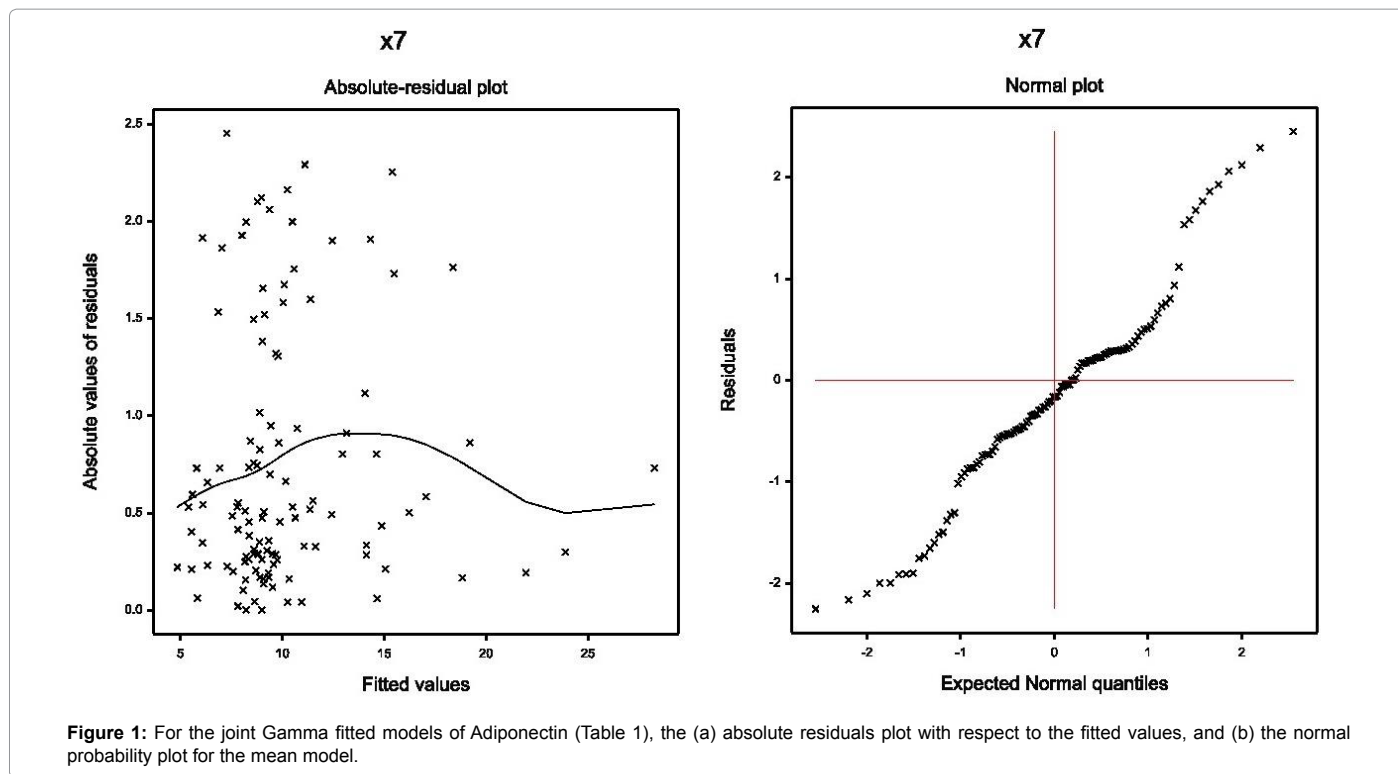
The summarized form JGLMs fitted outcomes for both Log-normal and Gamma models are displayed in Table 1. The following outcomes are related to the Gamma fitted models in Table 1. It is derived herein that mean adiponectin is negatively associated with Age (P=0.0006), Body mass index (BMI) (P<0.0001), Resistin (P=0.0237) and interaction effect BMI*Leptin (P=0.1729) (partially significant), while it is positively associated with Leptin (P=0.1202) (partially significant), interaction effects Age*BMI (P=0.0017) and BMI*Resistin (P=0.0615). Variance of adiponectin is partially positively significantly associate with Age (P=0.1233).

Gamma fitted Adiponectin mean ($\hat{\mu}$) model (from Table 1) is $\hat{\mu} = \exp(6.7778 - 0.0617 \text{ Age} - 0.1475 \text{ BMI} + 0.0020 \text{ Age} * \text{BMI} + 0.0282 \text{ Leptin} - 0.0662 \text{ Resistin} + 0.0018 \text{ BMI} * \text{Resistin} - 0.0008 \text{ BMI} * \text{Leptin})$, and Gamma fitted Adiponectin variance ($\hat{\sigma}^2$) model is $\hat{\sigma}^2 = \exp(-2.318 + 0.017 \text{ Age})$.

These two equations present the mean and variance relationship of Adiponectin. It is noted that mean Adiponectin is expressed by Age, BMI, Leptin, Resistin, Age*BMI, BMI*Resistin, BMI*Leptin, while variance of Adiponectin is explained by only Age. Note that adiponectin is modeled by JGLMs. Here mean & variance both are modeled simultaneously by iterative method [18]. The significance of regression coefficients are tested by t-statistic, as usual multiple regression analysis.

Model	Covariate	Log-normal fit				Gamma fit			
		Estimate	S.E.	t-value	P-value	Estimate	S.E.	t-value	P-value
Mean	Constant	6.8667	1.0012	6.858	<0.0001	6.7778	0.9853	6.879	<0.0001
	AGE	-0.0627	0.0178	-3.525	0.0006	-0.0617	0.0174	-3.550	0.0006
	BMI	-0.1512	0.0367	-4.122	<0.0001	-0.1475	0.0361	-4.087	<0.0001
	AGE*BMI	0.0020	0.0006	3.067	0.0027	0.0020	0.0006	3.214	0.0017
	LPT	0.0217	0.0184	1.179	0.2409	0.0282	0.0180	1.566	0.1202
	RST	-0.0701	0.0296	-2.371	0.0195	-0.0662	0.0289	-2.293	0.0237
	BMI*RST	0.0020	0.0010	2.003	0.0476	0.0018	0.0010	1.886	0.0615
	BMI*LPT	-0.0006	0.0006	-0.976	0.3312	-0.0008	0.0006	-1.372	0.1729
Dispersion	Constant	-2.325	0.6674	-3.483	0.0007	-2.318	0.6595	-3.515	0.0006
	AGE	0.019	0.0114	1.690	0.0939	0.017	0.0112	1.553	0.1233
Above are the final models		AIC=673.8				AIC=673.368			
Additional two variables Glucose & Insulin are included below to examine their significance									
Mean	Glucose	-0.0011	0.0029	-0.379	0.7054	-0.0015	0.0029	-0.536	0.5930
	Insulin	0.0052	0.0057	0.914	0.3627	0.0034	0.0056	0.609	0.5438

Table 1: Results for mean and dispersion models for Adiponectin from Log-Normal and Gamma fit.



Discussion

Final fitted results for both the distributions are given in Table 1, and also the Gamma fitted mean and variance models of Adiponectin are given above. These two models of Adiponectin (Table 1) conclude the following.

- The mean Adiponectin (ANT) (MANT) is negatively associated with AGE ($P=0.0006$), indicating that ANT is higher for younger women than older. This is observed in practice.
- MANT is negatively associated with BMI ($P<0.0001$), concluding that ANT is higher for women with lower BMI. This is also observed in practice.
- MANT is positively associated with the interaction effect AGE*BMI ($P=0.0017$), indicating that ANT increases as the interaction effect AGE*BMI increases. Note that both the marginal effects AGE & BMI are negatively associated, while their interaction effect is positively associated with ANT.
- MANT is partially positively associated with Leptin (LPT) ($P=0.1202$), interpreting that ANT increases as LPT increases.
- MANT is negatively associated with Resistin (RST) ($P=0.0237$), implying that ANT increases as RST decreases.
- MANT is positively associated with the interaction effect BMI*RST ($P=0.0615$), indicating that ANT increases as the interaction effect BMI*RST increases. Note that both the marginal effects BMI & RST are negatively associated, while their interaction effect is positively associated with ANT.
- MANT is partially negatively associated with the interaction effect BMI*LPT ($P=0.1729$), indicating that ANT increases as the interaction effect BMI*LPT decreases. Note that the marginal effect BMI is negatively, while LPT is positively, but

their interaction effect is negatively associated with ANT.

- Variance of Adiponectin is partially positively associated with Age ($P=0.1233$), concluding that Adiponectin variance is higher for older women than younger.

Interpretations of the Adiponectin analysis outcomes have been displayed above. The associations of age, BMI, breast cancer biomarkers such as Leptin and Resistin are shown with Adiponectin. It is found herein that Adiponectin levels are higher for younger women with lower BMI, lower Resistin levels and higher Leptin levels. It is derived herein that lower age, lower BMI, and their joint interaction effect (AGE*BMI) increase Adiponectin. Similarly, it is also derived herein that lower BMI, lower Resistin, and their joint interaction effect (BMI*RST) increase Adiponectin. Note that Adiponectin has no association with glucose levels, insulin levels, MCP-1 and HOMA. Many articles have pointed that Adiponectin has association with glucose and insulin levels, but the present findings have shown that Adiponectin has no association with them (last two rows are added in Table 1 to show their association) [2,11,12,14]. The report has derived many joint interaction effects, which have not been pointed in earlier reports. In addition, there are a few similar earlier studies, so it is very difficult to compare the present findings with the earlier findings. For the given data set [14], adiponectin level is insignificant for the subject type. The report is unable to focus any association of adiponectin with many diabetes markers and cardiac factors, as the considered data set [14] does not contain such characters.

Conclusion

The associations of Adiponectin with age, BMI and other breast cancer biomarkers have been derived herein with probabilistic modeling. Mean and variance models of Adiponectin have been explained by Age, BMI, Leptin, Resistin and their interaction effects. The final mean and variance models of Adiponectin have selected based on comparison of

the Log-normal and Gamma distributions, lowest AIC value, model checking plots, and small standard error of the estimates (Table 1). Therefore, the final fitted models are approximately correct to the true unknown models, and the interpretations which have been drawn based on the fitted models are exactly true. In addition, the findings support the real situations and some earlier results. Hence, research should have greater faith on these results than those emanating from simple correlation, simple, multiple and Logistic regression models. The report has derived that Adiponectin levels are higher for younger women, with lower BMI, lower Resistin levels & higher Leptin levels. It is derived herein that lower age, lower BMI, and their joint interaction effect (AGE*BMI) increase Adiponectin. Similarly, it is also derived herein that lower BMI, lower Resistin, and their joint interaction effect (BMI*RST) increase Adiponectin. In addition, the report has shown that Adiponectin has no association with glucose, insulin, MCP-1 and HOMA.

The associations (Table 1) of Adiponectin with age, BMI and other breast cancer biomarkers are valid for the data set in [14]. For different similar data sets, fitted models may be different (with respect to regression coefficients), but the conclusions may be identical. It is not examined herein as we have not similar data sets. Moreover, the data set [14] does not contain diabetes markers 2-hours post plasma glucose, HbA1c and random plasma glucose. The reported data set does not contain many diabetes markers and cardiac factors. Future research reports may examine the associations of Adiponectin with all possible diabetes, cardiac and breast cancer biomarkers along with age and BMI. These studies will present the interrelationship of blood biochemical parameters with diabetes, breast cancer and cardiac diseases.

The report has shown that Adiponectin has no association with glucose and insulin (last two additional rows in Table 1). These are contradictions to earlier findings [2,11,12,14]. The report has supported some earlier findings (association between Adiponectin and BMI). Many interaction effects have been identified which have not been reported in any previous articles. Medical practitioners may be able to know the different influential factors of Adiponectin from the report. Every woman should reduce her BMI, and care should be taken on Adiponectin levels at older ages.

Conflict of Interest

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

Acknowledgement

The authors are very much indebted to the referees who have provided valuable comments to improve this paper. 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).

References

- Kelesidis I, Kelesidis T, Mantzoros CS (2006) Adiponectin and cancer: A systematic review. *Br J Cancer* 94: 1221-1225.
- Schmidt S, Monk JM, Robinson LE, Mourtzakis M (2015) The integrative role of leptin, oestrogen and the insulin family in obesity-associated breast cancer: Potential effects of exercise. *Obes Rev* 16: 473-487.
- Lorincz AM, Sukumar S (2006) Molecular links between obesity and breast cancer. *EndocrRelat Cancer* 13: 279-292.
- Rose DP, Vona-Davis L (2010) Interaction between menopausal status and obesity in affecting breast cancer risk. *Maturitas* 66: 33-38.
- Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, et al. (2003) Association of serum adiponectin levels with breast cancer risk. *Clin Cancer Res* 9: 5699-5704.
- Chen DC, Chung YF, Yeh YT, Chaung HC, Kuo FC, et al. (2006) Serum adiponectin and leptin levels in Taiwanese breast cancer patients. *Cancer Lett* 237: 109-114.
- Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ (2001) Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control* 12: 47-59.
- Morimoto LM, White E, Chen Z, Chlebowski RT, Hays J, et al. (2002) Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 13: 741-751.
- Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, et al. (2001) Association of family history and other risk factors with breast cancer risk among Japanese premenopausal and postmenopausal women. *Cancer Causes Control* 12: 349-358.
- Tung HT, Tsukuma H, Tanaka H, Kinoshita N, Koyama Y, et al. (1999) Risk factors for breast cancer in Japan, with special attention to anthropometric measurements and reproductive history. *Jpn J Clin Oncol* 29: 137-146.
- Awadhi SAA, Khaldi RMA, Rammah TA, Kapila K, Mojiminiyi OA (2012) Associations of adipokines & insulin resistance with sex steroids in patients with breast cancer. *Indian J Med* 135: 500-505.
- Danthala M, Rajesh GR, Gundeti S, Raju GS, Chandran P, et al. (2018) Obesity and breast cancer: Association of serum adiponectin, leptin, and adiponectin-leptin ratio as risk biomarkers. *Indian J Med Paediatr Oncol* 39: 292-296.
- Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, et al. (2003) Association of Serum Adiponectin Levels with Breast Cancer Risk. *Clin Cancer Res* 9: 5699-5704.
- Patrício M, Pereira J, Crisóstomo J, Matafome P, Gomes M, et al. (2018) Using Resistin, glucose, age and BMI to predict the presence of breast cancer. *BMC Cancer* 18: 18-29.
- Wolberg WH, Mangasarian OL (1990) Multi surface method of pattern separation for medical diagnosis applied to breast cytology. *Proc Natl AcadSci USA* 87: 9193-9196.
- Zheng BC, Yoon SW, Lam SS (2014) Breast cancer diagnosis based on feature extraction using a hybrid of K-means and support vector machine algorithms. *Expert Syst Appl* 41: 1476-1482.
- Maglogiannis I, Zafiroopoulos E, Anagnostopoulos I (2009) An intelligent system for automated breast cancer diagnosis and prognosis using SVM based classifiers. *Appl Intell* 30: 24-36.
- Lee Y, Nelder JA, Pawitan Y (2006) Generalized Linear Models with Random Effects (Unified Analysis via H-likelihood). London: Chapman & Hall 2006.
- Das RN, Lee Y (2009) Log-normal versus gamma models for analyzing data from quality-improvement experiments. *Quality Engineering* 21: 79-87.
- Das RN, Lee Y (2010) Analysis strategies for multiple responses in quality improvement experiments. *International Journal of Quality Engineering and Technology* 1: 395-409.
- Das RN (2014) Robust Response Surfaces, Regression, and Positive Data Analyses. London: Chapman & Hall 2014.
- Das RN, Lee Y, Bhattacharyya G (2018) Effects of Plasma Volume and Red Cell Index on Cardiac Parameters for Shock Patients. *J Blood Lymph* 8: 228.
- Hastie T, Tibshirani R, Friedman J (2001) The Elements of Statistical Learning, Springer-Verlag.