Oncology
and Radiotherapy ©
1 (46) 2019: 005-009 • RESEARCH ARTICLE

Association of monocyte chemoattractant protein-1 with age, glucose, BMI, insulin and other breast cancer biomarkers

Jinseog Kim[1], Rabindra Nath Das[2], Youngjo Lee[3], Ranjan Kumar Sahoo[4]

[1] Department of Applied Statistics, Dongguk University, Gyeongju, Korea
[2] Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India
[3] Department of Statistics, College of Natural Science, Seoul National University, Seoul, Korea
[4] Department of Statistics, Utkal University, Bhubaneswar, Odisha, India

SUMMARY

Breast cancer is in most cases noticed over the world as the second cause of cancer-allied death in women. Monocyte chemoattractant protein-1 (MCP-1) plays an essential role in the opening and advancement of cancer. The report derives the association of MCP-1 with age, BMI, insulin, glucose and other breast cancer biomarkers such as leptin, resistin, adiponectin, HOMA based on a real data set. It is obtained herein that mean MCP-1 is positively associated with BMI ($p<0.0001$), resistin ($p<0.0001$) and the interaction effect of insulin and leptin (i.e., insulin*leptin) ($p<0.0001$), while it is negatively associated with insulin ($p<0.0001$) and leptin ($p<0.0001$). The variance of MCP-1 is positively associated with age*insulin ($p=0.0025$), leptin*resistin ($p=0.0176$) and glucose*leptin ($p=0.0819$), while it is negatively associated with age ($p=0.0706$), homeostasis model assessment score (HOMA) ($p=0.0055$), leptin ($p=0.0198$) and resistin ($p=0.0777$). Only three partially significant effects (approximately 8% level of significance) are included in the Gamma variance model, while they are significant in the Log-normal variance model. These are accounted as a confounder in the model in view of Epidemiology. It is concluded herein that MCP-1 is higher for women with high BMI, higher levels of resistin, low levels of both insulin and leptin, along with their high interaction effect.

Key words: adiponectin, breast cancer, HOMA, insulin, leptin, 0MCP-1, resistin

Address for correspondence:

Professor Rabindra Nath Das, Department of Statistics, University of Burdwan, West Bengal, India, email: rabin.bwn@gmail.com

Word count: 3507 **Tables:** 1 **Figures:** 1 **References:** 29

Received: - 19 February, 2019

Accepted: - 08 March, 2019

Published: - 15 March, 2019

INTRODUCTION

Leukocytes infiltrate a number of mouse and human cancers [1, 2]. MCP-1 is a chemokine with potent monocyte chemotactic activity [2]. Initially, it was purified from the culture supernatant of a monocytic leukemic cell line [3], and a human malignant glioma [4]. Later on, it was suggested as identical to the earlier described tumor cell-derived chemotactic factor [5]. Therefore, tumor cells are a root of MCP-1. It is suggested that MCP-1 produced by tumors is accountable for the collection of immunosuppressive macrophages that enhance tumor growth [6 - 9]. So, it plays a major role in the opening and advancement of colitis-associated colon carcinogenesis [10]. It was found that inhibition of MCP-1 resulted in shortened the growth of breast cancer [11], prostate cancer [12 - 14] and lung cancer [15] in mice. Therefore, the neutralization of MCP-1 is a cancer treatment target [16]. A meta-analysis has been adopted to establish the association between MCP-1 expression, overall survival, clinical staging, and disease-free survival among patients with solid tumors [17].

MCP-1 is an authentic element of the inflammatory process and reveals a potential therapeutic treatment target, not only in breast cancer but also in obesity [11, 17]. The relationship of MCP-1 with glucose, insulin, age, BMI and other breast cancer biomarkers are little studied simultaneously in earlier literature. Considering only any two covariates, there are some studies. But for a multivariate data set, simple correlation between any two covariates is meaningless, without eliminating the effects of the other covariates. This type of association can only be studied adopting suitable modeling. Best of our knowledge, in earlier studies there is no such probabilistic model for MCP-1 with its many associated covariates. The relationship of MCP-1 with age, MBI, glucose, insulin, and other breast cancer biomarkers are derived herein based on probabilistic modeling. The effects of MCP-1 on the other covariates are investigated in the current report.

MATERIALS AND METHODS

Materials

The relationship of MCP-1 with its related covariates such as insulin, glucose, age, BMI and many other breast cancer biomarkers is derived in the report adopting a real data set of 116 (52 healthy and 64 breast cancer) women with 10 covariates.

The data set can be viewed in the UCI Machine Learning Repository. A detailed illustration of the patient population and data collection process is noted in [18], which is not redisplayed herein. For essential use of covariates, they are redisplayed as Insulin (μU/mL), Age (years), Glucose (mg/dL), BMI (kg/m^2), Adiponectin (μg/mL), Leptin (ng/mL), HOMA, MCP-1 (pg/dL), Resistin (ng/mL), Class of subjects (1=healthy; 2=patients).

Statistical methods

The relationship of MCP-1 with its related covariates is derived herein with probabilistic modeling. Note that the response MCP-1 is positive continuous and non-constant variance, which can be modeled by adopting variance stabilization transformation, when the variance is stabilized by the applied transformation. Otherwise, it should be modeled adopting Joint Generalized Linear Models (JGLMs) using both the distributions such as Log-normal and Gamma, which is illustrated in [19 - 22]. Note that the variance of MCP-1 is not stabilized by any transformation, which is modeled herein by JGLMs that has been explicitly illustrated in many books and research articles. It is not redisplayed in details herein, and interested researchers can visit [19, 21]. Very shortly, two JGLMs for both Log-normal and Gamma are displayed as follow.

JGLMs with Log-normal distribution: Suppose a continuous positive response variable y_i's with $E(y_i) = \mu_i$ (mean parameters), and heteroscedastic variance σ_i^2 (dispersion parameters), satisfies the relationship $Var(Y_i) = \sigma_i^2 \mu_i^2 = \sigma_i^2 V(\mu_i)$ say. For this situation, practically, the log transformation $Z_i = \log(Y_i)$ is adopted to stabilize the variance $Var(Z_i \approx) \sigma_i^2$ $Var(Zi \approx) \sigma_i^2$, but in practice, the variance may not be stabilized always. Under this situation, JGLMs for mean and dispersion are frequently adopted to derive the appropriate model, assuming the response distribution as Log-normal or Gamma. For the response (Y_i) having Log-normal distribution (with $Z_i = \log Y_i$), JGLMs for mean and dispersion are presented by

$$E(Z_i) = \mu z_i \text{ and } Var(Z_i) = \sigma_{zi}^2,$$
$$\mu z_i = X_i^t \beta \text{ and } \log\left(\sigma_{zi}^2\right) = g_i^t \gamma,$$

Where x_i^t and g_i^t are the explanatory variable vectors connected with the regression coefficients β (mean model) and γ (variance model), respectively.

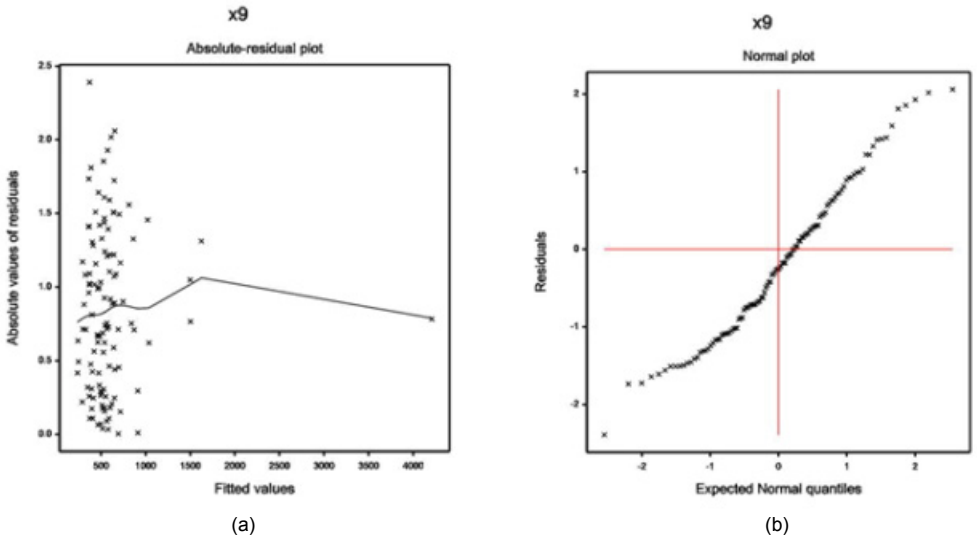
JGLMs with Gamma distribution: The above stated continuous positive random response y_i, satisfies $V(y_i) = \sigma_i^2 V(\mu_i)$, where $V(.)$ presents the variance function with two GLM components such as σ_i^2 (independent of means) and $V(\mu_i)$ (depends on means). Practically, GLM family distribution is represented by $V(\mu_i)$. For illustration, if $V(\mu) = \mu$, it is Poisson, Normal if $V(\mu)$=1, and Gamma if $V(\mu) = \mu^2$ etc. Therefore, Gamma JGLMs for mean and dispersion if $V(\mu) = \mu^2$ are

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

Where $g(\cdot)$ and $h(\cdot)$ are GLM link functions connected to the mean and dispersion linear predictors respectively, and x_i^t, w_i^t is the explanatory variable vectors, related to the mean and dispersion parameters respectively. The Maximum Likelihood (ML) and the restricted ML (REML) method are adopted respectively, for calculating the mean and dispersion parameters [19].

Statistical and graphical analysis

In this section, MCP-1 has been modeled using JGLMs adopting both the Log-normal and Gamma distributions. MCP-1 is considered as the dependent variable, while the others are considered as the explanatory variables. Smallest Akaike information criterion (AIC) value (within each class) selects the final model, which minimizes both the squared error loss and predicted additive errors [23]. All included factors in the mean model are significant. In the variance model, some insignificant effects such as insulin, glucose, and resistin are included following the marginality rule given by Nelder [24 - 29], which suggests that if any interaction effect is significantly included in the model, then all its lower order effects should be included. In Epidemiology, partially significant effects are named as a confounder. Treated as a confounder, age and interaction effect glucose*leptin are included in the Gamma fitted variance model, but they are significant in the Log-normal variance model. Note that in Log-normal fitted variance model all effects are significant except insulin and glucose, which are included in



(a) (b)

Fig. 1. For the MCP-1 Gamma fitted models (Table 1), the (a) absolute residuals plot with respect to MCP-1 fitted values, and (b) the normal probability MCP-1 mean model plot

the model due to marginality rule by Nelder [24 - 29]. MCP-1 analysis outcomes for JGLMs with both Log-normal and Gamma models are presented in Table 1. In addition, both models give identical interpretations. In view of AIC rule, Gamma model (AIC=1572.816) shows a better fit than Log-normal (AIC=1575).

Finally accepted model always reveals valid interpretations. Thus, it must be adopted based on model checking diagnostic plots. Here, Gamma fitted MCP-1 model is accepted as the final model which is examined by Figure 1, which contains absolute residuals and mean normal probability plots. The absolute residuals are plotted with respect to the MCP-1 Gamma fitted values (Table 1) in Figure 1a, which is an approximately flat straight line with the running means, concluding that variance is constant. Figure 1b shows the Gamma fitted MCP-1 mean normal probability plot (Table 1), which does not reveal any discrepancy in the fitting. Thus, both the plots argue that Gamma fitted MCP-1 model (Table 1) is near to its true model.

RESULTS

The outcomes of MCP-1 analysis are tabulated in Table 1 for both the models. It is observed from Table 1 that all the included factors in the mean model for both the distributions are highly significant. Mean MCP-1 is positively associated with BMI ($p<0.0001$), resistin ($p<0.0001$) and the interaction effect of insulin and leptin (i.e., insulin*leptin) ($p<0.0001$), while it is negatively associated with insulin ($p<0.0001$) and leptin ($p<0.0001$). The variance of MCP-1 is positively associated with age*insulin ($p=0.0025$), leptin*resistin ($p=0.0176$) and glucose*leptin ($p=0.0819$), while it is negatively associated with age ($p=0.0706$), HOMA ($p=0.0055$), leptin ($p=0.0198$) and resistin ($p=0.0777$). Note that age ($p=0.0383$), glucose*leptin ($p=0.0056$) and resistin ($p=0.0215$) are significant in the Log-normal fitted variance model, while they are partially significant in Gamma fitted variance model.

Gamma fitted MCP-1 mean (μ) model (from Table 1) is μ = exp (5.1791+0.0455 BMI - 0.0265 Insulin - 0.0192 Leptin+0.0009 Insulin*Leptin+0.0220 Resistin), and Gamma fitted MCP-1dispersion ($\hat{\sigma}^2$) model is $\hat{\sigma}^2$ = exp (0.7374-0.0293 Age-0.0868 Insulin+0.0051 Age*Insulin-0.8286 HOMA+0.0053 Glucose-0.0997 Leptin+0.0007 Glucose*Leptin-0.0405 Resistin+0.0010 Leptin*Resistin).

Mean and dispersion relationship of MCP-1 are expressed by the above two equations. Mean MCP-1 is explained by BMI, insulin, leptin, insulin*leptin and resistin, while the dispersion of MCP-1 is explained by age, insulin, age*insulin, HOMA, glucose, leptin, glucose *leptin, resistin, leptin*resistin. The mean and dispersion of MCP-1 are modeled simultaneously by the iterative method [19]. For testing the significance of regression coefficients, t-statistic is used (Table 1).

DISCUSSION

Summarized results of MCP-1 analysis are presented in Table 1. The detailed conclusions of MCP-1 analysis are displayed in this section. Mean MCP-1 model concludes the following:

- Mean MCP-1 is positively associated with BMI ($p<0.0001$), concluding that MCP-1 levels are higher as BMI increases. This is reported in many articles [9, 17]
- Mean MCP-1 is negatively associated with insulin ($p<0.0001$), implying that MCP-1 levels rise as insulin decreases. This is very little reported in earlier articles
- Mean MCP-1 is negatively associated with leptin ($p<0.0001$), indicating that MCP-1 levels rise as leptin decreases, which is little reported in earlier articles
- Mean MCP-1 is positively associated with insulin*leptin ($p<0.0001$), implying that MCP-1 levels increase as the joint interaction effect insulin*leptin increases. Note that its two marginal effects insulin and leptin are negatively associated with MCP-1, while their joint effect is positively associated with it. This is not reported in earlier articles
- Mean MCP-1 is positively associated with resistin ($p<0.0001$), interpreting that MCP-1 levels increase as resistin levels increase. This is very little reported in earlier articles. Variance model of MCP-1 concludes

Tab. 1. Results for mean and dispersion models for MCP.1 from Log-Normal and Gamma fit

Model	Covariate	Gamma model				Log-normal model			
		estimate	s.e.	t-value	P-value	Estimate	s.e.	t-value	P-value
Mean model	Constant	5.1791	0.27784	18.641	<0.0001	4.9439	0.28594	17.29	<0.0001
	BMI	0.0455	0.01066	4.265	<0.0001	0.0465	0.01101	4.226	<0.0001
	Insulin	-0.0265	0.00449	-5.9	<0.0001	-0.0225	0.00494	-4.566	<0.0001
	Leptin	-0.0192	0.00336	-5.73	<0.0001	-0.0174	0.00345	-5.038	<0.0001
	Insulin*Leptin	0.0009	0.00017	5.458	<0.0001	0.0009	0.00018	4.846	<0.0001
	Resistin	0.022	0.00348	6.327	<0.0001	0.0239	0.00345	6.923	<0.0001
Dispersion Model	Constant	0.7374	1.5228	0.484	0.6293	1.011	1.5513	0.652	0.5158
	Age	-0.0293	0.0161	-1.826	0.0706	-0.0328	0.0156	-2.097	0.0383
	Insulin	-0.0868	0.0733	-1.184	0.239	-0.0613	0.072	-0.851	0.3966
	Age*Insulin	0.0051	0.0016	3.098	0.0025	0.0054	0.0015	3.488	0.0008
	HOMA	-0.8286	0.2928	-2.83	0.0055	-0.9607	0.2825	-3.4	0.0009
	Glucose	0.0053	0.0144	0.371	0.7113	0.0069	0.0143	0.483	0.63
	Leptin	-0.0997	0.0421	-2.365	0.0198	-0.1177	0.0416	-2.826	0.0056
	Glucose*Leptin	0.0007	0.0004	1.756	0.0819	0.0008	0.0004	2.091	0.0388
	Resistin	-0.0405	0.0227	-1.781	0.0777	-0.0524	0.0224	-2.332	0.0215
	Leptin*Resistin	0.001	0.0004	2.411	0.0176	0.0013	0.0004	3.114	0.0024
		AIC=1572.816				AIC=1575			

the following, which is not reported in earlier articles

- The variance of MCP-1 is negatively associated with age (p=0.0706), concluding that MCP-1 variance is higher at younger women. Note that it is significant under the Log-normal model
- The variance of MCP-1 is positively associated with age*insulin (p=0.0025), interpreting that it increases as the interaction effect age*insulin increases. Note that age is negatively associated while insulin is insignificant, but their joint interaction effect is positively associated with it
- The variance of MCP-1 is negatively associated with HOMA (p=0.0055), implying that it increases if HOMA levels decrease
- The variance of MCP-1 is negatively associated with leptin (p=0.0198), indicating that it increases as insulin levels decrease
- The variance of MCP-1 is positively associated with glucose*leptin (p=0.0819), interpreting that it increases as the interaction effect glucose*leptin increases. Note that leptin is negatively associated while glucose is insignificant, but their joint interaction effect is positively associated with it
- The variance of MCP-1 is negatively associated with resistin (p=0.0777), concluding that it increases as resistin levels decrease
- The variance of MCP-1 is positively associated with leptin*resistin (p=0.0176), interpreting that it increases as the interaction effect leptin*resistin increases. Note that both leptin and resistin are negatively associated with it, while their joint interaction effect is positively associated

The current MCP-1 analysis shows that it is significantly associated with age, BMI, diabetes markers (insulin and glucose), and also other breast cancer biomarkers (resistin, leptin, HOMA). Here it is observed that mean MCP-1 is significantly positively associated with BMI (supports earlier findings) and resistin. On the other hand, BMI and resistin analyses have revealed a similar association with MCP-1. Note that mean MCP-1 is negatively significantly associated with insulin and leptin. But leptin analysis has revealed a similar association with MCP-1, while MCP-1 is associated with the variance of insulin. The current MCP-1 analysis shows no association with adiponectin, while adiponectin analysis has revealed similar results. In addition, present analysis has shown that the interaction effect insulin*leptin is positively associated with MCP-1, which is not mentioned in any previous article. Moreover, there are many factors such as age, age*insulin, HOMA, leptin, glucose*leptin, resistin, leptin*resistin are highly associated with the variance of MCP-1 (Table 1) which were not noted in any previous article. Diabetes markers such as glucose and insulin are associated with the mean and variance of MCP-1. These diabetes markers jointly with leptin (i.e., insulin*leptin and glucose*leptin) and age (age*insulin) are associated with mean and variance of MCP-1 (Table 1). In addition, MCP-1 is also associated with other breast cancer biomarkers such as leptin, resistin, and HOMA. Leptin and resistin are marginally and jointly associated with the mean and variance of MCP-1, while HOMA is only marginally associated with the variance of MCP-1 (Table 1). Best of our knowledge, little previous studies have focused the associations of MCP-1 with many other breast cancer and diabetes markers adopting probabilistic modeling, thus the present findings are little compared with the previous results.

The current outcomes of MCP-1 analysis are completely associated with the data set in [18]. It is hoped that the present results will be valid for similar data sets, which is not examined herein. The considered data set does not take on many other breast cancer biomarkers and diabetes markers such as 2-hours post plasma glucose, random plasma glucose, and HbA1c. So, the present study is unable to derive any association of MCP-1 with HBA1c, random plasma glucose, and 2-hours post plasma glucose. Future researchers can consider much more diabetes and breast cancer biomarkers including age and BMI.

CONCLUSION

The associations of MCP-1 with BMI, insulin, glucose, age and other breast cancer biomarkers have been derived herein with probabilistic modeling. The final MCP-1 model has been adopted on comparison of both the Log-normal and Gamma models, small standard error of the parameter estimates, based on the smallest AIC value, and examining model checking plots. The standard error of the mean parameter estimates of MCP-1 is lower in the final selected Gamma model than Log-normal, while the scenario is completely reverse for the variance models except for the intercept. Both models have very similar results. Thus, the final selected MCP-1 model is very close to its true model. Therefore, the derived associations from the MCP-1 model are true to the best of our knowledge. The derived results have supported many earlier results and real situations. The report has shown that mean MCP-1 is associated with BMI, insulin, leptin, resistin, and insulin*leptin, while the variance of MCP-1 is associated with age, age*insulin, HOMA, leptin, glucose*leptin, resistin leptin*resistin. These associations cannot be derived based on simple correlation, simple and multiple regression, meta-analysis, logistic regression, odds ratio, etc. Hence, the research should have greater faith in the current MCP-1 analysis outcomes than those emanating from meta-analysis, simple and multiple regression, odds ratio, logistic regression, etc.

It has been derived that MCP-1 is higher for high BMI women along with high levels of resistin, including low levels of leptin and insulin. If both the insulin and leptin levels are low indicating that their joint interaction effect (insulin*leptin) is positive, which also increases the MCP-1 levels (Table 1). Most of the findings related to MCP-1 analysis herein are completely new in the breast

cancer literature. The present findings will be helpful to the medical practitioners, researchers, patients as well as healthy women. Women with high BMI should care on MCP-1levels along with resistin, insulin and leptin levels.

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).

REFERENCES

1. Mortazavi H, Baharvand M, Mehdipour M. Oral potentially malignant disorders: an overview of more than 20 entities. J Dent Res Dent Clin Dent Prospects. 2014;8:6-14.
2. Amagasa T. Oral premalignant lesions. Int Clin Oncol. 2011;16:1-4.
3. George A, BSS SS, Varghese SS, Thomas J, Gopakumar D, et al. Potentially malignant disorders of oral cavity. OMPJ. 2011;2:95-100.
4. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. J Oral Sci. 2010;52:251-256.
5. Tannirandorn Y, Rodeck CH. New approaches in the treatment of haemolytic disease of the fetus. Baillieres Clin Haematol. 1990;3:289-320.
6. Vasudev S, Vakade CD, Paramesh RC, Belgal P. Role of curcumin in management of potentially malignant disorders: A review of literature. J Adv Clin Res Insights. 2016;3:152-155.
7. Neville BW. Oral and maxillofacial pathology. Philadelphia, PA: W.B. Saunders, 2002.
8. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002;52:195-215.
9. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer. 1975;36:1021-1028.
10. Gupta VK, Malhotra S, Patil R, Tripathi A. Oral submucous fibrosis at pediatric age, now time to think: Series of two cases. Indian J Med Paediatr Oncol. 2013;34:107-110.
11. Angadi PV, Rekha KP. Oral submucous fibrosis: A clinicopathologic review of 205 cases in Indians. Oral Maxillofac Surg. 2011;15:15-19.
12. Abbate G, Foscolo AM, Gallotti M, Lancella A, Mingo F. Neoplastic transformation of oral lichen: Case report and review of the literature. Acta Otorhinolaryngol Ital. 2006;26:47-52.
13. Cawson RA, Odell EW. Cawson's Essentials of Oral Pathology and Oral Medicine. Edinburgh; Toronto: Churchill Livingstone, 2008.
14. Thomas G, Hashibe M, Jacob BJ, Ramadas K, Mathew B, et al. Risk factors for multiple oral premalignant lesions. Int J Cancer. 2003;107:285-291.
15. Chung CH, Yang YH, Wang TY, Shieh TY, Warnakulasuriya S. Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan. J Oral Pathol Med. 2005;34:460-466.
16. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26:612-619.
17. Deepa DA, Anita B, Sreelatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemo protective agents in oral submucous fibrosis: A clinical and histopathological evaluation. JIAOMR. 2010;22:88-92.
18. Nagpal M, Sood S. Role of curcumin in systemic and oral health: An overview. J Nat Sci Biol Med. 2013;4:3-7.
19. Kopuri RK, Chakravarthy C, Sunder S, Patil RS, Shivraj W, et al. A comparative study of the clinical efficacy of lycopene and curcumin in the treatment of oral submucous fibrosis using ultrasonography. J Int Oral Health. 2016;8:687-691.
20. Ramirez-boscα A, Soler A, Gutierrez MA. Antioxidant curcuma extracts decrease the blood lipid peroxide levels of human subjects. Age. 1995;18:167-169.
21. Agarwal N, Singh D, Sinha A, Srivastava S, Prasad RK, et al. Evaluation of efficacy of turmeric in management of oral submucous fibrosis. J Indian Acad Oral Med Radiol. 2014;26:260-263.
22. Shivakumar GC, Sahana S, Fatima N, Chaurasia A. Comparative evaluation of curcumin extracts and lycopene in leukoplakia. J Dent Educ. 2016;9:153-157.
23. Singh V, Pal M, Gupta S, Tiwari SK, Malkunje L, et al. Turmeric-A new treatment option for lichen planus: A pilot study. Natl J Maxillofac Surg. 2013;4:198-201.