

Risk factors of reflux esophagitis observed in tertiary care centre of Nepal

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Abstract

Introduction: Gastroesophageal reflux disease (GERD) is considered to be common disease in western countries. The prevalence of GERD is believed to be less in Asia than in Western countries. Upper GI Endoscopy is the valuable tools in the evaluation of reflux esophagitis which is a common complication of GERD. The present study aimed to determine the risk factor of Reflux Esophagitis in Nepalese with Gastroesophageal Reflux disease symptoms.

Methods: It was a cross sectional observational study conducted in the department of Gastroenterology at Tribhuvan University, Institute of Medicine. Patients were recruited as per inclusion and exclusion criteria. The study involved data on 166 patients with Gastroesophageal reflux disease symptoms. After fulfilling the criteria of validated GERD questionnaire, patient were divided into two groups those having reflux esophagitis and Non erosive reflux disease according to the upper Gastrointestinal Endoscopy. Association of reflux esophagitis with different variables including patient characteristics, clinical features of GERD and endoscopic findings were tested using Chi-square test for discrete variables and continuous variables are measured as Mean $\pm$ SD. Multivariate analysis was performed for the association of risk factors with reflux esophagitis using logistic regression analysis. p value <0.05 was considered statistically significant.

Results: Among the total of 166 patients with GERD, 63.3% were female and 36.7% were male. Mean BMI of the patient was 23.47 ± 4.59 . Of the total 7.8% had history of smoking and 12% patients were alcohol consumer. 27.7% patients were found to have reflux esophagitis. There was statistically significant difference between gender of the patients between the two group (p value =0.05). There was significant association found between current smoking and reflux esophagitis ($p=0.03$), also, between alcohol consumer and reflux esophagitis ($p=0.021$). While comparing the endoscopic findings Hiatus hernia was found significantly associated with Reflux esophagitis ($p=0.004$), Mean BMI and presence of peptic ulcer disease was not significantly associated with Reflux esophagitis ($p=0.9$) and ($p=0.36$).

Conclusion: The frequency of Reflux esophagitis is 27.7% in our Nepalese patient. Reflux esophagitis is more common in male, predominantly in current smoker and alcoholics and those who are having hiatus hernia. Abstinence of smoking and alcohol drinking along with lifestyle modification might be important steps for prevention of Reflux esophagitis.

Key words: Gastroesophageal reflux disease, Upper GI endoscopy, Reflux esophagitis

Introduction

Gastro esophageal reflux disease (GERD) is a common chronic disorder prevalent in many countries. It is

one of the most prevalent diseases seen in Western countries.¹ It is defined by the abnormal reflux of gastro duodenal content into the esophagus, occurring

on a daily, weekly or yearly basis, which may lead to other complications including Esophagitis, esophageal ulcer, upper gastrointestinal bleeding and Barrett's esophagus.²⁻⁴

Esophagitis is only present in a subset of patients with GERD⁵ and is viewed increasingly as a complication rather than a presentation of the disease.

The consensus panel proposed a definition of GERD during Asia-Pacific Digestive Week 2003⁶ as "GERD is a disorder in which gastric contents recurrently reflux into the esophagus causing heartburn and other symptoms." In Japan, however, the accepted definition of GERD extends to include damage to the esophageal mucosa.⁷

Published studies indicate that the prevalence of GERD is lower in the Asian population and the spectrum of the disease is mild.⁹ A systematic review identified a 10–20% prevalence of GERD (at least weekly heartburn and or regurgitation) in the western countries; while in Asia, the prevalence was at <5%.⁹ It has been suggested that there is an increasing trend in the prevalence of GERD over the last two decades and that reflux disease is more common in Asian countries than previously recognized.^{10,11} Age, male sex, obesity, and hiatus hernia (HH) were the proposed risk factors for GERD. (1) Changes in preference to a more Westernized diet and lifestyle were considered responsible for the increase in reflux disease in Asia.¹² Epidemiologic data from the Indian subcontinent; Africa, South America, and the Middle East are sparse.¹

The prevalence of GERD among Nepalese residing in Brunei Darussalam was 7.2%.¹³ The study by Kasyap AK, et al. from NAMS, Nepal enrolled 127 reflux esophagitis after endoscopic diagnosis to find the association between BMI and GERD. They determined no significant association among age, sex, smoker, alcoholics, hernia and severity grade of esophagitis ($p>0.05$) (14)

There are a number of studies regarding GERD, its prevalence and risk factor in general population in world literature. There are very few studies in Nepalese regarding GERD but there are no such studies identifying the frequency of RE among GERD patients. So, we conducted this study to determine the

possible risk factors of endoscopic Reflux Esophagitis in Nepalese with Gastroesophageal Reflux disease symptoms. Identifying the risk factor this study may have role in prevention of complication of GERD like Reflux Esophagitis, Barrett esophagus, stricture of lower Esophagus and Adenocarcinoma of the Esophagus which are the dreadful complication of prolong GERD.

Methods

This Cross sectional descriptive study was conducted in the Gastroenterology Unit, Department of Medicine, TUTH, Kathmandu Nepal from March 2017 to June 2017. Patients attending outpatient >16 years who fulfilled the validated criteria for GERD questionnaire¹⁵ were referred for UGI endoscopy. Gastroesophageal Reflux symptoms defined as heart burn and acid regurgitation were included in the study after providing written and informed consent. Patient with history of Abdominal Surgery, Gastrointestinal Carcinoma, Inflammatory Bowel disease and Concomitant medical condition like advanced Liver and Renal disease were excluded. The study was approved by the Institutional Review Board of Tribhuvan University, Institute of Medicine, and Kathmandu, Nepal. Patients fulfilling inclusion criteria were enrolled in the study after obtaining informed and written consent.

We screened 166 patients with Gastro esophageal reflux symptoms having Regurgitation or Heartburn who fulfilled the GerDQ questionnaire through direct interviewing. The selected patients were recruited for Upper Gastro Intestinal endoscopy. Severity of Reflux esophagitis was graded according to Los Angeles classification, Grade A to D and associated complications like Barrets esophagus, esophageal stricture and esophageal carcinoma. NERD is defined as no mucosal breaks in the esophagus and the patients have typical Reflux symptoms.

Hiatus hernia (HH) was defined as present when the distance from the proximal end of the gastric folds to the diaphragm was greater than 1 cm. Endoscopic findings, such as gastric ulcer, duodenal ulcer, ESEM, and HH were assessed.

The following variables were included: age and sex, body mass index (BMI), occupation, Tea drinking habits,

Current smoking status, and alcohol consumption habits (>21 drinks per week in men and >14 drinks per week in female, 1 alcoholic drink ~ 10 gram of alcohol per one drink unit). Heartburn, Regurgitation, epigastric pain, nausea, early-satiety and Night symptoms. Endoscopic findings like Reflux esophagitis, Hiatus Hernia, PUD. BMI was classified according to World Health Organization BMI criteria as normal (18.5 to < 24.9 kg/m²), overweight (24.9 -29.9 kg/m²), and obese ($\geq$ 30 kg/m²).

Statistical analysis

Statistical analysis in this study was conducted using the SPSS version 23.0 software package (SPSS, Chicago, IL, USA). Statistical analysis was performed using the chi-square test for comparison of discrete variables, and the t-test was used for comparison of continuous variables. Continuous variables measured in this study are expressed as the mean $\pm$ SD. Multivariate analysis was performed using logistic regression. To examine the risks of potential confounders for erosive esophagitis, multivariate models included adjustment for age, sex, BMI $\geq$ 25, current smoking, alcohol consumption, and HH. The odds ratio (OR) and 95% confidence interval (95% CI) are given for each variable. A two-tailed *P* value < 0.05 was considered statistically significant.

Results

The present prospective study included a total of 166 patients with gastroesophageal reflux symptoms who were undergoing upper gastrointestinal endoscopy. Among the study population 105 (63.3%) were female and 61(36.7%) were male. In the present study female to male ratio is 1.72:1

Age of the patients ranged from 18 to 101 years, mean age was 43.11 $\pm$ 1.06 years. 29 patients (17.5%) were in the age group greater than 60years. Mean BMI of the patients was 23.47 $\pm$ 4.59 (range from 16 to 46). 13(7.8%) patients had history of smoking and 20 (12%) patients were alcohol consumer and 108 (65.1%) of the patient were regular tea consumer, more than two cups per day. Among the study patients, 5.4% were Hypertensive and 2.4 % were diabetic. Regarding diet,

13% were vegetarian and 92.2% are non vegetarian. All basic characteristics of the patient are shown in the table below (Table 1).

Table 1: Basic characteristic of the patient (n=166)

Clinical characteristics	
Age Mean (SD)	43.11 (1.06)
<45y	102 (61.4%)
46-60y	35 (21.4%)
>60y	29 (17.5%)
Male gender	61 (36.7%)
Female gender	105 (63.3%)
Mean BMI(SD)kg/m ²	23.47 (4.59)
<18.4	16 (9.6%)
18.5-24.9	96 (57.8%)
25-29.9	42 (25.3%)
>30	10 (6%)
Diabetes	4 (2.4%)
Hypertension	9 (5.4%)
Current smoking	13 (7.8%)
Non vegetarian	153 (92.2%)
Vegetarian	13 (7.8%)
Tea consumer	108 (65.1%)
Alcohol consumer	20 (12%)

Of the 166 study patient typical symptoms like heart burn was present in 69.3%, regurgitation in 77.7%, both heart burn and regurgitation in 48.2% and water brash in 25.9%. Atypical symptoms like epigastric pain present in 59.6%,

All 166 patients with reflux symptoms underwent Upper gastro intestinal endoscopy among them, 46 (27.7%) patients were found to have reflux esophagitis. Using Los Angeles classification for differentiation of severity of reflux esophagitis, 33 (19.9%) of the patient with reflux esophagitis showed grade A esophagitis, 6 (3.6%) of them showed grade B esophagitis, 6(3.6%) of them showed grade C esophagitis and one (0.6%) of them showed grade D esophagitis. 36 (21.7%) of patients were found to have Hiatus Hernia.

Table 2: Patients characteristics associated with development of reflux esophagitis

Principal parameters	Patients with RE	Patients with NERD	P value
Mean age (SD)*	45.96±19.65	42.02±15.51	0.1
Age<60y	35 (25.6%)	102(74.4%)	0.13
Age>60y	11 (38%)	18 (62%)	
Male	22 (36%)	39 (64%)	0.05
Female	24 (21%)	89 (79%)	
BMI (mean)±SD*	23.41±5.50	23.49±5.21	0.9
BMI>25kg/m2	16 (31%)	36 (69%)	0.33
BMI<25kg/m2	30 (29%)	84 (81%)	
smoker	7 (54%)	6 (46%)	0.03
Non smoker	39 (25%)	114 (75%)	
Alcoholic	10 (50%)	10 (50%)	0.021
Non alcoholic	36 (25)	110 (75)	
Non- vegetarian	40 (26)	113 (74)	0.11
vegetarian	6 (46%)	7 (54%)	
Tea consumer	33 (31%)	74 (69%)	0.16
Non consumer(Tea)	13 (22%)	45 (78%)	

Based on the upper GI endoscopy findings patients were assigned into two groups, patient with reflux esophagitis and Patient with non erosive reflux disease (NERD) mean age group are 45.96±19.65 (RE group) and 42.02±15.51 (NERD) group which were comparable and no statistical difference found between these two groups ($p=0.1$). There was statistically significant difference between gender of the patients between the two group (p value =0.05). Mean BMI between the two groups are 23.41±5.50 and 23.49±5.21 which were comparable and no statistical difference found ($p=0.9$). Similarly, the percentage of BMI ≥ 25 was not significantly associated with Reflux esophagitis, ($P=0.33$). Table 2

There was significant association found between current smoking and reflux esophagitis ($p=0.03$) similarly between alcohol consumer and reflux esophagitis ($p=0.021$). There was no statistically significant association found between diet (vegetarian or non vegetarian of the patient and tea consumer with reflux esophagitis).

Table 3: Typical and atypical symptoms associated with the development of reflux esophagitis

Parameter	Reflux esophagitis	Patients with NERD	P value
Heart burn	34 (30%)	81(70%)	0.27
Without heart burn	12 (24%)	39 (76%)	
Regurgitation	39 (30)	90 (70%)	0.12
Without regurgitation	7 (19%)	30 (81%)	
Epigastric pain	26 (26%)	73 (74%)	0.36
Without epigastric pain	20 (30%)	47 (70%)	
Nausea	19 (24%)	59 (76%)	0.23
Without nausea	27 (31%)	61 (69%)	
Early satiety	14 (26)	39 (74)	0.47
Without early satiety	32 (28%)	81 (72%)	
Nocturnal symptoms	14 (25%)	41 (75%)	0.39
Without noct.sym.	32 (30%)	79 (70%)	

While comparing the typical clinical features like Heart burn and regurgitation with the reflux esophagitis both were statistically not significant ($p=0.27$) and ($p=0.12$). Similarly while comparing the atypical clinical features like epigastric pain, early satiety, Nausea and nocturnal symptoms with the reflux esophagitis none of these were found to be statistically significant (p value >0.05). Table 3

Table 4: Endoscopic findings associated with development of reflux esophagitis

Parameters	Reflux esophagitis	NERD	P Value
PUD	4 (36%)	7 (64%)	0.36
Without PUD	42 (27%)	113 (73%)	
Hiatus Hernia	17 (47%)	19 (53%)	0.004
Without hiatus hernia	29 (22%)	101 (78%)	

While comparing the endoscopic findings Hiatus hernia was found significantly associated with Reflux esophagitis ($p=0.004$) similarly presence of peptic ulcer disease was not significantly associated with Reflux esophagitis ($p=0.36$). Table 4

Table 5: Univariate and multivariate analysis for comparing risk factor of reflux esophagitis

parameter	Patient with RE(n=46)	NERD (n=120)	Univariate analysis			Multivariate analysis		
			OR	95% CI	P value	OR	95% CI	P value
Male gender	22 (36%)	39 (64%)	0.525	0.263-1.051	0.050	0.327	0.087-1.227	0.100
Age ≥ 60 y	11 (38)	18 (62)	1.781	0.767-4.136	0.131	0.557	0.226-1.375	0.204
BMI ≥ 25	16 (31%)	36 (69%)	1.244	0.605-2.560	0.339	0.872	0.393-1.934	0.737
Current smoking	7 (54%)	6 (46%)	3.410	1.080-10.764	0.035	0.327	0.087-1.227	0.098
Alcohol consumption	10 (50%)	10 (50%)	3.056	1.177-7.932	0.021	0.606	0.190-1.934	0.398
Hiatus Hernia	17 (47%)	19 (53%)	3.116	1.437-6.755	0.004	0.299	0.133-0.673	0.004

Finally risk factor of Reflux esophagitis like Male gender, Age >60 , BMI >25 , Smoking and Alcohol consumer and Hiatus hernia are analyzed and summarized in (Table 5). According to the Univariate analysis male gender smoking, alcohol consumer and hiatus hernia were significant risk factor (p value <0.05). During Multivariate analysis however Hiatus hernia was the only significant risk factor for reflux esophagitis ($p=0.004$) while male gender, smoking, alcohol consumer, age greater than 60 years and BMI >25 were not found to be significant risk factor for Reflux Esophagitis.

Discussion

Gastro esophageal reflux disease has traditionally been considered as a disease of wealthy people. Hence, in developing countries like Nepal, GERD isn't considered as significant health problem until now. To date very few study has been conducted regarding gastroesophageal reflux disease. Therefore, we performed this prospective study to identify the frequency, severity and risk factor of reflux esophagitis in patient presented with GERD symptoms. Gastro esophageal reflux disease is a common disease especially in the western countries than in the Asian countries. For the last few decades

its increasing prevalence is seen in Asian subcontinent probably due to westernized lifestyle and preference for western diet.

The prevalence of Reflux esophagitis was reported as 34% in United States,¹⁶ 45% in Spain¹⁷ and 62% in Finland studies.¹⁸ But there is low prevalence of Reflux esophagitis in Asian countries among the patient with gastro esophageal reflux symptoms and there is very less patient with severe esophagitis as compared to mild esophagitis.¹⁹ Reflux esophagitis was reported as 20% in Japan.²⁰ A study from Egypt reported 24 % of the patient had RE among patient presenting with reflux symptoms.²¹ Similarly studies from Taiwan reported incidence of 17.3 %.²² Study from Pakistan reported an incidence of 42% of Endoscopically proven GERD²³ among obese.

Several studies on GERD have been conducted from the Indian Subcontinent and interestingly, the reported rates vary. A multicenter study in Indians reported a rate 7.6% based on symptoms experienced at least once a week.²⁴ Another study from Northern Indian hospital reported a rate of 16.2% based on a GERD questionnaire study.²⁵ However, unlike our study these Indian studies only evaluate the prevalence of GERD symptoms. Similarly, the prevalence of GERD among Nepalese society residing in Brunei Darussalam was 7.2 %.¹³

In the current study 166 patients with gastroesophageal reflux disease symptoms fulfilling the GERD questionnaire were recruited for upper gastrointestinal endoscopy. The frequency of reflux esophagitis was 27.7%, which was higher than Taiwanese study 2012 (17.3%), Japanese study (7.1%) and also Egyptian study (24%). Most of our patient have grade A esophagitis (19.9%) and few patient have grade B (3.6%) and grade C (3.6%) esophagitis similarly grade D was seen in 0.6% only.

Complications of Gastro esophageal reflux disease include Reflux esophagitis and Barrett's esophagus. The importance of Reflux esophagitis rests in its potential for masking underlying Barrett's Esophagus. Barrett's esophagus is a condition clearly associated with adenocarcinoma of esophagus with adenocarcinoma is asymptomatic most of the time. Older age >60, male gender, smoking, alcohol drinking, overweight and Hiatus hernia identified as a risk factor associated with reflux esophagitis.^{26,27}

Twenty seven percent of Reflux esophagitis and 0.6% of Barrett's esophagus were consistent with other several studies in Asia and which is different from studies from western countries. The strength of our study is the interview-based design where we have recorded the symptoms of GERD and evaluated heartburn and regurgitation using a symptom score. This has the advantage of bypassing the shortcoming of self-administered questionnaires, particularly, the misinterpretation of non-reflux dyspeptic symptoms for GERD when the responder fills the questionnaire.

This study showed Male gender was significantly associated with Reflux esophagitis ($p=0.05$) which was similar to the other studies.²² Study by Kashyap et al did not find any association of gender with the development and severity of reflux esophagitis.¹⁴ But the study among the Nepalese residing in Brunei found significant relation between GERD symptoms and female gender ($p=0.005$).¹³

The effect of obesity on the prevalence of Gastro esophageal reflux disease symptoms is unclear. There is conflicting evidence that obesity per se predisposes to gastro esophageal reflux disease. Our study shows no significant association of GERD complication, Reflux esophagitis with increasing BMI >25 that is in line with the findings in other Nepalese studies¹⁴ who concluded that obesity as measured by BMI had no significant association with the severity of esophagitis ($p=0.44$). Although some large cross sectional population based studies examining relationship between body mass index and GERD found that increasing BMI was strongly positively related to the frequency of symptoms of and the severity of GERD.²⁸

Taiwanese study by Jian Lin shows the strong association of obesity with the reflux esophagitis.²² The mechanism by which obesity leads to esophagitis remain unknown possible explanation include the development of hiatus hernia and increase intra abdominal pressure, increase frequency of transient lower esophageal sphincter relaxation and high acid secretion rates.²⁹

Association between smoking and GERD is controversial. Several reports showed direct relationship of GERD with smoking,^{30,31} similarly, In our study we found cigarette smoking to be a risk factor for the development of reflux esophagitis ($p=0.035$). Several experimental studies revealed reductions in lower esophageal sphincter pressure and frequent reflux episodes during smoking.³² The previous study by

Kashyap et al found no association of smoking with the development of reflux esophagitis ($p=0.5$). Similarly study from Brunei found no significant association between GERD symptoms and cigarette smoking. Also Indian studies by Sharma et al²⁵ did not find any association of cigarette smoking and GERD symptoms ($p>0.05$).

Similar to smoking, alcohol use has been shown to evoke reflux episodes.^{22,33} In our study we found significant association of alcohol consumption with presence of reflux esophagitis. But the previous study by Kashyap et al and study from Brunei in Nepalese did not find any association of alcoholism with the reflux esophagitis.

During both Univariate and Multivariate analysis we found Hiatus Hernia as an important risk factor for the development of Reflux esophagitis ($p=0.004$). This finding is supported by other studies. Gado et al²¹ from Egypt and Jian-Lin et al²² from Taiwan both found significant association of Hiatus hernia for the development of reflux esophagitis. But previous study by Kashyap et al did not find significant association of Hiatus Hernia with Reflux esophagitis.

It was established that Crural diaphragm is important in prevention of gastroesophageal reflux during the period of lower esophageal sphincter pressure. Hiatus Hernia results in malfunction of gastroesophageal barrier. Patient with hiatus hernia have more reflux episodes during lower LES pressure,³⁴ swallow associated normal LES relaxation, deep inspiration, and strain in presence of GERD. Hiatus Hernia increases esophageal acid exposure because it impairs the Lower esophageal sphincter, reduces the LES pressure and length, and alters the opening characteristic of Gastroesophageal junction.³⁵

Conclusion

In conclusion, this hospital based study supported by questionnaire and upper gastrointestinal endoscopy showed that GERD and its complication, reflux esophagitis is common condition in our Nepalese patient though the disease burden is less than that of Western world. The frequency of Reflux esophagitis is 27.7% in our Nepalese patient at TUTH (IOM). This frequency is similar to the other Asian countries but less than European and American studies. In our study Reflux esophagitis is more common in male, predominantly in current smoker and alcoholics and those who are having hiatus hernia.

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References

1. Sharma P, Wani S, Romero Y, Johnson D, Hamilton F. Racial and geographic issues in gastroesophageal reflux disease. *Am J Gastroenterol* 2008; 103:2669–80.
2. Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastro-oesophageal reflux disease in an adult population. *Ann Med*. 1995; 27(1):67–70.
3. Kennedy T, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. *Aliment Pharmacol Ther*. 2000; 14(12):1589–94.
4. Nouraei M, Razjouyan H, Assady M, Malekzadeh R, Nasseri-Moghaddam S. Epidemiology of gastroesophageal reflux symptoms in Tehran, Iran: a population-based telephone survey. *Arch Iran Med*. 2007; 10(3):289–94.
5. Kang JY, Tay HH, Yap I, et al. Low frequency of endoscopic esophagitis in Asian patients. *J Clin Gastroenterol* 1993; 16:70–73.
6. Fock KM, Talley N, Hunt R, et al. Report of the Asia-Pacific consensus on the management of gastroesophageal reflux disease. *J Gastroenterol Hepatol* 2004; 19:357–367.
7. Hongo M, Nomura T. Modern perspectives on pathophysiology and treatment of gastroesophageal reflux disease. *J Clin Exp Med* 2001; 198:131–134.
8. Wong WM, Lai KC, Hui WM, Hu WH, Huang JQ, Wong NY, et al. Pathophysiology of gastroesophageal reflux diseases in Chinese—role of transient lower esophageal sphincter relaxation and esophageal motor dysfunction. *Am J Gastroenterol* 2004; 99:2088–2093.
9. Dent J, El-Serag HB, Wallander MA. Epidemiology of gastroesophageal reflux disease: a systematic review. *Gut* 2005; 54:710–7.
10. El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2007; 5:17–26.
11. Wong BC, Kinoshita Y. Systematic review on epidemiology of gastroesophageal reflux disease in Asia. *Clin Gastroenterol Hepatol* 2006; 4:398–407.
12. Kim BJ, Cheon WS, Oh HC, Kim JW, Park JD, Kim JG. Prevalence and risk factor of erosive esophagitis observed in Korean national cancer screening program. *J Korean Med Sci* 2011; 26:642–6.

13. Chong V, Padam B, Hermanta R, Anand J. Gastro-oesophageal reflux disorders among Nepalese residing in Southeast Asia. *Med j Malaysia*. 2013; 68(3):234-8.
14. Kasyap AK, Sah SK, Chaudhary S, Shrestha R, Shrestha D. Association between Body Mass Index and Gastroesophageal Reflux Symptoms in Nepalese Adult Population- A Single Centered Hospital Based Study. *JCMS Nepal*. 2015; 11(2):23-26
15. C. Jonasson, B.Wernersson, D.A.L. Hoff, J. G. Hatlebakk. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2013; 37: 564–572.
16. WO JM, Mendez C, Harrel Setel et al. Clinical impact of upper endoscopy in management of patient with Gastro Esophageal Reflux Disease. *Am J Gastroenterol* 2004; 99:2311-6
17. Garrido Serrano A, Guerrero Igea FJ, Lepe Jimenez JA et al. Clinical features and endoscopic progression of Gastroesophageal reflux disease. *Rev Esp Enferm. Dig* 2003; 95:712-6
18. Voutilainen. M, Sipponen P, Mecklin JP et al. prevalence, clinical, endoscopy and hisstopathological findings in 1,128 consecutive patients referred to endoscopy due to dyspeptic and reflux symptoms. *Digestion* 2000;61:6-13
19. Wong WM, Lai KC, Hui WM, et al. Pathophysiology of gastroesophageal reflux diseases in Chinese – role of transient lower esophageal sphincter relaxation and esophageal motor dysfunction. *Am J Gastroenterol* 2004; 99:2088–93.
20. Komoto K, Iwakiri R, Mori M, Hara M, Oda K, Dango A et al. Clinical symptoms in endoscopic reflux esophagitis: evaluation in 8031 adult subjects. *Dig Dis Sci* 2003; 48: 2237-41
21. Ahmed Gado, Basel Ebeid, Aido Abdelmohsen et al. Prevalence of reflux esophagitis among patients undergoing endoscopy in a secondary referral hospital. *Alexandria Journal of Medicine* (2015) 51, 89–94
22. Jian-lin, Chin Chin ju, Ping–I HSU et al. Prevalence and risk factor of erosive esophagitis in Taiwan. *Journal of the Chinese Medical Association* 75 (2012) 60e64
23. Ssjid Nisar, Shahbaz Piracha, Faisal Masud The Frequency of Gastroesophageal Reflux Disease among obese. *P J M H S* 2010; 4: 455-59
24. Bhatia SJ, Reddy DN, Ghoshal UC, et al. Epidemiology and symptom profile of gastroesophageal reflux in the Indian population: Report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol* 2011; 30:118-27
25. Sharma PK, Ahuja V, Madan K, Gupta S, Raizada A, Sharma MP. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in northern India. *Indian J Gastroenterol*.2011; 30: 118-27.
26. Chan TS, Chang FY. The prevalence and risk factor of reflux esophagitis among adult Chinese population in Taiwan. *J C Gastroenterol* 2007; 41:819-22
27. Cho J, Kim H, Ko G et al. Old age and male sex are associated with increased risk of asymptomatic erosive esophagitis. *J Gastroenterol Hepatol* 2011; 26:1034-8
28. EI- Serag HB, Graham DY, Satia JA et al. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J of gastroenterol* 2005; 100:1243-50
29. WU JC, Mvi LM, Cheung CM et al. Obesity is associated with increased transients lower esophageal sphincter relaxations. *Gastroenterology* 2007; 132:883-9
30. Nelson M, Johnsen R, Ye W, Hveem K, Lagergren J. Life style related risk factors in etiology of gastroesophageal reflux *Gut* 2004; 13: 1730-5
31. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastro-oesophageal reflux- a population based study. *Aliment Pharmacol Ther* 2006; 23: 169-174.
32. Kadakia SC, Kikendall JW, Maydonovitch. Effect of cigarette smoking on Gastro esophageal reflux measure by 24-h ambulatory esophageal ph monitoring. *Am J Gastroenterol* 1995; 90:1785-90
33. Beom Jin Kim, Won Seok Cheon I, Hyoung-Chul Oh, Jeong Wook Ki, Jung Duck Park, Jae G. Kim. Prevalence and Risk Factor of Erosive Esophagitis Observed in Korean National Cancer Screening Program. *J Korean Med Sci* 2011; 26: 642-646
34. Van Herwaarden MA, Samsom M, Smout AJPM. Excess Gastroesophageal reflux in patient with hiatus hernia is caused by mechanism other than transient LES relaxations. *Gastroenterology* 2000; 119:1439-46
35. Gordon C, Kang JY, Neild PJ, Maxwell JD. The role of hiatus hernia in Gastro-esophageal reflux disease. *Aliment Pharmacol Ther* 2004; 20: 719-32