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Study of Serum Pepsinogen 1 And Pesinogen1 to Pepsinogen 2 Ratio Level as A Screening for Atrophic Gastritis and Gastric Cancer

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Abstract

Objective:To evaluate pepsinogen1 (Pg 1) level in serum and pepsinogen1 to pepsinogen2 ration (Pg 1/2) in patients with AG and GC and compare them to gold standard endoscopic examination in those patients, to detect the sensitivity and specify of these markers to evaluate their value as a future seromarker or tumor marker.

Patients and Method: This was an observational case-control comparative study that included 60 patients diagnosed with atrophic gastritis and gastric carcinoma. A clinical and endoscopic examination were used to make the diagnosis, and gastric biopsies were examined histologically to confirm it.Two separate groups of patients were formed, with 30 patients involved within group 1 having AG and 30 patients in group 2 having GC. As a control group, 30 healthy volunteers were enlisted. Informed written consent will be taken from all patients.

Results: Serum Pg 1 and Pg 1/2 in AG and GC patients were comparable *(p= .098, 0.976, respectively)*, however, compared to healthy controls, they were statistically considerably lower*(p< 0.001 for all).* The optimum cut-off values for diagnosing AG or GC were Pg 1 18.96 and Pg 1/2 2.25; these values may produce a 100% sensitivity (94-100), 100% specificity (88.4-100), positive predictive value (PPV) that was 100%, and 100% negative predictive value (NPV).

Conclusion:For AG and GC diagnosis, serum Pg exhibited a very high diagnostic value.

Keywords: Serum pepsinogen, Gastric cancer, Atrophic gastritis.

Introduction

Gastric cancer (GC) was discovered to be the fourth most prevalent cancer-related death factor .[1, 2]However, if it is discovered from the early lesions that are likely to be precancerous, such as atrophic gastritis, a common progressive illness, It has a great prognosis and is treatable..[3, 4]

When it comes to high-risk GC conditions, atrophic gastritis (AG) can progress from modest lesions at first to moderate and severe ones.[5]Therefore, it is essential to carry out early detection of the high-risk group suffering moderate and severe AG related lesions in order to lower the risk of GC.However, these AG related lesions are most probably asymptomatic in populations, making it hard to be detected with recommended current methods like guided biopsies or endoscopy. In order to screen programs for AG lesions, non-invasive techniques are now required.[3, 4]

As a result of the stomach lumen's acidic pH, pepsinogen (Pg), a proenzyme that is abundantly released by the gastric mucosal cells, is transformed into pepsin. There are two Pgimmunological categories: Pg 1 and alsoPg 2. Additionally, the pepsinogen ratio Pg 1/2 was calculated.[6]Approximately, One percent of the pepsinogens produced into the stomach lumen are able to enter the bloodstream and are subsequently found in the serum. By using serum Pg levels, this technique enables investigation of the morphological and functional state of the stomach mucosa.Atrophy of the mucosal glands in the antrum and/or corpus lowers the Pg I/II ratio and influences Pg 1 and Pg 2 levels.[7]

Currently, Pg has been found to be the most reliable non-invasive biomarker for the diagnosis of severe AG or GC.[8-11]However, its application is still controversial,[12, 13]and it is advised to utilize it carefully and with caution[8]since the populations' cut-off values vary.[11, 14]

Accordingly, we aimed to evaluate serum Pg1 and Pg1/2 in patients with AG and GC and compare them to gold standard endoscopic examination in those patients, to detect the sensitivity and specify of these markers to evaluate their value as a future seromarker or tumor marker.

Patients involved and Methods used:

This case-control observational study included 60 adults over the age of 18 with GC and AG. Clinical and endoscopic evidence supported the diagnosis, which was then supported by a histological review of gastric biopsies.Patients were chosen from outpatient clinics and were scheduled for upper GIT Endoscopy in Endoscopy unit in Gastroenterology Unit in Internal Medicine Department, Alexandria University Hospital.After clearly informing all patients, their written consent was obtained. There were two groups of patients: group 1, which contained 30 AG diagnosed patients, and group 2, which had 30 patients with GC. 30 healthy people were enlisted as a control group.

Patients who had undergone partial or total gastrectomy, patients who were undergoing chemotherapy or radiotherapy, patients with gastric polyps, patients suffering gastric lymphoma, and patients suffering gastric carcinoid were all excluded from the study. Patients who had taken inhibitors of proton pump or nonsteroidal anti-inflammatory medicines within the earlier six weeks before enrolment were also excluded.

Each patient underwent a full medical history review as well as a regional and local clinical abdominal examination. All patients underwent upper gastrointestinal endoscopy using traditional and narrow band imaging endoscopy with biopsy. Biopsy samples were collected using the most recent Sydney system of classification.[(15)]Five biopsy samples were obtained: Two were taken from the antrum, which is 2 to 3 cm from the pylorus; one was taken from the lesser distal curvature, and the other from the greater distal curvature; two were taken from the corpus, which is 8 cm away from the cardia; one was taken from the lesser curvature; and one was taken from the incisura angularis. classification of AG using the Sydney system of grading.[(15)]Serum Pg 1 and Pg 2 assay was estimated by Enzyme-linked immunosorbent assay (ELIZA) andPg1/2was calculated. Finally, Pylori Antibodies IgG in blood and Pylori Ag in the stool were assessed.

Results

Table 1 represents patients' demographic data and H. Pylori tests findings. When compared to controls, Pg 1 and Pg1/2 were both lowersignificantly among the group diagnosed with AG and GC group (p 0.001 for all), according to statistical analysis. In contrast, there was difference of no statistical significance in Pg 1 and Pg1/2 among the AG group and the GC group (p=.098, 0.976, respectively). (Table 2)

The Sydney classification found that antrum AG was reported in 10 patients (33.33%), with mild gastritis being described in two patients (20%), moderate gastritis in four patients (40%), and severe gastritis in four patients (40%).Corpus AG was detected in 6 patients (20%), distributed as mild, moderate, and severe AG in one patient (16.67%), three patients (50%), and two patients (33.33%) respectively.Multifocal AG was seen in 14 patients (46.67%), distributed as mild gastritis in three patients (21.43%) moderate gastritis in six patients (42.86%), and severe gastritis in five patients (35.71%).

In terms of Pg1 and Pg1/2, there was difference that was not significant statistically between males and females with p-values= 0.383 and 0.623, respectively). Regarding Pg1 and Pg1/2, there was a difference that was statistically not significant among H. pylori positiveand also negative individuals (p= 0.633 and p= 0.331, respectively). (Table 3)

Pg1 levels were statistically higher in patients with severe exercise than in those with low and moderate activity (p=0.001 and p0.001, respectivelyPg1/2 was statistically significantly lower in patients with severe activity compared to those with light and moderate activity levels (p=0.017 and p=0.023, respectively). However, there was no statistically significant difference in the Pg1/2 and Pg1 ratios between patients who exercised lightly and moderately (p=0.278 and 0.58, respectively). (Table 3)

In AG patients, Pg1 and age had a statistically significant high negative correlation (r= -0.806, p0.001). (Figure 1)In contrast, the Pg1/2 ratio and age did not have a statistically significant relation among AG patients (r=-0.304, p=0.102).

According to histological examination, gastric adenocarcinoma was categorized into two types; intestinal type in 22 patients (73.33%) and diffuse type in 8 patients (26.67%). Accordingtolocation, gastric cancer was found in the antrum within 14 patients (46.67%), body within 7 patients (23.33%), fundus within 4 patients (13.33%), cardia in 3 patients (10%), and pylorus in two patients (6.67%).

In terms of Pg1 and Pg1/2, there was difference of no statistical significance among both the males and the females with p-values = 0.154 and 0.95, respectively.Regarding Pg1 and Pg1/2, there was no significant difference statistically among both H. pylori positive and negative individuals (p=0.4 and p=0.92, respectively).(Table 4)

In GC patients, there was high significant negative connection statistically between Pg1 and age. *(r= -0.95, p<0.001)*. (Figure 2) In contrast, the Pg1/2 ratio and age did not have a

correlation of statistical significance in GC patients (r=-0.133, p=0.48).

Overall model including (age, sex, H. pylori, and disease) is statistically significantinpredictingPg1and Pg1/2 ratio as(F=1486.88,p<0.001),The model explains 98.5 percent of the Pg1 variability and (F= 1724.448, p<0.001), model explains(99%) ofPg1/2 ratio variability. (Table 5)

Table 6 shows the ROC curve analysis of Pg 1 and Pg1/2 ratio. It shows that pg1 (ng/l) can significantly discriminate between patients having AG or GC and healthy individuals as diagnostic accuracy ((AUC)= 1.00 (95% CI), p <0.001), as cut of point which has highest sensitivity, specificity ≤18.96 (sensitivity = 100, specificity = 100). Also, Pg1/2 ratio (ng/l) can significantly discriminate between patients having AG or GC and healthy individuals as diagnostic accuracy ((AUC) = 1.00 (95% CI), p <0.001), as cut of point which has highest sensitivity, specificity ≤2.25 (sensitivity = 100, specificity = 100).

Discussion

To date, it remains debatable for using Pgas a non-invasive biomarker for diagnosing AG or GC.[12, 13]In the present work, although the means of Pg 1 in AG (16.95 ± 1.12 ng/ml) and GC (17.83 ± 0.85 ng/ml) patients were comparable *(p= .098)*, however, they were highly statistically significantly lower than healthy controls (47.23 ± 3.69 ng/ml) *(p< 0.001 for both).* Also, the mean of Pg 1/2 in the AG group (2.02 ± 0.08 ng/ml) was nearly equal to that in the GC group (2.05 ± 0.07 ng/ml) *(p= 0.976)*, but they were highly statistically significantly lower than healthy controls (4.53 ± 0.32 ng/ml) *(p< 0.001 for both).* These results suggest a possible relationship between Pg 1 and Pg 1/2 ratio in diagnosing AG and GC.

These findings confirm those ofMansour-Ghanaei et al.[10]who discovered that patients suffering GC had considerably lower Pg 1serum levels and Pg 1/2 ratio than did healthy individuals. Additionally, Kim et al.[16]found that among 95 patients, patients diagnosed with AG had significantly lower Pgserum levels and also ratio.Similar to this, Nguyen et al.[17]assessed how Pg in serum can help in mild and severe AG diagnosis among the Vietnamese population. They came to the conclusion that the serum PGII lacked diagnostic significance while the Pg 1 level and Pg 1/2 ratio were found to be significant indicators for diagnosing AG. Our findings, however, contrast from those of an Iranian study by Hosseini et al.[13]which found no link between Pg 1 serum level and AG but find correlation that was

statistically significant among AG and Pg 2 and Pg 1/2 ratio levels.

A correlation that was not significant statistically between Pg1 and Pg1/2 and H. pylori was noticed in the current study, whether in AG patients or GC patients. The results of this investigation, however, contradict past reports[18, 19]that suggested a substantial correlation between Pg levels and H pylori infection. According to research reported by Yuan et al.[20]patients with active H. pylori infection had greater blood Pg levels and lower Pg 1/2 levels than patients without the illness.Also, Cai et al.[21]observed that in patients with gastric mucosal atrophy, H. pylori-positive subjects showed considerably statistically significant higher Pg 1 and Pg 2 serum levels and a statistical significant lower P 1/2 in comparison to H. pylori-negative patients (P 0.05). That could be explained by the inconsistent findings of tests performed to find H pylori and the presence of additional variables that could alter the results, such as gender, BMI, and drugs taken (such as proton pump inhibitors).

Regarding the relation between AG activity and Pg1 and Pg 1/2 levels our findings were consistent with Nguyen et al.[17] We found that in AG patients, the disease activity is related to Pg1 and Pg 1/2 where the lowest levels of Pg1 and Pg 1/2 were reported in the severe active disease. According toNguyen et al.[17]the moderate to severe AG group had serum Pg 1 levels that were lowersignificantly more than those of mild AG group.Similar to this,Tonget al.[22]assessed Pg levels in the serum and examined the link with finding of both endoscope and histology in a prospective study of asymptomatic patients. They found that when compared to the groups with mild atrophy and no atrophy, Pg levels in the group with severe AG reduced significantly (p 0.01). There is debate regarding the relationship between other variables including age and gender and pepsinogen levels. Results of a research including 6596 "healthy" participants were reported by Huang et al.[23]According to the study, pepsinogen levels rose in men and fell in women as people aged. The study revealed that values of pepsinogen diminished with age and increased more in males than females.However, Zhang et al.[24]did not discover any statistically significant age- and sex-related values of P 1/2 in their investigation of 2568 healthy individuals. They did note a modest increase in Pg 1 and Pg 2 with ageing in both sexes, though.

Several studies looked at the serum Pgdiagnostic value in the AG and GC diagnosis. In various investigations, the sensitivity ranges of Pgs range from 36.84%[25] to 90.91%[26] for the GCdetection and from 25%[27] to 91.18%[28] to AG detection.In this study, we discovered that serum Pg has a very high diagnostic value for GC and AG. The best cut-off values for diagnosing AG or GC were PGI 18.96 and Pg 1/2 2.25, which might result in 100%

sensitivity (94-100), 100% specificity (88.4-100), 100% PPV, and 100% NPV. This result appears to be consistent with those of earlier studies[8, 9, 11, 17, 22]which found that Pg 1 and Pg 1/2 have a diagnostic value in identifying AGAdditionally, this outcome was comparable to that stated by Mansour-Ghanaei et al.[10]which discovered that both Pg 1 and Pg 1/2 are the only selective and sensitive for GC screening.According to Nguyen et al.[17]For the investigation of moderate and severe AG, the serum Pg 1 and Pg 1/2 ratios showed an accurate diagnostic value, with the Pg 1/2 ratio being preferable.They discovered that the optimal diagnostic AG cut-off valueswere (Pg 169.0) and (Pg 1/24.6), which could yield results with a final accuracy of 82.4% and sensitivity, specificity, PPV, and NPV of 73%, 83.9%, 41.5%, and 95.2% based on images of gastroscopy. The optimum cut-off values for GC diagnosis were Pg 1 63.5 and Pg 1/2 5.2, which might result in final accuracy of 72.9% and sensitivity of 49.4%, specificity of 82.1%, PPV of 52.1%, NPV of 80.5%, and 82.1%specificity.A meta-analysis involving 30,000 patients from 13 different Eastern and Western nations was carried out to evaluate the accuracy of Pg in AG and GC diagnosis.[9] Huang et al. results showed that,[9]Pg 1 had a 69% sensitivity and 73% specificity for diagnosis of intestinal GC and 69% sensitivity and 88%specificity for diagnosis of AG. Although the authors acknowledged it as a limitation, the research heterogeneity in respect of diagnostic methodologies and the various cut-off values for these procedures.Blood Pg levels were used in astudy by Broutet et al.[29]on 284 patients suffering dyspeptic related complaints in 14 European countriesto assess the severity of multifocal AG. They claimed that the only precancerous stomach lesions biomarker that may be used as a screening test is the Pg 1/2 ratio. The following outcomes were reported in relation to the Pg 1/2: having a5.6cut-off point, and 65.0% sensitivity and 77.9%. specificity. Since we evaluated a cut-off value of pepsinogen levels ranging from mild to moderate and severe AG up to GC, our study's Pg 1 and Pg 1/2 cut-offs were lower than those reported in the literature. As a result, as compared to what is reported in the literature, Pg 1 and Pg 1/2 have higher sensitivity and specificity for diagnosing AG and GC. Some researchers have discovered outcomes that are not significant or are weak, in contrast to our findings.One of these is a study by Ricci et al.[30]which found that Pg 1 and Pg 1/2 cannot distinguish between patients with and without antrum-predominant AG. Similarly, Colarossi et al.[31]showed that none of the biomarkers could distinguish between patients who had atrophy and those who did not. Age, H. pylori infection, AG activity, the GC cardia/non-cardia nature, and AG alone or combined with metaplasia that was intestinally involved, are some of the variables that may contribute to these variances. These variables can also change the serum pepsinogens levels. Additionally, the great variation in Pg serum testing methods

makes it challenging to interpret the data. The most used technique is ELISA, but some researchers also utilize immunoturbidimetry, radioimmunoassay, chemiluminescent assay, and the latex agglutination test.[32]

This study only used a limited sample size, therefore that is one of its limitations. Serum pepsinogen in AG and GC were not separately evaluated for their diagnostic value (sensitivity and specificity).

Conclusion

Serum Pg demonstrated a very high diagnostic value for the diagnosis of AG and GC. In which it was discovered that the Pg 1/2 ratio and Pg 1 level were helpful biomarkers for the diagnosis of patients with AG and GC...

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Table1: Comparison of the three study groups based on demographic parameters.

Sociodemographicdata	**Atrophicgastritis(n=30)**		**Gastriccancer (n=30)**		**Controls(n=30)**		**Test ofsignificance(p)**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Sex							
Male	16	53.3	16	53.3	15	50.0	χ^2= 0.089, p= 0.956
Female	14	46.7	14	46.7	15	50.0	
Age(years)							
Mean±SD	49.47 ±10.56		58.23 ±9.25		50.17 ±11.82		F= 6.342,p=0.003*
Median(Min–Max)	49.5 (34 – 66)		55.5 (45 – 77)		48.0 (33 – 69)		
Significancebet.groups	p1= 0.005*, p2=0.965, p3= 0.011*						
H.pylori:							
Negative	15	50.0	16	53.3	14	46.7	χ^2=0.267, p=0.875
Positive	15	50.0	14	46.7	16	53.3	

χ2;Chi-square test to compare the three involved study groups
F; One-Way ANOVA test, pairwise comparison was done using Tukey testp1;
p valuebetween atrophicgastritis and gastric cancer
p2;pvaluebetweenatrophicgastritisandcontrols
p3; p value between gastric cancer and controls.
SD;standard deviation, *significant(p<0.05)

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Table 2: Comparison of the Pg1 and Pg1/2 ratio biomarkers among the three involved study groups

	Atrophic gastritis(n=30)	**Gastric cancer(n= 30)**	**Controls (n=60)**	**Testof significance (p)**
Pg 1 (ng/ml)				
Mean± SD	16.95 ±1.12	17.83 ±0.85	47.23 ±3.69	H= 63.900,p< 0.001*
Median (Min– Max)	16.3(15.74-18.84)	17.9 (16.14-18.9)	47.4 (41.28-52.14)	
Significancebet.Groups	p1= .098, p2< 0.001*, p3< 0.001*			
Pg1/2(ng/ml)				
Mean± SD	2.02 ±0.08	2.05 ±0.07	4.53±0.32	H= 60.308,p< 0.001*
Median (Min– Max)	2.02 (1.89 -2.25)	2.05 (1.91 -2.21)	4.52(4.01 -5.12)	
Significancebet.Groups	p1= 0.976, p2< 0.001*, p3< 0.001*			

H;KruskalWallistest,pairwise comparisonwas doneusingBonferronitest
p1;p valuebetween atrophicgastritis and gastric cancer
p2;pvaluebetweenatrophicgastritisandcontrols
p3; p value between gastric cancer and controls.
SD;standard deviation, * significant(p<0.05)

Table 3: Distribution of Pg1 and Pg1/2 ratio with different variables among AG patients.

Variables	Pg1(ng/ml)		Test ofsignificance(p)	Pg1/2ratio(ng/ml)		Test ofsignificance(p)
	Mean± SD	Median (Min-Max)		Mean± SD	Median (Min-Max)	
Sex						
Male	16.79 ± 1.12	16.17(15.75-18.84)	U=91.0 p=0.383	2.0 ±0.08	2.02(1.9-2.18)	t= -0.497 p=0.623
Female	17.12 ± 1.13	16.74(15.74-18.66)		2.03 ±0.09	2.02(1.89-2.25)	
H.pylori						
Positive	17.01 ±1.19	16.24(15.88-18.84)	U=101.0 p=0.633	2.0 ±0.07	2.02(1.89-2.18)	t= -0.990 p=0.331
Negative	16.88 ±1.08	16.44(15.74-18.52)		2.03 ±0.09	2.02(1.92-2.25)	
Activity						
Mild	18.45 ±0.23	18.47(18.2-18.84)	H= 23.055p<0 .001*	2.07 ±0.09	2.04(2.0-2.25)	H=7.566p =0.023*
Moderate	17.11 ±0.93	17.06(16.11-18.66)		2.04 ±0.07	2.02(1.94-2.18)	
Severe	15.92 ±0.12	15.95(15.74-16.1)		1.96 ±0.06	1.95(1.89-2.03)	
Significant bet.groups	p1=0.278, p2<0.001*, p3=0.001*			p1=0.58, p2<0.017*, p3=0.023*		

U;Mann-Whitney test,t; independentttest
H;KruskalWallistest,pairwisecomparisonwas doneusingBonferronitestp1;p valuebetweenmild and moderate
p2;p valuebetween mild and severe
p3;pvaluebetweenmoderateandsevere.SD;standarddeviation,*significant(p<0.05)

Table 4: Both Pg1 and Pg1/2 ratio distribution among the GC group according to sociodemographic traits.

Variables	Pg1(ng/ml)		Test ofsignificance(p)	Pg1/2ratio(ng/ml)		Test ofsignificance(p)
	Mean± SD	Median (Min-Max)		Mean± SD	Median (Min-Max)	
Sex						
Male	17.6± .9	17.2(16.14-18.19)	(U=147, P=0.154)	8.67±.5	8.7(7.9-9.4)	(U=113.5, P=0.95)
Female	18.11± .71	18.2(16.7-18.9)		8.7±.5	9.04(7.8-9.23)	
H.pylori						
Positive	17.68±.94	17.9(16.14-18.96)	(U=91.5, P=0.4)	8.72±.53	9(7.9-9.4)	(U=109.5, P=0.92)
Negative	17.9±.78	18(16.7-18.9)		8.73±.54	9(7.8-9.3)	

U; Mann-Whitneytest.
SD;standard deviation,* significant($p<0.05$)

Table 5: Linear regression model for predictors of Pg1 and Pg 1/2 among the studied sample

Predictors	UnstandardizedCoefficientsBstd. error		StandardizedCoefficientsBeta	t	Significance	95% CI
Pg1						
Constant	53.158	1.164			<0.001*	
Age	-0.131	0.017	-0.103	-7.736	<0.001*	-0.165 –-0.098
Sex[a]	0.509	0.376	0.018	1.355	0.179	-0.238 – 1.257
H.pylori[b]	-0.174	0.368	-0.006	-0.473	0.638	-0.906 – 0.558
Disease[c]	-29.354	0.395	-0.971	-74.405	<0.001*	-30.138 – -28.569
Pg½						
Constant	1.305	0.409		3.186	0.002*	
Age	0.0	0.002	0.003	0.185	0.854	(-0.003-0.003)
Sex[a]	0.015	0.026	0.006	0.565	0.574	(-0.038-0.068)
H.pylori[b]	-0.028	0.026	-0.012	-1.080	0.283	(-0.079-0.023)
Disease[c]	-0.475	0.223	-0.188	-2.126	0.036*	(-0.919 –-0.031)
Pg1	0.068	0.008	0.810	8.971	<0.001*	(0.053-0.083)

[A]ref;Female
[B]ref;negativeH.pylori
[C]ref;not-disease

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Table 6: ROC curve analysis for Pg1 and Pg1/2 (ng/l) in diagnosing AG or GC patients

AUC	95% CI	Point of Cut off	Sensitivity (95% CI)	Specificity (95% CI)	+PV	-PV	p
1.000	0.960 – 1.000	≤18.96	100 (94 – 100)	100 (88.4 – 100)	100	100	<**0.001***
AUC	**95% CI**	**Point of Cut off**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**+PV**	**-PV**	**p**
1.000	0.960 – 1.000	≤ 2.25	100 (94 – 100)	100 (88.4 – 100)	100	100	<**0.001***

AUC: Area under the curve
+PV: positive predictive value
-PV: negative predictive value

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Figures

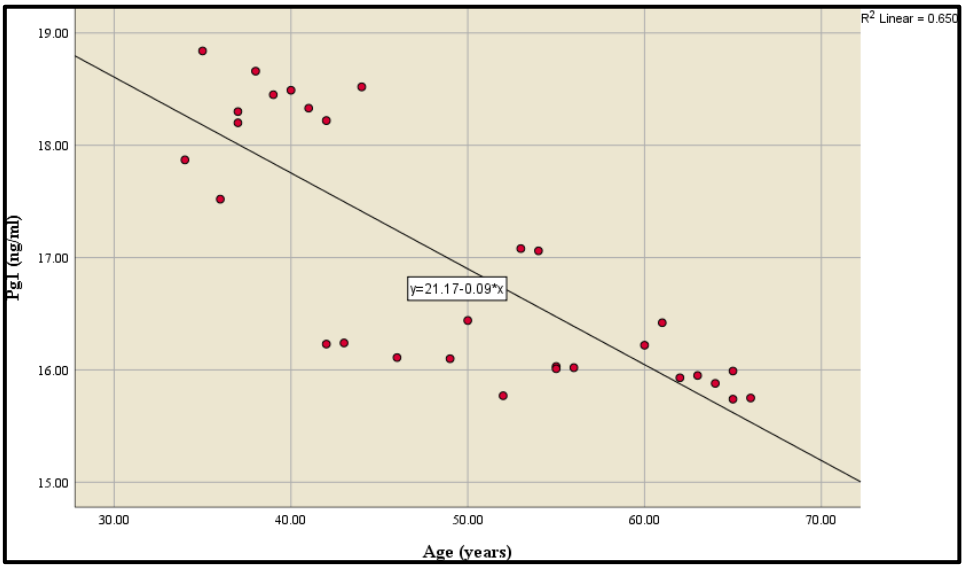

Figure 1: Correlation between Pg1 and age among AG group

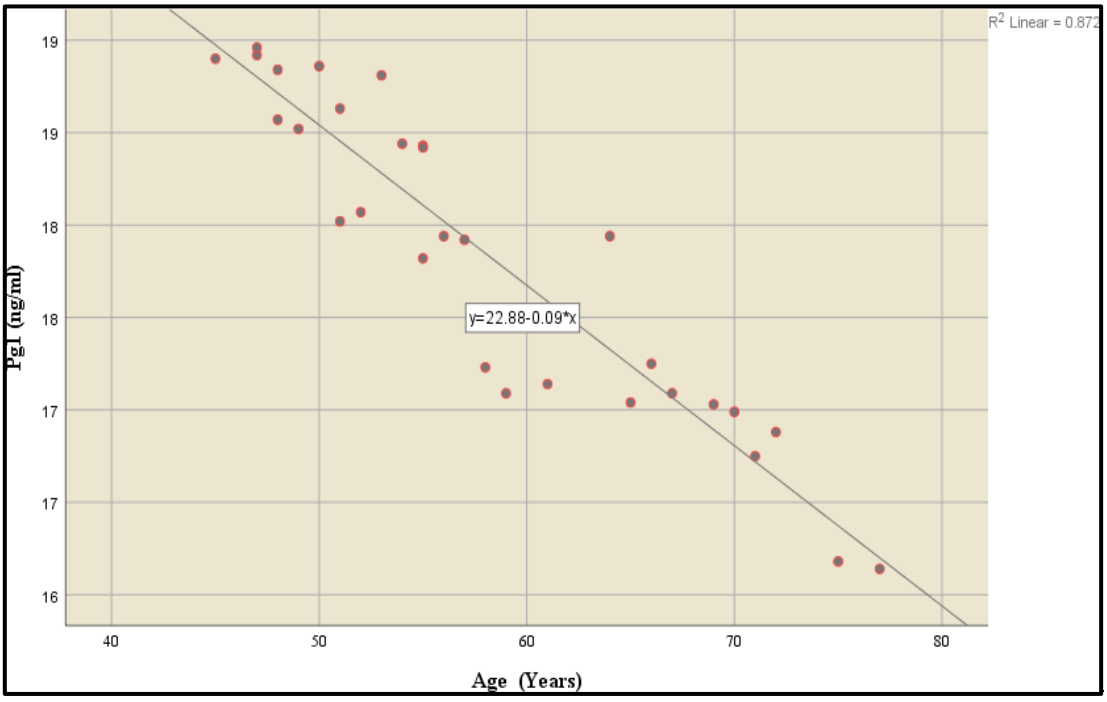

Figure2: Correlation betweenPg1and ageamongGCgroup