SAS Journal of Surgery ISSN 2454-5104
SAS J. Surg., Volume-3; Issue-6 (Jun, 2017); p-154-164
Available online at http://sassociety.com/sasjs/

Original Research Article

A Clinicopathological Study of Gallbladder Carcinoma with Special Emphasis on Correlation of Serum Ca 19-9 Level to Staging

Dr. Visazotuo Yano[1], Dr. Souvik Basak[2*], Prof (Dr.) Kashinath Das[3]
[1]Junior Specialist, Community Health Centre, Chennai
[2]RMO cum Clinical Tutor
[3]Professor and Head, Department of Surgery, Medical College, Kolkata
Department of Surgery, Medical College, Kolkata 88, College Street, Kolkata -700073

***Corresponding author**
Dr. Souvik Basak
Email: sb009cmc@gmail.com

Abstract: Carcinoma gallbladder has traditionally been considered an incurable disease with a poor prognosis. The aim of this study was to study the clinical presentation and pathology of carcinoma gallbladder and to correlate serum CA 19-9 to staging which may help in its better diagnosis and further treatment. It was seen that the mean age of presentation was 52.6 years and was found to be more common in female with the male to female ratio of 1:3.7. Most of the patients belonged to low socioeconomic class (56%). The most common clinical feature was pain (86.7%). Stage IVb was the most common stage (53.3) and adenocarcinoma the most common histological type. It was seen that CA 19-9 was raised in 96.6% of the patients, with the mean of 795.13 U/ml. CA 19-9 did not significantly correlate with gender, pain, jaundice, weight loss, anaemia, nausea/vomiting, abdominal lump and gall stone but significantly correlated with nodal stage (p-value = 0.001), metastasis (p-value = 0.015), stage (p-value = 0.000) and socioeconomic status (p-value = 0.001). Higher stages are associated with poorer prognosis, therefore, it can be stated that high serum CA 19-9 value has poor prognosis. In any case of gallbladder pathology with raised CA 19-9 it is essential to rule out gallbladder malignancy and diagnosed preoperative patients should also have serum CA 19-9 evaluated for monitoring, recurrence and follow up.
Keywords: Gallbladder Cancer, CA 19-9.

INTRODUCTION:

Gallbladder cancer is an aggressive malignancy that carries an extremely poor prognosis [1]. It is the most common malignancy of the biliary tract and the fifth most common gastrointestinal tract malignancy [4]. It accounts for about 2–4 % of gastrointestinal malignancies, its occurrence in random autopsy series is about 0.4% and approximately 1% of patients undergoing biliary tract operations have carcinoma gallbladder either as anticipated diagnosis or found incidentally. It is two to three times more common in female then in male with the peak incidence in seventh decade of life [2].

Carcinoma gallbladder has traditionally been considered an incurable disease with a poor prognosis. The pessimism associated with gallbladder carcinoma is due to late presentation, often with disseminated disease, dismal prognosis and lack of effective therapy. It uniquely can spread through biopsy tracks and wounds apart from early lymphatic spread, haematogenous, direct route, and peritoneal seeding. The median survival of untreated gallbladder cancer is generally between 2 to 5 months [3]. Ninety percent of gallbladder cancer originates in the fundus or body so most do not produce symptoms. Early symptomatic patients have better prognosis. Symptomatic patients may have biliary colic or cholecystitis. Weight loss, jaundice and abdominal mass are associated with late stage [1]. In most cases by the time a diagnosis is made the disease is progressed way beyond cure and possibility of surgical resection is low. Diagnosis is straightforward in advanced cases but it remains elusive in early cases despite our evolving ability and innovative techniques of imaging the biliary tract. A high index of clinical suspicion and complete biochemical and radiological work-up can help in establishing the diagnosis and an early diagnosis alone can offer a chance for cure in patients with gallbladder carcinoma [3].

Systemic chemotherapy remains relatively ineffective but the role of radical resection has shown to be effective in selected patients. Thus early detection has a key role in the management of gall bladder cancer. With improvement in imaging, staging, hepatic and biliary resection, there is now hope for patients with non-metastatic gallbladder carcinoma [3]. It is therefore

important to use some tumor markers that can help in better management of gallbladder cancer. One such tumor marker that can help reduce the burden of gallbladder cancer is CA 19-9. Carbohydrate antigen 19-9 (CA 19-9) is a kind of glycosphingolipid that is a specific dialyzed derivative of the Lea blood group and shown as Lexa. The CA 19-9 antigen was first isolated by Koprowski *et al.;* using a monoclonal antibody generated against colonic carcinoma cell lines. Subsequently, a radio immunometric assay was developed by Del Villano *et al.;* to quantify CA 19-9. CA 19-9 is most valuable as a serum marker for pancreatic and biliary cancer, but increased concentrations occur in several other gastrointestinal (GI) malignancies, e.g. gastric, colorectal and liver cancer and also in breast, lung and gynaecological cancers. However, elevated levels may also occur in benign diseases [5].

It is critical for the surgeons to understand natural history, biology, staging and surgical treatment of this tumour, so that appropriate decisions are made at the time of initial diagnosis, at the same time it is also important to understand the limitation of surgical resection so that operation with unreasonably high morbidity but minimal chance of success can be avoided [3].

MATERIAL AND METHODS:

This was an institution-based, prospective and comparative study where the material consisted of cases admitted in Medical College and Hospital, Kolkata from January 2012 to June 2013 (18 months). During this period, 30 non-randomized cases were selected for our study purpose, all of which were diagnosed with Gallbladder cancer. Informed consent was taken from all the patients. The study got clearance from Institutional Ethical Committee.

Inclusion Criteria: The following patients were included in the study population: -

a) Both sexes.
b) All age groups.
c) Patients admitted in Medical College and Hospital during this period with diagnosed Gallbladder cancer by cytological examination and by radiological method.

Exclusion Criteria: The following patients were excluded from the study population: -

a) Patients on chemotherapy or radiotherapy for gallbladder cancer.
b) Patients whose Gallbladder tumor has been resected.
c) Patients with pancreatitis.
d) Patients with liver cirrhosis.
e) Patients with hepatitis.
f) Patients with other co-existing malignancy.
g) Patient with common bile duct obstruction due to stone.
h) Patients who refuses to be part of study.

Several parameters needed measurement or qualitative analysis during the progress of this study viz. clinical presentations of the patients, HPE examination of the tissue sample, radiological findings relevant to the staging of the tumor and serum CA19-9. Apart from these several other parameters were also measured like blood biochemistry (TC, DC, ESR, Haemoglobin levels), ECG in high risk cardiac patients, serology (Australia antigen, anti HCV, HIV I & II). Study tools comprised of Ultrasonography and computed tomography of whole abdomen, Fine needle aspiration cytology of the Gallbladder, Serum for CA 19-9. All statistical analyses were performed with SPSS® software version 21.0 for Windows 8.1 (SPSS, Chicago, IL, USA). Several statistical tests were performed like Fisher's exact t-test. Spearman's rho correlation coefficient was also calculated. P-value of < 0.05 was considered significant.

RESULTS:

In this study, 30 patients who were admitted with gallbladder cancer were studied. Out of them 8 (26.6%) were male and 22 (73.3%) were female. The male: female ratio was 1:3.7.

Descriptive statistics:

Age:

In this study mean age was 52.6 years with standard deviation (S.D.) 13.4 years. The range was from 25 to 74 years. The most of patients were between 41-50 and 61-70 years, followed by 51-60 years.

Table 1: Descriptive Statistics of Age

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	30	25	74	52.63	13.415

Table 2: Age Frequency table

Age in years	Frequency	Percent
21-30	3	10.0
31-40	2	6.7
41-50	8	26.7
51-60	7	23.3
61-70	8	26.7
71-80	2	6.7
Total	30	100.0

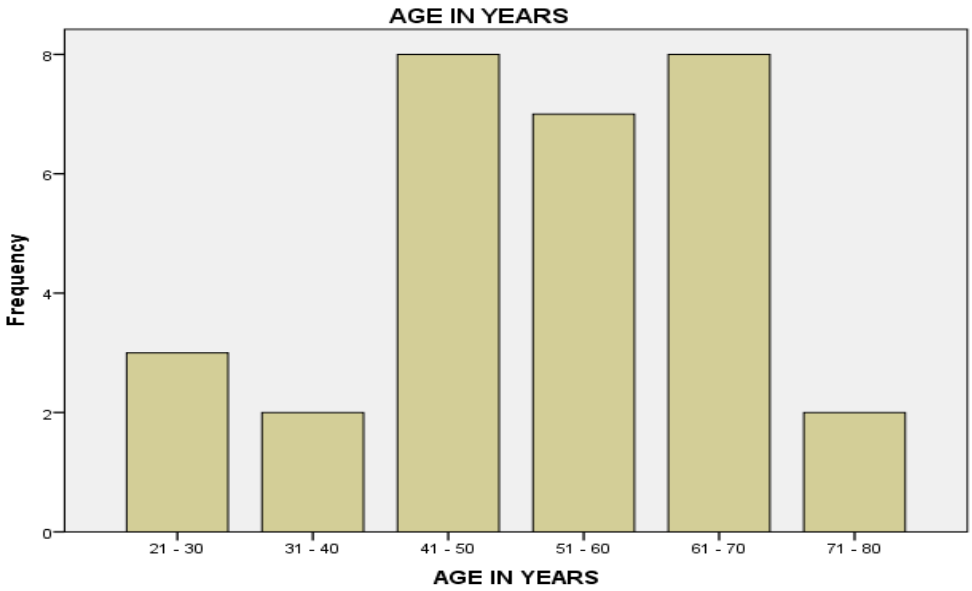


Chart 1: Age Frequency Bar Diagram.

Socioeconomic Status:

In this study 2 patients (6.7%) belonged to high socioeconomic status, 11 (36.7%) to medium socioeconomic status and 17 (56.7%) to low socioeconomic status.

Table 3: Descriptive Statistics of Socioeconomic Status.

Socioeconomic Status	Frequency	Percent
Low	17	56.7
Medium	11	36.7
High	2	6.7
Total	30	100.0

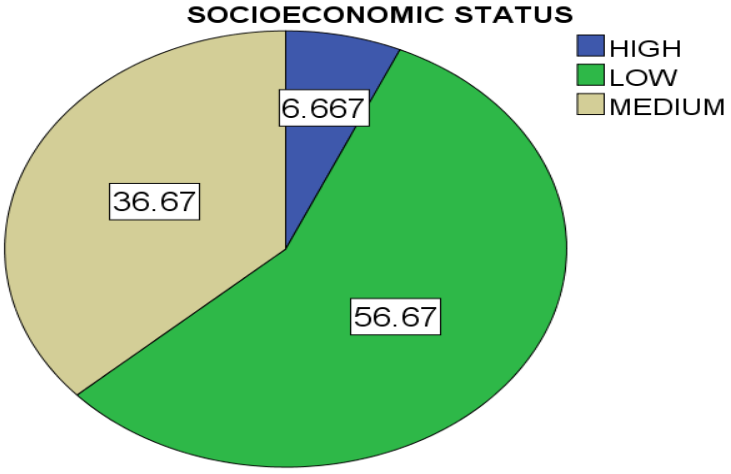


Chart 2: Pie chart of Socioeconomic Status distribution.

Pain:

In this study 26 (86.7%) patients had pain and 4 (13.3%) patients had no pain.

Table 4: Descriptive Statistics of pain

Pain	Frequency	Percent
No pain	4	13.3
Pain present	26	86.7

Jaundice:

In this study, 21 (70%) patients had jaundice and 9 (30%) patients had no jaundice.

Table 5: Descriptive Statistics of Jaundice

Jaundice	Frequency	Percent
Jaundice	21	70.0
No jaundice	9	30.0

Weight Loss:

In this study, 9 (30%) patients had weight loss but 21 (70%) had no weight loss.

Table 6: Descriptive Statistics of Weight Loss

Weight loss	Frequency	Percent
No weight loss	21	70.0
Weight loss present	9	30.0

Anaemia:

In this study, 3 (10%) had anaemia and 27 (90%) had no anaemia.

Table 7: Descriptive Statistics of Anaemia

Anaemia	Frequency	Percent
Anaemia present	3	10.0
No anaemia	27	90.0

Nausea/Vomiting:

In this study, 14 (46.7%) had nausea/vomiting and 16 (53.3%) had no nausea/vomiting.

Table 8: Descriptive Statistics of Nausea/Vomiting

Nausea/Vomiting	Frequency	Percent
Nausea/Vomiting	14	46.7
No nausea/vomiting	16	53.3

Abdominal lump:

In this study, 23 (76.7%) had abdominal lump and the remaining 7 (23.3%) had no lump.

Table 9: Descriptive Statistics of Abdominal Lump

Abdominal lump	Frequency	Percent
Abdominal lump	23	76.7
No abdominal lump	7	23.3

Gallstone:

In this study, 21 (70%) patients had gallstone and the remaining 9 (30%) had no gallstone.

Table 10: Descriptive Statistics of Gallstone

Gallstone	Frequency	Percent
Gall stone	21	70.0
No gallstone	9	30.0

Primary tumor (T):

In this study, 3 (10%) patients belonged to T2, 11 (36.6%) belonged to T3 and 16 (53.3%) belonged to T4.

Table 11: Descriptive Statistics of Primary Tumor (T)

Primary tumor (T)	Frequency	Percent
T1	0	0
T2	3	10.0
T3	11	36.7
T4	16	53.3

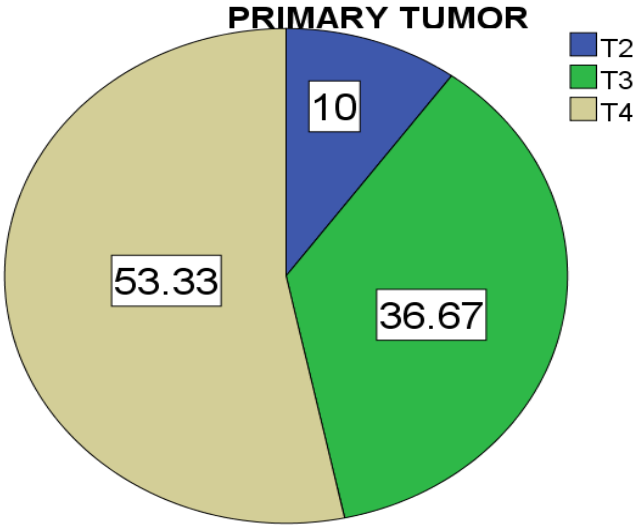


Chart 3: Pie chart of tumor distribution.

Nodal Status:

In this study, 7 (23.3%) patients belonged to N0, 10 (33.3%) belonged to N1 and 13 (43.3%) belonged to N2.

Table 12: Descriptive Statistics of Nodal Status

Nodal status (N)	Frequency	Percent
N0	7	23.3
N1	10	33.3
N2	13	43.3
Total	30	100.0

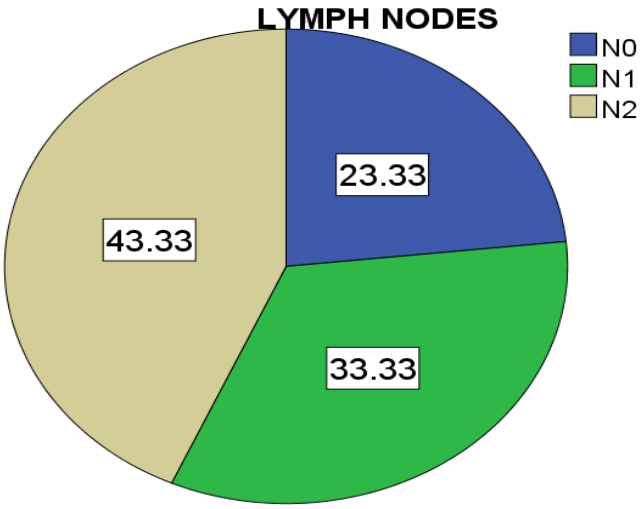


Chart 4: Pie chart of lymph node status.

Metastasis:

In this study, 20 (66.6%) patients had no metastasis, 10 (33.3%) has metastasis

Table 13: Descriptive Statistics of Metastasis

METASTASIS	Frequency	Percent
M0	20	66.7
M1	10	33.3

Stage:

No case of stage I or II were found. In this study, 3 (10%) patients were in stage IIIa, 4 (13.3%) patients in stage IIIb, 7 (23.3%) patients in stage IVa and 16 (53.3%) patients in stage IVb.

Table 14: Descriptive Statistics of Stage of tumor

STAGE	Frequency	Percent
IIIA	3	10.0
IIIB	4	13.3
IVA	7	23.3
IVB	16	53.3

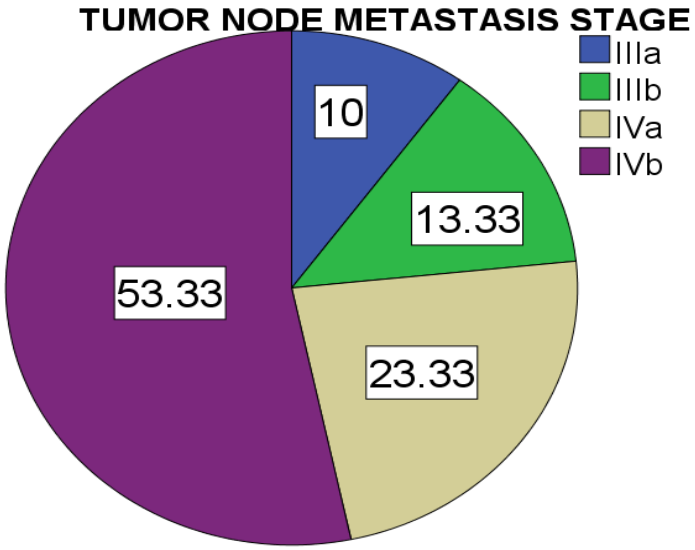


Chart 5: Pie chart of stage distribution.

FNAC:

In this study 9 (30%) were of moderately Differentiated adenocarcinoma, 6 (20%) were of poorly differentiated adenocarcinoma and 15 (50%) were of well differentiated adenocarcinoma.

Table 15: Descriptive Statistics of Grade of tumor from FNAC

FNAC GRADE	Frequency	Percent
Well differentiated	15	50
Moderately differentiated	9	30
Poorly differentiated	6	20
Total	30	100.0

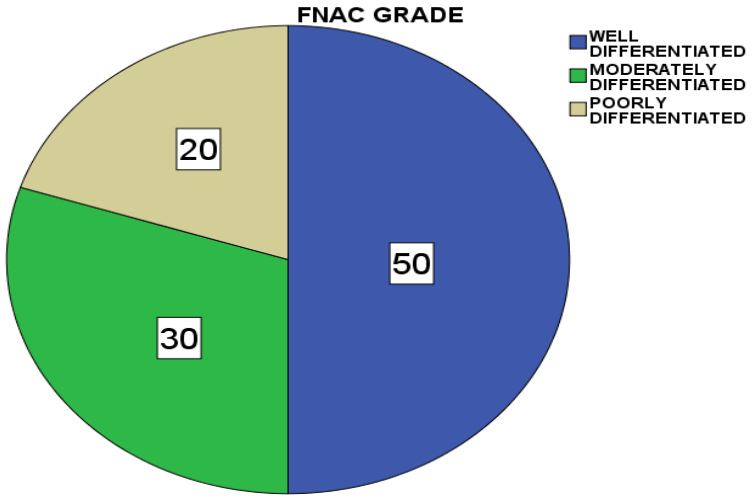


Chart 6: Pie chart of FNAC grade distribution.

CA 19-9:

The mean of serum CA 19-9 was 795.13 U/ml, median of 525 U/ml and a standard deviation of 873.7. Most of the patients had serum CA 19-9 value lower than 1500U/ml.

Table 16: Descriptive Statistics of Grade CA 19-9

VALUES	MEAN	MEDIAN	STD.DEVIATION
CA 19-9	795.13	525.00	873.739

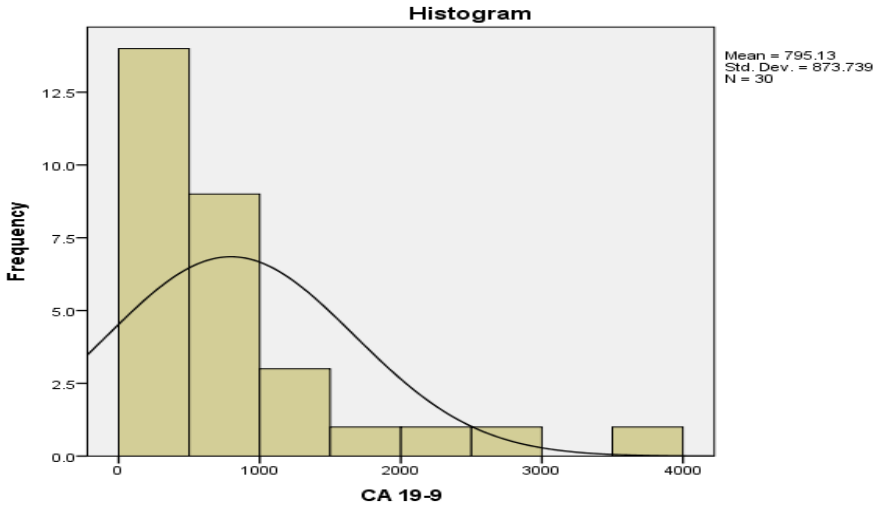
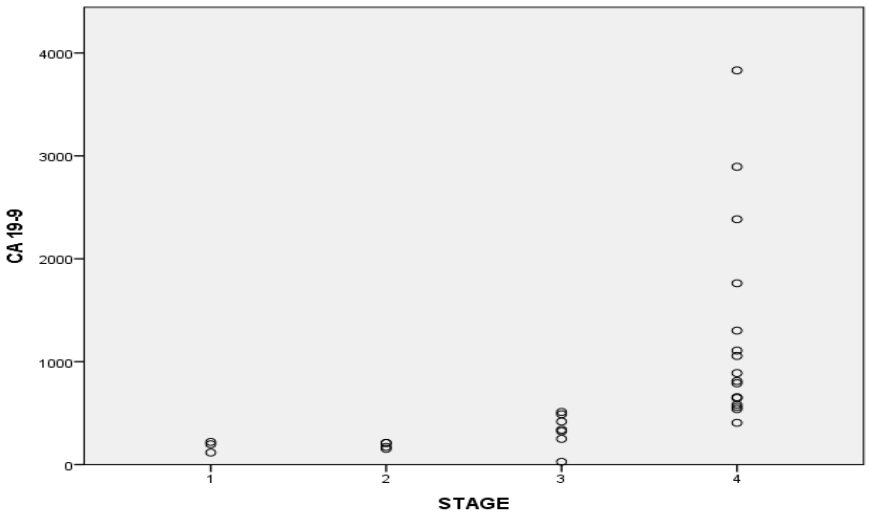


Chart 7: Distribution Histogram of CA 19-9

Table 17: Serum CA 19-9 level at each stage

STAGE	IIIa	IIIb	IVa	IVb
NUMBER	3	4	7	16
MEAN	178 U/ml	186.5 U/ml	336.86 U/ml	1263.5 U/ml
MEDIAN	197 U/ml	191 U/ml	339 U/ml	850.5 U/ml
STD. DEVIATION	54.1 U/ml	28.78 U/ml	165.22 U/ml	978.53 U/ml

The serum CA 19-9 value was seen increasing with stage.



1 = IIIa, 2 = IIIb, 3 = IVa, 4 = IVb.

Chart 8: Scattered diagram of CA 19-9 and stage.

Correlation studies:

Correlation of CA 19-9 with age and FNAC:

Table 18: Correlation table of CA 19-9 with age and FNAC

			AGE	FNAC GRADE
Spearman's Rho	CA 19-9	Correlation coefficient	-.163	-.139
	CA 19-9	Sig.(2 tailed)	.389	.464

In this study, age and FNAC did not significantly correlate with serum CA 19-9 level.

Correlation of CA 19-9 with Tumor, nodes, stage and metastasis:

Table 19: Correlation of CA 19-9 with Tumor, nodes, stage and metastasis

			PRIMARY TUMOR	NODAL STATUS	METASTASIS	STAGE
Spearman's Rho	CA 19-9	Correlation Coefficient	.081	.577	.441	.862
		Sig. (2-tailed)	.669	.001	.015	.000

In this study, serum CA 19-9 correlate with nodal status, metastasis and stage with p-value of .001,.015 and .000 respectively. But there was no correlation between CA 19-9 and primary tumor.

Correlation of socioeconomic status with CA 19-9:

Table 20: Correlation of socioeconomic status with CA 19-9

Socioeconomic status	Asymp. Sig. (2-sided)
Pearson Chi-Square	.001

Socioeconomic status correlates with serum CA 19-9 level.

Correlation of CA 19-9 with gender, pain, jaundice and weight loss:

Table 21: Correlation of CA 19-9 with gender, pain, and jaundice and weight loss

		GENDER	PAIN	JAUNDICE	WEIGHT LOSS
Fisher's Exact Test	Exact Sig. (2-sided)	1.000	1.000	.300	1.000

In this study, there was no correlation of serum CA 19-9 with gender, pain, jaundice, weight loss.

Correlation of anaemia, nausea/vomiting, abdominal lump and gallstone:

Table 22: Correlation of anaemia, nausea/vomiting, abdominal lump and gallstone

		ANAEMIA	NAUSEA/ VOMITING	ABDOMINALLUMP	GALLSTONE
Fisher's Exact Test	Exact Sig. (2-sided)	1.000	.467	1.000	.300

In this study, there was no correlation of serum CA 19-9 level to anaemia, nausea/vomiting, lump and gallstone.

DISCUSSION:

In this study the mean age of 30 patients was 52.6 years and a standard deviation of 13.4. The youngest patient was of age 25 and maximum of age was 74 years. The maximum number of patients was between 41-50 and 61-70 years, followed by 51-60 years. In India, however, the majority of gallbladder carcinomas are discovered at an advanced stage during ultrasonography for upper abdominal symptoms [10, 16, 27]. We can see from the study that gallbladder cancer increases after the age of 40 years. There is a slight variation with the western literatures but according to Indian literatures, the mean age is in accordance with the literatures that are available at present [28, 29]. It was seen that gallbladder cancer occurs in both gender but more commonly seen in females [3, 10, 29]. In this study it was found out that gallbladder cancer was more common in female with male: female ratio of 1:3.7. These findings were slightly higher than the studies done earlier but are similar. In this study of 30 patients 17 (56.7%) belonged to low socioeconomic status, 11 (36.7%) belonged to moderate socioeconomic status and 2 (6.7%) belonged to high socioeconomic status. The findings have been found to be similar to earlier studies [43].

Pain is the main presenting symptom of gallbladder cancer and was found in most of the patients. The pain was seen in right upper abdomen. In this study of 30 patients, it was seen that 26 patients were having some degree of pain (i.e. 86.7 %) which is similar to the findings in other literatures [3, 30]. The finding of Jaundice is a sign of advanced Gallbladder cancer. In this study jaundice was found in 70% of the patients, it is higher in comparison to other literature because the sample included in this study contains more of advanced stage [3, 31]. Weight loss occurs in patients due to malignancy or other factors such as vomiting, anorexia etc. In this very study, 9 out of 30 had weight loss and 21 out of 30 had no sign of weight loss. This finding is consistent with findings in other literatures [3]. Anemia is not a very common finding in case of gallbladder cancer. In this study anemia was found in 3 (10%) patients, out of 30 and the remaining 27 (90%) patients had no anemia. This value shows similarity with other studies [3]. In this study 46.7 percent were found to be having nausea and vomiting. The value in this study is in accordance with other literatures [4].

Abdominal lump may not be found in early stage of gallbladder cancer but with advancing stage, the mass may be palpable. The lump may be due to the gallbladder cancer mass alone or involvement of adjacent organ. But in this study abdominal lump was found in 76.7% of the patients. There is increase of percentage in this study as compared to others because the samples taken were of advanced Gallbladder cancer (stage III and IV) [4, 28, 31]. In this study gallstone was found in 70 % of the patient with gallbladder cancer. The percentage of gallstone in gallbladder cancer is in accordance with the other studies [4, 41, 42]. In this study, the tumor stage of T1 was not found, T2 stage was seen in 10%, T3 in 36.6% and T4 in 56.3 % of the patients. Due to absence of symptoms in early stage or symptoms of mild degree, the patients tend to neglect the severity of the disease resulting it into a late stage disease. The nodal status was negative in 23.3%, N1 in 33.3 % and N2 in 43.3 %. In this study metastasis was seen in 33.3 % and the remaining patients were without metastasis.

Gallbladder cancer is usually diagnosed in the late stage. In this very study, the early stages were not included because all the patients presented in later stages. So this study included stage III and IV, which were further divided in IIIa, IIIb, IVa and IVb. Among these 30 patients, 3 (10%) belonged to stage IIIa, 4 (13.3%) to stage IIIb, 7 (23.3%) to stage IVa and 16 (53.3 %) to stage IVb. Adenocarcinoma is the most common type of gall bladder cancer accounting for nearly 90 %. It can be divided into well differentiated, moderate differentiated and poorly differentiated and the worst prognosis being the poorly differentiated. In this study of 30 patients, all the patients had adenocarcinoma. 15 (50%) patients had well differentiated adenocarcinoma, 9 (30%) had moderately differentiated adenocarcinoma and 6 (20%) patients had poorly differentiated carcinoma. The finding in this study is similar with the studies done earlier [27, 32].

In this study, among 30 cases, 29 cases were positive for CA 19-9, above 37 U/ml and only 1 was below 37u/ml. The lowest was 27 U/ml and the highest value of 3831 U/ml with mean being 795.13 U/ml and median 525.00. The standard deviation was 873.739. The mean in this study was higher that the study done by Shukla *et al.;* because with advanced stage it has been observed that CA 19-9 value increase, and this study sample contained mostly of the advanced stages i.e. III and IV [20]. It has also been seen in this study that there was gradual increase from stage IIIa to IIIb and to IVa but in stage IVb there was an abrupt increase in serum CA 19-9 reaching to a maximum of 3831 U/ml. The median CA19-9 level with pancreatobiliary tumours was 910 U/ml in a study done by Mann DV *et al.;* in 2000 [26]. In another study done it was found that that serum CA 19-9 value was 11704 U/ml [25]. Considering all these studies it can be concluded that the serum CA 19-9 level of this study has a similarity with findings in other studies.

Using Spearman's Rho, CA 19-9 was correlated with age, FNAC, primary tumor, nodal status, and metastasis and TNM stage. Pearson chi-square test was used for socioeconomic status. Fisher's exact test was used to correlate CA 19-9 with gender, pain, jaundice, weight loss, anaemia. Using Fisher's exact test CA 19-9 was found not to correlate with gender, pain, jaundice, weight loss, anaemia, nausea/vomiting, abdominal lump and gallstone. Using Spearman's rho, it was found that serum CA 19-9 had negative correlation with age (Correlation coefficient of -0.163) but statistically it was not found to be significant. Serum CA 19-9 had negative correlation with FNAC grade but it was also not significant. Using Pearson Chi-Square test CA 19-9 was found correlating significantly with socioeconomic status (p-value = 0.001). Primary tumor showed no significant correlation with serum CA 19-9 level. The nodal status showed a Correlation coefficient value of 0.577 and a p-value of 0.001 which was significant, which means that with increase in lymph nodal stage the serum CA 19-9 will increase.

Distant metastasis was correlated with serum CA 19-9 and the correlation showed the p-value of 0.015 (significant) and a Correlation coefficient value of 0.441. This also means that when gallbladder cancer has metastasis the serum CA 19-9 will also increase and it can be used as a marker for metastasis. It was found using Spearman's rho that the Correlation coefficient was 0.862 and the p-value was 0.000 in case of correlation of CA 19-9 with staging. This means that the p-value is highly significant and with the rise in stage there is also rise in the serum CA 19-9 level and with decrease in stage the serum CA 19-9 falls too. This correlation is the most significant of all the above correlations. In this study the serum CA 19-9 correlated with staging with a high coefficient value. The serum CA 19-9 gradually increased with not much difference between stage IIIA and IIIb and after reaching stage IVa the CA 19-9 escalated so high as to a value of 3831U/ml. This study has much in resemblance with the study by Sharada R *et al.;* in 2013 [40].

CONCLUSION:

In this study it was seen that the mean age was 52.6 years and most of patients were in the range between 41-50 years and 61-70 years. Gallbladder cancer was found to be more common in female with the male to female ratio of 1:3.7. Most of the patients belonged to low socioeconomic class (56%), followed by 36.6 % belonging to medium socioeconomic class and 6.7 % belonging to high socioeconomic status. The most common clinical features were pain (86.7%) followed by jaundice (70%), weight loss (30%), anaemia (10%) nausea/vomiting (46.7%) and abdominal lump (76.7%). Stage IVb was the most common stage (53.3%), followed by stage IVa (23.3%), stage IIIb (13.3%) and the least is stage IIIa. The most common histological type was adenocarcinoma, which was subdivided into well differentiated (50%), moderately differentiated (30%) and poorly differentiated (15%). It was seen that CA 19-9 was raised in 96.6% of the patients, with the mean of 795.13U/ml. CA 19-9 did not significantly correlate with gender, pain, jaundice, weight loss, anaemia, nausea/vomiting, abdominal lump and gall stone but CA 19-9 significantly correlated with nodal stage (p-value = 0.001), metastasis (p-value = 0.015), stage (p-value = 0.000) and socioeconomic status (p-value = 0.001).

Since serum CA 19-9 correlates significantly with nodal stage, metastasis and TNM stage, finding higher value will indicate that Gallbladder cancer has either higher nodal status or has metastasis or as a higher TNM stage. Serum CA 19-9 should be estimated in all patients presenting with gallbladder cancer, to know the extent of the disease through its raised value. Higher stages are associated with poorer prognosis, therefore, it can be stated that high serum CA 19-9 value has poor prognosis. In any case of gallbladder pathology with raised CA 19-9 it is essential to rule out gallbladder malignancy and manage like wise. Diagnosed preoperative patient also should have serum CA 19-9 evaluated for monitoring, recurrence and follow up.

REFERENCES:

1. Sabiston Textbook of Surgery, 19/e (Vol. II)
2. Schwartz's Principles of Surgery, Ninth Edition
3. Surgery of the liver, biliary tract, and pancrease: L.Blumgart
4. Gallbladder Cancer Editors: Manoj Pandey and Vijay K Shukla
5. Korkmaz M, Ünal H, Selçuk H, Yilmaz U. Extraordinarily elevated serum levels of CA 19-9 and rapid decrease after successful therapy: a case report and review of literature. The Turkish journal

of gastroenterology: the official journal of Turkish Society of Gastroenterology. 2010 Dec; 21(4):461-3.
6. Pathology and genetics of tumours of the digestive system: Edited by Hamilton SR, Aaltonen LA. Lyon
7. Human Anatomy:B.D.Chaurasia, fourth edition.ch-22-273 t0 293
8. Hamdani NH, Qadri SK, Aggarwalla R, Bhartia VK, Chaudhuri S, Debakshi S, Baig SJ, Pal NK. Clinicopathological study of gall bladder carcinoma with special reference to gallstones: our 8-year experience from eastern India. Asian Pacific Journal of Cancer Prevention. 2012; 13(11):5613-7.
9. Kim WS, Jang KT, Choi DW, Choi SH, Heo JS, You DD, Lee HG: Clinicopathologic analysis of adenosquamous/squamous cell carcinoma of the gallbladder. J Surg Oncol. 2011 Mar 1; 103(3):239-42.
10. Singh S, Ansari MA, Narayan G. Pathobiology of gall bladder cancer. J Sci Res. 2012; 56:35-45.
11. Silk YN, Douglass Jr HO, Nava HR, Driscoll DL, Tartarian GA. Carcinoma of the gallbladder. The Roswell Park experience. Annals of surgery. 1989 Dec; 210(6):751.
12. Hatzaras I, Schmidt C, Muscarella P, Melvin WS, Ellison EC, Bloomston M. Elevated CA 19-9 portends poor prognosis in patients undergoing resection of biliary malignancies. Hpb. 2010 Mar 1; 12(2):134-8.
13. O'Connor R, Harding B, Greene D, Coolican J. Primary carcinoma of the gall bladder associated with ulcerative colitis. Postgraduate medical journal. 1986 Sep 1; 62(731):871-2.
14. Singh S, Tang SJ, Sreenarasimhaiah J, Lara LF, Siddiqui A. The clinical utility and limitations of serum carbohydrate antigen (CA19-9) as a diagnostic tool for pancreatic cancer and cholangiocarcinoma. Digestive diseases and sciences. 2011 Aug 1; 56(8):2491-6.
15. Korkmaz M, Ünal H, Selçuk H, Yilmaz U. Extraordinarily elevated serum levels of CA 19-9 and rapid decrease after successful therapy: a case report and review of literature. The Turkish journal of gastroenterology: the official journal of Turkish Society of Gastroenterology. 2010 Dec; 21(4):461-3.
16. Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. The lancet oncology. 2003 Mar 31; 4(3):167-76.
17. Rottenberg Y, Nisman B, Peretz T. Extreme high levels of CA19-9 associated with adenocarcinoma of the lung. IMAJ. 2009; 11(2):116-7.
18. Kim HR, Lee CH, Kim YW, Han SK, Shim YS, Yim JJ. Increased CA 19-9 level in patients without malignant disease. Clinical chemistry and laboratory medicine. 2009 Jun 1; 47(6):750-4.
19. Mehmet ŞAHİN, Erkan CÜRE a, Mehmet İŞLER, İbrahim BAR: Elevated Ca 19-9 Levels in Patient with Cholecystitis. Fırat Tıp Dergisi 2007;12(1): 81-83
20. Shukla VK, Gurubachan, Sharma D, Dixit VK, Usha:Diagnostic value of serum CA242, CA 19-9, CA 15-3 and CA 125 in patients with carcinoma of the gallbladder. Trop Gastroenterol. 2006 Oct-Dec; 27(4):160-5.
21. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, Pinto E, Roviello F.: CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg. 2009 Sep; 198(3):333-9.
22. Kotoh T, Arima S, Futami K: A case of retroperitoneal lymph node recurrence with gallbladder cancer responding to UFT and CDDP combination chemotherapy. Gan To Kagaku Ryoho. 1994 May; 21(6):881-4.
23. Strom BL, Iliopoulos D, Atkinson B, Herlyn M, West SL, Maislin G, Saul S, Varello MA, Rodriguez-Mart: Pathophysiology of tumor progression in human gallbladder: flow cytometry, CEA, and CA 19-9 levels in bile and serum in different stages of gallbladder disease.inez HA, Rios-Dalenz J, *et al* J Natl Cancer Inst. 1989 Oct 18;81(20):1575-80.
24. Stefanović D, Novaković R, Perisić-Savić M, Djordjević Z, Zivanović M, Stajić S. The evaluation of tumor markers levels in determination of surgical procedure in patients with gallbladder carcinoma. Medicinski pregled. 1992 Dec; 46:58-9.
25. Ono T, Komatsu M, Hoshino T, Ishii T, Fujii T, Oshima S, Mikami KI, Umeki Y, Enomoto K, Masamune O. Alpha-fetoprotein, carcinoembryonic antigen, and carbohydrate antigen 19-9-producing gallbladder cancer. Journal of gastroenterology. 1996 Oct 10; 31(5):742-6.
26. Mann DV, Edwards R, Ho S, Lau WY, Glazer G Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol. 2000 Aug; 26(5):474-9.
27. Srivastava V, Patel B, Kumar M, Shukla M, Pandey M. Cyclin D1, retinoblastoma and p16 protein expression in carcinoma of the gallbladder. Asian Pac J Cancer Prev. 2013 Jan 1; 14(5):2711-5.
28. Lobo L, Prasad K, Satoskar RR. Carcinoma of the gall bladder: a prospective study in a tertiary hospital of Bombay, India. J Clin Diagn Res. 2012; 6(4 Suppl 2):692-5.
29. George RA, Godara SC, Dhagat P, Som PP. Computed tomographic findings in 50 cases of gall bladder carcinoma. Medical Journal Armed Forces India. 2007 Jul 31; 63(3):215-9.
30. A. Mohamed; F. Emran; N. Ghanem; A. Mohamed: Gallbladder Carcinoma, Improving Diagnosis and Outcome. Internet Journal of Surgery Vol: 23, No: 2, 2010.
31. Qayyum A. Patients with gall bladder cancer: A clinical experience. Pakistan Journal of Medical Sciences. 2007 Apr 1; 23(2):298.

32. Bazan F, Sanchez J, Aguilar G, Radosevic A, Busto M, Zuccarino F, Pijuan L, Risueño N. Metastatic gallbladder adenocarcinoma with signet-ring cells: A case report. Journal of medical case reports. 2011 Sep 14; 5(1):458.
33. Shukla VK, Khandelwal C, Roy SK, Vaidya MP. Primary carcinoma of the gall bladder: A review of a 16-year period at the university hospital. Journal of surgical oncology. 1985 Jan 1; 28(1):32-5.
34. Pandey M, Gautam A, Shukla VK. ABO and Rh blood groups in patients with cholelithiasis and carcinoma of the gall bladder. BMJ. 1995 Jun 24; 310(6995):1639.
35. Shukla VK, Pandey M, Kumar M *et al*: Ultrasound guided fine needle aspiration cytology for malignant gallbladder masses. Acta Cytol 41: 1654-58, 1997.
36. Kasper, Braunwald, Fauci. Harrison's Principles of Internal Medicine, 16th edition. P-438, table 66-5.
37. Ashraf A. Tabll; Mohamed El-Sadany; Tallat Ibrahim; Ibrahim El-Dosoky; Samia Salem; Abdelfattah M. Attallah International Journal of Cancer Research Vol: 3, No: 3, 2007[Page 151-156].
38. Long XY, Li YX, Wu W, Li L, Cao J. World J Gastroenterol. 2010 Oct 21; 16(39):4998-5004.
39. Sonoda T, Milsom JW. Section 5: Gastrointestinal tract and abdomen.
40. Kankonkar SR, Joshi SV, Deshpande RR. Significance of tumour markers in cancer of gall bladder. Open Journal of Immunology. 2013 Mar 13; 3(01):33.
41. Cavallaro A, Piccolo G, Panebianco V, Menzo EL, Berretta M, Zanghì A, Di Vita M, Cappellani A. Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. World Journal of Gastroenterology: WJG. 2012 Aug 14; 18(30):4019.
42. William R Beltz, Roberte Condon: Primary Carcinoma of the Gallbladder. Department of Surgery, University of Iowa, College of Medicine, Iowa City, Iowa: November 21, 1973.
43. Dwivedi S, Madeshiya A, Singh D, Singh S, Krishna A. Gall Bladder Cancer and some epidemiological factors: A cross sectional study. Biomedical Research. 2013; 24(1).