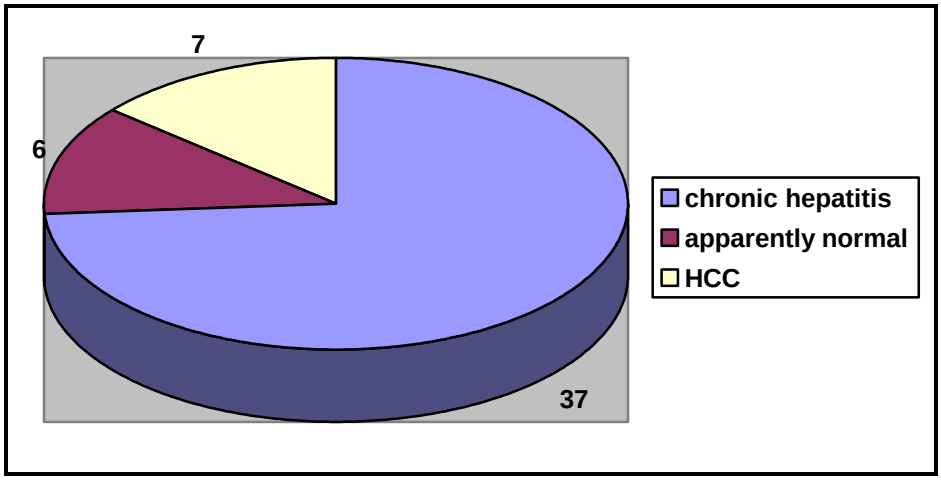
RESULTS

This retrospective study included fifty liver biopsies; composed of 6 biopsies of apparently normal liver tissue as a control group ,selected 37 biopsies of chronic viral C hepatitis (the study group) ,in addition to 7 biopsies of hepatocellular carcinoma (HCC) on top of cirrhosis as another control group.

Graph (1): Study groups



Clinical Results

1-Age distribution in Chronic viral C hepatitis cases:

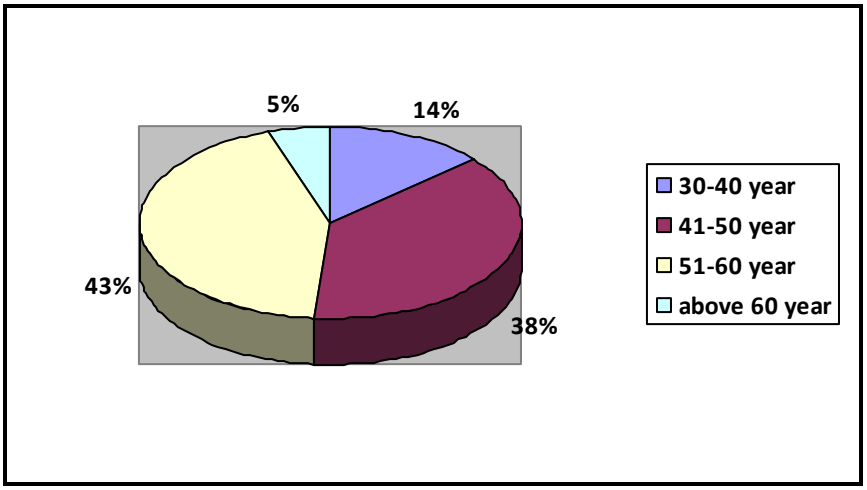
Ages of the studied 37 cases of chronic hepatitis ranged from 32 to 65 years with mean age (48.41, SD ± 8.64).

Among the chronic viral C hepatitis cases, 5 cases (14%) aged between (30-40 years), 14 cases (38%) were between ages 41-50 years. Maximum age group was 16 cases (43%) between age 51-60 and only 2 cases (5%) aged above 60 years.

Table (3): Age distribution of chronic viral C hepatitis cases:

Age group	NO.	%
30-40	5	14%
41-50	14	38%
51-60	16	43%
Above 60	2	5%
Total	**37**	**100%**

Graph (2): Age distribution of chronic viral C hepatitis cases



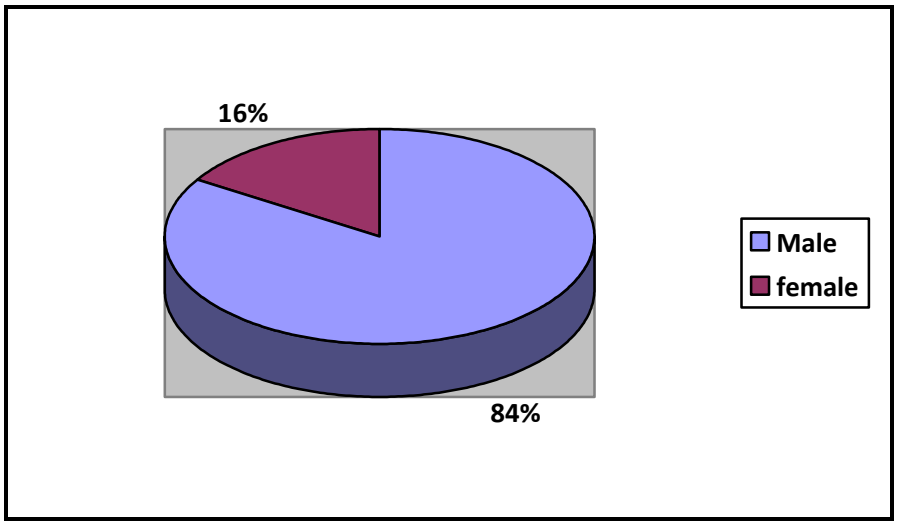
2-Gender distribution of chronic viral C hepatitis cases:

Out of 37 cases, 31 cases were males (84%) and 6 cases were females (16%).

Table (4): Gender distribution of chronic viral C hepatitis cases:

Sex	NO.	%
Male	31	84%
Female	6	16%
Total	**37**	**100%**

Graph (3): Gender distribution of chronic viral C hepatitis cases.



HISTOPATHOLOGICAL RESULTS

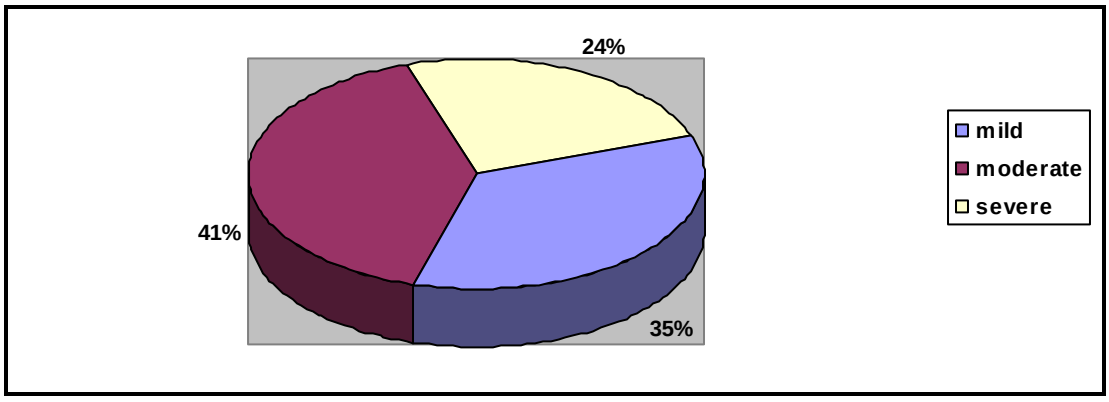
1-Hepatitis activity index (HAI), according to modified Ishak scoring system:

According to modified Ishak scoring system: out of 37 cases of chronic hepatitis, 13 cases (35.1%) showed mild activity, 15 cases (40.5%) showed moderate activity and 9 cases (24.4%) showed severe activity.

Table (5): shows percent of the study group cases regarding hepatitis activity index (HAI), according to modified Ishak scoring system:

HAI	No.	%
Mild	13	35%
Moderate	15	41%
Severe	9	24%
Total	**37**	**100%**

Graph (4): shows distribution of the studied cases regarding hepatitis activity index (HAI), according to modified Ishak scoring system:



2-Fibrosis/cirrhosis (according to Ishak staging):

According to Ishak staging system, Out of 37 cases of chronic hepatitis:

-One case (3%) showed no fibrosis (score 0).

- One case (3%) showed fibrous expansion of some portal areas with short fibrous septa (score 1).

-Three cases (8%) showed fibrous expansion of most portal areas with or without fibrous septa (score 2)

-Three cases (8%) showed fibrous expansion of some portal areas with occasional portal to portal bridging (score 3)

- one case (3%) showed fibrous expansion of portal areas with marked bridging (portal to portal & portal to central (score 4)

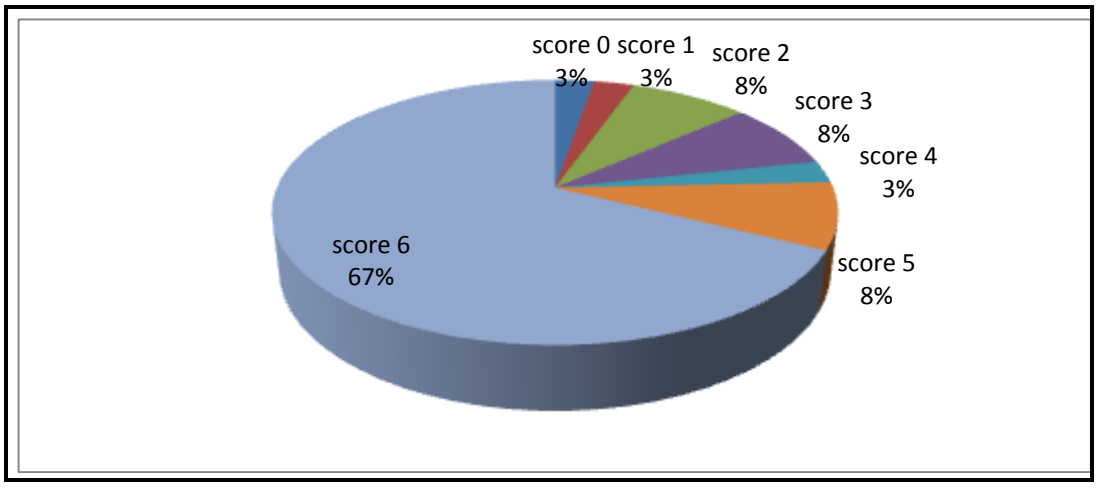
- Three cases (8%) showed fibrous Marked bridging (portal to portal and / or portal to central) with occasional incomplete nodules (incomplete cirrhosis) (score 5)

- Twenty five cases (67%) showed established cirrhosis (score 6)

Table (6): shows number and percent of the studied cases regarding the Ishak scoring system for fibrosis:

Fibrosis stage	No.	%
Stage 0	1	3%
Stage 1	1	3%
Stage2	3	8%
Stage 3	3	8%
Stage 4	1	3%
Stage 5	3	8%
Stage 6	25	67%
Total	**37**	**100%**

Graph (5): shows distribution of the studied cases regarding the Ishak scoring system for fibrosis:



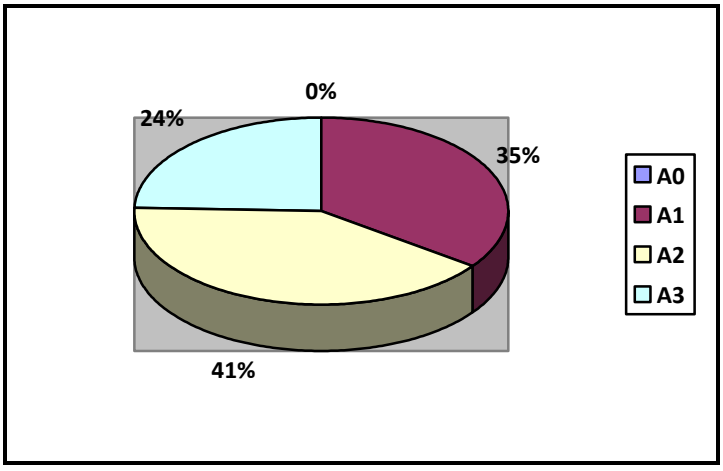
3-Hepatitis activity, according to Metavir scoring system:

According to Metavir system, Out of 37 cases of chronic hepatitis: No case (0%) had no activity (A0) ;13 cases (35%) showed mild activity (A1), 15 cases (41%) showed moderate activity (A2), 9 cases (24%) showed severe activity (A3).

Table (7): shows number and percent of the studied cases regarding hepatitis activity score according to Metavir system:

HAI	No.	%
A0	0	0%
A1	13	35%
A2	15	41%
A3	9	24%
Total	**37**	**100%**

Graph (6): shows distribution of the studied cases regarding hepatitis activity score according to Metavir system:



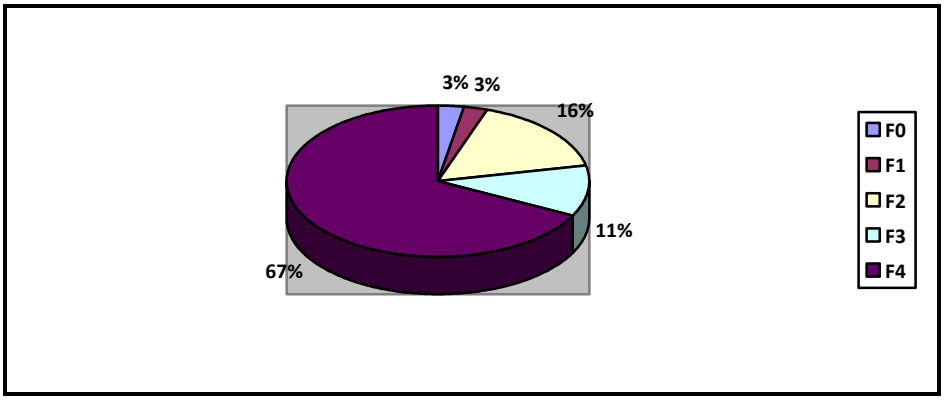
4-Fibrosis staging according to Metavir scoring system:

According to Metavir system; Out of 37 cases of chronic hepatitis: one case (3%) showed no fibrosis (F0), one case (3%) showed minimal scarring (F1), 6 cases (16%) showed scarring that extends outside the areas in the liver that contains blood vessels (F2), 4 cases (11%) showed spreading bridging fibrosis (F3); 25 cases (67%) showed cirrhosis or advanced scarring of the liver (F4).

Table (8): shows number and percent of the studied cases regarding Metavir staging system for fibrosis:

Stage of fibrosis	No.	%
F0	1	3%
F1	1	3%
F2	6	16%
F3	4	11%
F4	25	67%
Total	37	100%

Graph (7): shows distribution of the studied cases regarding the Metavir scoring system for fibrosis:



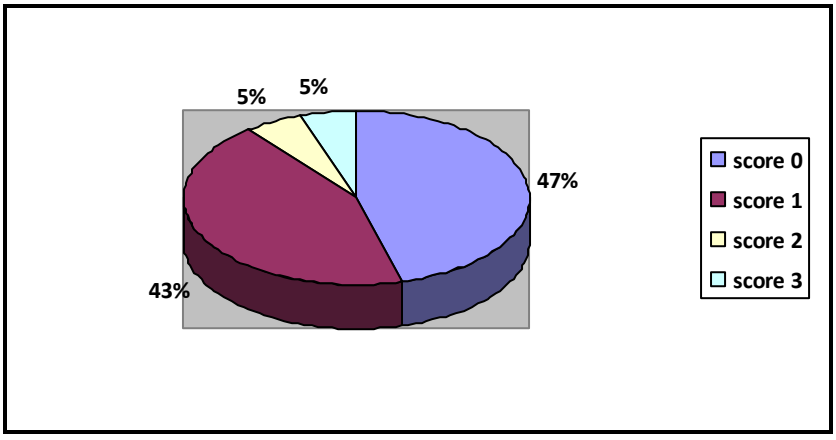
5-Steatosis:

According to ***Andrew et al .,(2005);****Out of 37 cases*: 17 cases (47%) were scored 0 (less than 5% of hepatocytes affected),16 cases (43%) were scored 1 (5-29% of hepatocytes affected) ,2 cases (5%) were scored 2 (30-70% of hepatocytes affected),and 2 cases (5%) got score 3 (more than 70 %of hepatocytes affected).

Table (9): shows percent of studied cases regarding the degree of steatosis:

Steatosis score	NO.	%
Score 0	17	47%
Score 1	16	43%
Score 2	2	5%
Score 3	2	5%
Total	**37**	**100%**

Graph (8): shows distribution of the studied cases regarding the degree of steatosis.



Histopathological variants

Table (10): Number and percent of the study group cases in relation to different histopathological variants:

Variable	NO.	Percent
Grade of activity: **a- Modified Ishak system:**		
Mild	13	35%
Moderate	15	41%
Severe	9	24%
b- Metavir system:		
A0	0	0%
A1	13	35 %
A2	15	41%
A3	9	24 %
Fibrosis stage **a- Ishak staging:**		
Stage 0	1	3%
Stage 1	1	3%
Stage2	3	8%
Stage 3	3	8%
Stage 4	1	3%
Stage 5	3	8%
Stage 6	25	67%
b- Metavir		
F0	1	3%
F1	1	3%

F2	6	16%
F3	4	11%
F4	25	67%
Steatosis score (*Andrew et al.,(2005)*)		
Score 0	17	47%
Score 1	16	43%
Score 2	2	5%
Score 3	2	5%

Hepatocellular carcinoma (HCC) cases (control group):

Out of seven cases of HCC, 6 cases exhibited trabecular pattern, and one case exhibited pseudoglandular pattern. All studied HCC cases were moderately differentiated (*according to* ***Hirohashi et al., (2000)***) with no detectable vascular invasion.

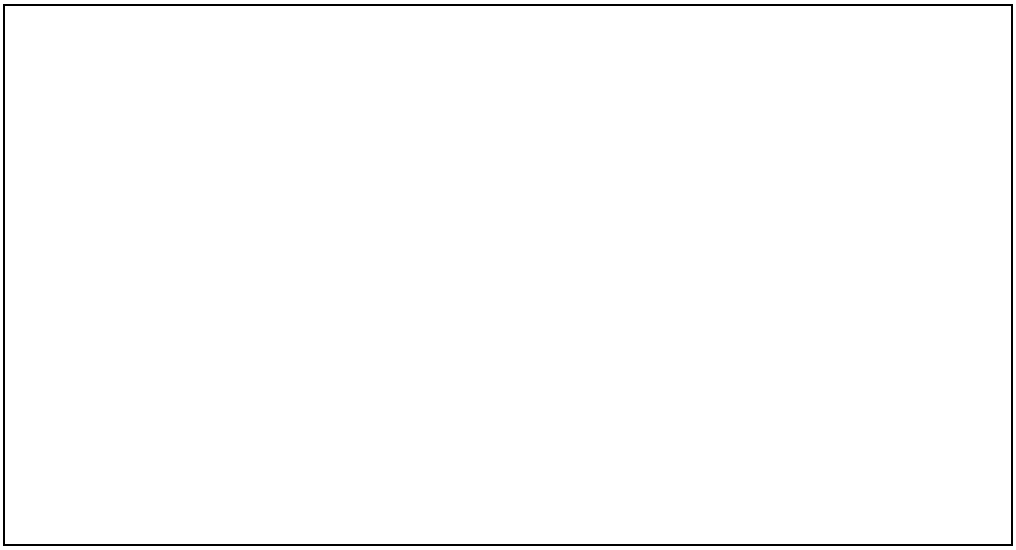


Figure (24): **Chronic hepatitis showing fibrous expansion of portal area with early septation; surrounding hepatocytes show mild hydrobic changes (Ishak stage of fibrosis 2/6). (H&E X200).**

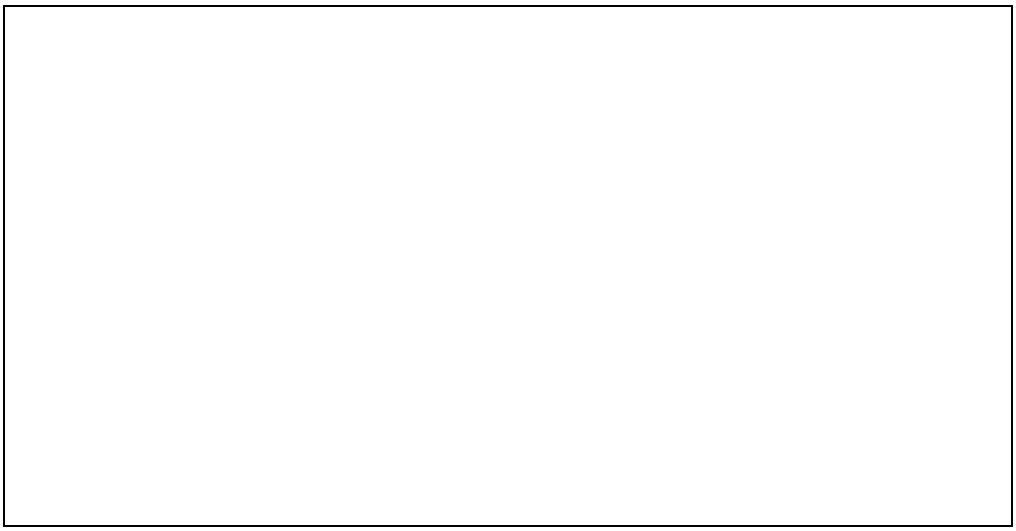


Figure (25): **Chronic hepatitis showing moderate to marked portal tract inflammation with portal-portal bridging fibrosis; surrounding hepatocytes show hydrobic changes (modified Ishak score for portal tract 3/4, Ishak stage of fibrosis 3/6) (H&E X200).**

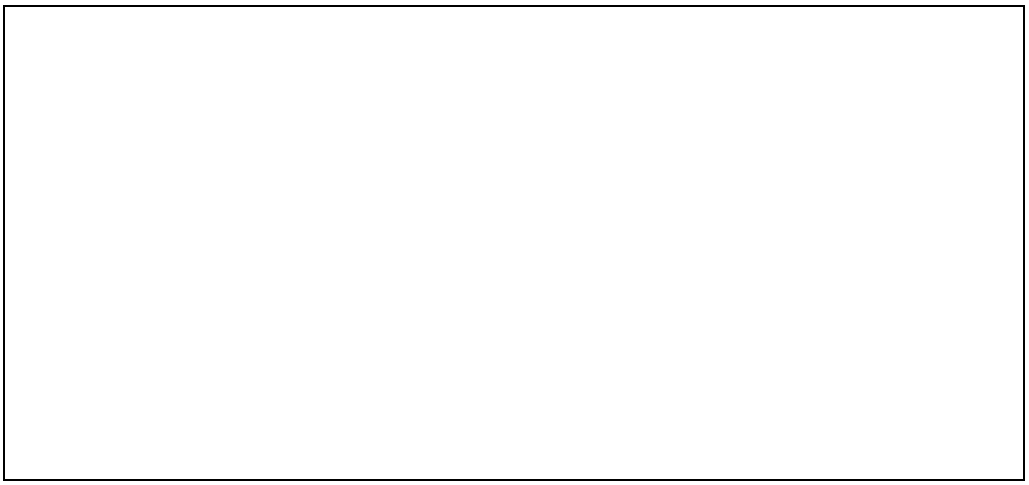


Figure (26): Chronic hepatitis showing marked portal tract inflammation up to lymphoid follicle formation with incomplete nodules formation (modified Ishak score for portal tract 4/4, Ishak stage of fibrosis 5/6).The surrounding hepatocytes show hydrobic changes and macrovesicular steatosis (steatosis score 1) (H&E X100).

Figure (27): Chronic hepatitis showing moderate to marked portal tract inflammation with complete nodules formation (modified Ishak score for portal tract ¾, Ishak stage of fibrosis 6/6) (H&E X100) .

Figure (28): Chronic hepatitis showing moderate portal tract inflammation (modified Ishak score for portal tract 2/4) .The surrounding hepatocytes show no steatosis (score 0) (H&E X200).

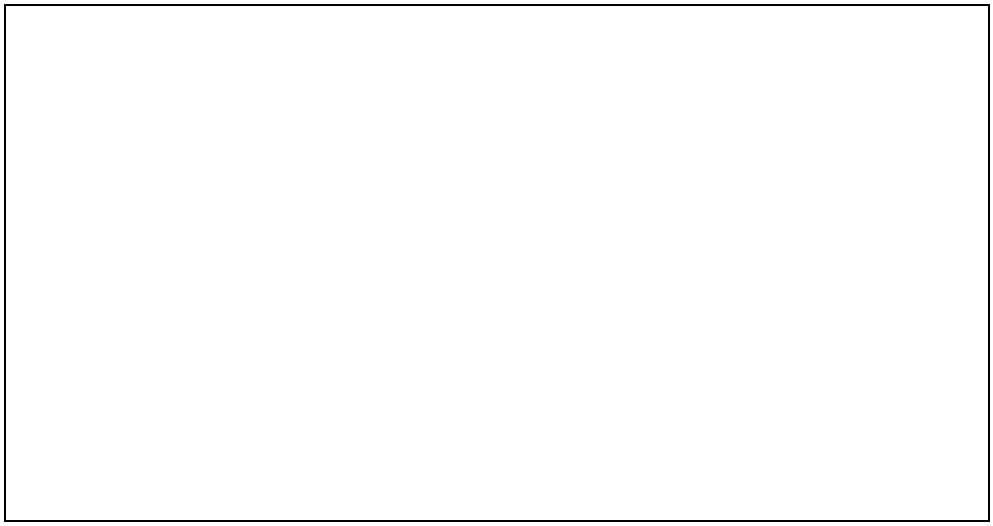


Figure (29): Chronic hepatitis showing marked portal tract inflammation up to lymphoid follicle formation (modified Ishak score for portal tract inflammation 4/4). Steatosis scored 0 (H&E X100).

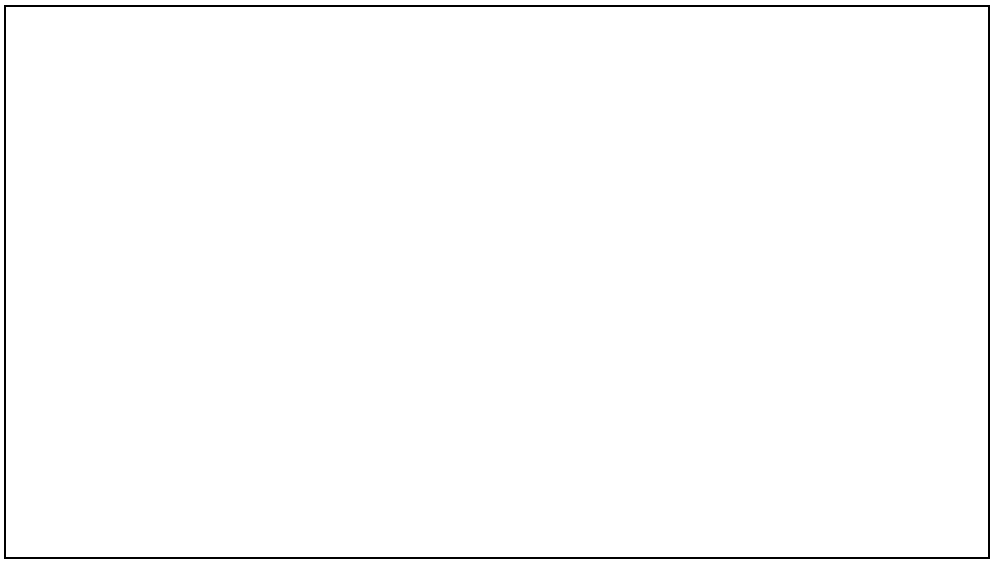


Figure (30): Chronic hepatitis showing interface hepatitis identified by irregular portal area outlines (modified Ishak score for interface hepatitis 2/4) (H&E X 200).

Figure(31):Chronic hepatitis showing apoptotic cells at interface hepatitis that appear as shrunken cells surrounded by clear halo with nuclear hyperchromasia (A);or cells with intensely eosinophilic cytoplasm(B)(H&EX1000Oil immersion lens)

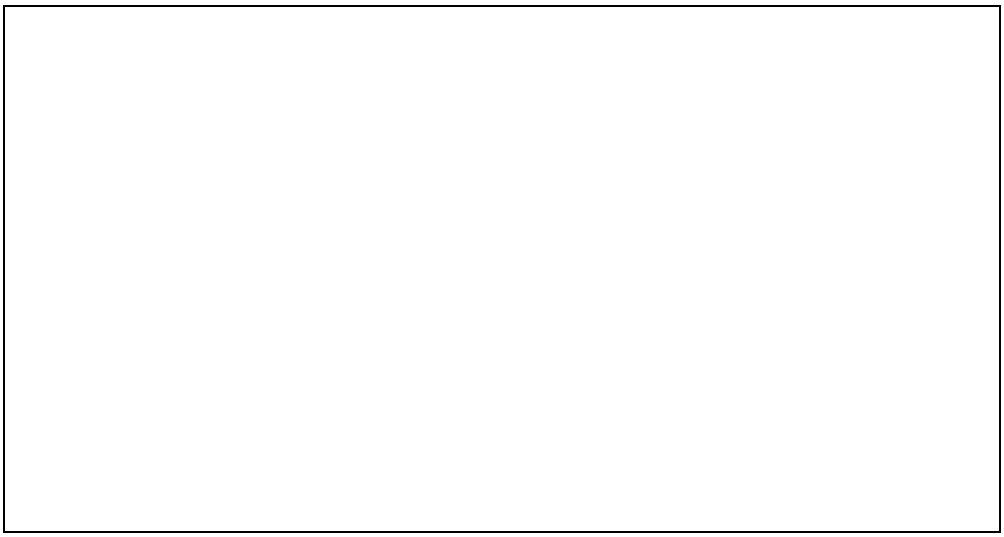


Figure (32): Chronic hepatitis showing necro-inflammatory foci identified by clusters of lymphocytes surrounding dying hepatocytes (H&E X400).

Figure (33): Chronic hepatitis showing confluent necrosis identified as dropped out contiguous hepatocytes, with heavy inflammatory infiltration. Surviving hepatocytes show hydrobic changes (modified Ishak score for confluent necrosis 2/6)(H&E X400).

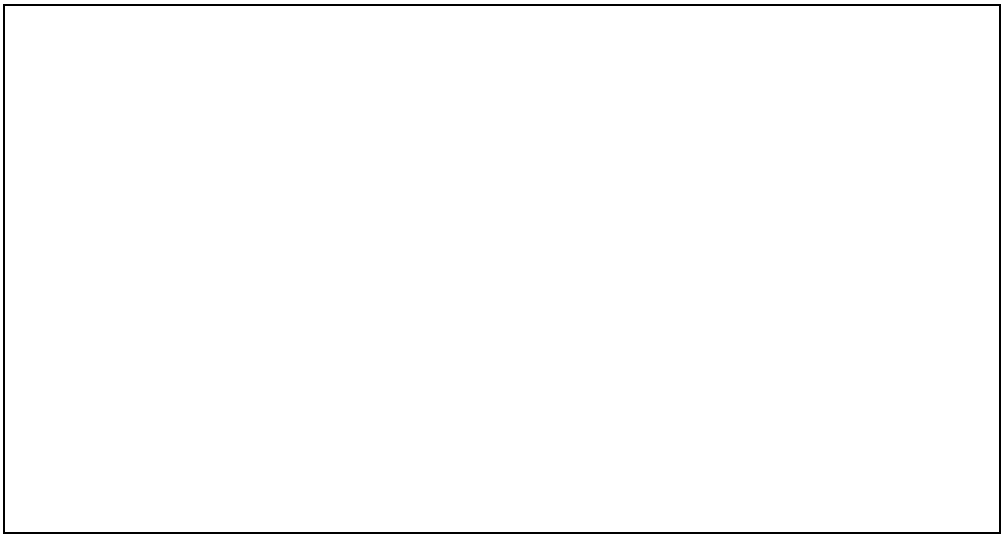


Figure (34): Chronic hepatitis showing macrovesicular steatosis ranging from 30-70% (score 2) (H&E X200).

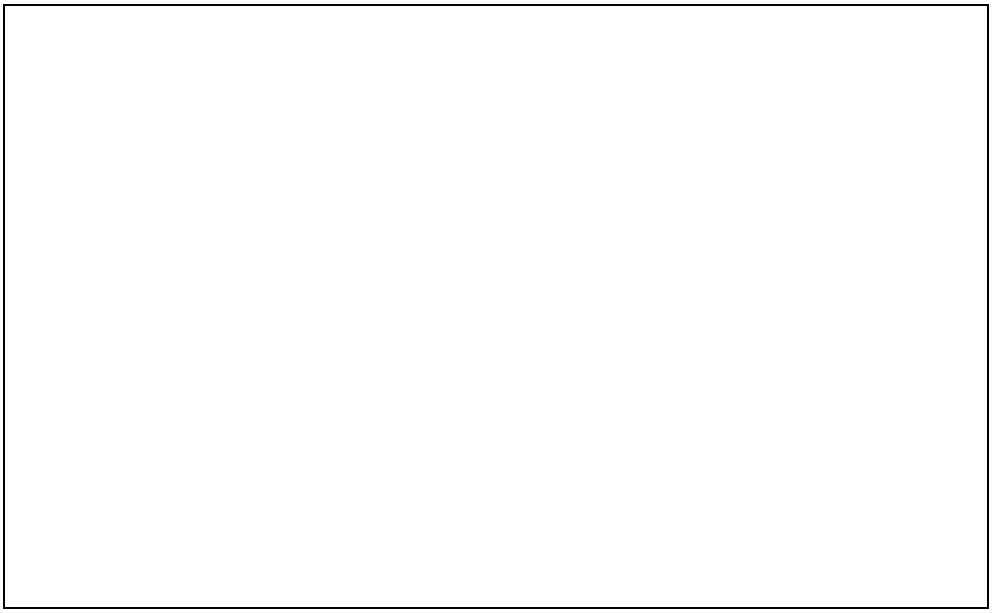


Figure (35): Chronic hepatitis showing macrovesicular steatosis >70% (score 3) (H&E X200).

Immunohistochemical results for detection of singular hepatic progenitor cells (HPCs) and atypical ductular reaction

In apparently normal liver group:

Neither singular hepatic progenitor cells nor atypical ductular reaction could be detected in examined apparently normal liver tissue.

In cases of chronic viral C hepatitis:

Both singular hepatic progenitor cells (HPCs) and atypical ductular reaction were detected in all chronic viral C hepatitis cases, through their positivity for cytokeratin 19.Such positivity appeared diffuse brownish cytoplasmic staining to anti-cytokeratin 19 (anti CK19).

Morphology of detected hepatic progenitor cells and atypical ductular reaction:

Singular hepatic progenitor cells were smaller than hepatocytes, oval in shape with oval nuclei, scant cytoplasm and positive cyoplasmic staining for cytokeratin 19 (CK19) **(Fig 40).** While atypical reactive ductules were irregular ductular structure with ill-defined lumen, lined by flattened to oval cells showing positive cytoplasmic staining for CK19 **(Fig 41).**

Distribution of detected hepatic progenitor cells and atypical ductular reaction in chronic viral C hepatitis cases:

Both singular hepatic progenitor cells and atypical ductules were mainly seen within portal areas and expanding fibrous septa with high concentration at their periphery and at the interface between connective tissue and the

parenchyma. Some HPCS and atypical reactive ductules were seen extending to hepatic parenchyma. Close association of atypical ductular reaction to singular HPCs was noted. Close proximity of singular HPCs and atypical reactive ductules to inflammatory cells was also observed **(Fig 42).**

Number of hepatic progenitor cells and atypical reactive ductules in chronic viral C hepatitis cases:

In chronic viral C hepatitis cases, the average number of detected hepatic progenitor cells (HPCs) ranged from 0.3 to 5.2/HPF with mean number of 2.02± 1.22.

While the average number of atypical reactive ductules ranged from 0.3 to 10/HPF with mean number of 3.44 ± 2.35

In hepatocellular carcinoma (HCC) group:

Both singular hepatic progenitor cells and atypical ductular reaction were detected in all cases of hepatocellular carcinoma, exhibiting the fore mentioned morphologic criteria as chronic viral C hepatitis.

Cytokeratin 19 positive singular cells were detected among the malignant parenchymal cells. Both singular hepatic progenitor cells (HPCs) and atypical ductular reaction were seen within the intratumoral fibrous stroma. Similar to chronic viral C hepatitis; close association between singular hepatic progenitor cells and atypical reactive ductules was observed.

The average number of singular HPCs in cases of HCC ranged from 5 to 8.3/HPF with mean number of 6. 2 ±1.07.While the average number of atypical ductular reaction in cases of HCC ranged from 7.1 to 15.7/HPF with mean number of 10.0 ± 3.22.

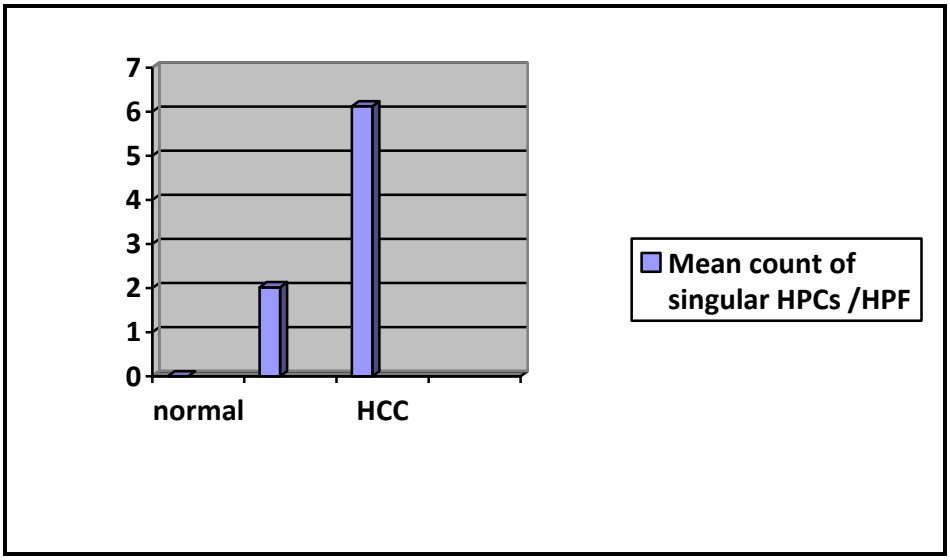
- ***Number of singular hepatic progenitor cells (HPCs) in all examined cases:***

No singular hepatic progenitor cells (HPCs) could be detected in examined normal liver tissue while singular hepatic progenitor cells (HPCs) were found in chronic hepatitis cases with mean count 2.02±1.22.Their mean count increased in hepatocellular carcinoma (HCC) cases to be 6.12±1.07.

Table (11): Mean and standard deviation (SD) of singular HPC /HPF in all examined cases:

Study group	No. of cases	Mean
± Normal liver	6	0.00±0.00
Chronic viral C hepatitis	37	2.02±1.22
HCC	7	6.2±1.07

Graph (9): Mean count of singular HPCs /HPF in all examined cases:



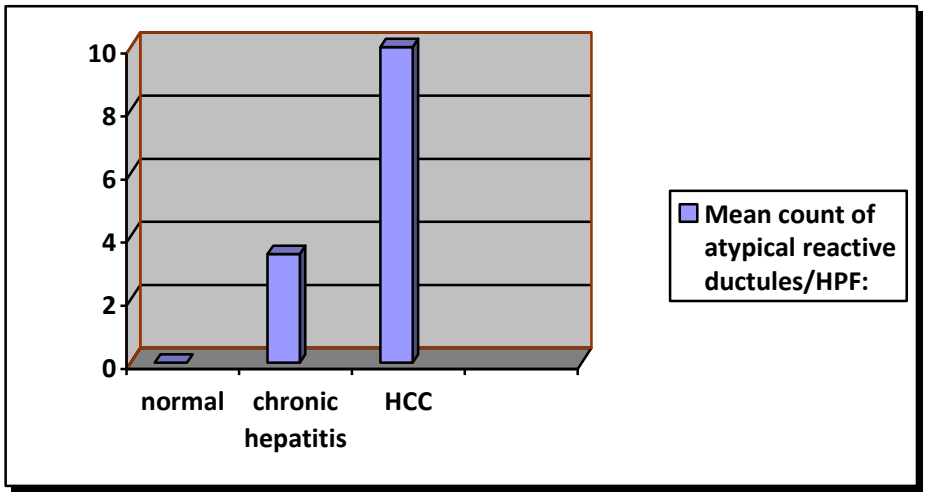
-Number of atypical reactive ductular in all examined cases:

No atypical reactive ductules could be detected in examined normal liver tissue while atypical reactive ductules were found in chronic hepatitis cases with mean count 3.44±2.35.Their mean count increased in hepatocellular carcinoma (HCC) cases to be 10±3.22.

Table (12): Mean and standard deviation (SD) of atypical reactive ductular count/ HPF all examined cases:

Study group	No. of cases	Mean count of atypical reactive ductules/HPF:
± Normal liver	6	0.00±0.00
Chronic Viral C hepatitis	37	3.44±2.35
HCC	7	10.00±3.22

Graph (10): Mean count of atypical reactive ductular /HPF in all examined cases:



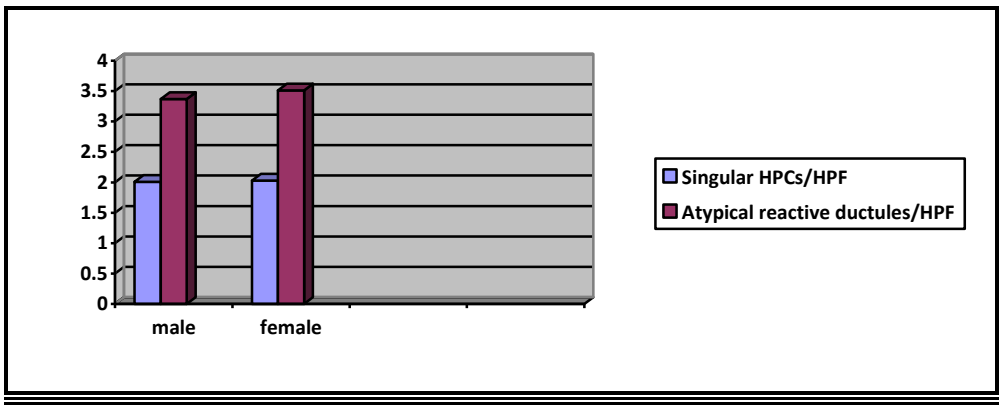
-Comparison of the mean number of each of singular HPCs and atypical reactive ductules/HPF between both sexes:

There was no significant difference in neither mean count of singular HPCs/ HPF nor mean count of atypical reactive ductules/HPF between both sexes.

Table (13): Comparison of the mean number of each of singular HPCs and atypical reactive ductules/HPF between both sexes.

Sex	No. of cases &% of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules / HPF
Male	31 (84%)	2.01±1.19	3.37±2.49
Female	6 (16%)	2.03±1.04	3.51±2.00
Total	**37 (100%)**	**-**	**-**

Graph (11): Comparison of the mean number of each of singular HPCs and atypical reactive ductules/HPF between both sexes.



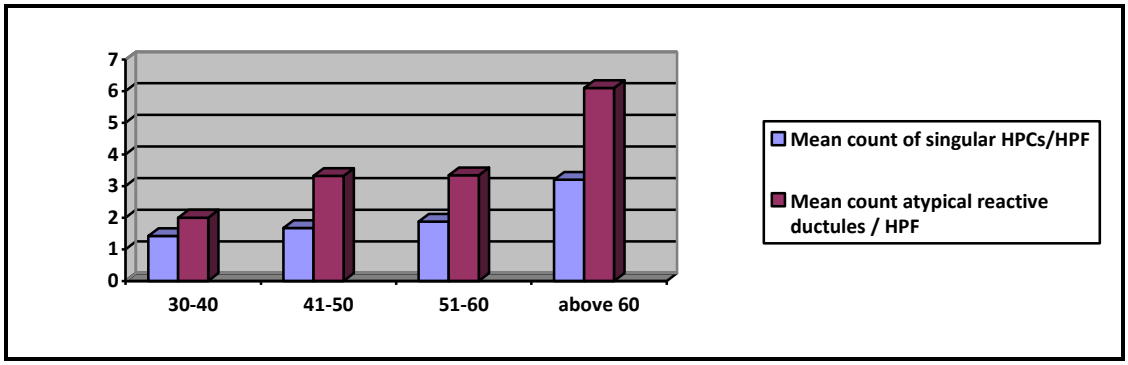
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to age:

The mean count of singular HPCs/HPF increases gradually with increased age, however it was ***statistically insignificant (P=0.203)*** .Similarly; the mean count of atypical reactive ductules/HPF increases gradually with increased age, however it was ***statistically insignificant (P=0.867).***

Table (14): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to age:

Age group	NO.&% of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules / HPF
30-40	5 (14%)	1.42±0.42	2.0±1.42
41-50	14(38%)	1.67±1.096	3.32±2.36
51-60	16(43%)	1.87±0.981	3.34±0.53
Above 60	2 (5%)	3.20±2.757	6.10±5.58
Total	**37 (100%)**	**P =*0.203*(*insignificant*)**	**P=*0.867*(*insignificant*)**

Graph (12): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to age.



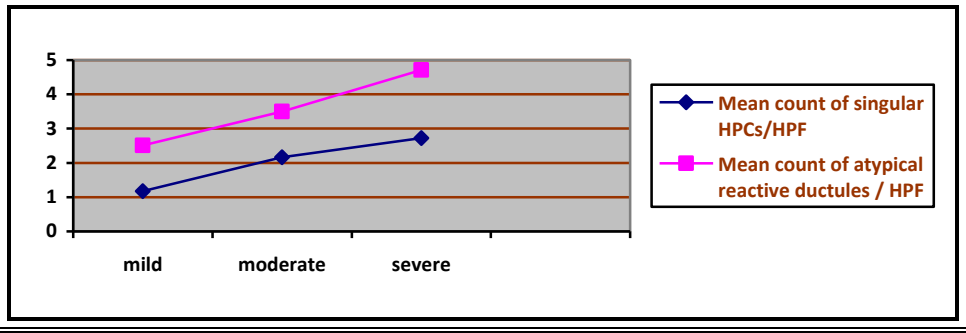
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (according to modified Ishak scoring system):

The mean number of each of singular HPCs/ HPF and atypical reactive ductules/HPF increased gradually with increasing grades of chronic hepatitis activity with ***statistically significant positive correlation for both (P=0.002,0.029 respectively)*** .

Table (15): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (according to modified Ishak scoring system):

Grade (modified Ishak)	No.&%of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules /HPF
Mild	**13 (**35%)	1.18±0.34	2.50±1.35
Moderate	**15 (**41%)	2.16±1.28	3.48±2.14
Severe	**9 (**25%)	2.72±1.33	4.71±3.28
Total	**37 (**100%)	***P=0.002(significant)***	***P=0.029(significant)***

Graph (13): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (according to modified Ishak scoring system):



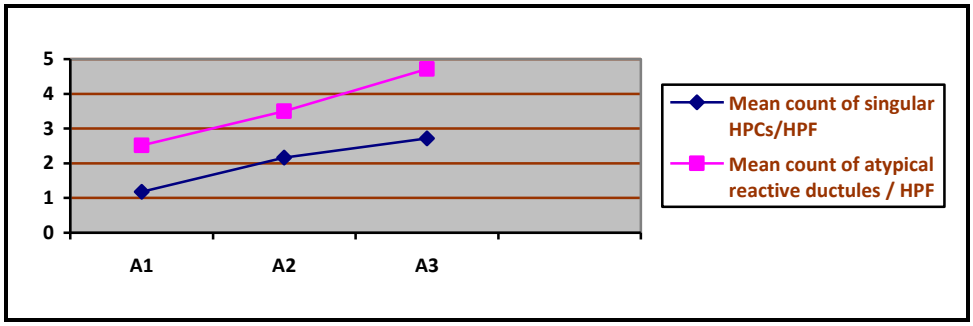
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (according to Metavir scoring system):

The mean number of each of singular HPCs and atypical reactive ductules/HPF increased gradually with increasing grades of chronic hepatitis activity with ***statistically significant positive correlation for both (P=0.002,0.029 respectively)*** .

Table (16): Correlation the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (*according to Metavir scoring system*):

Grade (modified Ishak)	No.&%of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules /HPF
A1	**13 (**35%)	1.18±0.34	2.50±1.35
A2	**15 (**41%)	2.16±1.28	3.48±2.14
A3	**9 (**25%)	2.72±1.33	4.711±3.28
Total	**37** (100%)	***P=0.002 (significant)***	***P=0.029(significant)***

Graph (14): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the grade of chronic hepatitis (*according to Metavir scoring system*):



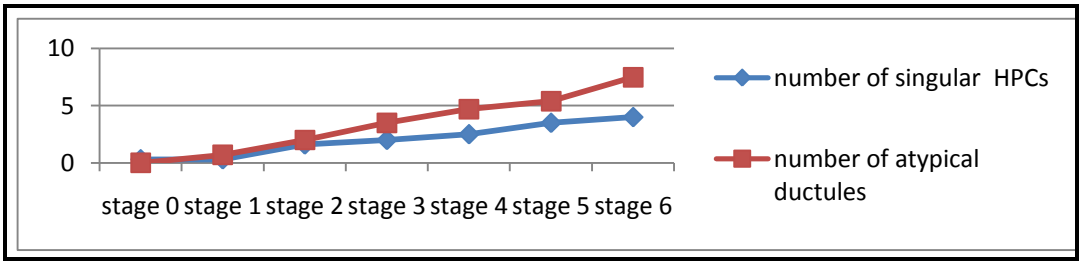
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis (according to Ishak scoring system):

The number of proliferating HPCs and atypical reactive ductules were increasing with increased degree of fibrosis up to established cirrhosis. There was ***statistically significant positive correlation*** between the mean count of each of singular HPCs and atypical reactive ductules/HPF and the stage of fibrosis (***P=0.001 and 0.008 respectively)***.

Table (17): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis (according to Ishak scoring system):

Stage	No.&%of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules / HPF
Stage 0	1 (3%)	0.3± 0.00	0.00±0.00
Stage 1	1 (3%)	0.3±0.00	0.7±0.00
Stage 2	3 (8%)	1.6±0.5	2±0.85
Stage 3	3 (8%)	2 ±0.9	3.5±0.89
Stage 4	1 (3%)	2.5±0.00	4.7±0.00
Stage 5	3 (8%)	3.5±1.5	5.4 ±3.6
Stage 6	25 (67%)	4.00±1.46	7.5±2.38
Total	**37**(100%)	***P=0.001(significant)***	***P=0.008(significant)***

Graph (15): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis (according to Ishak scoring system):



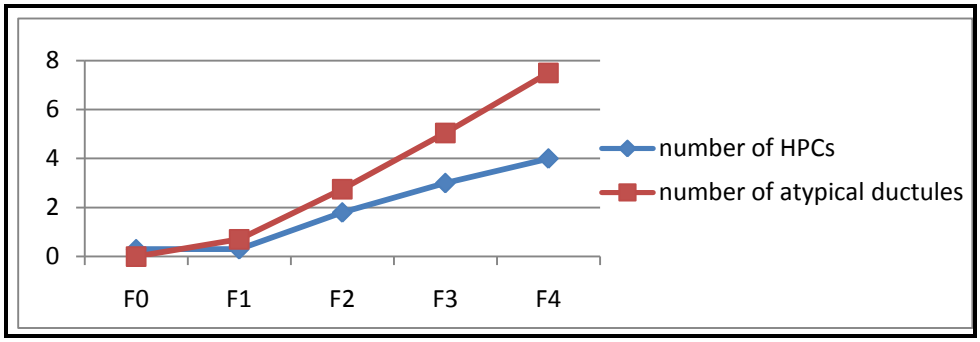
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis/cirrhosis (according to Metavir scoring system):

The number of proliferating HPCs and atypical reactive ductules were increasing with increased degree of fibrosis up to established cirrhosis. There was ***statistically significant positive correlation*** between the mean count of each of singular HPCs and atypical reactive ductules/HPF, and the stage of fibrosis ***(P =0.003 and 0.013 respectively)***.

Table(18):Correlation the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis/cirrhosis (according to Metavir scoring system):

Stage	No.&%of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules / HPF
F 0	1 (3%)	0.3± 0.00	0.00±0.00
F 1	1 (3%)	0.3±0.00	0.7±0.00
F 2	6 (16%)	1.8±0.5	2.75±0.85
F 3	4 (11%)	3.00±0.76	5.05±0.8
F 4	25 (67%)	4.00±1.46	7.5±2.38
Total	37(100%)	***P=0.003(significant)***	***P=0.013(significant)***

Graph (16): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the stage of fibrosis/cirrhosis (according to Metavir scoring system):



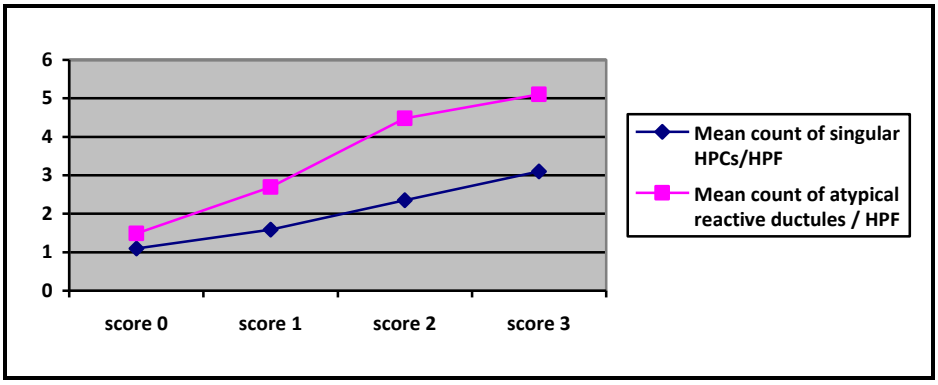
-Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the degree of steatosis:

The mean count of each of singular HPCs and atypical reactive ductules/HPF showed gradual increase with the degree of steatosis. ***Statistically significant positive correlation*** was found between the mean count of each of singular HPCs and atypical reactive ductules/HPF, and the degree of steatosis ***(P=0.004 and 0.045 respectively).***

Table(19):Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the degree of steatosis:

Degree of steatosis	No.&% of cases	Mean count& SD of singular HPCs/HPF	Mean count & SD of atypical reactive ductules / HPF
0	17 (47%)	1.1±0.99	1.49±0.345
1	16 (43%)	1.59±1.25	2.69±2.804
2	2 (5%)	2.35±0.21	4.48±4.472
3	2 (5%)	3.1±0.91	5.10±1.82
Total	**37** (100%)	***P=0.004****(significant)*	***P=0.045****(significant)*

Graph (17): Correlation of the mean number of each of singular HPCs and atypical reactive ductules/HPF to the degree of steatosis:



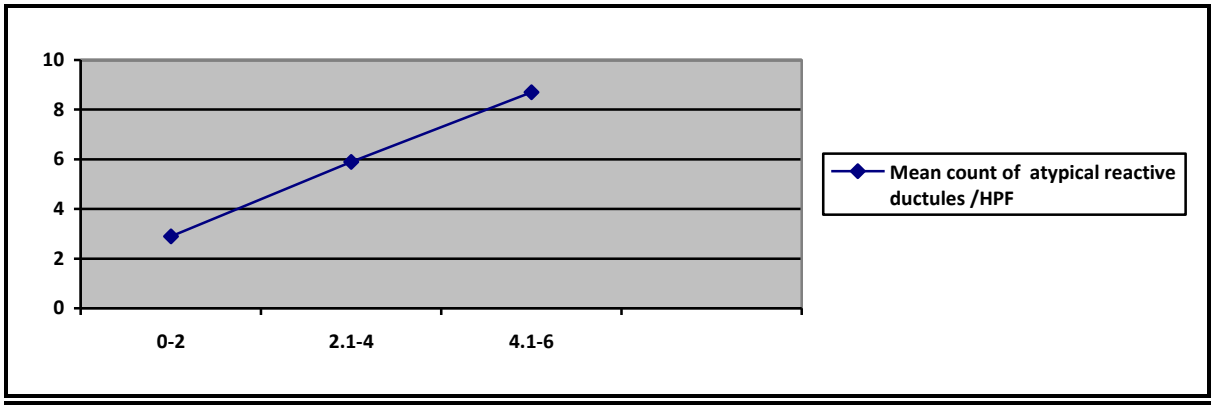
- Correlation of the mean count of singular HPCs / HPF to the mean count of atypical reactive ductules /HPF:

The mean count of atypical reactive ductules /HPF showed parallel increase to the mean count of singular HPCs / HPF**.** ***Highly statistically significant positive correlation*** was found between mean count of singular HPC /HPF and mean count of atypical reactive ductules /HPF ***(P=0.004***).

Table (20): Correlation of the mean count of singular HPCs / HPF to the mean count of atypical reactive ductules /HPF:

Mean Singular HPCs count/HPF	No. of cases	Mean count of atypical reactive ductules /HPF
0-2	24 (67.6%)	2.09±1.04
2.1-4	10 (21.6%)	5.09±1.8
4.1-6	3 (10.8%)	8.7±1.15
Total	**37** (100%)	***P=0.004****(significant)*

Graph (18): Correlation of the mean count of singular HPCs /HPF to the mean count of atypical reactive ductules /HPF.



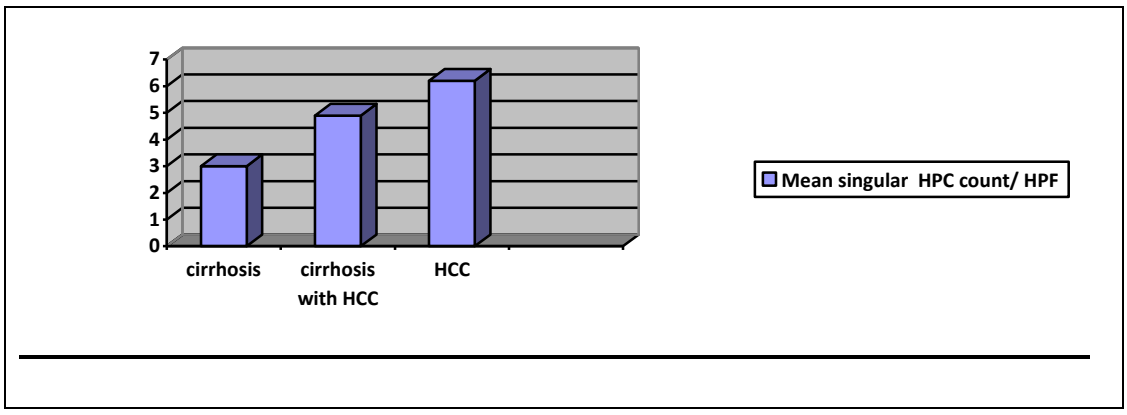
Comparison between the mean counts of singular HPCs /HPF in cirrhosis without tumor, cirrhosis adjacent to tumor and HCC on top of cirrhosis:

Mean Singular HPCs count/HPF showed gradual increase from cirrhosis (Ishak stage 6/6) without yet tumor development, to cirrhosis adjacent to tumor to reach the maximum in HCC on top of cirrhosis. ***Statistically positive significant correlations were found between cirrhosis & cirrhosis adjacent to tumor and between cirrhosis & HCC regarding the mean count of singular HPCs /HPF (P=0.017 and 0.0001 respectively).***

Table (21): Comparison between the mean counts of singular HPCs / HPF in cirrhosis without tumor, cirrhosis adjacent to tumor and HCC on top of cirrhosis:

Lesion	NO.&%of cases	Mean singular HPCs count/ HPF	P value
Cirrhosis without tumor	18 (41.86%)	3±0. 89	***P=0.017(cirrhosis&cirrhosis adjacent to HCC).*** ***P=0.0001(cirrhosis&HCC).***
Cirrhosis adjacent to tumor	**7 (**16.27%)	4.9±1.50	
HCC on top of cirrhosis	7 **(**16.27%)	6.2±1.053	

Graph (19): Comparison between the mean count of singular HPCs /HPF in cirrhosis without tumor, cirrhosis adjacent to tumor and HCC on top of cirrhosis.



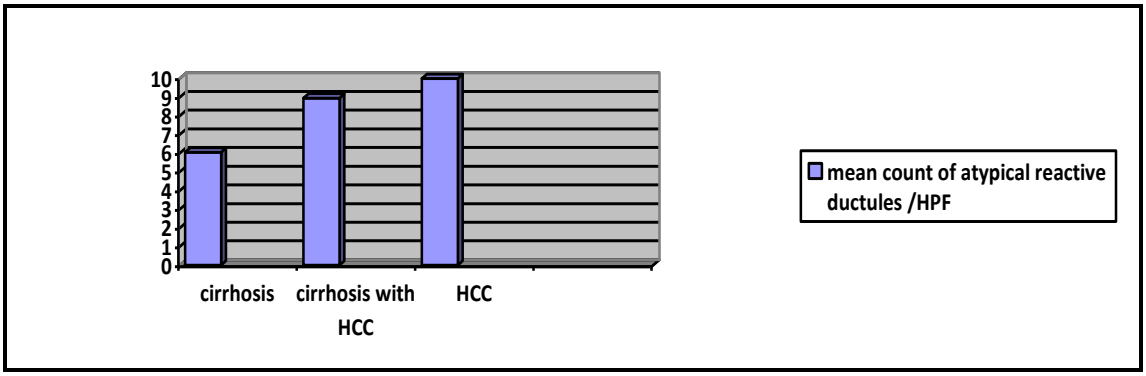
Comparison between the mean counts of atypical reactive ductules /HPF in cirrhosis without tumor, cirrhosis adjacent to tumor and HCC on top of cirrhosis:

The mean count of atypical reactive ductules /HPF showed gradual increase from cirrhosis (Ishak stage 6/6) without yet tumor development to cirrhosis adjacent to tumor to reach the maximum in HCC on top of cirrhosis. ***Statistically significant positive correlations were found between cirrhosis&cirrhosis adjacent to tumor and between cirrhosis & HCC regarding the mean count of atypical reactive ductules /HPF (P=0.014 and 0.0001 respectively).***

Table (22): Comparison between the mean counts of atypical reactive ductules/HPF in cirrhosis without tumor,cirrhosis adjacent to tumor and HCC on top of cirrhosis:

Lesion	NO. of cases	mean count of atypical reactive ductules /HPF	P value
Cirrhosis without tumor	18 (41.86%)	6.05±1.69	***P=0.014(cirrhosis&cirrhosis adjacent to HCC).***
Cirrhosis adjacent to tumor	7 (16.27%)	8.95±2.52	***P=0.0001(cirrhosis&HCC).***
HCC	7 (16.27%)	10±3.17	

Graph (20):Comparison between the mean counts of atypical reactive ductules /HPF in cirrhosis without tumor,cirrhosis adjacent to tumor and HCC on top of cirrhosis.



<u>Table (23):</u> shows the mean numbers of singular HPCs/HPF and atypical reactive ductules/ HPF in all examined cases:

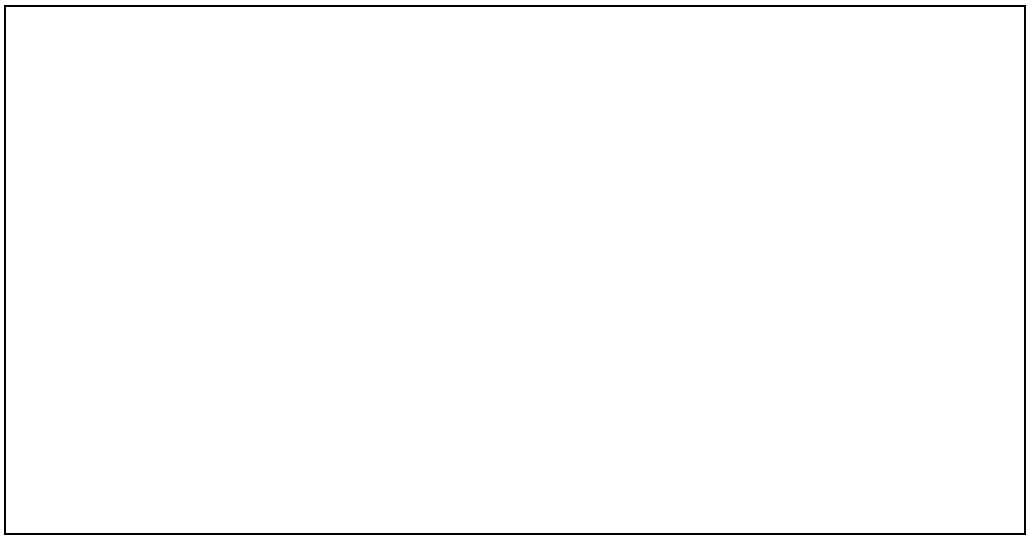
Chronic viral C hepatitis (mild activity) (no of cases:13)		*Chronic viral C hepatitis (moderate activity) (no of cases:15)*		*Chronic viral C hepatitis (marked activity) (no of cases:9)*		*HCC (control) (no of cases7)*	
Singular HPCs	*Atypical reactive ductules*	*Singular HPCs*	*Atypical reactive ductules*	*Singular HPCs*	*Atypical reactive ductules*	*Singular HPCs*	*Atypical reactive ductules*
1.3	2.7	2.7	3.7	3.7	8	6.3	8
1.3	2.7	2.4	4.3	4.6	6.3	5.3	7.1
0.7	4	2.7	2.7	3.3	7.8	6.5	9
1.3	2.7	1.3	2.7	2.7	3.7	6	8.8
1.3	2.3	1.7	2	1.7	0.7	5.5	12.7
1.3	1.7	2.5	5.7	3.2	7.3	5	15.7
1	1.3	2.9	2.9	1	1.2	8.3	8.9
1.3	1.7	4	5	1.8	2.7		
0.3	0.7	1.33	2	2.5	4.7		
0.3	0	0.3	2.1				
2.7	6.6	5.2	10				
1.3	2	0.6	1.8				
1.3	4.3	1.3	2				
		1.2	2.7				
		2	2.6				

Table (24): ***Correlation of mean count of singular HPCs /HPF and mean count of atypical reactive ductules/HPF to different clinical and histopathologiacal variants:***

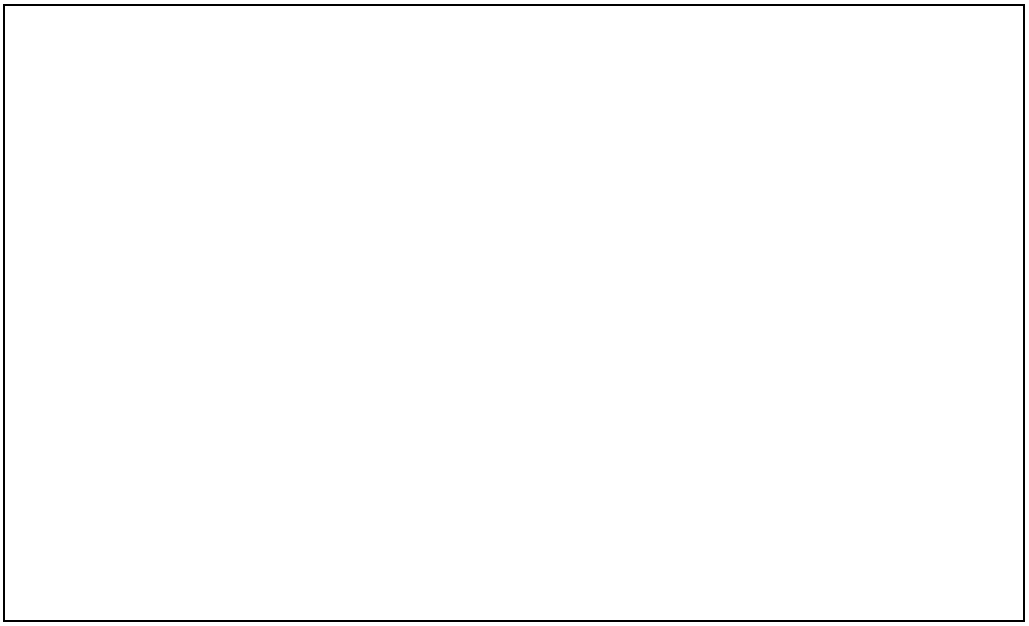
Clinical &Hisopathological variants			**Mean count of singular HPCs /HPF**	**P value**	**Mean count of atypical reactive ductules/ HPF**	**P value**
Sex		**Male**	2.01		3.37	
		Female	2.03		3.51	
Age		**30-40**	1.42	***P=0.203 insignificant***	2.0	***P=0.867 insignificant***
		41-50	1.67		3.32	
		51-60	1.87		3.34	
		More than 60	3.20		6.10	
Grade of activity	**ISHAK**	**Mild**	1.18	***P=0.002 (Significant)***	2.50	***P=0.029 (Significant)***
		Moderate	2.16		3.48	
		Severe	2.72		4.711	
	METAVIR	**A1**	1.18	***P=0.002 (Significant)***	2.50	***P=0.029 (Significant)***
		A2	2.16		3.48	
		A3	2.72		4.71	

stage of fibrosis	**ISHAK**	**Stage 0**	0.3	***P=0.001 (significant)***	0.00	***P=0.008 (Significant)***
		Stage 1	0.3		0.7	
		Stage 2	1.6		2	
		Stage 3	2		3.5	
		Stage 4	2.5		4.7	
		Stage 5	3.5		5.4	
		Stage 6	4.00		7.5	
	METAVIR	**F 0**	0.3	***P=0.003 (significant)***	0.00	***P=0.013 (significant)***
		F 1	0.3		0.7	
		F 2	1.8		2.75	
		F 3	3.00		5.05	
		F 4	4.00		7.5	

Steatosis	**Score 0**	1.1	***P=0.004*** ***(Significant)***	1.49	***P=0.045*** ***(significant)***
	Score 1	1.59		2.69	
	Score 2	2.35		4.48	
	Score 3	3.1		5.10	
	Cirrhosis without tumor	3	***P=0.017*** ***(Significant)***	6.05	***P=0.014*** ***(Significant)***
	Cirrhosis adjacent to tumor	4.9	***P=0.0001*** ***(Significant)***	8.95	***P=0.0001*** ***(Significant)***
	HCC	6.2		10	



Figure(36): Apparently normal liver tissue with no detectable singular hepatic progenitor cells or atypical ductular reaction. Septal bile duct is seen;highlighted by anti-CK19 immunostain, with its lumenal diameter greater than 100 µm, (ABC X400).



Figure(37): shows interlobular bile duct, highlighted by anti-CK19 immunostain ,with its lumenal diameter is 64.5 µm (between 50-100 µm) (ABC X400) .

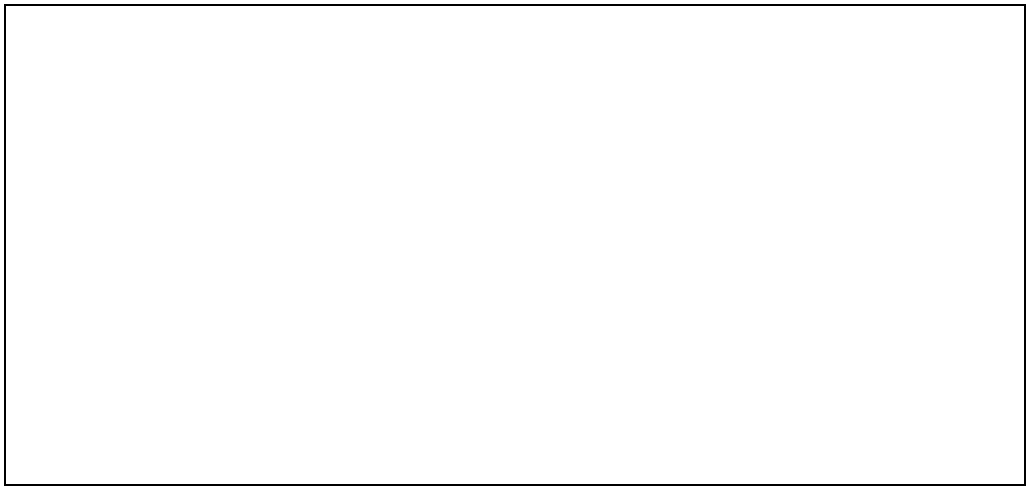
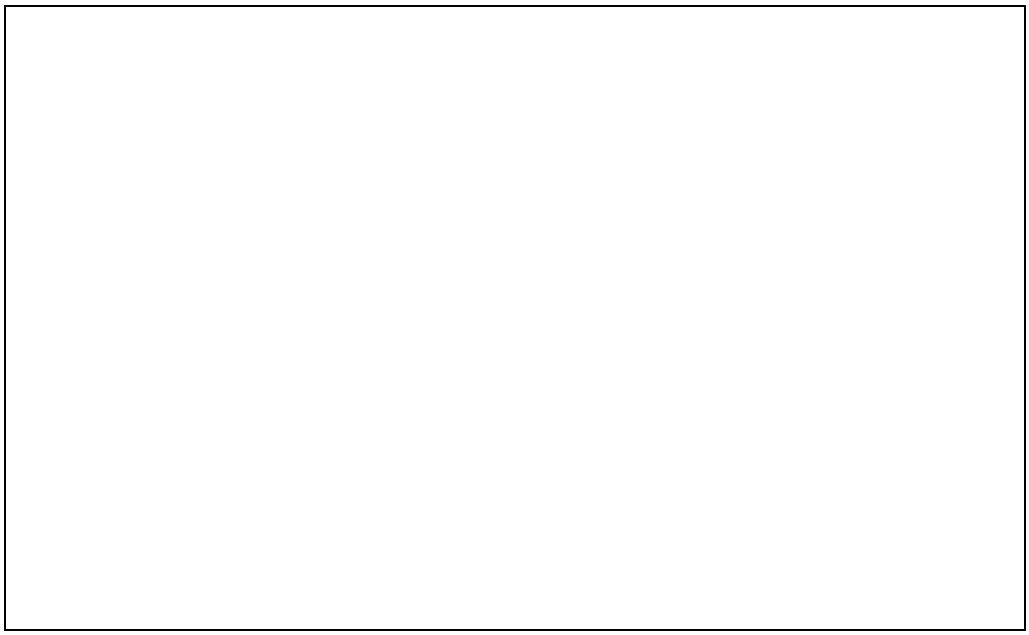
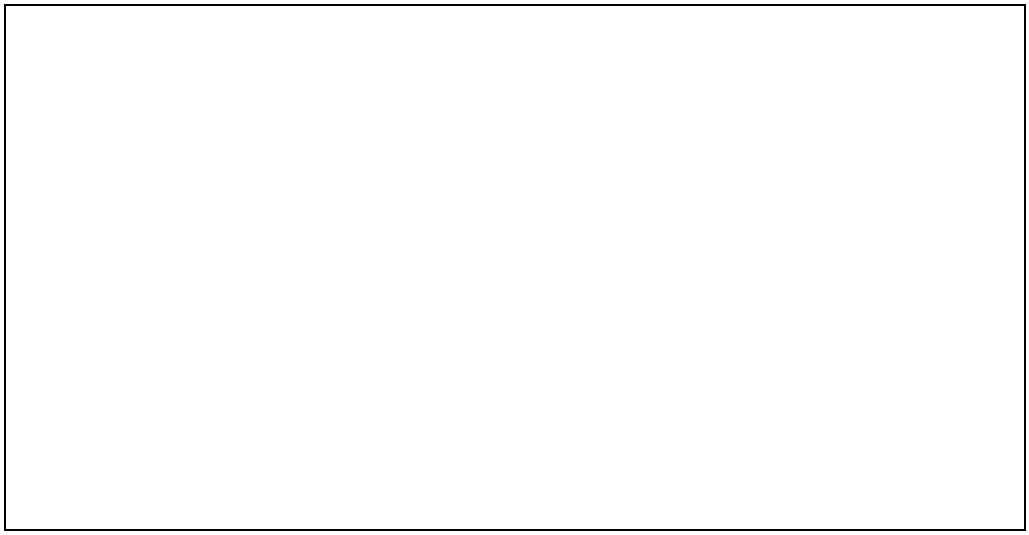


Figure (38): shows bile ductules; highlighted by anti-CK19 immunostain,with well formed ductular profiles, cuboidal lining and discernible lumen of maximal diameter less than 50 µm. (ABCX400).

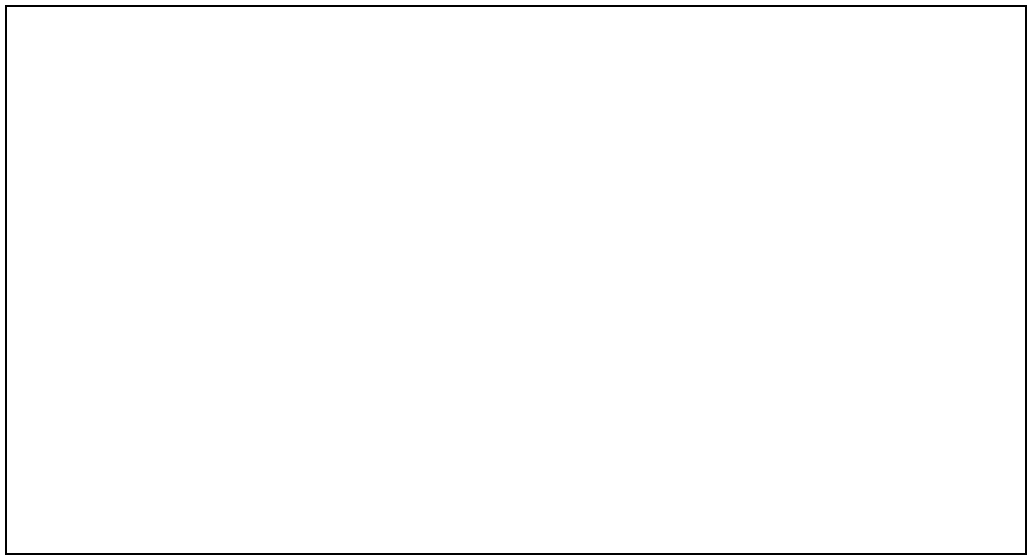
Figure (39): A case of chronic hepatitis showing atypical ductular reactions with ill defined lumen, ill formd ductular profile& oval cell lining. Singular HPCs are also seen. Both are immunostained with anti-CK19, in. (ABC X200).



<u>Figure (40)</u>: shows singular hepatic progenitor cells (HPCs) with cytoplasmic expression of CK19 (ABCX1000 oil immersion lens).



<u>Figure (41):</u> shows singular hepatic progenitor cells (A) together with irregular atypical ductular reaction (B). Both show cytoplasmic expression of CK19 (ABCX1000 oil immersion lens).



Figure(42): shows distribution of hepatic progenitor cells (HPCs) and atypical ductular reaction, immunostained with anti-CK19, within portal tracts, fibrous septa with more dense distribution toward the periphery or even extending to hepatic parenchyma (ABC x100).

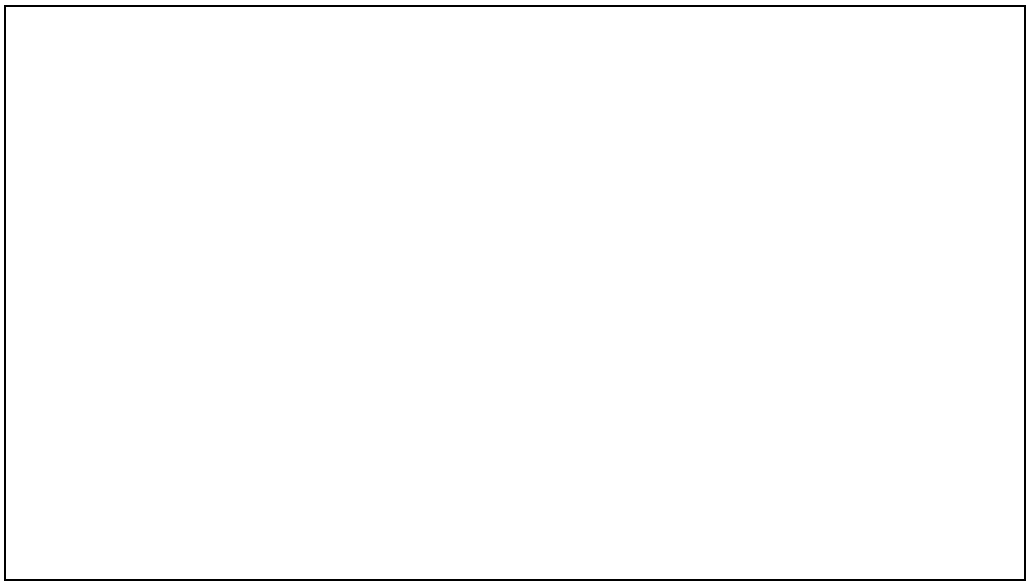


Figure (43): Chronic hepatitis, with Ishak score for fibrosis 1/6 showing low count of both singular HPCs and atypical ductular reaction, immunostained by anti-CK19 (ABC X200).

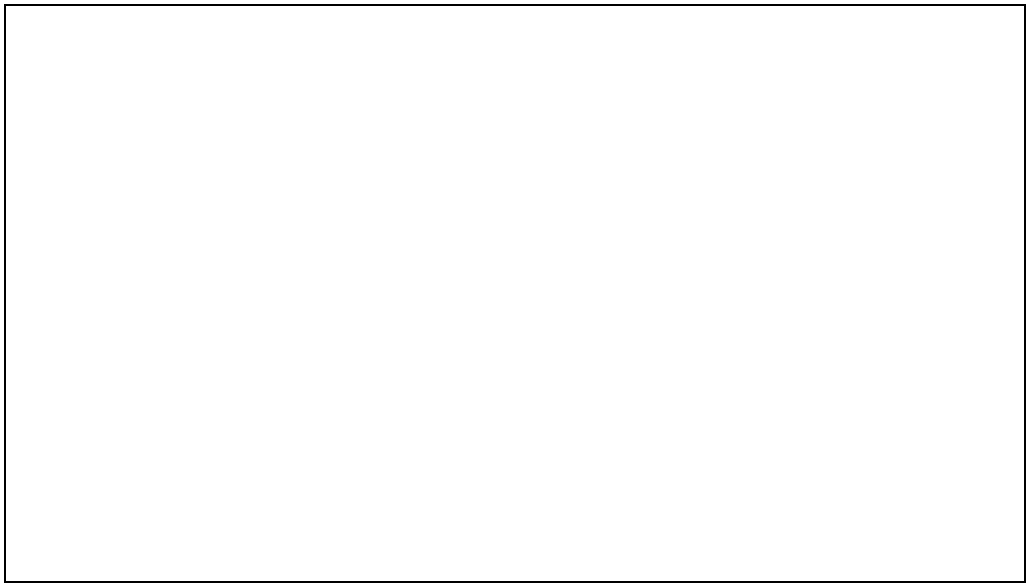


Figure (44): Chronic hepatitis, with Ishak score for fibrosis 6/6, showing high count both singular HPCs and atypical ductular reaction, immunostained by anti-CK19 (ABC X200).

Figure (45): Chronic hepatitis, with modified Ishak score for HAI 6/18 (mild activity), showing low count of both singular HPCs and atypical ductular reaction, immunostained by anti-CK19 (ABCX200).

Figure (46): Chronic hepatitis, with modified Ishak score for HAI 9/18 (moderate activity), showing moderate count of both singular HPCs and atypical ductular reaction, immunostained by anti-CK19 (ABC X200).

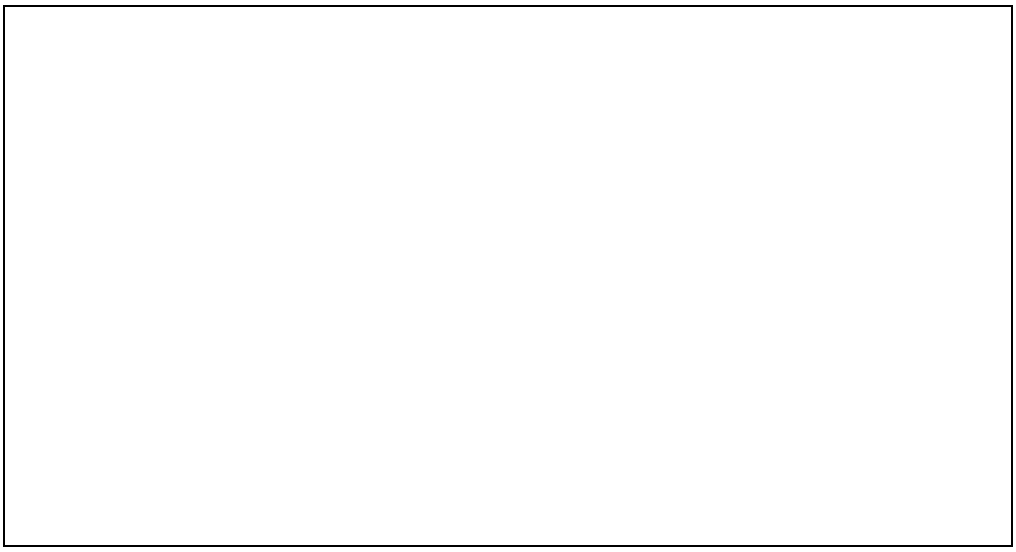


Figure (47): Chronic hepatitis, with modified Ishak score for HAI 13/18 (marked activity), showing higher count of both singular HPCs and atypical ductular reaction, immunostained by anti-CK19. (ABCX200).

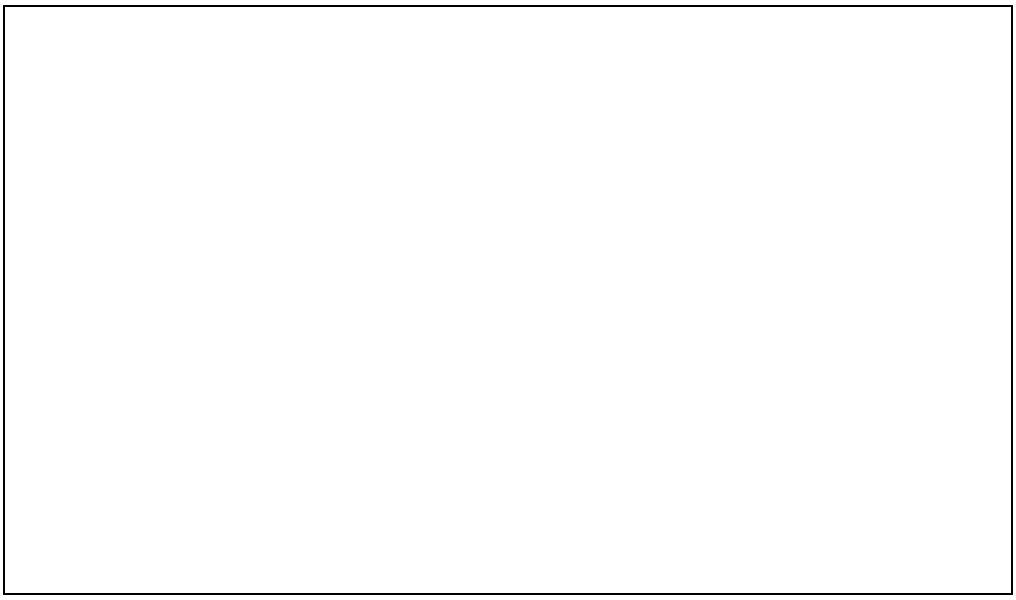
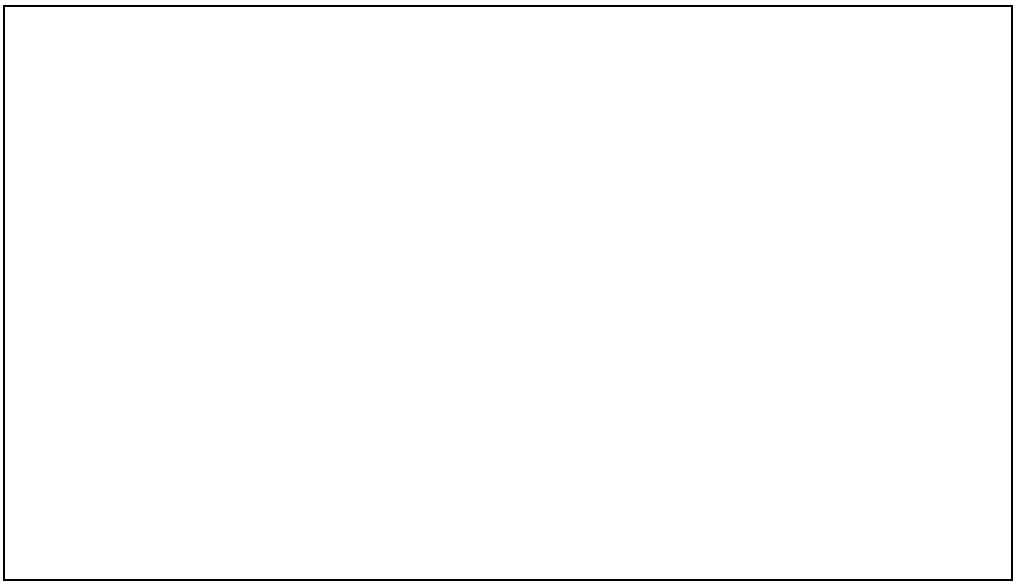
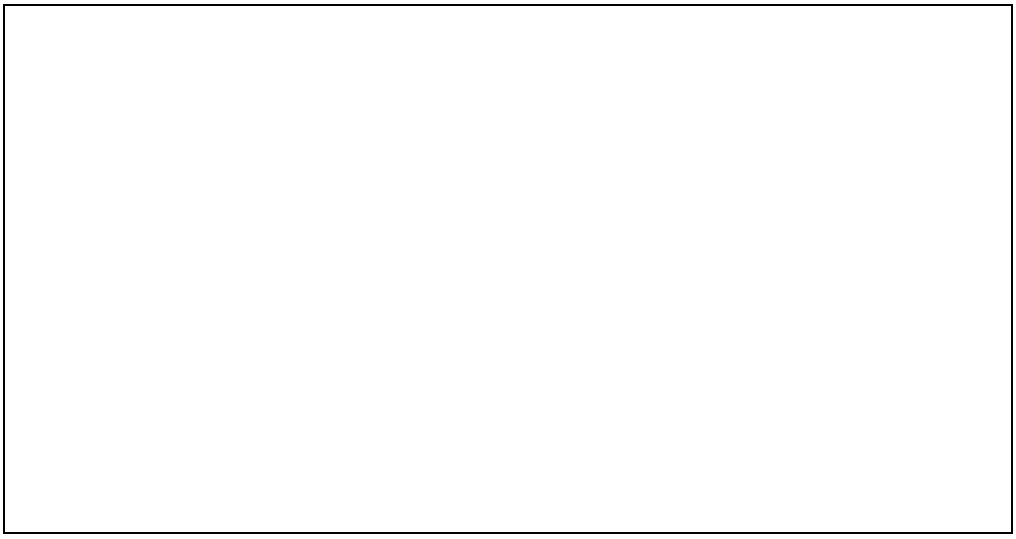


Figure (48): shows proliferated singular HPCs and atypical reactive ductules , immunostained with anti-CK19, in cirrhosis adjacent to HCC (ABC X100).



<u>Figure (49):</u> shows both singular HPCs and atypical reactive ductules, immunostained with anti-CK19 in HCC, pseudoglandular pattern (ABCX100)



<u>Figure (50):</u> shows both singular HPC and atypical reactive ductules immunostained with anti-CK19 in HCC, trabecular pattern (ABCX100).