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PREVALENCE OF THROMBOCYTOPENIA IN EGYPTIAN PATIENTS WITH CHRONIC HEPATITIS C VIRUS

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Abstract

Thrombocytopenia is defined as a platelet count less than 150.000/mm^3. It is a common finding in subjects with chronic hepatitis as HCV antibody-positive individuals are 2.6 times more likely to have a low platelet count than those who are HCV-antibody negative. However, controversy still exists concerning the mechanism of HCV-associated thrombocytopenia

This work studied the thrombocytopenia prevalence in Egyptian patients with chronic HCV. Data of 100 patients with chronic hepatitis C presented to Tropical Medicine department, Al-Azhar University, included full history, clinical assessment, laboratory investigations (complete blood count, liver biochemical profile, kidney function tests and PCR), abdominal ultrasound and liver biopsy.

The prevalence of thrombocytopenia among patients was 24/100 (24%), mild thrombocytopenia was the commonest grade (17%) then moderate one (6%) and lastly severe thrombocytopenia (1%). Thrombocytopenia significantly occurred more in older ages with high AST and ALT levels. The prevalence of thrombocytopenia significantly increased with abnormality liver Echopattern and with the progress of fibrosis and activity in liver biopsy.

Key words: Egyptian Patients, Thrombocytopenia, Chronic HCV

Introduction

Hepatitis C virus is a major cause of chronic liver disease, infecting 200 Million persons worldwide (Mc Huchison *et al,* 2004). In Egypt, HCV antibody was around 12% nationwide in 1999 (Egypt, Ministry of Health and population, 1999). The epidemic was attributed to mass campaigns of parentral antischistosomiasis treatment (PAT) in rural areas in the 1960s-70s (Frank *et al,* 2000), in Egypt high HCV rates in several populations reached up to 20% (Mohamed *et al*, 2005; Seif El-Nasr *et al*, 2006).

On the other hand, thrombocytopenia is a common finding in subjects with chronic hepatitis as HCV antibody-positive individuals are 2.6 times more likely having a low platelet count than those who are HCV-antibody negative. But, controversy existed concerning the mechanism of HCV-associated thrombocytopenia (Wang *et al,* 2004).

Several mechanisms have been proposed as contributing to thrombocytopenia: sequestration of platelets in the enlarged spleen (Sanjo *et al,* 2003), platelet destruction mediated by platelet-associated IgG might lead to se-

questration in the reticuloendothelial system and related to hypersplenism (Pockros *et al,* 2002), impaired hepatic production of thrombopoietin (TPO) (Martin *et al,* 1997; Ishikawa *et al,* 1998) and a direct viral effect since a positive correlation between thrombocytopenia and HCV association with platelets was reported (De Almeida *et al,* 2004).

Thrombopoietin is the main stimulus for thrombopoiesis, regulates platelet production, stimulating megakaryocyte proliferation and maturation. It is produced primarily in the liver and degraded by circulating platelets (Streiff *et al,* 2002). Administration of thrombopoietin is currently under investigation for management of thrombocytopenia in patients with liver disease, or during treatment with interferon therapy to counteract the myelosuppressive effects of the drug (Garcia-Suarez *et al,* 2000).

Patients, Materials and Methods

The present study is cross sectional study included 100 patients with chronic HCV, from El-Sayed Galal and Al-Hussein Hospitals, Al-Azhar University from November 2010 to July 2011. Patients were selected due to the following criteria: a- age between 18-75 years old, and b- presented with chronic HCV proved by HCV Ab and quantitative PCR. Excluding criteria were patients with HBV infection, or with autoimmune hepatitis, or with hepatocellular carcinoma, or with cirrhosis or with history of antiviral treatment or now on antiviral treatment.

Every patient was subjected to: 1- Full history taking and clinical assessment, and 2- Laboratory investigations for CBC (Hb, WBC & Platelet count), 2i- Blood film, 2ii- Coagulation profile (PT, PC & INR), 2iii- Assessment of liver biochemical profile (ALT, AST, Total protein, Serum albumin and Bilirubin), 2iv- Serum creatinin and blood urea, 2-v HbsAg and HCVAb, 2-vi- Alpha feto-protein, 2vii- ANA, ASMA, LKMA, 2vii-Qantitative PCR for HCV (Wahib *et al*, 2006). 3- Pelvi-abdominal ultrasound, and 3- Liver biopsy.

Thrombocytopenia was defined as patients with platelet count <150000 / µl. Prevalence was assessed as patients' ratio with thrombocytopenia in all chronic HCV patients at the time of data collection.

Results

The results are shown in tables (1 to 16) and figures (1 to 16).

Table 1: Prevalence of thrombocytopenia in chronic HCV patients.

	Thrombocytopenia	Normal platelet count	Total
Frequency	24 (24%)	76 (76%)	100 (100%)

Table 2: Grades of thrombocytopenia in patients.

PLT	N	%
normal	76	76.00
mild thrombocytopenia	17	17.00
moderate thrombocytopenia	6	6.00
sever thrombocytopenia	1	1.00
Total	100	100.00

These tables showed that prevalence of thrombocytopenia among patients was (24%) and thrombocytopenia was mild in most cases.

Table 3: Thrombocytopenic & non-thrombocytopenic patients as regard residence.

Residence		N	Mild	Moderate	Severe	Total
Rural	%	42	8	2	0	52
	N	55.26	47.06	33.33	0.00	52.00
Urban	%	34	9	4	1	48
	N	44.74	52.94	66.67	100.00	48.00
Total	%	76	17	6	1	100
	X^2	100.00	100.00	100.00	100.00	100.00
Chi-square	P-value	2.411				
	P-value	0.492				

NS=Non significant (p>0.05).

No significant difference in prevalence of thrombocytopenia in rural or urban areas.

Table 4: Thrombocytopenic and non- thrombocytopenic patients as regard sex.

sex		Normal	Mild	Moderate	Severe	Total
Male	N	55	13	4	1	73
	%	72.37	76.47	66.67	0.00	72.00
Female	N	21	4	2	0	27
	%	27.63	23.53	33.33	100.00	28.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	2.830				
	P-value	0.419 (NS)				

Thrombocytopenia was more in males but without significant (P = 0.419).

Table 5: Thrombocytopenic and non-thrombocytopenic patients as regard age.

PLT	AGE		ANOVA	
	Range	Mean ± SD	f	P-value
Normal	20 - 59	38.316 ± 10.896	12.319	0.000 (HS)
Mild	37 - 58	50.000 ± 6.452		
Moderate	46 - 58	50.667 ± 4.719		

Thrombocytopenia was more in older age with high significant above 50 years.

Table 6: Thrombocytopenic and non-thrombocytopenic patients as regard smoking.

Smoking		Normal	Mild	Moderate	Severe	Total
No	N	63	12	5	1	81
	%	82.89	70.59	83.33	100.00	81.00
Yes	N	13	5	1	0	19
	%	17.11	29.41	16.67	0.00	19.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X2	1.631				
	P-value	0.652 (NS)				

No significant difference in prevalence of thrombocytopenia and grades between smoker and non-smokers.

Table 7: Thrombocytopenic and non-thrombocytopenic patients as regard DM.

DM		Normal	Mild	Moderate	Severe	Total
No	N	73	13	5	1	92
	%	96.05	76.47	83.33	100.00	92.00
Yes	N	3	4	1	0	8
	%	3.95	23.53	16.67	0.00	8.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	11.966				
	P-value	0.167 (NS)				

No significant difference in prevalence of thrombocytopenia and grades between diabetic and non-diabetic patients.

Table 8: Thrombocytopenic and non-thrombocytopenic patients as regard HTN.

HTN		Normal	Mild	Moderate	Severe	Total
No	N	74	13	6	1	94
	%	97.37	76.47	100.00	100.00	94.00
Yes	N	2	4	0	0	6
	%	2.63	23.53	0.00	0.00	6.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	11.238				
	P-value	0.123 (S)				

No significant difference in prevalence of thrombocytopenia and grades between hypertensive and non-hypertensive patients.

Table 9: Thrombocytopenic & non-thrombocytopenic patients as regard complains.

Complain		Normal	Mild	Moderate	Severe	Total
Accidently	N	37	3	3	1	44
	%	48.68	17.65	50.00	100.00	44.00
Fatigue	N	18	9	2	0	29
	%	23.68	52.94	33.33	0.00	29.00
Rt. hypochond pain	N	16	2	1	0	19
	%	21.05	11.76	16.67	0.00	19.00
Dyspepsia	N	5	3	0	0	8
	%	6.58	17.65	0.00	0.00	8.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	11.827				
	P-value	0.223 (NS)				

No significant difference in prevalence of thrombocytopenia and grades as regard presenting complains.

Table 10: Thrombocytopenic and non-thrombocytopenic patients and ALT levels.

ALT		Normal	Mild	Moderate	Severe	Total
Normal	N	33	2	0	0	35
	%	43.42	11.76	0.00	0.00	35.00
Elevated	N	43	15	6	1	65
	%	56.58	88.24	100.00	100.00	65.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	10.172				
	P-value	0.017 (S)				

(S)= significant p-value ≤ 0.05.

This table shows significant differences in prevalence of thrombocytopenia and ALT levels.

Table 11: Thrombocytopenic and non-thrombocytopenic patients and AST levels.

AST		Normal	Mild	Moderate	Severe	Total
Normal	N	62	0	0	0	62
	%	81.58	0.00	0.00	0.00	62.00
Elevated	N	14	17	6	1	38
	%	18.42	100.00	100.00	100.00	38.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	51.524				
	P-value	0.000 (HS)				

This table shows highly significant differences in prevalence of thrombocytopenia and AST levels.

Table 12: Thrombocytopenic & non-thrombocytopenic patients as regard viraemia.

PLT	PCR For Hepatitis c Virus		ANOVA	
	Range	Mean ± SD	f	P-value
Normal	1 - 3	1.658 ± 0.684	0.881	0.418 (NS)
Mild	1 - 3	1.882 ± 0.600		
Moderate	1 - 3	1.833 ± 0.753		

No significant difference in prevalence of thrombocytopenia and viraemia level.

Table 13: Thrombocytopenic & non-thrombocytopenic patients and liver Echopattern.

CHOPATERN		Normal	Mild	Moderate	Severe	Total
Normal	N	53	2	0	0	55
	%	69.74	11.76	0.00	0.00	55.00
Bright	N	22	7	1	0	30
	%	28.95	41.18	16.67	0.00	30.00
Coarse	N	1	8	5	1	15
	%	1.32	47.06	83.33	100.00	15.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	58.650				
	P-value	0.000 (HS)				

This table shows highly significant differences in prevalence of thrombocytopenia and Echopattern of liver levels.

Table 14: Thrombocytopenic and non-thrombocytopenic patients as liver size by ultrasound.

PLT	Size of Liver				ANOVA	
	Range	Mean	±	SD	f	P-value
Normal	1 - 2	1.145	±	0.354	1.388	0.255 (NS)
Mild	1 - 2	1.059	±	0.243		
Moderate	1 - 2	1.333	±	0.516		

1=Normal (Rt. Lobe upto 16cm) 2=Enlarged (Rt. Lobe more than 16 cm)

No significant difference in prevalence of thrombocytopenia and liver size.

Table 15: Thrombocytopenic and non-thrombocytopenic patients as regard activity in liver biopsy

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	A (Activity)	Normal	Mild	Moderate	Severe	Total
1	N	51	2	0	0	53
	%	67.11	11.76	0.00	0.00	53.00
2	N	23	7	0	0	30
	%	30.26	41.18	0.00	0.00	30.00
3	N	2	8	6	1	17
	%	2.63	47.06	100.00	100.00	17.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	61.458				
	P-value	0.000 (HS)				

This table shows highly significant differences in prevalence of thrombocytopenia and its grades as regard activity in liver biopsy.

Table 16: Thrombocytopenic and non-thrombocytopenic patients as regard fibrosis in liver biopsy.

	F (Fibrosis)	Normal	Mild	Moderate	Severe	Total
0	N	16	0	0	0	16
	%	21.05	0.00	0.00	0.00	16.00
1	N	40	1	0	0	41
	%	52.63	5.88	0.00	0.00	41.00
2	N	18	5	0	0	23
	%	23.68	29.41	0.00	0.00	23.00
3	N	2	11	6	1	20
	%	2.63	64.71	100.00	100.00	20.00
Total	N	76	17	6	1	100
	%	100.00	100.00	100.00	100.00	100.00
Chi-square	X^2	68.325				
	P-value	0.000 (HS)				

This table shows highly significant differences in prevalence of thrombocytopenia and degree of fibrosis in liver biopsy.

Discussion

Globally, HCV is a serious worldwide public health problem affecting an estimated 120-170 million individuals (Shepard *et al,* 2005). Several extrahepatic manifestations have been reported in the natural history of hepatitis C virus infection (Galossi *et al,* 2007). Up to 40-74% of patients infected with

HCV might develop at least an extrahepatic manifestation during the disease course (Agnello and De Rosa, 2004). Dietrich and Spivak (2003) reported that thrombocytopenia is one of several extrahepatic manifestations associated with chronic HCV infection. Thrombocytopenia (platelet count of <150, 000/µl) was one of the commonest hematological abnormalities in patients with chronic liver disease (Giannini, 2006).

In the present study, a variety of pathogenic mechanisms were reported to be implicated in thrombocytopenia related to chronic HCV infection: sequestration of platelets in the enlarged spleen secondary to portal hypertension or hypersplenism (Kirby *et al,* 2013), deregulation of the host immune system triggering the production of autoantibodies against platelet glycoproteins (Pockros *et al,* 2002), inadequate production of thrombopoietin in advanced stage liver disease (Adinolfi *et al,* 2001), infection of platelets (Hamaia *et al,* 2001) and megakaryocytes (Bordin *et al,* 1995).

The prevalence of thrombocytopenia among in the present patients was 24 (24%) out of 100 (100 %). Roomer *et al.* (2010) reported that severe bleedings did not occur in patients with platelet counts below 50,000/microl; based on these findings, treatment with peginterferon alfa and ribavirin appeared to be safe in patients with platelet counts below 50,000/microl although platelet counts below 25,000/microl were rare. Nagamine *et al.* (1996) diagnosed thrombocytopenia (<$15x10^4$ platelets/µl) in 151/368 patients (41%) with chronic HCV (cirrhotic and non-cirrhotic). Wang *et al*. (2004) evaluated association between HCV infection and thrombocytopenia (<100,000/mm^3), the prevalence was 1.3% among seronega-tive subjects, and 10.2% among anti-HCV-positive ones. The present low frequency of thrombocytopenia could be due to the definition of thrombocytopenia used. Afdhal *et al.* (2008) classified thrombocytopenia based on clinical significance into mild (>75,000/µl-<150,000/µl), which was minimal and usually did not interfere with treatment or management decisions, moderate (50,000/µl-75,000/µl) which increased the risk of bleeding during invasive diagnostic procedures such as liver biopsy, particularly in patients with coexistent coagulopathy, and could limit treatment of chronic HCV infection with pegylated interferon (PEG-IFN) and severe thrombocytopenia (<50,000 /µl) can significantly increase bleeding the risk.

In the present study, mild thrombocytopenia was the most common grade as we find its prevalence (17%) followed by moderate thrombocytopenia (6%) and lastly severe thrombocytopenia (1%). Analyzing the demographic data it was found that patients with older ages were more likely to have thrombocytopenia which was highly statistically significant (p=0.000). On the other hand, thrombocytopenia was more prevalent in males than females but without significant (p=0.419*),* also no significance between patients from rural or urban area (p=0.492). This agreed with Lu *et al*. (2006) who reported that among anti-HCV positive

individuals, older persons were likely to have thrombocytopenia more than other age groups. This might be related to poor compensation for platelet production especially in individuals with severe liver disease (Another possibility might be that older individuals in an area hyper-endemic with HCV have been infected by it longer and, therefore, are more likely to have significant liver impairment (Wang *et al,* 2004). But, this data disagreed with Sandler (2004) who reported significant differences in demographic characteristics of HCV patients with thrombocytopenia regarding old age and equally distributed among sexes.

Analyzing of the presenting symptoms showed no significance between degrees of thrombocytopenia and comorbid diseases. Also, there were high significance between AST levels and thrombocytopenia (P=0.000) and between ALT level and thrombocytopenia (P=0.017). This agreed with Wang *et al.* (2004) who reported that elevated ALT & AST levels were strongly associated with thrombocytopenia, indicating that thrombocytopenia highly correlated with hepatocellular damage. This agreed with Shepard *et al*. (2005) who reported that HCV related thrombocytopenic patients were more likely to have mild elevations of ALT & AST as compared with HCV sero-negative patients.

In the present study, there was no significance between viral load by PCR and thrombocytopenia's degree (p= 0.418). Ultrasonography showed a non-invasive prediction of liver histological findings with a high sensitivity (89%-100%) and specificity (89%-93%), a feasible practice in the community, and was appropriate for the screening and follow-up observation of patients with chronic liver disease or hepatic fibrosis. The correlation between ultrasound finding as regard liver condition and size on one hand and prevalence of thrombocytopenia on the other hand there was highly statistically significance (p =0.000) between Echopattern of the liver and prevalence of thrombocytopenia, on the other hand there was no statistically significant difference between liver size and thrombocytopenia (p =0.255*)*. The results agreed with Wang *et al.* (2004) who stated that the prevalence of thrombocytopenia in patients with anti-HCV increased from 2.3% among those with sonographic evidence of a normal liver to 5.1% among those with bright liver, 20.3% among those with coarse liver and 31.8% among those with advanced liver disease (including liver cirrhosis and hepatoma).

Liver biopsy proved the most accurate method to determine the state of liver condition. In our study we found that there is high statistically significance between activity and fibrosis in liver biopsy on one hand and the prevalence of thrombocytopenia on the other hand (p =0.000). These results agreed with Adinolfi *et al.* (2001) who stated that there is an inverse correlation between serum thrombopoietin (TPO) levels and grade of liver fibrosis (**p <0.0001**) with thrombocytopenia occurring with greater frequency and severity in patients with grade 3 or 4 liver fibrosis than in those with grades 0,1

and 2 liver fibrosis. The results agreed with Giannini *et al.* (2002) who reported inverse correlation between platelet count and the severity of hepatic fibrosis due to chronic HCV (p=0.005). Patients with advanced fibrosis had significantly lower mean platelet counts compared to those having stage 0, 1 & 2 hepatic fibrosis also, agreed with Bashour *et al.* (2000) who reported that thrombocytopenia was higher in cirrhosis patients as compared to non-cirrhosis ones.

Conclusion

The outcome data showed that HCV was strongly associated with thrombocytopenia, which is directly correlated with hepatocellular damage and hepatic fibrosis. In most of thrombocytopenic patients degree of hepatocellular damage, as indicated by ALT & AST levels was more deteriorated in thrombocytopenic than non-thrombocytopenic ones reflecting that thrombocytopenia correlate with severity of liver disease.

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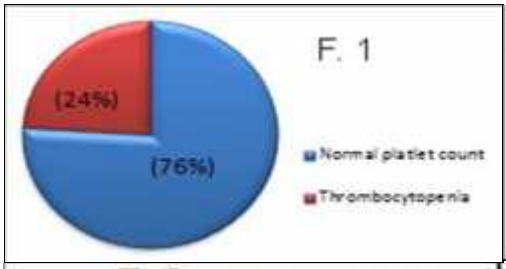

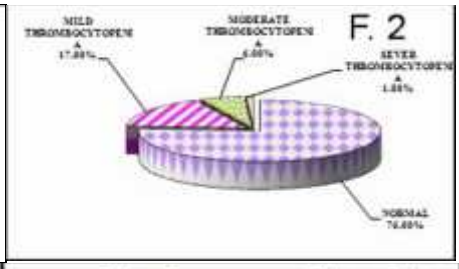

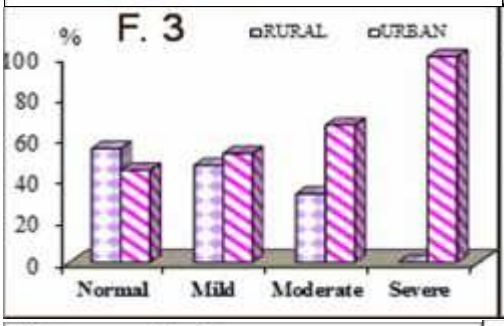

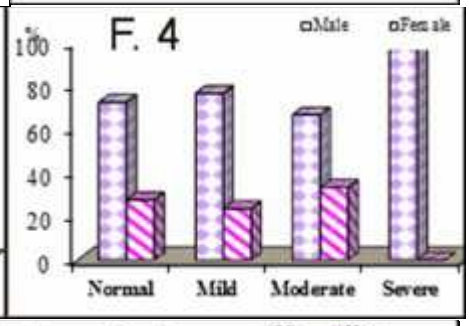

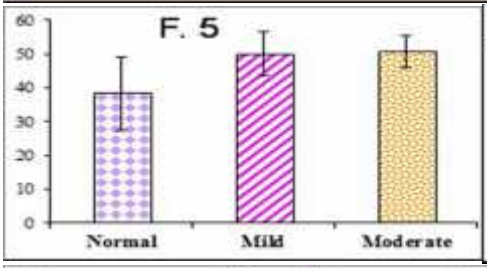

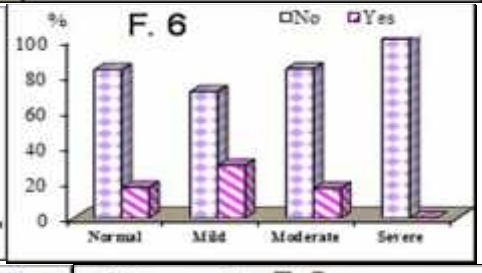

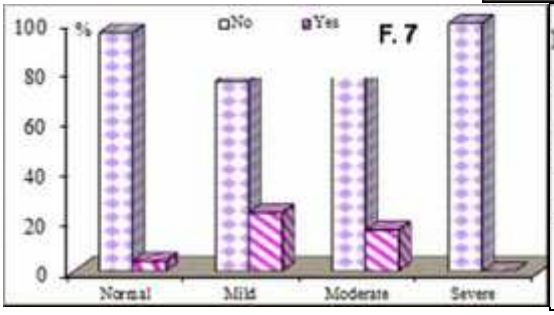

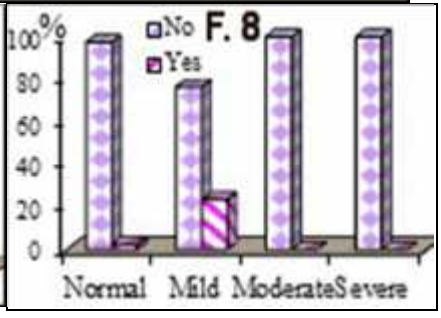

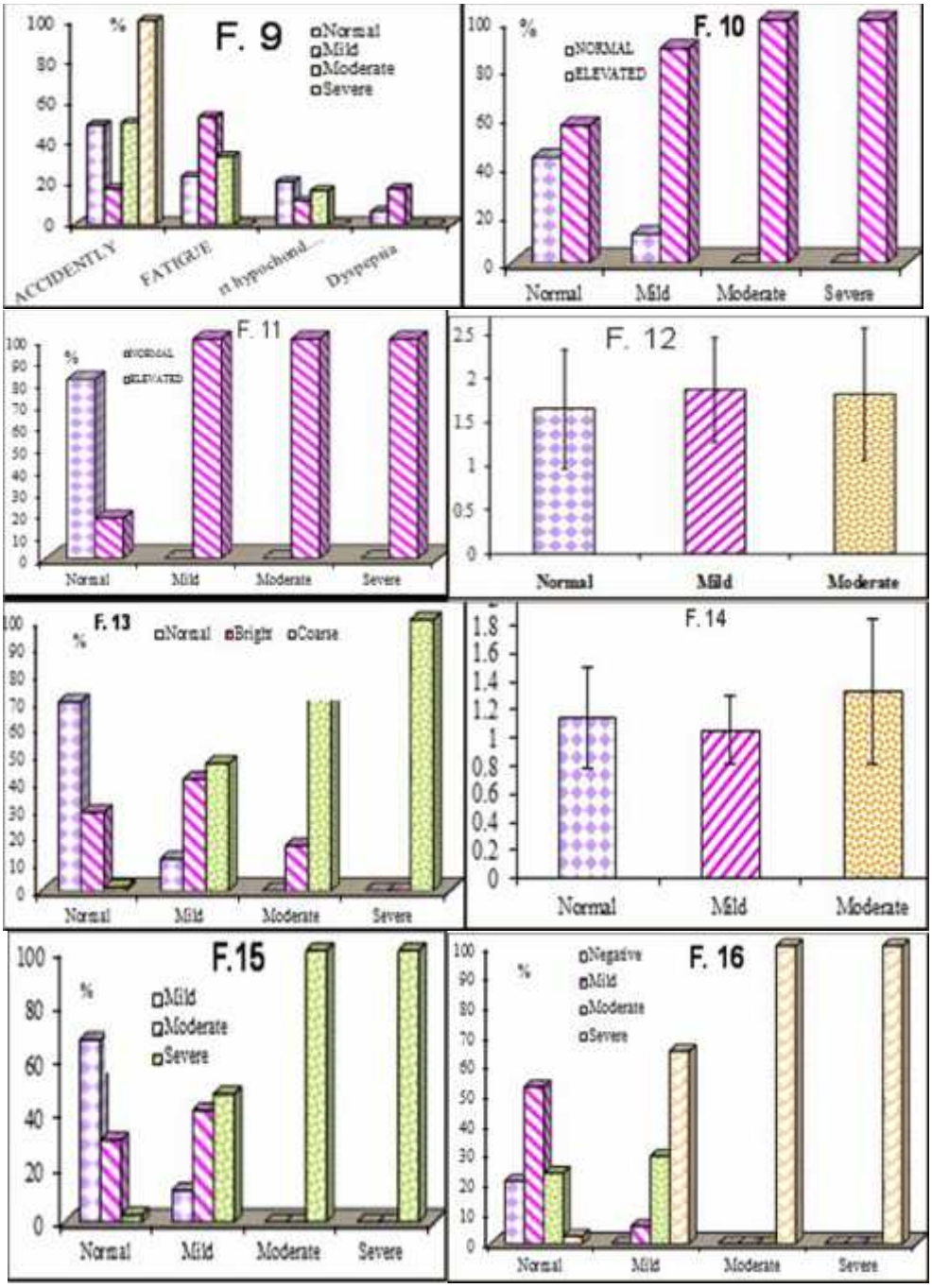
F. 9
Normal
Mild
Moderate
Severe
ACCIDENTLY
FATIGUE
Dyspepsia
F. 10
NORMAL
ELEVATED
Normal
Mild
Moderate
Severe
F. 11
NORMAL
ELEVATED
Normal
Mild
Moderate
Severe
F. 12
Normal
Mild
Moderate
F. 13
Normal
Bright
Course
Normal
Mild
Moderate
Severe
F. 14
Normal
Mild
Moderate
F.15
Mild
Moderate
Severe
Normal
Mild
Moderate
Severe
F. 16
Negative
Mild
Moderate
Severe
Normal
Mild
Moderate
Severe