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Study of Prevalence of Autoimmune Manifestations of Chronic Hepatitis C Infection in Beni-Suef Governorate

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ABSTRACT

Background: Although most patients with chronic hepatitis C are asymptomatic, an appreciable number will experience symptoms that are due to liver disease and /or extrahepatic manifestations of HCV infection. Recognition of these symptoms will lead to early diagnosis and treatment of hepatitis C. **Objective:** This study aimed to assess the prevalence of extrahepatic manifestations in patients with chronic hepatitis c infection in Beni-Suef Governorate. **Patients and methods:** 200 patients with CHC are studied, their ages ranged between 20-60 years. They are collected randomly from Beni-Suef University and general hospitals and outpatient clinics. **Results:** There is a wide range of prevalence of EHMS of HCV infection, 8% were asymptomatic and accidentally discovered to have HCV. 92% of the total number of patients have at least one EHM. The commonest extrahepatic manifestations are rheumatological 51%, hematological 26%, fatigue 20%, dermatological 19%, neurological 16%, DM11%, cryoglobulinemia 9% and less common chest, renal, lymphoproliferative disorders, cardiac, thyroid dysfunction. **Conclusion**: Extrahepatic manifestations appear earlier than hepatic manifestations of HCV patients. Age and liver fibrosis are considered major risk factors of EHMs. Health professionals should be aware of these HCV-associated complications and presentations.

Keywords: HCV, Autoimmune manifestations, Drugs, Hepatic manifestations.

INTRODUCTION

Egypt had one of the highest prevalence rates of HCV in the world with about 10% chronic HCV infection among people aged 15 to 59 years [1, 2]. The Ministry of Health revealed that the prevalence of HCV in 2021 reached 2%, marking a drop compared to7% in 2018 after the conduction of multiple national programs to control HCV infection [3]. Although hepatitis C virus (HCV) infection primarily affects the liver, other organ systems can become involved, which may result in a variety of clinical complications, including cryoglobulinemia which may be asymptomatic or presented with a triad of purpura, myalgia, and arthralgia (Meltzer's triad) is the most common presentation with HCV-related mixed cryoglobulinemia [4]. Cutaneous disorders are known to be linked to HCV infection including mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda, and necrolytic acral erythema. Besides these dermatoses, HCV can also be associated with autoimmune cutaneous diseases such as vitiligo and psoriasis [5]. Arthralgia and arthritis are frequently observed EMS with no erosive joint changes with rheumatoid factor activity may be found, but antibodies to cyclic citrullinated peptides are absent [6], renal manifestations of CHC mostly include type I membranoproliferative glomerulonephritis (MPGN) with sub-endothelial deposits [7].

Lymphoproliferative disorders, including monoclonal gammopathies in addition to mixed cryoglobulinemia and B-cell NHL. Patients positive for anti-HCV antigen had a 2.5-fold increased risk of NHL versus controls [8]. Neuropsychiatric manifestations include peripheral polyneuropathy, central nervous system manifestations and neuropsychological/ psychiatric manifestations [9], and a higher prevalence of mental illness and substance abuse [10]. Ocular manifestations include a dry eye syndrome similar to Sjögren syndrome, and ischemic retinopathy [11]. Hematological manifestations such as thrombocytopenia: may be due to a variety of non-immune and immune mechanisms such as hypersplenism and coombs-positive autoimmune hemolytic anemia [12].

Endocrinal manifestations; thyroid disorder including chronic thyroiditis, hypothyroidism, and hyperthyroidism and increased levels of serum anti-thyroperoxidase and anti-thyroglobulin autoantibody and diabetes Mellitus up to one-third of patients with chronic hepatitis C virus (HCV) develop type 2 diabetes mellitus (DM). Further, HCV seropositivity in patients with DM appears to be higher than in the general population [13, 14]. Cardiac involvement HCV infection is a proven independent risk factor for the development of cardiovascular disorders and Idiopathic pulmonary fibrosis is a serious condition with HCV infection histologically by interstitial inflammation with dense collagen fibrosis [15].

These many HCV-associated extrahepatic manifestations can have a major impact on morbidity, mortality, and medical costs [6].

Need for Recognition: Clinicians must consider the potential for HCV to cause extrahepatic manifestations in persons with chronic HCV infection. An awareness of the range of potential extrahepatic manifestations could facilitate earlier diagnosis, more appropriate and timely treatment of these disorders, and makes the need for DAA treatment of HCV considered urgent [16]. Although both public plans and commercial policies regarding approval for HCV treatment are constantly changing, these payers typically cover DAA therapies when any extrahepatic manifestation exists, despite the level of hepatic fibrosis.

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This study aimed to assess the prevalence of extrahepatic manifestations in patients with chronic hepatitis c infection in Beni-Suef Governorate.

PATIENTS AND METHODS

The study included 200 Egyptian patients with chronic hepatitis C who did not start specific antiviral treatment in Beni-Suef Governorate, selected randomly from Beni-Suef University and general hospitals and outpatient clinics.

Exclusion criteria:

1. Con concomitant HBV or HIV infections, autoimmune liver disease, or with previously diagnosed autoimmune disease as (SLE, RA, primary SJOGREN syndrome).
2. Patients with age more than 60 or less than 20 years.
3. Patients on regular hemodialysis.
4. Patients with ANA positive are excluded from the analysis.
5. Patients who already started direct antiviral therapy, or treated with interferon as it has many autoimmune side effects that mimic extrahepatic manifestations of HCV.

All patients are subjected to:

1- Full history taking for details of HCV infection and other extrahepatic manifestations if present as (fatigue, arthralgia, arthritis, fibromyalgia, Rayunds, cryoglobulinemia, lichen planus, urticaria, livedo reticularis, porpheria cutenea tarda, renal affection, DM, lymphoma, pulmonary fibrosis, thyroid dysfunction, sicca syndrome, Moorens ulcer, paraesthesia, etc).

2- Thorough complete clinical examination of whole-body systems to detect signs of liver disease or other EHMS. Abdominal sonar was done for all patients.

3- The diagnosis of chronic HCV infection is based on both positive testing for serum anti HCV antibody and HCV RNA.

4-The diagnosis of extrahepatic manifestations is based on clinical and laboratory data as follows (specific labs were done for patients who have obvious symptoms of one of the extrahepatic manifestations).

5-Blood urea & Serum creatinine level, (24 hours' urinary proteins renal biopsy in certain cases with renal symptoms).

6-Thyrotropic hormone (TSH, free T3, free T4), anti-thyroid antibody.

7-Complete blood picture (hemoglobin concentration-platelet and leucocytic count) Coombs test and bone marrow biopsy (in AIHA, or cases of pancytopenia), anti-platelet antibody.

8-Random blood glucose level as screening for DM then FBS, 2HPP to confirm the diagnosis of DM.

9-Serum cryoglobulin is detected using precipitation method (Unfortunately, there are no universally accepted methodologies for cryoglobulin measurements, but simple standardized indications are often sufficient for testing cryoglobulinemia Since cryoglobulins present a high thermal instability, the measurement of Ig cryoprecipitate should be performed immediately in the same place where the blood is sampled for a correct evaluation of serum cryoglobulins [17].

10-Skin disorders are diagnosed through the examination of the skin, oral mucosa, hair, and nails by dermatologists, or even skin biopsy if needed.

11-For detection of lymphoma (clinical examination for enlarged lymph nodes or splenomegaly, lymph node biopsy for histopathology).

12-Complete ophthalmological examination, Schirmer test, fundus examination (for Sjogren syndrome or Moorens ulcer)

13-Chest X-ray, pulmonary functions to assess symptomatizing chest patients.

14-ECG, echocardiography to detect cardiomyopathy or carditis associated with HCV patients as EHMS.

Ethical consideration:

Approval of the study was obtained from Beni-Suef University academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Methods

Data obtained from the present study are presented as number and percent, mean and standard deviation (SD), or median and interquartile range (IQR). Categorical variables were compared using the Chi-square test while numerical variables were compared using one-way ANOVA or Kruskal-Wallis test as appropriate. All statistical tests were computed using SPSS 25 (IBM, USA) with a p-value less than 0.05 considered statistically significant.

RESULTS

Table (1) illustrates the frequency of different gender with 54% females and 46% males among the study group and its mean age is (39.4 ±10.6) years, and mean disease duration is (35.3±45.7) months among the study group.

Table (1): Demographic data among study group (sex, age, duration of disease)

Variables	Minimum	Maximum	Mean	±SD
Age (years)	20	59	**39.4**	10.6
Duration of disease (months)	1	180	**35.3**	45.7
Sex	**Number** (total n=200)		**%**	
Male	92		46%	
Female	108		54%	

Table (2) illustrates that there is a statistically significant difference with a p-value <0.05 between both sexes regarding the presence of EHM with a high percentage of EHM among females.

Table (2): Comparisons of gender between patients with and without EHMs.

Sex	**No EHM** (n=16)		**EHM** (n=184)		p-value	Sig.
	No.	**%**	**No.**	**%**		
Male	16	**100%**	76	41.3%	**<0.001**	**HS**
Female	0	0%	108	**58.7%**		

HS---highly significant

Table (3) illustrates the prevalence of different extra-hepatic manifestations among the study group with a high percentage for rheumatologic and hematologic manifestations (46%, 26%) respectively then followed by fatigue (20%) and dermatologic l manifestation (19%) and the least common are renal, lymphoma thyroid dysfunction 2%cardiac1%.

Table (3): Prevalence of extrahepatic manifestations (clinical and labs) among the study group

Extrahepatic manifestations	**Number** (n=200)	**%**
(No EHMs)	16	8%
Rheumatological (total)	102	51%
-Arthralgia	46	
- Ocular		
-Sjogren′syndrome (schirmmers test)	30	
-Moorens ulcer	0	
-Arthritis	18	
-Fibromyalgia	8	
Hematological (total)	52	26%
-Thrombocytopenia	24	
-Leucopenia	20	
-Anemia of chronic disease	16	
-Autoimmune hemolytic anemia	4	
-Pancytopenia	4	
Fatigue	40	20%
Dermatological (total)	38	19%
-Urticaria	14	
- Eucocytoclasticvasculitis (aspurpura)	12	
-Lichen planus	6	
-Livedo reticularis	4	
-Porpheria cutenea tarda	2	
Neurological (total)	32	16%
-Paraesthesia (P.N)	16	
-Headache	22	
Diabetes mellitus (total)	22	11%
-Type 1	2	
-Type 2	20	
Cryoglobulins (total)	18	9%
GIT (total)	18	9%
-Chronic diffuse abd. pain	18	
-Inflamatory bowel disease	0	
Chest	10	5%
-Interstitial pulmonary fibrosis	4	
-Chronic obstructive pulmonary disease	6	
Renal manifestation (Membrano proliferative GN)	4	2%
Lymphoproliferative	4	2%
-Hodjken lymphoma	2	
-Non-Hodjken lymphoma	2	
Thyroid dysfunction	4	2%
-Hypothyroidism	2	
-Antithyroid antibody	2	
Cardiac	2	1%
-Carditis	0	
-Cardiomyopathy	2	

Table (4) illustrates that there is no statistically significant difference with p-value >0.05 between two EHM groups as regards ultrasound findings.

Table (4): Comparison of ultrasound findings among different study groups

Ultrasound finding	No EHM (n=16)		EHM (n=184)		p-value	Sig.
	No.	%	No.	%		
Normal US	6	37.5%	72	39.1%	0.1	NS
Bright liver	8	50%	38	20.7%		
Coarse liver	2	12.5%	22	12%		
HSM (hepatosplenomegaly)	0	0%	20	10.9%		
HM (hepatomegaly)	0	0%	10	5.4%		
SM (splenomegaly)	0	0%	16	8.7%		
Peri-portal fibrosis	0	0%	6	3.3%		

Table (5) illustrates that there is a statistically significant difference between patients' cryo- globulin positive, and negative with p-value <0.05, regarding sex it shows that a higher percentage of the positive cases were females.

Table (5): Comparison of cryoglobulin test outcome among different sexes

sex	Cryoglobulin				p-value	Sig.
	Negative (n=182)		Positive (n=18)			
	No.	%	No.	%		
Male	88	48.4%	4	22.2%	**0.05**	**S**
Female	94	51.6%	14	**77.8%**		

Table (6) illustrates that there is a statistically significant difference between different cryoglobulin manifestations groups with a p-value <0.05 as regards viral load with a high mean among positive cryoglobulin. On the other hand, there is a non-statistical significant difference as regards age and liver enzymes level.

Table (6): Comparison of age and PCR, and liver enzymes among different cryoglobulin positive and negative patients.

Variables	Cryoglobulin				p-value	Sig.
	Negative (n=182)		Positive (n=18)			
	Mean	±SD	Mean	±SD		
Age (years)	38.9	10.5	43.4	10.3	0.09	NS
PCR 1000IU/ml	294.94	58.98	118.47	24.43	**<0.001**	**HS**
ALT (up to 43) IU/ml	23.6	5.4	27.7	6.9	0.3	NS
AST (up to 45) IU/ml	22.9	5.9	29.1	6.5	0.1	NS

Table (7) illustrates that there is a statistically significant difference with p-value <0.05 in liver enzymes level and viral load between different groups of fatigue with high mean among the non-fatigue group.

Table (7): Comparison of PCR and liver enzymes among patients with and without fatigue

Variables	Fatigue				p-value	Sig.
	Negative (n=160)		Positive (n=40)			
	Mean	±SD	Mean	±SD		
PCR 1000IU/ml	416.34	95.172	209.73	46.61	0.2	NS
ALT IU/ml	**25.3**	7.4	18.3	4.4	**0.001**	**HS**
AST IU/ml	**24.8**	5.9	18.4	3.4	**0.002**	**HS**

Table (8) illustrates that there is a statistically significant difference with p-value <0.05 in liver enzymes level and viral load between different groups of lymphoproliferative manifestations with high mean among the positive group as regards to ALT level and the negative group as regards to AST level.

Table (8): Comparisons of PCR and liver enzymes among patients with and without lymphoproliferative manifestation

Variables	Lymphoproliferative manifestations				p-value	Sig.
	Negative (n=196)		Positive (n=4)			
	Mean	±SD	Mean	±SD		
PCR 1000IU/ml	378.46	36.51	206.51	44.63	0.7	NS
ALT IU/ml	23.9	4.4	**24.5**	2.9	**0.04**	**S**
AST IU/ml	**23.6**	5.2	20	4.6	**0.02**	**S**

The multivariate logistic regression model analysis was conducted to explore the explanatory power of different risk factors in the prediction of EHM among hepatic patients and it illustrates that there were statistical significance predictors with p-value <0.05 to age with OR =0.92 and to liver tissues biopsy with OR= 2.5.

Table (9): Stepwise multivariate regression analysis to determine the risk factors of EHM among the study group

Variables	B	SE	Sig.	RR
Constant	42.2	-----	-----	----
Age	-0.087	0.039	**0.02**	**0.92**
Duration of disease	0.001	0.006	0.9	1
Sex	-19.8	3553.5	0.9	0.0
PCR	0.0	0.0	0.6	1
Liver tissues biopsy (Metavir F4 for fibrosis)	0.95	7107	**0.03**	**2.5**

DISCUSSION

Hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality worldwide and represents a major public health problem. According to different studies, 40-74% of patients infected with HCV may develop at least one extrahepatic manifestation (EHM) during the disease.

In this study, we assess the prevalence of extrahepatic manifestations in 200 patients with chronic hepatitis c infection in the Beni-Suef governorate. In our study group, we try to find a relationship between cryoglobulins positivity and prevalence of EHMs but, it was non-significant. So, it could not be considered as a risk factor for EHMs. The multivariate logistic model analysis of our study groups determines older age and liver fibrosis by liver tissue biopsy as risk factors for EHMs while, duration of disease, sex, and viral load are not risk factors.

Rasheed *et al.* [18] on their cross-sectional study on 100 patients at the Rheumatology Department of Pakistan Institute of Medical Science with HCV infection, there were (37%) males and (63%) females. the mean age was (41.39±10.191) years. Myalgia was the most common found in 79% followed by arthralgia in 49%, fibromyalgia 33%, Raynaud's phenomenon 11%, paraesthesia 22%, numbness 46%, neuropathy 3%, vasculitis 0%, dry Eyes 4%, and dry mouth in 32% of patients. Inflammatory arthritis was present in 14 patients. High titers of anti-CCP antibodies were found in 3 patients who met the ARA criteria for rheumatoid arthritis. Low titers of anti-CCP antibodies were present in 2 patients.

Rheumatic manifestations are present in 20 % of the patients with hepatitis C. These include myalgias, arthralgias, arthritis, fibromyalgia, and cryoglobulinemic vasculitis. Hepatitis C-related arthritis may present as monoarthritis, oligoarthritis, and polyarthritis resembling rheumatoid arthritis.

According to **Hamdy *et al.*** [19] across a sectional study among 306 Egyptian patients with chronic HCV infection were performed to assess the prevalence of rheumatological manifestations (16.39%) and results were as follows, chronic fatigue syndrome 9.5%, sicca syndrome 8.8%, arthralgia 6.5%, fibromyalgia 1.9%, myalgia 1.3%, arthritis 0.7%, cryoglobulins 0.7%, thrombocytopenia 0.7%, chronic fatigue syndrome, and sicca syndrome being the most common rheumatological EHM with no significant correlation of liver disease or viral load.

According to **Soliman *et al.*** [20]**,** overt symptoms of cryoglobulinemic vasculitis develop in only approximately 5% of chronic HCV infection cases**,** circulating mixed cryoglobulin complexes are much more common in about 40–50% in chronic HCV-infected patients**.** MC tends to correlate with the duration of HCV infection and older age. However, cryoglobulinemia in the serum of HCV patients has been associated with an increased risk of advanced fibrosis, the severity of hepatic steatosis on liver biopsy, and cirrhosis, irrespective of age or disease duration.

In our study we agree with **Soliman *et al.*** [20] as the number of patients with overt symptoms and serology of cryoglobulinemic vasculitis are 18 patients with percent(9%) male percent is 22.2%, female percent 77,8%, mean age (43.4±10.3 years). Cryoglobulins are associated with a high viral load as the relation between MC and PCR has a significant P-value (<0.001). Out of 18 patients with positive cryo, there were 4 cases had renal manifestations in form of hypertension, proteinuria, rarely hematuria, or elevated creatinine

level renal biopsy is taken for histopathology which represents membranoproliferative GN which is the commonest renal pathology with HCV with or without cryoglobulins. But here we have a strong correlation with a significant P-value between cryoglobulins and renal manifestations in HCV patients. Other 4 cases with positive cryo have paresthesia in form of tingling and numbness which is also commonly associated with it.

According to **Zignego *et al.*[(8)],** the prevalence of HCV infection in B-cell NHL has given conflicting results**.** In several countries data ranges from 9% to 37%.

In our study we disagree with this article as the percent of lymphoproliferative disorders reached 4% (2 cases of non-Hodgkin lymphoma and 2 cases of Hodgkin lymphoma) proved by lymph node biopsy as patients presented with generalized lymphadenopathy cervical, inguinal, epi-trochlear, and abdominal. Cervical LN biopsies were taken for histopathology, routine labs had done, HCV ab positive, no other EHMs were found.

HCV infection in patients with porphyria is high, 40-50% depending on the country **Cacoub *et al.*[(21)]** suggested that cirrhosis may play a role in its development, reporting that the highest rates of PCT were in patients with HCV related liver cirrhosis.

In our study dermatological manifestations represent about 19%, the prevalence of PCT represents 5.3% of all dermatological manifestations, lichen planus 15.8%, leukocytoclastic vasculitis 31.6%, urticarial 36.8%, livedoreticularis 10.5%. So the commonest dermatological manifestations were urticarial, LCV, LP, and less is PCT only 2 cases were reported.

Zarebska- Michaluk *et al.* [(22)] studied 340 consecutive patients (mean age 42 years) with untreated chronic HCV evaluated at the infectious disease unit in Poland from 2010 to 2016. Results were, 210 patients with CHC (61.7%)presented at least 1 EHM including, mixed cryoglobulinemia (37.1%), thrombocytopenia (27.6%), thyroid autoimmunity (16.2%) dermatological disorders (4.1%), type 2 DM (4.1%), other EHM such as sicca syndrome, nephropathy, lymphomas, neuropathy had much lower prevalence.

The univariate analysis showed that the main factors associated with the presence of EHM were older age, longer duration of HCV, AST, GGT activity lower platelet count, higher inflammatory activity and advanced fibrosis. The multivariate analyses revealed that only a lower platelet count was associated with the presence of EHM.

In our present study, the multivariate analysis showed that older age and increased liver fibrosis by biopsy are risk factors for EHMS but sex, duration of disease, and viral load are not risk factors.

Several studies have shown that thrombocytopenia is frequently observed in chronic hepatitis C. according to **Jadali1 and Alavian[(23)]** Thrombocytopenia is often thought to be due to hypersplenism or due to autoimmune reaction to platelet Chronic infection with HCV is one of the occurring conditions associated with nonmalignant secondary ITP**.**

In the present study, hematological manifestations were observed in 26% with a prevalence of thrombocytopenia of 12%. We detected 24 cases with symptomatizing thrombocytopenia by epistaxis, ecchymosis with low PLT count <100 000. There were 4cases with antiplatelet antibodies, BM biopsy was done and revealed 10 cases of picture suggestive ITP and 14 cases with hyperactive BM secondary to hyper-splenisim.

CONCLUSION

The clinical focus of HCV infection is typically related to the liver (the primary organ involved), but an awareness of the extrahepatic manifestations of HCV infection is important. With the growing prevalence of HCV worldwide, health professionals should be aware of these HCV-associated complications and presentations.

The commonest extrahepatic manifestations are rheumatological, hematological, fatigue, dermatological, neurological, DM, cryoglobulinemia, and less common chest, renal, lymphoproliferative disorders, cardiac, thyroid dysfunction.

Extrahepatic manifestations appear earlier than hepatic manifestations of HCV infection so they can be considered as early markers during screening for HCV patients. Age and liver fibrosis are considered major risk factors of EHM.

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REFERENCES

1. **El-Daly M, Ibrahim H, Labib E *et al.* (2019):** Significance of DEPDC5 and MICA Variants in Hepatocellular Carcinoma risk related Hepatitis C Virus patients in Egypt. EJMO., 3(4):274–280.
2. **El-Assal M, Al Hassanin S, Hussein A (2015):** Epidemiological and clinical characteristics of Egyptian patients with hepatocellular carcinoma: A single-center study. Inter J Med Health Sci Res., 2:177-86.
3. **Elbahrawy A, Ibrahim M, Eliwa A *et al.* (2021):** Current situation of viral hepatitis in Egypt. Microbiology and Immunology, 65: 352-372.
4. **Iannuzzella F, Vaglio A, Garini G (2010):** Management of hepatitis C virus-related mixed cryoglobulinemia. Am J Med., 123:400-8.
5. **Wiznia L, Laird M, Franks A (2017)**: Hepatitis C virus and its cutaneous manifestations: treatment in the direct-acting antiviral era. J Eur Acad Dermatol Venereol., 31: 1260-1270.
6. **Cacoub P, Saadoun D (2021):** Extrahepatic Manifestations of Chronic HCV Infection. N Engl J Med., 384:1038-52.

7. **Dalrymple L, Koepsell T, Sampson J *et al.* (2007):** Hepatitis C virus infection and the prevalence of renal insufficiency. Clin J Am Soc Nephrol., 2:715–721.
8. **Zignego A, Giannini C, Gragnani L (2012):** HCV and lymphoproliferation. Clin Dev Immunol., 12:980942.
9. **Ferri C, Ramos-Casals M, Zignego A *et al.* (2016):** International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev., 15:1145–1160.
10. **Negro F, Forton D, Craxì A *et al.* (2015):** Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology, 149: 1345–1360.
11. **Zegans M, Anninger W, Chapman C (2002):** Ocular manifestations of hepatitis C virus infection. Curr Opin Ophthalmol., 13(6):423-427.
12. **Srinivasan R (2001):** Autoimmune hemolytic anemia in treatment-naïve chronic hepatitis C infection. J Clin Gastroenterol., 32(3):245-247.
13. **Fallahi P, Ferrari S, Giuggioli D *et al.* (2014):** Thyroid involvement in hepatitis C - associated mixed cryoglobulinemia. Hormones (Athens), 13:16–23.
14. **Bahtiyar G, Shin J, Aytaman A (2004):** Association of diabetes and hepatitis C infection: epidemiologic evidence and pathophysiologic insights. Curr Diab Rep., 4(3):194-198.
15. **Gill K, Ghazinian H, Manch R *et al.* (2016):** Hepatitis C virus as a systemic disease: reaching beyond the liver. Hepatol Int., 10:415-423.
16. **Younossi Z, Park H, Henry L *et al.* (2017):** Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. Gastroenterology, 150:1599-1608.
17. **Ferri C, Zigneego A, Pileri S (2002):** Cryoglobulinaemia. J Clin Pathol., 55:4-13.
18. **Rasheed U, Nisar A, Aziz W *et al.* (2013):** Rheumatological manifestation of HCV infection a tertiary care hospital. Ann Pak Inst Sci., 9(2):57-60.
19. **Hamdy R, Ibrahim H, Gamal A *et al.* (2016):** Prevalence of rheumatologic manifestations of chronic hepatitis C virus infection among Egyptians. Clin Rheumatol., 29: 1373-1380.
20. **Soliman A, El Hawaii S, Refaey M *et al.* (2016):** Extrahepatic manifestation of hepatitis C virus: An extending list. Aro-Egypt J Infect Endem Dis., 2(1):36-53.
21. **Cacoub P, Buggisch P, Carrión J *et al.* (2018):** Direct medical costs associated with the extrahepatic manifestations of hepatitis C infection in Europe. J Viral Hepat., 25:811-17.
22. **Zarebska-Michaluk D, Lebensztejn D, Kryczka W *et al.* (2017):** Extrahepatic manifestations associated with chronic hepatitis C infections in Poland. Adv Med Sci., 55(1):67-73.
23. **Jadali Z, Alavian S (2016): Autoimmune** diseases co-existing with hepatitis C virus infection. Iranian Journal of Allergy, Asthma, and Immunology, 16: 191-206.