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Research Article

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IL-21R polymorphism and virological response to Peg-INF treatment in chronic hepatitis C Egyptian patients.

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Abstract

Background: Hepatitis C virus (HCV) is a major cause of chronic hepatitis C (CHC) and different HCV genotypes show characteristic variations in their pathological properties. Egypt has the highest reported rates of HCV infection (predominantly genotype 4) in the world. Interleukin-21 (IL-21) is a cytokine that has potent regulatory effects on cells of the immune system, including natural killer (NK) cells and cytotoxic T cells that can destroy virally infected or cancerous cells. Interleukin-21 receptor (IL-21R) gene polymorphism is recently studied as pretreatment predictor in CHC patients treated with Pegylated interferon (**Peg-INF**) plus ribavirin. This study was designated to assess whole blood interleukin-21Rpolymorphism in CHC genotype 4 patients and investigate it is benefit as a pre treatment predictor of antiviral response in Egyptian patients. **Methods:** Eighty patients infected with HCV genotype 4 were recruited for the study. All 80 CHC patients are subjected to treatment in National Hepatology & Tropical Medicine Research institute. All the patients were subjected to clinical and laboratory assessment, abdominal ultrasound, and liver biopsy. All the patients were treated with combined therapy of (Pegylated interferon and ribavirin) and followed up to sustained virological response (SVR) end of treatment and. Viral titer was determined during and at the end of the treatment by using real-time polymerase chain reaction (RT PCR) technique. The eighty patients were divided into two groups. The first group containing patients who responded to treatment, and it was consisted of 44 patients (Responders) while the second group containing patients who didn't responded to treatment, and it was consisted of 36 patients (Non responders). IL-21R gene polymorphism was estimated using (RT PCR) and also standard laboratory investigations were undertaken to characterize liver function. **Results:** Our study on 80 CHC patients who subjected to Peg-interferon treatment and divided into responders and non responders showed that, the Mean ± SD of ALT was 48.68 ± 18.205 and 53.97 ± 15.601, AST 55.43 ± 23.611 and 56.99 ± 21.255 and AFP 15.00 ± 18.728 and 12.58 ± 14.463 respectively. 52.27% of responders were CC genotype and 33.33% of non responders were CC genotype. **Conclusion:** Patients with IL-21R rs3093390 CC genotype had a higher sustained virological response to interferon treatment than those with non-CC genotypes.

Keywords: Hepatitis C virus, chronic hepatitis C, interleukin 21, interleukin 21 receptor.

Introduction

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with

comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures[1]. HCV is classified into eleven major genotypes (designated 1-11), many subtypes (designated a, b, c, etc). Genotype 4 is principally found in the Middle East, Egypt, and central Africa[2]. Chronic hepatitis C infection can result in progressive liver inflammation (viral hepatitis), which may progress to scarring (fibrosis and cirrhosis). If left untreated, inflammation can lead to mild, moderate, or serious liver disease and in some cases, liver cancer and liver failure [3].Pegylated interferon markedly improved the rates of SVR in chronic HCV-4.The host immune response plays an important role in viral clearance in patients who are chronically infected with hepatitis C virus (HCV) and are treated with interferon α. Activation of the immune system involves the release of pro and anti-inflammatory molecules that can be measured in plasma samples such as cytokines[4].A gene on chromosome 4q26-q27 that encodes IL-21, a cytokines with immunoregulatory activity that may promote the transition between innate and adaptive immunity. IL-21 induces the production of IgG1 and IgG3 in B cells, and may play a role in proliferation and maturation of natural killer cells in synergy with IL-15 [5].CHC patients have higher serum IL-21 levels than healthy adults. Higher pretreatment serum IL-21 levels and IL-21R polymorphisms may serve as potential factors predictive of treatment outcomes in CHC patients with interferon-based therapy [5].Recent studies reported that IL-21R (rs3093390) CC polymorphism could be used as a novel predictor of response to HCV treatment so this study was aimed to evaluate the association between IL-21R (rs 3093390) CC gene polymorphism and virological response to interferon-based treatment in Egyptian CHC patients.

Patients and Methods

Patients:

This prospective study was carried out on 80 patients with chronic hepatitis C genotype 4 (CHC) (male = 53, female= 27) divided into two groups. The first group comprised 44 patients (male= 29, female = 15, mean age 41.70 ± 8.992 years; range 28–54 years, BMI 26.000 ± 8.6616) who responded to treatment with ribavirin-pegylated Interferon alpha-2a (180 mcg subcutaneously once weekly) for 48 weeks (Responders), and the second group comprised 36 patients (male= 24 female= 12 mean age 39.31 ± 6.907 years; range 20-69 years, BMI 24.028 ± 8.4633) who non responded to treatment (Non responders) patients.

Exclusion criteria:

Patients who are younger than 18 years, older than 60 years, have co-infection with hepatitis B virus, alcohol intake, clinically evident liver cirrhosis, esophageal varices, hepatic encephalopathy, hepatocellular carcinoma, any end organ failure, hematological diseases, major psychiatric disorder, pregnant and breast feeding women were excluded from the study.

Methods:

Blood sampling and biochemical analysis:

Blood sampling:

Fasting venous blood samples (~7ml) were collected by trained laboratory technicians. A portion of blood was allowed to clot and then centrifuged at 3500 g for 5 minutes to separate the serum and used for assessment of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, AFP, viral infection status, and glucose concentrations. Serum aliquots were stored at - 80°C until assayed for HCV RNA.A portion of blood samples was collected in vacutainer tubes containing citrate to separate plasma used for the assay of albumin. The last portion was collected in vacutainer tubes containing EDTA as anticoagulant to obtain non coltted whole blood sample whish used for the assay of IL-21R gene polymorphism by using RT PCR technique.

Biochemical analysis:

AST, ALT activities, total bilirubin, direct bilirubin, albumin and glucose concentrations were assayed using Beckman CX4 chemistry analyzer (NY, USA, supplied by the Eastern Co. For Eng. & Trade-Giza, Egypt). AFP and viral status (HbsAg and Anti-HCV) were measured using Abbott, Axyam (USA, Supplied by al kamal company Cairo, Egypt).

Quantitative real time PCR for determination of HCV viremia:

RNA was extracted from patients' blood using the QIAmp Viral RNA Mini Kit (QIAGEN, Santa Clarita, U.S.A) according to the manufacturer's instructions, then quantitative Real time polymerase chain reaction was performed using previously standardized real time protocol for HCV, supplied from applied Biosystems (USA) .

Extraction of genomic DNA and rs 3093390 genotyping:

All 80 patients samples were genotyped for SNP (rs 3093390). Genomic DNA was extracted by standard protocols with red blood cell lysis, DNA binding, washing and elution by using Qiagen DNA extraction Mini Kit (Qiagen, Germany, supplied by clinilab, Cairo, Egypt). Extracted DNA normalized to 20 ng/µl was obtained. DNA quality (concentration and purity) was assayed by calculating the absorbance ratio optical density 260nm /280 nm using Nanodrop2000 spectrophotometer (Thermoscietific, USA, supplied by analysis for life,

Cairo, Egypt). The SNP rs 3093390 were genotyped by using Taq Man master mix Mini Kit and Taq Man allelic discrimination 100 test kit (Applied Biosystems, USA, supplied by analysis for life, Cairo, Egypt) using 7500 real time PCR (Applied Biosystems, USA, supplied by analysis for life, Cairo, Egypt).

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing 2 groups and one way analysis of variance (ANOVA) test with posthoc multiple 2-group comparisons in comparing more than 2 groups. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, -ve predictive value, and overall accuracy. *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

A total of 80 adult CHC patients were subjected to treatment with ribavirin-pegylated Interferon alpha-2a (180 mcg subcutaneously once weekly) for 48 weeks and were divided into two groups, the first group consisted of 44 patients who were responders to treatment with Peg - Interferon alpha-2a and the second group consisted of 36 patients who were non responders to treatment.

Results of the demographic feature:

The mean age of CHC responder patients to ribavirin-pegylated Interferon alpha-2a treatment was 41.70 ± 8.992 years with the range between 28 and 54 years. In the non responder patients the mean age was 39.31 ± 6.907 years with a range between 20 and 69 years. There was male predominance among the responder and non responder patients, between responder patients, 29 men (65.9%) versus 15 women (34.1%), with a male-to-female ratio of 1.933 : 1, among the non responder patients, 24 men (66.67%) versus 12 women (33.33%), with a male-to-female ratio of 2 : 1, but there was no significant difference in the sex ratios of responder and non responder patients (p=0.943) Fig 1.the results also showed that the body mass index (BMI) had no statistically significant difference between the two groups (P=0.309) (Table 1) Fig 2.

Table 1. Demographic features of the studied patients group

	Responders N = 44 (55 %) Mean ± SD	**Non responders N = 36 (45 %) Mean ± SD**	**All patients N = 80 (100 %) Mean ± SD**	**P-value**
Age (Year)	41.70 ± 8.992	39.31 ± 6.907	40.63 ± 8.16	0.193
Sex Female Male Female : Male	 15 29 1 : 1.933	 12 24 1 : 2	 27 53 1 : 1.963	0.943
BMI (Kg/m^2)	26.000 ± 8.6616	24.028 ± 8.4633	25.11 ± 8.5758	0.309

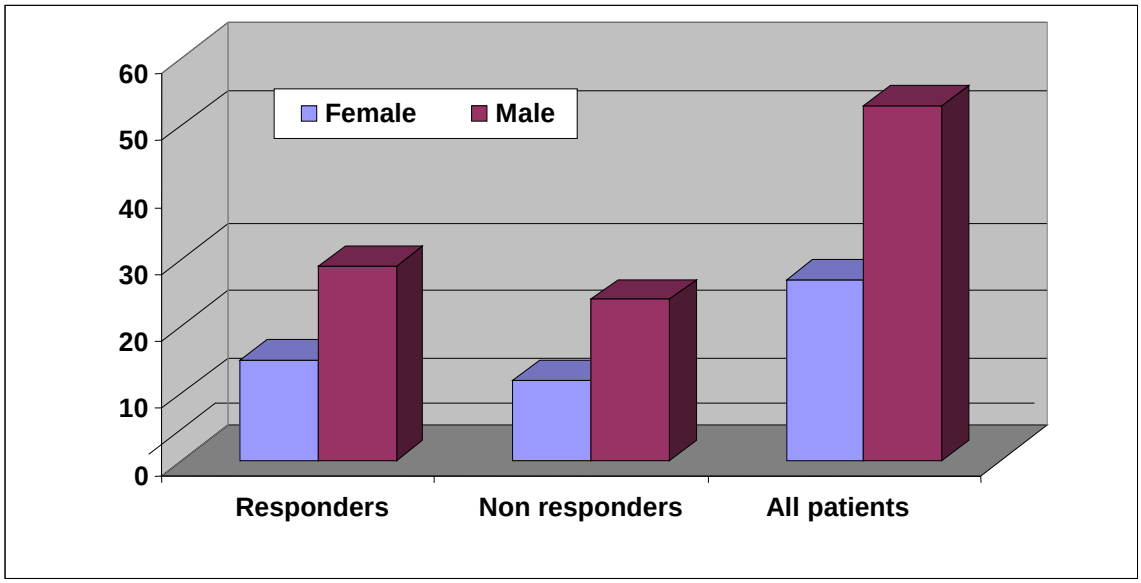

Fig 1. Correlation between response to ribavirin-pegylated Interferon alpha-2a and sex.

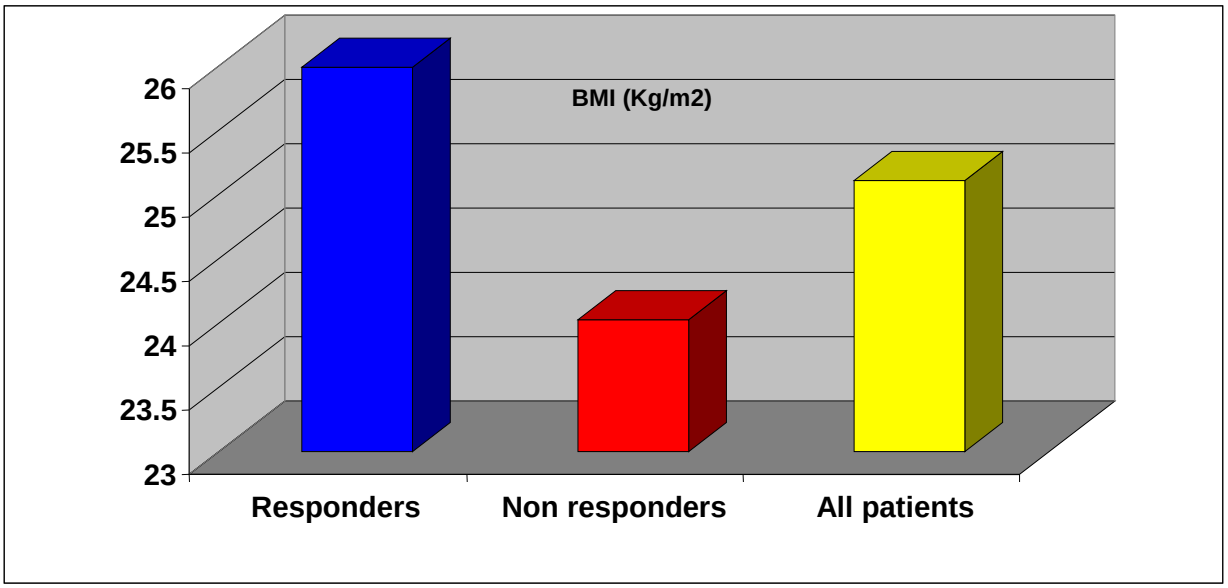

Fig 2. Correlation between response to interferon treatment and BMI.

Study of biochemical:

The biochemical characteristics of responding and non responding two patient groups to treatment with Pegylated interferon plus ribavirin were illustrated in table 2.As showed in the table our study found no statistically significant difference between the two studied groups and different biochemical parameters including liver (AST, ALT, TBIL, DBIL, ALB, ALP and AFP), kidney (creatinine) function tests and TSH, but we can noticed that the levels of ALT and AST were lower in responders group than non-responders one, with P-values respectively (P=0.172 and P=0.473) Fig 3.

Study of blood picture and blood glucose:

In our study we found that there is statistically significant difference between the two studied groups and WBCs (P=0.003) and platelets count (P=0.037) as showed in table 3, but there is no significant difference in blood glucose between the two groups (P=0.904) Fig 4.

Correlation between genotype and response:

Our study estimated that patients with IL-21R rs3093390 CC genotype (wild genotype) had a higher sustained virological response to interferon treatment than those with non-CC genotypes

(mutant genotypes) as showed in table 4, and there are significant correlation between CC genotype and response to interferon treatment in CHC genotype 4 Egyptian patients (P=0.089) Fig 5.

Study correlation between SNP and AFP:

There is no significant correlation between SNP and other studied parameters (demographic features, biochemical characteristics, blood picture and blood sugar) except only in the case of AFP (P=0.05) (table 5) Fig 6.

Table 2. Biochemical characteristics of the studied patient groups.

	Responders N = 44 (55 %) Mean ± SD	Non responders N = 36 (45 %) Mean ± SD	All patients N = 80 (100 %) Mean ± SD	P-value
AST (IU/ml)	55.43 ± 23.611	58.89 ± 18.114	56.99 ± 21.255	0.473
ALT (IU/ml)	48.68 ± 18.205	53.97 ± 15.601	51.06 ± 17.183	0.172
TBIL (mg/dl)	2.009 ± 6.6495	1.114 ± .0.3965	1.606 ± 4.9333	0.423
D.BIL (mg/dl)	0.236 ± 0.2081	0.244 ± 0.1382	0.240 ± 0.1790	0.842
Albumin (g/dl)	3.67 ± 0.653	3.78 ± 0.337	3.72 ± 0.534	0.367
ALP (Unit/mL)	114.43 ± 41.327	114.31 ± 46.652	114.38 ± 43.518	0.990
AFP (ng/mL)	15.00 ± 18.728	12.58 ± 14.463	13.91 ± 16.883	0.528
Creatinine (mg/dl)	1.064 ± 0.2324	1.017 ± 0.1699	1.043 ± 0.2067	0.315
TSH (mIU/L)	3.639 ± 1.0253	3.786 ± 0.9181	3.705 ± 0.9753	0.505

AST=aspartate aminotransferase, ALT=alanine aminotransferase, TBIL=total bilirubin, D.BIL=direct bilirubin, ALP=alkaline phosphatase, AFP=alfa feto protein, TSH=thyroid stimulating hormone.

Table 3. blood picture and blood glucose among studied patient groups.

	Responders N = 44 (55 %) Mean ± SD	Non responders N = 36 (45 %) Mean ± SD	All patients N = 80 (100 %) Mean ± SD	P-value
Hb (gm/dl)	11.205± 2.0779	11.728 ± 1.7819	11.440 ± 1.9559	0.236
WBCs (cell/cmm)	664.57 ± 194.432	788.06 ± 160.781	720.14 ± 189.344	**0.003***
PLTs (cell/cmm)	258.48 ± 76.721	293.39 ± 69.033	274.19 ± 74.971	**0.037***
Glucose (mg/dl)	99.18 ± 25.017	99.78 ± 17.398	99.45 ± 21.791	0.904

*p-value <0.05 Significant, Hb=hemogloubin, WBCs=white blood cells, PLTs=platelets

Table 4. Correlation between genotype and response

	Wild (CC)	Mutant (CT,TT)	p-value
Responder	52.27%	47.72%	0.089
Non responder	33.33%	66.67%	

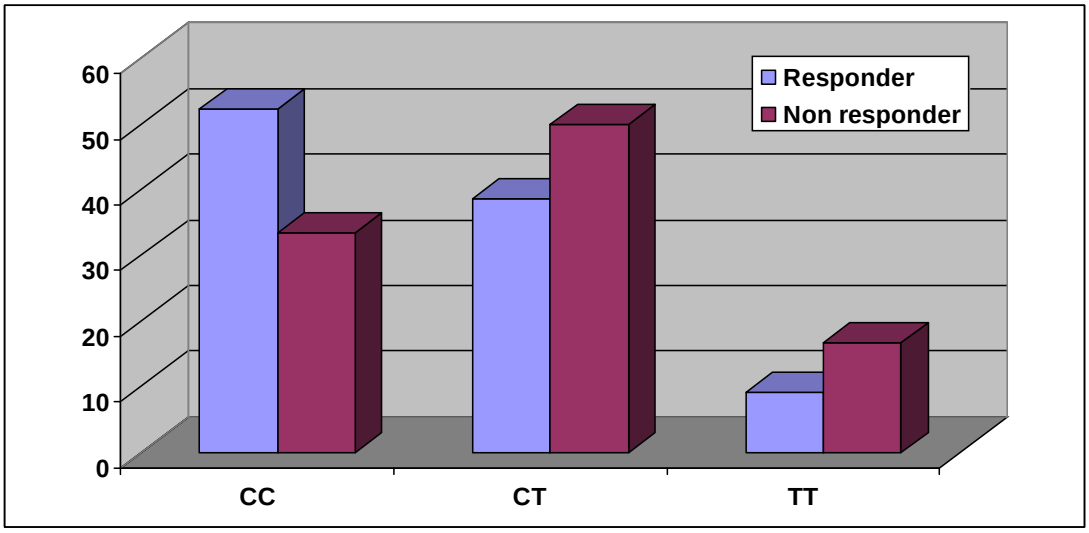

Fig 5. Correlation between response to interferon treatment and different genotypes

Discussion

Hepatitis C virus (HCV) is considered the most common etiology of chronic liver disease (CLD) in Egypt, where prevalence of antibodies to HCV (anti-HCV) is approximately 10-fold greater than in the United States and Europe [17].

The prevalence of genotype 4 as the main HCV genotype with different subtypes as well as different virological, biochemical and histopathological responses to treatment in comparison to the other well-known isolated 5 genotypes; made it an important and interesting task for many researchers to study the interaction between the viral genome and the anti-viral preparations specially IFN which has many preparations and has both an anti-viral as well as an immune-modulator role in combating the virus [18]. As a result of the continuing research for better medications; the development of new and efficient medications remained an important concern of many research institutions in the field of hepatology. Interferon alpha (IFN alpha) has been widely used as therapy for chronic hepatitis C. The attachment of an inert Poly Ethylene Glycol (PEG) molecule to the standard IFN had resulted in the production of long acting IFN which was named Pegylated Interferon (PEG-IFN). Standard treatment with pegylated alpha IFN in combination with the nucleoside analogue ribavirin leads to a sustained virologic response in approximately half of the patients [17]. Although the efficacy of antiviral therapy in chronic hepatitis C has improved since interferon was introduced, non response to this therapy remains common. Several factors have been shown to influence response [19]. The biological activity of interferon (IFN) is mediated by the induction of intracellular antiviral proteins, such as 2'-5' oligoadenylatesynthetase, dsRNA-activated protein kinase and MxA protein [20].Intercellular adhesion molecule is a protein regulating the inflammatory cells movement.

The receptor complex for IL-21 is composed of IL-21R, which specifically binds IL-21, together with the common cytokine receptor -chain [6, 7]. In contrast to the cytokine, IL-21R is expressed on multiple cell types in the immune system [8, 9, 10], including T cells, B cells, NK cells, macrophages, and dendritic cells [11, 12].

In our study, we report on the genetic association between a SNP in IL21R (rs3093390) and virological response to interferon treatment in Egyptian patients with chronic hepatitis C (CHC).

From our study we found that patients with IL-21R rs3093390 CC genotype had a higher sustained virological response to interferon treatment than those with non-CC genotypes (P=0.089). These results were agreed with *C-S HSU et al, 2013* who found that patients with rs3093390 CC genotype has comparable RVR, EVR and SVR rates to those with CT or TT genotypes (P= 0.031)[13]. Our results also estimate the correlation between percentage of response to treatment and different genotypes, where 52.27% of responder patients have CC genotype versus 47.72% non CC genotype (CT, TT). On the other hand only 33.33% of non responder patients have CC genotype versus 66.67% non CC genotype (CT, TT).

Our study estimated that the mean age of responder patients was (41.70 ± 8.992) vs (39.31 ± 6.907) in non-responder. The difference was not statistically significant (p=0.193). also BMI had no significant difference between responders and non-responders (26.000 ± 8.6616) vs. (24.028 ± 8.4633) respectively (P=0.309).

According to our data there are other factors associated with SVR as low blood platelets count, it showed statistically significant correlation with treatment response (P=0.037). These results are in agreement with previous studies, which reported that the low platelets count and splenomegaly is a path gnomonic sign of chronic liver disease so the patients will obviously show a poor response with interferon therapy[14]. Khairy *et al.* (2012) reported that low platelets count was associated with poor response to INF treatment [15]. But Del Campo *et al.* (2012) found no significant relation between platelets and Sustained Virological Response (SVR) in patients with HCV genotypes 1&4[16].

Conclusion

Patients with IL-21R rs3093390 CC genotype had a higher sustained virological response to interferon treatment than those with non-CC genotypes.

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Competing interests

All The authors declare that they have no competing interests.

Authors' contributions

Dr/ Amal A. Mohamed: Carried out the lab analysis, participated in study design.
Dr/Magda Ahmed Abd-Allah: Helped in the manuscript preparation.
Dr/Heba Kamal Mohamed: Helped to draft the manuscript.
Dr/Lamiaa Ahmed Fouad: Helped in practical work and manuscript writing.
Dr/Mohamed Said Abdul Aziz: Coordinated and performed Ultra sound for all patients.
Dr/Nagwa M AbdelWahab: performed the Statistical analysis .

References

1.WHO,2015(http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html)
2. M. El Nahas, S. Kassim and N. Shikoun, "Profile HiddeMarkov Model for Detection and Prediction of Hepatitis CVirus Mutation," IJCSI, vol. 9, no. 3, pp. 251-256, 2012. S. C. Ray, R. R. Arthur, A. Carella, J. Bukh and D. L. Thoma.
3. Dubuisson J, Penin F, Moradpour D. Interaction of hepatitis C virus proteins with host cell membranes and lipids. Trends Cell Biol 2002; 12: 517-523.
4. Moura AS[1], Carmo RA, Teixeira AL, Teixeira MM, Rocha MO. Soluble inflammatory markers as predictors of virological response in patients with chronic hepatitis C virus infection treated with interferon-α plus ribavirin.. Mem Inst Oswaldo Cruz. 2011 Feb;106(1):38-43.
5. Segen's Medical Dictionary. © 2012 Farlex, Inc. All rights reserved.
6. Asao H, Okuyama C, Kumaki S, Ishii N, Tsuchiya S, Foster D, et al. Cutting edge: the common -chain is an indispensable subunit of the IL-21 receptor complex. J Immunol 2001;167:1–5.
7.HabibT,SenadheeraS,WeinbergK,KaushanskyK.The common chain is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry 2002;41:8725–31
8. Parrish-Novak J, Dillon SR, Nelson A, Hammond A, Sprecher C, Gross JA, et al. Interleukin 21 and its receptor are involved in NK cell expansion and regulation of lymphocyte function. Nature 2000;408:57–63.
9.Kasaian MT, Whitters MJ, Carter LL, Lowe LD, Jussif JM, Deng B, et al. IL-21 limits NK cell responses and promotes antigenspecific T cell activation: a mediator of the transition from innate to adaptive immunity. Immunity 2002;16:559–69.
10. Ozaki K, Kikly K, Michalovich D, Young PR, Leonard WJ. Cloning of a type I cytokine receptor most related to the IL-2 receptor chain. Proc Natl Acad SciUSA2000;97:11439–44.
11.Brandt K, Bulfone-Paus S, Foster DC, Ruckert R. Interleukin-21 inhibits dendritic cell activation and maturation. Blood 2003;102: 4090–8.
12. Brandt K, Bulfone-Paus S, Jenckel A, Foster DC, Paus R, Ruckert R. Interleukin-21 inhibits dendritic cell-mediated T cell activation and induction of contact hypersensitivity in vivo. J Invest Dermatol 2003;121:1379–82.
13. Ching-Sheng Hsu, Shih-Jer Hsu, Wei-Liang Liu, Chi-Ling Chen, Chun-Jen Liu, PeiJer Chen, Ding-Shinn Chen, Jia-Horng Kao, Antiviral Therapy 2013; 18:599-606 (doi:10.3851/IMP2502).
14. Sharma SK, Aggarwal R. Prediction of large esophageal varices in patients with cirrhosis of liver using clinical, laboratory and imaging parameters. J Gastroenterol Hepatol 2007; 22:1909-15.
15. Khairy, M., M. Abdel-Rahman, M. El-Raziky, W. El-Akel and N. Zayed *et al., 2012.* Non-invasive prediction of hepatic fibrosis in patients with chronic HCV based on the routine pre-treatmennnt workup. Hepat. Mon.,12:e6718-e6718. DOI:10.5812/hepatmon.6718
16. del Campo, J.A., M. Garcia-Valdcasas, L. Rojas and M. Romero-GÓmez, 2012. The hepatitis C virus modulates insulin signaling pathway *in vitro* promoting insulin resistance. PLoS One, 7:e47904-e47904.DOI: 10.1371/journal.pone.0047904

17. Strickland GT, Elhefni H, Salman T, Waked I, Abdel-Hamid M, Mikhail NN, et al(2002). Role of hepatitis C infection in chronic liver disease in Egypt. Am.J. Trop. Med. Hyg;67(4):436-442.
18. Khuroo MS, Khuroo MS, Dahab ST(2004). Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. Aliment PharmacolTher;20(9):931-8.
19. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçales FL Jr, et al (2002). Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med;347(13):975-82.
20. Tokumoto Y, Hiasa Y, Horiike N, Michitaka K, Matsuura B, Chung RT, et al (2007).Hepatitis C virus expression and interferon antiviral action is dependent on PKR expression. J Med Virol;79(8):1120-7.

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