Prevalence of hepatitis C virus infection in a cohort of Egyptian patients with rheumatoid arthritis

Thesis
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بسم الله الرحمن الرحيم

صدق الله العظيم

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Mahmoud Elzalabany

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List of Abbreviations

Abb.	*Meaning*
AASLD	American Association for the Study of Liver Diseases
ACPA	Anti-citrullinated protein antibodies
ACR	Americal college of Rheumatology
AFP	α-fetoprotein
ALT	Alanine transaminase
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-MCV	Anti-mutated citrullinated vimentin
AST	Aspartate transaminase
CBC	Complete blood count
CRP	C-reactive protein
DAAs	Direct Acting Antivirals
DAS28	Disease Activity Score in 28 joints
DHEA	Dehydroepiandrosterone
DIP	Distal interphalangeal
DMARDs	Disease modifying antirheumatic drugs
EASL	European association for the study of the liver
EBV	Epstein-Barr virus
EDHS	Egyptian Demographic Health Survey
EHIS	Egyptian Health Issues Survey
EHMs	Extrahepatic manifestations

EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbant assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and drug administration
FSH	Follicular stimulating hormone
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCQ	Hydroxychloroquine
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IDUs	Intravenous drug users
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
ILD	Interstitial lung disease
IV	Intravenous
LDL	Low density lipoprotein
LFL	Leflunomide

LFTs	Liver function tests
LH	Luteinizing hormone
MC	Mixed cryoglobulinemia
MCP	Metacarpophalangeal
MOH	Ministry of Health
MPGN	Membrano-proliferative glomerulonephritis
MRI	Magnetic resonance imaging
MTP	Metatarsophalangeal
MTX	Methotrexate
NAT	Nucleic acid testing
NCCVH	National committee for control of viral hepatitis
NSAIDs	Non-steroidal anti-inflammatory drugs
NTRs	Nontranslated regions
OBV	Ombitasvir
ORF	Open reading frame
PAT	Parenteral antischistosomal therapy
PCR	Polymerase chain reaction
Peg-IFN	Pegylated interferon
PI	Protease Inhibitors
PIP	Proximal interphalangeal
PTV	Paritaprevir
RA	Rheumatoid arthritis

RBV	Ribavirin
RF	Rheumatoid factor
RIBA	Recombinant immunoblot assay
RT-PCR	Reverse transcriptase Polymerase chain reaction
SD	Standard deviation
SLZ	Sulfasalazine
SMV	Simeprevir
SOF	Sofosbuvir
SR-BI	Scavenger receptor B type I
SVR	Sustained virologic response
TB	Tuberculosis
TNF	Tumor necrosis factor
VLDL	Very low density lipoprotein
WBCs	White blood cells

Introduction

Introduction

Hepatitis C virus (HCV) is an enveloped RNA virus of the family Flaviviridae that was first characterized in 1989 **(*Choo et al., 1989*)**. HCV infection is a major public health problem affecting approximately 3% of the world's population with about 130-150 million people chronically infected worldwide **(*WHO, 2015*)**.

Egypt has the highest prevalence of HCV in the world of about 14.7% **(*El-Zanaty & Way, 2009*)**. This high prevalence was attributed to iatrogenic transmission during parenteral antischistosomal therapy (PAT) mass-treatment campaigns in the sixtieth till early eightieth **(*Frank et al., 2000*)**.

Hepatitis C virus is a strict blood-borne pathogen transmitted through exposure to contaminated blood. Transfusion of unscreened blood and blood products was a major risk factor for HCV transmission before 1994 when national blood screening program was started in Egypt. Other risk factors include occupational exposure among health care workers through needle sticks, IV Drug misuse, vertical transmission from infected mother to fetus, sexual contact and sharing toothbrushes and razors **(*Mohamoud et al., 2013*)**. Iatrogenic exposures as injections, surgical and dental procedures play an important role in the ongoing transmission of HCV infection nowadays in Egypt **(*Miller & Abu-Raddad, 2010*)**.

Most cases of acute HCV infections are asymptomatic and pass unnoticed. About 15-30% of the cases spontaneously clear the virus and the remaining 70-85% progress to chronic infection; which is defined as persistence of HCV RNA in the blood for six months after exposure. Once chronic HCV infection is established, it generally persists for life. Of those chronically infected, about 20% will develop cirrhosis within 10-20 years of which about 2-5% will develop primary hepatocellular carcinoma (HCC) **(*Seeff, 2002*)**.

The prevalence of anti-HCV antibodies in patients admitted to rheumatology ward in an Egyptian study was 18.5%, which is higher than the general population **(*El Garf et al., 2012*)**. There is no enough data about the prevalence of HCV infection in patients with rheumatoid arthritis in Egypt, a country with a unique HCV epidemic. Those patients are at increased risk of HCV infection due to immune suppression either by the disease itself or the drugs used in its treatment, in addition to their high exposure to invasive procedures. Many patients with chronic HCV infection may present for the first time with the rheumatic manifestations of the disease **(*Mohammed et al., 2010*)**.

Aim of the study

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The aim of the current study is to estimate the prevalence of HCV infection in a cohort of Egyptian patients with rheumatoid arthritis.

Review of literature

Chapter (1)

Hepatitis C Virus

Hepatitis C Virus

Hepatitis C virus (HCV) was first characterized in 1989 as the causative agent of the previously called "non-A, non-B" hepatitis. It is a hepatotropic enveloped RNA virus belonging to the genus hepacivirus of the Flaviviridae family **(*Bartenschlager et al., 2011*)**.

Epidemiology of HCV:

Hepatitis C virus infection represents a major public health concern with about 130-150 million people chronically infected with it all over the world. The average prevalence of HCV is 2-3%, but some countries like Egypt have a prevalence of more than 10%. It is estimated that 3-4 million cases are newly infected with HCV each year **(*WHO, 2015*)**.

Hepatitis C-related liver diseases cause about 500,000 deaths every year. HCV is responsible for 27% of cirrhosis and 25% of hepatocellular carcinoma (HCC) worldwide and it is the leading cause for liver transplantation **(*Perz et al., 2006*)**.

HCV prevalence is low (<1.5%) in Asia Pacific, Tropical Latin America and North America. It is moderate (1.5%-3.5%) in South and Southeast Asia, sub-Saharan Africa, Andean, Central, and Southern Latin America, Oceania, Australasia and Europe.

Central and East Asia, North Africa, and Middle East have high HCV prevalence (> 3.5%) **(*Hanafiah et al., 2013*) (Figure 1)**.

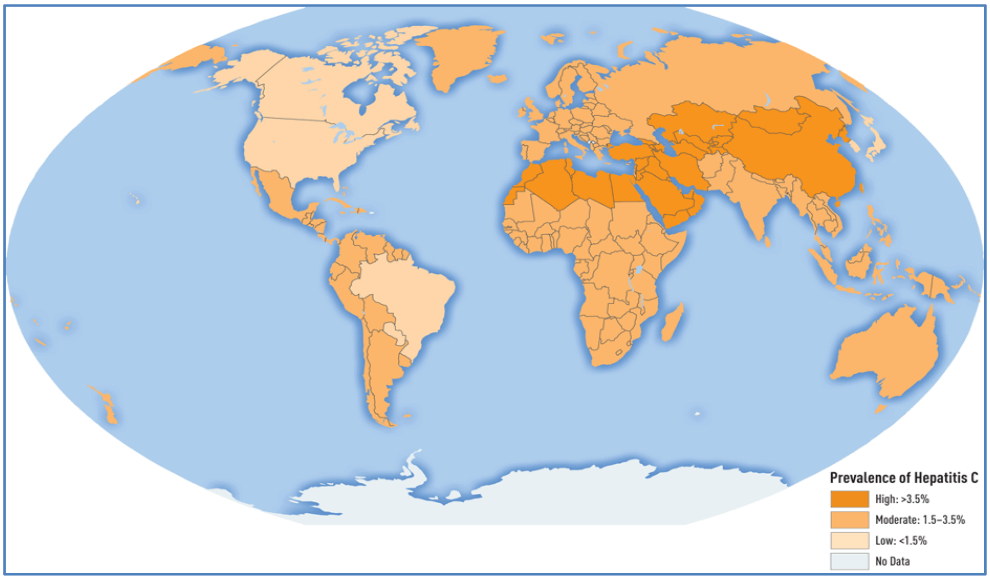


Figure (1): Global prevalence of chronic HCV infection (*Holtzman, 2015*).

HCV in Egypt:

A study published in 1992 estimated the prevalence of HCV antibodies in about 2000 Egyptian first time healthy blood donors to be 10.1%. This was a shocking number as it was 5-10 times more than any other country in the world. Another study was done in 1994 and included the entire population of a remote village in the northern Nile Delta. The overall anti-HCV antibodies prevalence in the village was 17.6%. In both studies, prevalence of anti-HCV antibodies increased strongly with age and was nearly similar in both sexes **(*Miller et al., 2015*)**.

Many similar studies were done in the following years in rural communities and selected health settings and confirmed the same finding of high HCV prevalence in Egypt. The cause of the HCV epidemic in Egypt is not clear, but thought to be due to campaigns of parenteral anti-schistosomiasis therapy (PAT) carried out in the sixtieth till early eightieth **(*Mohamoud et al., 2013*)**.

The Egyptian Ministry of Health (MOH) estimated that HCV incidence is about 100,000 new cases per year. A study estimated it to be about 500,000, while another study estimated it to be about 160,000 new cases per year **(*Miller et al., 2010; Breban et al., 2013*)**. Whatever the number is, but there is still an ongoing epidemic transmission of HCV in Egypt **(*Mostafa et al., 2010*)**.

Viral structure:

HCV has a spherical shape, 50 nm in diameter, with smooth outer surface and spike projections. The outer layer of the virus is formed of E1 and E2 proteins. It surrounds the lipid bilayer and the spherical nucleocapsid consisting of the HCV core (C) protein and containing the viral genome **(*Catanese et al., 2013*) (Figure 2)**.

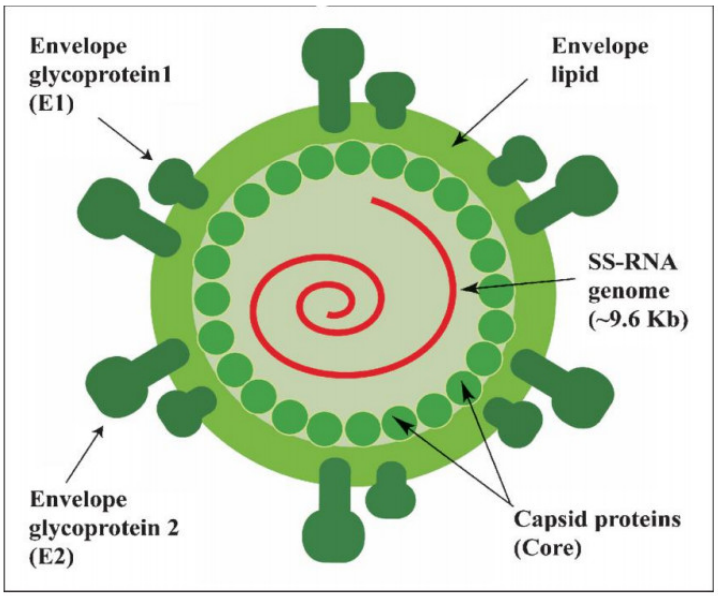


Figure (2): HCV particle structure (*Wakita et al., 2005*).

Viral genome:

Hepatitis C virus genome consists of one 9.6 kb single-stranded positive-sense RNA molecule which serves as a messenger RNA (mRNA) for the translation of viral proteins **(*Paul et al., 2014*)**.

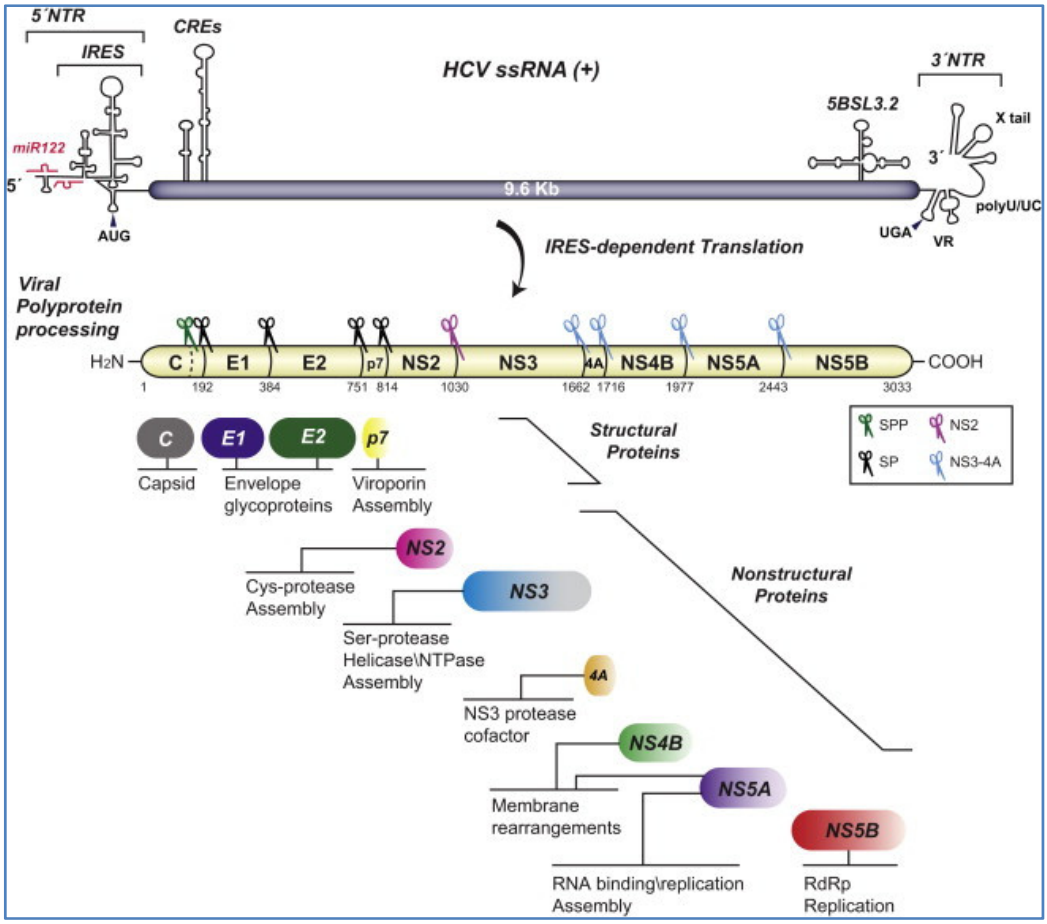


Figure (3): HCV genome organization (*Paul et al., 2014*).

The RNA molecule contains a single open reading frame (ORF) of about 9000 nucleotides coding for a precursor polyprotein of about 3000 amino acids. The ORF is flanked by 5' and 3' non-translated regions (NTRs) at each end **(Figure 3)**. The 5'NTR is the most conserved region in the genome, while the regions encoding envelope proteins (E1, E2) are the most variable ones **(*Kim and Chang, 2013*)**.

Viral proteins:

Table (1): HCV proteins and its functions (*Li & Lo, 2015*):

Viral protein	*Functions*
Core	It forms the viral capsid that contains the HCV genome and has regulatory functions.
E1 and E2	These envelope glycoproteins are responsible for adsorption of the virus to receptors on the host cell plasma membrane.
p7	It is a membrane protein which forms ion channels and plays an essential role in virus infection.
NS2	The NS2 and NS3 proteins form a cysteine protease which catalyzes the cleavage of the polyprotein precursor between NS2 and NS3.
NS3 and NS4A	The NS3 and NS4A proteins form a serine protease which is responsible for cleavage of the remaining HCV polyprotein. The C-terminus of NS3 has NTPase/helicase activity required for viral replication.
NS4B	The NS4B is an integral membrane protein. It appears to be responsible for the formation of the HCV RNA replication complex.
NS5A	The NS5A protein is a membrane-associated phosphoprotein that has multiple functions in HCV RNA replication, viral assembly, and virion release.
NS5B	NS5B serve as RNA-dependent RNA polymerase responsible for HCV replication. It lacks a proofreading mechanism leading to the conservation of mis-incorporated nucleotides.

The precursor polyprotein resulting from HCV RNA translation is cleaved during replication by viral and host enzymes into three structural proteins (core, E1, E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). The structural proteins are essential components of the HCV virions, whereas the non-structural proteins are involved in RNA replication and virion assembly **(*Li & Lo, 2015*) (Table 1)**.

HCV Life Cycle (Figure 4):

a) Adsorption and viral entry:

HCV lifecycle begins with the attachment of a virion to specific receptors on the surface of hepatocytes. Tetraspanin CD81, scavenger receptor B type I (SR-BI), tight junction protein claudin-1, and occluding are some known cellular receptors for HCV attachment. This process may be mediated by VLDL or LDL. After binding with its receptor, the virion is internalized via clathrin-mediated endocytosis. This is followed by release of the viral RNA into the cytoplasm of the cell **(*Douam et al., 2015*)**.

b) Translation and post-translational processing:

The HCV RNA binds to the 40S and 60S ribosomal subunits forming the translation complex at the endoplasmic reticulum. Translation of HCV RNA ORF results in a 3000 amino acids

polyprotein precursor. The precursor polyprotein is processed by four proteases to produce the 10 viral proteins **(*Kim and Chang, 2013*)**.

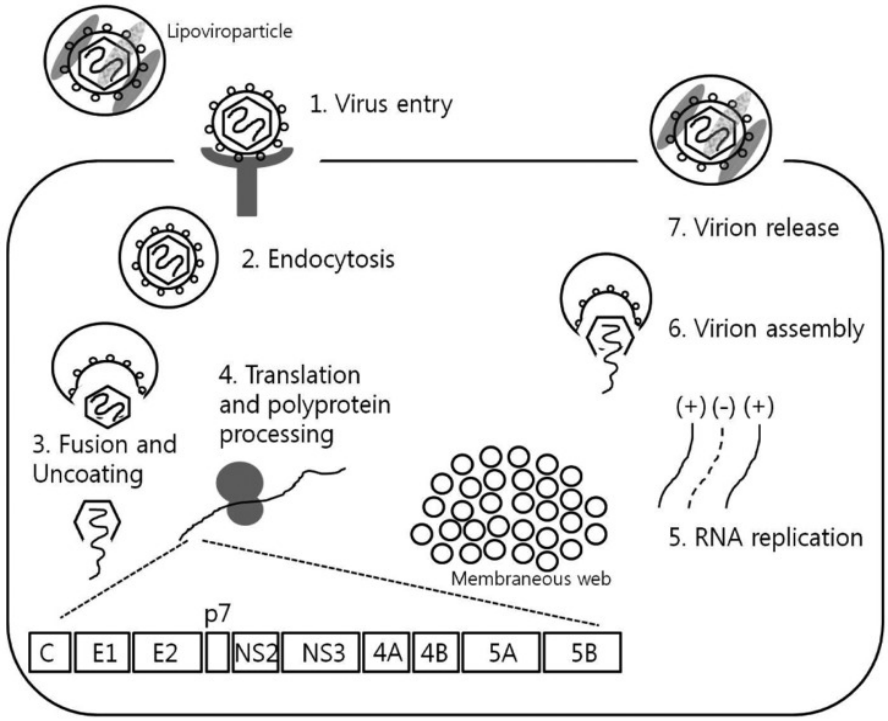


Figure (4): HCV life cycle (*Kim and Chang, 2013*).

c) HCV RNA replication:

HCV RNA-dependent RNA polymerase (NS5B) is the key enzyme for viral RNA replication. It uses the positive-strand HCV RNA as a template for the synthesis of a negative-strand RNA. The later is used in turn to synthesis numerous positive-strand RNA **(*Dubuisson and Cosset, 2014*)**.

d) Assembly and release:

After the viral proteins and the genomic HCV RNA have been synthesized, these single components have to be arranged in order to produce infectious virions. The HCV assembly and release process is not fully understood. However, it appears to be closely linked to lipid metabolism. The virion is a lipoviroparticle with a lipid composition that resembles VLDL and LDL with associated apoE and/or apoB, which are essential for the infectious virus assembly **(*Popescu et al., 2014*)**.

Genotypes and subtypes of HCV:

There is a high genetic diversity in HCV genome with about 6 major genotypes that differ at 30-35% of nucleotide sites and 67 confirmed subtypes differing at <15% of nucleotide sites **(*Simmonds et al., 2005*)**.

HCV genotypes show a large variability in geographic distribution. Genotype 1 is the most prevalent (46.2%), followed by genotype 3 (30.1%), while genotypes 2, 4, 5 and 6 represent the remaining 23.7% of HCV cases. Genotypes 1 and 3 dominate in most countries, while genotypes 4 and 5 dominate in low income countries. In Egypt, 91% of HCV cases are of genotype 4. This variation represents a challenge in developing vaccines and pan-genotypic treatments for HCV **(*Messina et al., 2015*)**.

Modes of Transmission of Hepatitis C:

HCV is a blood borne pathogen with exponential die off in 24 hours under laboratory conditions. It is less infectious than HBV and slightly more infectious than HIV **(*Song et al., 2010*)**. In many cases of newly diagnosed HCV infection no clear risk factor can be identified **(*Wasmuth, 2009*)**.

Injection drug use:

Injection drug use is the most common cause of acute HCV infection worldwide. The prevalence of anti-HCV antibodies in intravenous drug users (IDUs) may reach up to 70% **(*Sutton et al., 2008*)**. The number of IDUs in Egypt is not known although considered to be small **(*Miller et al., 2015*)**.

Blood transfusion:

In the past, transfusion of blood or blood products was a major risk factor for HCV transmission. In some cohorts 10% or more of patients who received blood transfusions were infected with hepatitis C **(*Alter, 2007*)**. In Egypt, the prevalence of anti-HCV antibodies was reported to be up to 54.9% in hospitalized multi-transfused children. The national blood donor HCV screening program, started in 1994, markedly reduced HCV transmission through blood transfusion **(*Moftah, 2002*)**.

Organ transplantation:

Transplant recipients who receive organs from HCV-positive donors have a high risk of acquiring HCV infection. Transmission rates in different cohorts vary from 30 to 80% **(*Miller et al., 2015*)**.

Hemodialysis:

Hemodialysis is one of the recognized risks for HCV transmission. In Egypt, from 46% to 100% of HCV negative dialysis patients could acquire HCV infection within a year in dialysis centers throughout the country. A lot of efforts have been done in this aspect and managed to reduce HCV transmission in dialysis centers **(*El Sayed et al., 2000*)**.

Sexual or household contact:

Sexual transmission of HCV is controversial and recovery of HCV from semen or other genital fluids was found to be difficult **(*Tohme & Holmberg, 2010*)**. Sexual transmission does not play a significant role in Egypt **(*Magder et al., 2005*)**.

No specific intra-familial exposure to HCV transmission has been identified. Familial sharing of any medical equipment such as syringe and needles or diabetic testing equipment could result in exposure to HCV transmission, but this remains to be established **(*Mohamed et al., 2005*)**.

Perinatal transmission:

The risk of perinatal transmission of HCV in HCV RNA-positive mothers is estimated to be 5% or less. In Egypt, it is estimated that there are 5000 newborns infected with HCV every year. Cesarean section doesn't reduce the transmission risk. HCV is not transmitted through breastfeeding; however it should be stopped if the nipples are cracked or bleeding **(*Benova et al., 2015*)**.

Needle sticks injury:

Accidental needle sticks from HCV positive patients have a probability of infection of about 3%, which is slightly greater than HIV but much lower than HBV infection **(*Talaat et al., 2003*)**.

Iatrogenic transmission:

Iatrogenic transmission can occur as a result of exposure to contaminated medical and dental instruments, sharps, needles, invasive procedures and contaminated multi-dose vials **(*Lavanchy, 2011*)**. Many reports identify iatrogenic transmission as the principal driver of the HCV epidemic in Egypt **(*Paez et al., 2010*)**.

Other rare transmission routes:

Other rare sources of HCV infection include scarification, cupping, tattooing, and body piercing **(*Kandeel et al., 2012*)**.

Natural History of HCV Infection:

The natural history of HCV has been very difficult to assess as most cases of acute HCV infection are asymptomatic and pass unnoticed. About 15-30% of the cases spontaneously clear the virus and the remaining 70-85% progress to chronic infection. In patients with chronic HCV infection, about 20% will develop cirrhosis within 10-20 years, of which about 2-5% will develop primary hepatocellular carcinoma **(*Westbrook and Dushieko, 2014*)**.

Clinical outcomes of HCV Infection:

1) Acute Hepatitis C:

After inoculation of HCV, there is a variable incubation period. HCV RNA in blood can be detected by PCR within several days to eight weeks. Aminotransferases become elevated approximately 6-12 weeks after exposure. HCV antibodies can be found first around 8 weeks after exposure although in some patients it may take several months to be detected **(*Vogel et al., 2009*)**.

The initial features of the acute illness are non-specific flu-like symptoms. More specific symptoms of viral hepatitis include jaundice, dark urine, anorexia and abdominal discomfort, and occur in a minority of cases. Fulminant hepatic failure due to acute HCV infection is very rare **(*Westbrook and Dushieko, 2014*)**.

2) Spontaneous Clearance of HCV:

Spontaneous Clearance of HCV occurs in around 15-30% of acute infections. Several host, viral and environmental factors are determinants of spontaneous clearance **(*Kong et al., 2014*)**. Female gender, young age at the time of infection and a history of icteric hepatitis are associated with increased spontaneous clearance, while African-American ethnicity, excess alcohol and illicit drug use are associated with low viral clearance rates **(*Grebely et al., 2014*)**.

Spontaneous clearance of HCV is increased in patients who are co-infected with Hepatitis B virus (HBV), while decreased in those co-infected with human immune deficiency virus (HIV). Many host genetic factors are associated with spontaneous clearance of HCV. The most important genetic factor is single-nucleotide polymorphisms around IL28B gene **(*Balagopal et al., 2010*)**.

A strong host immune response (innate and adaptive) is important for spontaneous HCV clearance **(*Diepolder, 2009*)**. During acute infection, HCV persistence can occur through evasion of the innate immune response. HCV could partly or completely counter the innate immune response by disrupting cellular signaling pathways that lead to interferon synthesis, and by subverting cellular signaling to restrict expression of interferon-stimulated genes and block their antiviral effects **(*Lemon, 2010*)**.

3) Chronic Hepatitis C:

Chronic hepatitis is the most common outcome of HCV infection, developing in 70-85% of patients. It is defined as persistence of HCV RNA in the blood after six months of the infection. Once chronic infection is established, there is a very low rate of spontaneous clearance **(*Watanabe et al., 2003*)**.

The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss. Aminotransferase levels can vary considerably over the course of chronic hepatitis C. Most patients have only slight elevations of transaminases and up to one third of patients have normal serum ALT. About 25% of patients have serum ALT concentration of between 2 and 5 times above the upper limit of normal. Elevations of 10 times the upper limit of normal are very rarely seen **(*Puoti et al., 2002*)**.

Chronic HCV is the leading cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the world. It is a slowly progressive disease characterized by persistent hepatic inflammation leading to the development of cirrhosis in approximately 10–20% of patients over 20–30 years. Patients could remain undiagnosed until they present with the complications of end stage liver disease **(*Hajarizadeh et al., 2013*)**.

4) Cirrhosis and hepatic decompensation:

Cirrhosis is defined pathologically as a diffuse process characterized by regenerative nodules that are separated from one another by bands of fibrosis and it is an end stage of most chronic liver diseases **(*Kleiner, 2005*)**.

Cirrhosis may be very difficult to diagnose clinically, as most cirrhotic patients will be asymptomatic as long as hepatic decompensation does not occur. Findings associated with cirrhosis on physical examination include hepatomegaly and/or splenomegaly, spider angioma, caput medusae, palmar erythema, testicular atrophy, and gynecomastia. Laboratory findings include elevated serum bilirubin, hypoalbuminemia, prolonged prothrombin time, and low platelets. Most of these findings are not sufficient to establish a diagnosis of cirrhosis. Therefore regular screening for liver fibrosis/cirrhosis e.g. with transient elastography is recommended by current guidelines **(*AASLD-IDSA, 2016*)**.

Once cirrhosis has developed there is a 3–6% annual risk of hepatic decompensation. Features of hepatic decompensation include ascites, jaundice, encephalopathy and bleeding from oesophageal varices. Once decompensation has developed the 5-year survival rate is roughly 50%. For this group of patients liver transplantation is the only effective therapy **(*Planas et al., 2004*)**.

5) Hepatocellular carcinoma (HCC):

Cirrhosis secondary to HCV is associated with the highest annual risk for developing HCC. Annual incidence rates of HCC in patients with HCV-related cirrhosis range widely from 1% to 5%. Elevated concentrations of α-fetoprotein (AFP) do not necessarily indicate HCC. Levels above (400 ng/mL) as well as a continuous rise in AFP over time are suggestive of HCC **(*El-Serag, 2004*)**.

6) Extrahepatic manifestations:

Around 40 to74% of patients with chronic hepatitis C has an extrahepatic manifestation of HCV. There is a wide variety of extrahepatic manifestations associated with HCV **(*Zignego and Craxi, 2008*)**:

- Hematologic manifestations (essential mixed cryoglobulinemia, lymphoma)
- Autoimmune disorders (thyroiditis, presence of various autoantibodies)
- Renal disease (membranoproliferative glomerulonephritis)
- Dermatologic disease (porphyria cutanea tarda, lichen planus)
- Rheumatologic manifestations
- Diabetes mellitus.

Diagnosis of HCV Infection

HCV infection is usually asymptomatic or presents with nonspecific symptoms and mostly diagnosed accidentally. It is estimated that only 30-50% of individuals infected with HCV are aware of their disease. HCV diagnostics should be performed thoroughly in all patients presenting with increased aminotransferase levels, with chronic liver disease of unclear etiology and with a history of risk factors for HCV transmission **(*Kamili et al., 2012*)**.

For the diagnosis of hepatitis C, both serologic and nucleic acid-based molecular assays are available. Serologic tests are sufficient when chronic hepatitis C is expected. Positive serologic results require testing for HCV RNA in order to differentiate between chronic hepatitis C and resolved HCV infection from the past. When acute hepatitis C is considered, serologic screening alone is insufficient because anti-HCV antibodies may develop late after transmission of the virus; in contrast HCV RNA is detectable within a few days of infection **(*Scott and Gretch, 2007*)**.

Serologic assays:

a) Enzyme immunoassay (EIA):

Antibodies against multiple HCV epitopes are detected by second and third generation enzyme-linked immunoassays (ELISA). In these tests, HCV-specific antibodies from serum samples are captured by recombinant HCV proteins and are then detected by secondary antibodies against IgG or IgM. These secondary antibodies are labeled with enzymes that catalyse the production of colored, measurable compounds. Second generation ELISA tests detect antibodies against antigens derived from the core, NS3 and NS4 regions with a sensitivity of about 95% and can detect HCV antibodies about 10 weeks after infection **(*Pawlotsky, 2003*)**.

Third generation ELISA tests have been developed adding an antigen from the NS5 region. This allows the detection of anti-HCV antibodies approximately 4-6 weeks after infection with a sensitivity of more than 99% **(*Colin et al., 2011*)**.

False positive serologic HCV test results are more frequent in patients with rheumatoid factors and in populations with a low hepatitis C prevalence. False-negative HCV antibody testing may occur in patients on hemodialysis or in severely immunosuppressed patients like in HIV infection or in hematological malignancies **(*Pawlotsky, 2003*)**.

b) Recombinant immunoblot assay (RIBA):

Several immunoblots are available for confirmation of positive HCV ELISA results, but these tests have lost their clinical role since the development of highly sensitive HCV RNA detection methods. Immunoblots are important for identification of false-positive serological tests **(*Carey, 2003*)**.

HCV Nucleic acid testing (NAT):

Measuring HCV RNA is the gold standard for diagnosis of active HCV infection. Both qualitative and quantitative HCV RNA Polymerase chain reaction (PCR) assays are available **(*Kamili et al., 2012*)**.

a) Qualitative HCV RNA PCR:

Qualitative assays for HCV RNA had lower limits of detection and lower costs compared to quantitative assays. They are used for the first diagnosis of acute hepatitis C, confirmation of chronic hepatitis C infection in patients with positive HCV antibodies, confirmation of virologic response after antiviral therapy, and in screening blood and organ donations for presence of HCV **(*Morishima et al., 2004*)**.

b) Quantitative HCV RNA PCR:

Quantitative HCV RNA detection assays offer the possibility of measuring the viral load exactly and are essential in treatment monitoring. Qualitative and quantitative HCV RNA assays have now been widely replaced by Real Time PCR-based assays that can detect HCV RNA over a very wide range, from 10 IU/ml up to 10 million IU/ml **(*Ghany et al., 2009*)**.

c) Reverse Transcriptase PCR (RT-PCR):

In reverse transcriptase PCR (RT-PCR) based assays; HCV RNA is used as a template for the synthesis of a single-stranded complementary cDNA by reverse transcriptase. The cDNA is then amplified by a DNA polymerase into multiple double-stranded DNA copies. Qualitative RT-PCR assays are expected to detect 50 HCV RNA IU/ml or less with equal sensitivity for all genotypes **(*Pawlotsky, 2003*)**.

HCV genotyping:

Because the currently recommended treatment regimen and its duration can depend on the HCV genotype, HCV genotyping is mandatory in every patient considered for antiviral therapy. In some countries like Egypt in which 90% of cases belong to genotype 4, HCV genotyping may not be necessary. The importance for HCV

genotyping may decline with the availability of pan-genotypic, all oral combination therapies in the future **(*Lange et al., 2014*)**.

Resistance testing during Direct Acting Antiviral therapies (DAAs):

HCV variants resistant to DAAs can emerge during antiviral therapy and result in treatment failure. Resistance testing prior to antiviral therapy can help select the optimal treatment regimen for individual patients **(*Schneider and Sarrazin, 2014*)**. For example, before starting simeprevir-based triple therapy, patients infected with HCV genotype 1a should be screened for the presence of the Q80K variant in NS3 region **(*Jacobson et al., 2013*)**.

Treatment of HCV infection:

The goal of antiviral therapy is to achieve sustained virologic response (SVR) which is defined as negative HCV RNA 6 months after the end of treatment. In 2011, the FDA accepted SVR-12 (HCV RNA negativity 12 weeks after the end of treatment) as endpoint for future trials because HCV relapse usually occurs within the first 12 weeks after treatment. More than 99% of patients who achieve SVR remain HCV RNA negative 4-5 years after the end of treatment and no signs of hepatitis have been documented **(*Swain et al., 2010*)**.

Long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality. Patients who achieved SVR have a similar life expectancy compared with the general population **(*Backus et al., 2011*)**. Achieving SVR can lead to improvement of liver function in patients with advanced and decompensated cirrhosis and may reduce the need for liver transplantation **(*Deterding et al., 2015*)**.

After discovery of HCV, Interferon (IFN) monotherapy was used for treatment of HCV with SVR rate of 5-20%. Then, a combination of IFN and ribavirin (RBV) was used with SVR rates of 40-50%. The approval of pegylated interferon (Peg-IFN) led to improved pharmacokinetics with once weekly dosage and higher SVR **(*Cornberg et al., 2016*)**.

The development of direct-acting antiviral agents (DAAs) against HCV has revolutionized the treatment of chronic hepatitis C. The main targets for DAAs are the NS3/4A protease, NS5B polymerase and the NS5A replication complex.

HCV NS3/4A Protease Inhibitors (PI):

In 2011, the first protease inhibitors boceprevir and telaprevir were approved for patients with HCV genotype 1 (GT1). When combined with Peg-IFN and Ribavirin, SVR rates improved to about 75% in treatment-naïve patients **(*Jacobson et al., 2011*)**.

In 2014, new DAAs were approved. Simeprevir (SMV) (Olysio®) was the first once-daily PI. The SVR rates for treatment-naïve GT1 patients increased to 80% with Peg-IFN/RBV plus SMV for 24 weeks with fewer side effects **(*Manns et al., 2014*)**.

Sofosbuvir (Sovaldi®):

Sofosbuvir (SOF), the first available once-daily NS5B polymerase inhibitor, was FDA approved in December 2013. Triple therapy with SOF/Peg-IFN/RBV for 12 weeks lead to 89% SVR in treatment-naïve GT1 patients, and 96-100% SVR in 35 GT4 patients. The resistance barrier of SOF is much higher compared to the available PIs **(*Lawitz et al., 2013*)**.

A combination of only SOF/RBV may be sufficient for some patients. SOF/RBV for 24 weeks resulted in 100% SVR for naïve and 87% for treatment experienced patients **(*Ruane et al., 2014*)**. With the introduction of more highly effective DAAs, this regimen is not recommended any more.

Sofosbuvir can also be combined with a protease inhibitor or a NS5A inhibitor. Treatment with sofosbuvir and simeprevir resulted in 92% SVR in GT1 patients **(*Lawitz et al., 2014*)**. The efficacy of this regimen has been confirmed in large real world cohorts **(*Dieterich et al., 2014*)**. The combination of SOF with the

NS5A inhibitor daclatasvir has also shown > 90% SVR **(*Sulkowski et al., 2014*)**.

Sofosbuvir/Ledipasvir (Harvoni®):

The single dose combination of sofosbuvir with the NS5A inhibitor ledipasvir has shown SVR > 90% (***Kowdley et al., 2014***). SYNERGY trial evaluated 12 weeks of sofosbuvir/ ledipasvir in 21 patients infected with HCV genotype 4, of whom 60% were treatment-naïve and 43% had advanced fibrosis. All of the 20 patients who completed treatment (100%) achieved an SVR12 **(*Kohli et al., 2015*)**.

Ombitasvir/Paritaprevir/Ritonavir (Qurevo®):

Ombitasvir/paritaprevir/ritonavir was FDA approved in December 2014 for GT1 and GT4 patients **(*Ferenci et al., 2014*)**. The PEARL-I study recruited 135 GT4 patients. Naïve patients received OBV/PTV/r with and without RBV for 12 weeks. Treatment-experienced patients were treated with OBV/PTV/r with ribavirin for 12 weeks. Naïve patients achieved 91% SVR without ribavirin and 100% SVR with ribavirin. All treatment-experienced patients were cured as well **(*Hezode et al., 2015*)**. The AGATE studies investigated patients with compensated cirrhosis. 12 weeks OBV/PTV/r with ribavirin showed SVR rates of 96-97% **(*Asselah et al., 2015a*)**.

Grazoprevir/Elbasvir (Zepatir®):

Sixty-six treatment-naïve genotype 4 patients have been treated with grazoprevir/elbasvir for 12 weeks with and without ribavirin. Overall 97% (64/66) achieved SVR12 **(*Asselah et al., 2015b*)**. C-EDGE evaluated 18 treatment-naïve genotype 4 patients who were treated with 12 weeks of grazoprevir/elbasvir. All 18 achieved SVR12 **(*Zeuzem et al., 2015*)**.

Sofosbuvir/Velpatasvir (Epclusa®):

Sofosbuvir/velpatasvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 4 infection in patients with and without cirrhosis. ASTRAL-1 included 64 genotype 4 treatment-naïve patients with and without cirrhosis, all of whom achieved SVR12 (100%) **(*Feld et al., 2015*)**.

AASLD-IDSA 2016 Guidelines for treatment of HCV genotype 4 infection (*AASLD-IDSA, 2016*):

The following recommendations are based on guidelines from the American Association for the Study of Liver Diseases [AASLD] and the Infectious Diseases Society of America [IDSA].

Treatment-naïve Patients with or without Compensated Cirrhosis:

- Ombitasvir/ Paritaprevir /Ritonavir + Ribavirin for 12 weeks
- Sofosbuvir/ Velpatasvir for 12 weeks
- Grazoprevir/ Elbasvir for 12 weeks
- Sofosbuvir/ Ledipasvir for 12 weeks

PegIFN/RBV treatment-experienced Patients without Cirrhosis:

- Ombitasvir/ Paritaprevir /Ritonavir + Ribavirin for 12 weeks
- Sofosbuvir/ Velpatasvir for 12 weeks
- Grazoprevir/ Elbasvir for 12 or 16 weeks
- Sofosbuvir/ Ledipasvir for 12 weeks

PegIFN/RBV treatment-experienced Patients with Compensated Cirrhosis:

- Ombitasvir/ Paritaprevir /Ritonavir + Ribavirin for 12 weeks
- Sofosbuvir/ Velpatasvir for 12 weeks
- Grazoprevir/ Elbasvir for 12 or 16 weeks
- Sofosbuvir/ Ledipasvir + Ribavirin for 12 weeks

Treatment of HCV in Egypt:

In Egypt, the national committee for control of viral hepatitis (NCCVH, established in 2006) started the national HCV treatment program in 2007. 26 treatment centers were established all over the country. From 2008 to 2014, around 360,000 patients received treatment with Peg-IFN/RBV with SVR rates of about 54% **(*El-Akel et al., 2017*)**.

In 2014, The NCCVH launched a website for HCV infected patients willing to receive the new oral agents. The first group of patients started receiving treatment in October 2014. Triple therapy with SOF/Peg-IFN/RBV was given for 12 weeks and SOF/RBV for 24 weeks for those ineligible for IFN. Priority was given to patients with advanced fibrosis (F3 & F4) **(*El-Akel et al., 2017*)**.

Treatment with the new DAAs showed great outcomes when compared to the previous Peg-IFN/RBV therapy. Of 8742 patients treated with SOF/Peg-IFN/RBV for 12 weeks, 94% achieved SVR12. Treatment with SOF/RBV for 24 weeks showed less favorable outcomes; only 78.7% of 5667 patients treated with this regimen achieved SVR12 **(*Elsharkawy et al., 2017*)**.

In May 2015, NCCVH updated its treatment protocol replacing SOF/RBV with sofosbuvir plus simeprevir (SOF/SMV) for 12 weeks due to the unfavorable outcomes of the first regimen.

94% of 6211 patients treated with the new regimen achieved SVR12 **(*Eletreby et al., 2017*)**.

In November 2015, The NCCVH updated its treatment protocol to all oral, IFN free regimens with sovosbuvir plus daklatasvir ± ribavirin for 12 or 24 weeks. In December 2016, The treatment protocol was updated again to include ombitasvir/paritaprevir/ritonavir (Qurevo®) + ribavirin for 12 weeks for easy to treat patients **(*NCCVH, 2016*) (Table 2)**.

Table (2): NCCVH updated Hepatitis C treatment protocol – December 2016 (*NCCVH, 2016*):

Patient Group	***Easy to treat***	***Difficult to treat***
Criteria	▪ Treatment naive ▪ S. Bilirubin ≤ 1.2 mg/dl ▪ S. Albumin ≥ 3.5 gm/dl ▪ INR ≤ 1.2 ▪ Platelet count ≥ 150,000	▪ Peg-IFN experienced ▪ S. Bilirubin > 1.2 mg/dl ▪ S. Albumin < 3.5 gm/dl ▪ INR > 1.2 ▪ Platelet count < 150,000
Regimen	▪ Ombitasvir/ Paritaprevir/ Ritonavir + Ribavirin ▪ Sovosbuvir + Daclatasvir	▪ Sovosbuvir + Daclatasvir + Ribavirin
Duration	12 weeks	12 weeks
The starting dose of ribavirin is 600 mg/day. A trial should be done to increase the dose to 1000 mg/day based on the patient tolerability.		

Table (3): Approved Direct Acting Antiviral Agents (DAAs) (*Cornberg et al., 2016*).

Drug	***Dose***	***Mechanism of Action***
Boceprevir (Victrelis®)	200 mg capsule (4 capsules / 8 hours)	NS3/4A protease inhibitor
Telaprevir (Incivo®)	375 mg tablet (2 tablets / 8 hours)	NS3/4A protease inhibitor
Simeprevir (Olysio®)	150 mg tablet (*once daily)*	NS3/4A protease inhibitor
Sovosbuvir (Sovaldi®)	400 mg tablet (*once daily)*	NS5B polymerase inhibitors (Nucleotide analogue)
Daclatasvir (Daclinza®)	60 mg tablet (*once daily)*	NS5A replication complex inhibitor
Sovosbuvir/ Ledipasvir (Harvoni®)	Sovosbuvir 400 mg / Ledipasvir 90 mg (*single tablet once daily)*	Sovosbuvir: NS5B polymerase inhibitors Ledipasvir: NS5A replication complex inhibitor
Ombitasvir/ Paritaprevir/ Ritonavir (Qurevo®)	Ombitasvir 12.5 mg / Paritaprevir 75 mg / Ritonavir 50 mg (*two tablets once daily)*	Ombitasvir: NS5A replication complex inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: prolong the action of paritaprevir
Grazoprevir/ Elbasvir (Zepatier®)	Grazoprevir 100 mg/ Elbasvir 50 mg (*single tablet once daily)*	Grazoprevir: NS3/4A protease inhibitor Elbasvir: NS5A replication complex inhibitor
Sofosbuvir/ Velpatasvir (Epclusa®)	Sovosbuvir 400 mg / Velpatasvir 100 mg (*single tablet once daily)*	Sovosbuvir: NS5B polymerase inhibitors Velpatasvir: NS5A replication complex inhibitor

Table (4): EASL 2016 Guidelines for treatment of HCV genotype 4 infection (*EASL, 2016*):

	Treatment Naiive (± compensated cirrhosis)	***Treatment Experienced*** (± compensated cirrhosis)	***Treatment Experienced*** (Ribavirin ineligible)
Option 1	Sovosbuvir/ Ledipasvir 12 weeks	Sovosbuvir/ Ledipasvir + Ribavirin* 12 weeks	Sovosbuvir/ Ledipasvir 24 weeks
Option 2	Sofosbuvir/ Velpatasvir 12 weeks	Sofosbuvir/ Velpatasvir 12 weeks	Sofosbuvir/ Velpatasvir 12 weeks
Option 3	Ombitasvir/ Paritaprevir/ Ritonavir + Ribavirin* 12 weeks	Ombitasvir/ Paritaprevir/ Ritonavir + Ribavirin* 12 weeks	----------
Option 4	Grazoprevir/ Elbasvir 12 weeks	Grazoprevir/ Elbasvir + Ribavirin* 12 or 16 weeks (if HCV RNA > 800,000 IU/ml)	----------
Option 5	Sovosbuvir + Daclatasvir 12 weeks	Sovosbuvir + Daclatasvir + Ribavirin* 12 weeks	Sovosbuvir + Daclatasvir 24 weeks
Option 6	Sovosbuvir + Simeprevir 12 weeks	Sovosbuvir + Simeprevir + Ribavirin* 12 weeks	Sovosbuvir + Simeprevir 24 weeks

(* *Ribairin dose: 1000mg daily in patients < 75 kg, 1200mg daily in patients ≥ 75 kg*)

Review of literature

Chapter (2)

Extra-hepatic Manifestations of HCV

Extrahepatic Manifestations of HCV

Table (5): Extrahepatic manifestations of chronic hepatitis C infection (*Cacoub et al., 2016*):

Organ/System	*Manifestation*
Rheumatic	▪ Mixed cryoglobulinemia / Cryoglobulinemic vasculitis ▪ Arthralgia / Myalgia ▪ Polyarthritis / Fibromyalgia ▪ Autoantibody production ▪ Sicca syndrome
Renal	▪ Glomerulonephritis ▪ Renal Insufficiency
Hematologic	▪ Lymphoproliferative disorders/Non-Hodgkin Lymphomas ▪ Monoclonal gammopathies ▪ Immune thrombocytopenia
Endocrine	▪ Autoimmune thyroiditis ▪ Diabetes Mellitus and insulin resistance
Dermatologic	▪ Palpable purpura ▪ Porphyria cutanea tarda (PCT) ▪ Lichen planus ▪ Pruritus
Other	▪ Chronic fatigue ▪ Neurocognitive disorders ▪ Cardiovascular disorders (i.e. stroke, ischemic heart disease)

Hepatitis C virus infection is considered as a systemic disease that doesn't affect the liver only and about two thirds of patients with chronic HCV infection develop a variety of extrahepatic manifestations (EHMs). EHMs may be the first presentation of HCV infection and include chronic fatigue, rheumatic, hematological, endocrine and dermatological disorders **(Table 5)** **(*Cacoub et al., 2016*)**.

Rheumatic Manifestations:

Mixed Cryoglobulinemia

Table (6): Types of Cryoglobulinemia (*Sene et al., 2004*):

Type	*Features*	*Associated with:*
Type I	Monoclonal immunoglobulins (IgG or IgM)	Lymphoproliferative disorders: - Multiple myeloma - B cell lymphoma - Waldenström macroglobulinemia
Type II	Polyclonal immunoglobulins (mainly IgG) Monoclonal IgM with rheumatoid factor activity	Chronic HCV
Type III	Polyclonal IgG and IgM	Chronic HCV

Cryoglobulinemia means the presence of abnormal immunoglobulins in the serum which precipitate at temperatures

below 37º C. Cryoglobulins are classified into three types **(Table 6)** **(*Sene et al., 2004*)**.

Cryoglobulinemic Vasculitis

Mixed cryoglobulinemia (MC) vasculitis (Cryovas) is a small vessel vasculitis involving mainly the skin, the joints, the peripheral nerve system and the kidneys **(*Vigano et al., 2007*)**.

Pathogenesis:

Infection of the lymphocytes by HCV or chronic stimulation induces B-cell clonal expansion leading to the production of antibodies, including rheumatoid factor. These antibodies (IgG & IgM) form immune complexes with complements and HCV particles and deposit in blood vessels causing tissue damage and vasculitis caused by T-cells **(Figure 5)** **(*Jacobson et al., 2010*)**.

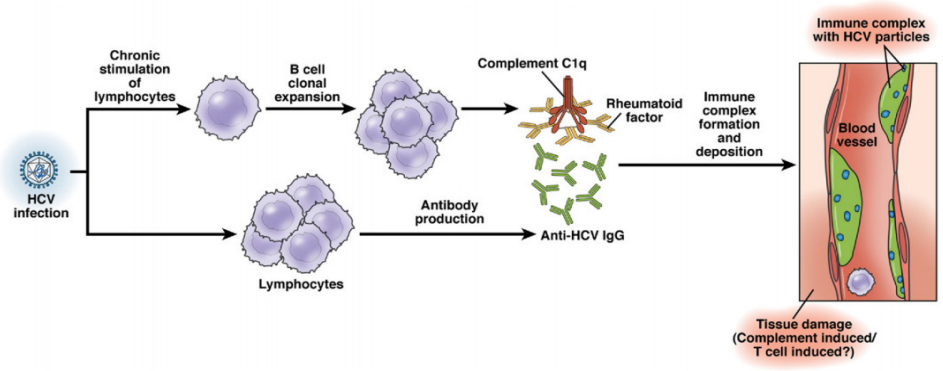


Figure (5): Pathogenesis of mixed cryoglobulinemic vasculitis (*Jacobson et al., 2010*).

Clinical Presentation:

HCV related-MC is asymptomatic in about 85% of cases but may turn into symptomatic disease leading to higher mortality. Symptoms may be mild (purpura, arthralgia) or may progress to severe complications (glomerulonephritis, systemic vasculitis) **(*Ferri et al., 2004*)**. Skin is the most frequently involved organ with manifestations including palpaple purpura, chronic ulcers and Raynaud's phenomenon. Peripheral neuropathy can also occur and it manifests as mononeuropathy or polyneuropathy and is mostly sensory **(*Lidove et al., 2001*)**.

Membrano-proliferative glomerulonephritis (MPGN) is the most common renal disorder associated with mixed cryoglobulinemia and is characterized by proteinuria, mild hematuria and mild renal insufficiency. In 15% of patients, MC-related nephropathy may progress to terminal chronic renal failure requiring dialysis **(*Terrier and Cacoub, 2013*)**.

Diagnosis:

Diagnosis is made by keeping the patient serum at 4°C for up to 7 days. If cryoglobulins present, a cryoprecipitate will be formed. Then, cryoglobulins can be purified and characterized using immunofixation electrophoresis.

The diagnosis of mixed cryoglobuluinemia is based on serologic, pathologic and clinical criteria **(*Neal and Gerond, 2007*) (Table 7)**.

Table (7): Diagnostic criteria of mixed cryoglobulinemia (*Neal and Gerond, 2007*):

Serologic	*Histopathologic*	*Clinical*
▪ Mixed type cryoglobulins ▪ Rheumatoid Factor positivity ▪ HCV Antibodies ▪ Low C4	▪ Leucocytoclastic vasculitis ▪ Monoclonal B cell infiltrates	▪ Purpura ▪ Fatigue ▪ Arthralgia ▪ Membranoproliferative GN ▪ Peripheral neuropathy

Treatment of MC:

Therapy should be initiated for patients with symptomatic MC, and is directed to both the virus and the immune-mediated inflammation **(*Cacoub et al., 2016*)**.

Antiviral therapy is the mainstay of treatment. Most HCV related-MC manifestations respond to clearance of HCV during antiviral therapy with pegIFN plus ribavirin. Some manifestations of HCV-MC, such as peripheral neuropathy or skin ulcers, may worsen with IFN-based therapy, so careful monitoring is mandatory **(*Saadoun et al., 2008*)**.

New interferon-free regimens of DAAs are now the standard of care for HCV infection with SVR rates > 95%. International guidelines recommend that treatment should be prioritized for patients with clinically significant extrahepatic manifestations **(*EASL, 2016*)**.

A randomized controlled trial showed that rituximab has a better efficacy than conventional treatment (***De Vita et al., 2012***). Addition of rituximab to pegIFN and ribavirin led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance **(*Dammacco et al., 2010*)**. Cyclophosphamide, chlorambucil or azathioprine can be used in life threatening organ involvement when there is no response to steroids. Plasmapheresis can be used with rituximab to control severe vasculitis **(*Saadoun et al., 2013*)**.

Sicca syndrome

Sicca symptoms (dry mouth and/or dry eyes) have been reported in 20-30% of patients with chronic HCV infection. Low titers of antinuclear antibodies and RF are common in patients with HCV-related sicca syndrome, but Sjogren's syndrome autoantibodies (anti-SSA/SSB antibody) and typical salivary gland histology are absent. There is no improvement of sicca symptoms after treatment of HCV **(*Ramos-Casals et al., 2001*)**.

HCV-related Arthropathy

Rheumatologic manifestations are common EHMs of HCV. Arthralgia is more common in patients with chronic HCV infection than overt arthritis and is reported in 19% of HCV patients. Overt arthritis includes arthritis associated with or without the presence of mixed cryoglobulinemia (MC) **(*Cacoub et al., 2016*)**.

Pathogenesis

HCV arthritis may be a part of MC or it may be directly or indirectly mediated by HCV infection. Direct invasion of synovial cells by the virus, causes local inflammatory response, cytokine induced disease or immune complex disease, particularly in genetically susceptible individuals. HLA-DR4 histocompatibility antigen is significantly elevated in HCV infected patients with autoimmune diseases, including RA **(*Buskila, 2000*)**.

Clinical Manifestations

The clinical picture of HCV related arthropathy may include polyarthralgia, monoarticular or oligoarticular intermittent arthritis, and symmetric chronic polyarthritis **(*Agarwal, 2008*)**.

HCV-related arthropathy can be clinically indistinguishable from recent onset RA, in which articular damage and deformities have not yet occurred. Most patients with HCV related arthropathy

may fulfill some of the American College of Rheumatology (ACR) criteria for RA diagnosis **(*Zehairy et al., 2012*)**.

HCV associated arthritis in contrast to RA has a benign course, typically not deforming, not associated with articular bony erosions, and involving predominantly small joints of the hands (metacarpo-phalangeal, proximal interphalangeals and wrists). In about 2/3 of the affected individuals, morning stiffness may be severe, resolving after more than an hour **(*Olivieri et al., 2003*)**.

Differences between true RA and HCV related arthritis:

Differentiation may be difficult. HCV related arthritis usually runs a relatively benign course that is typically non-deforming. Furthermore, unlike classic RA, ESR is elevated only in about half of the patients, articular bony erosions and subcutaneous nodules are absent, RF can be found in the setting of various rheumatic diseases, infections, other inflammatory diseases, and in some healthy people **(*Zuckerman et al., 2001*)**.

Anti-citrullinated protein antibodies (ACPA) have been reported as more specific serological markers of RA. They provide a superior alternative to the RF test in laboratory diagnostics of RA. This autoantibody family is an overlapping group of antibodies dependent on the citrullination of arginine residue **(*Klareskog et al., 2008*)**.

Due to the high clinical potential of ACPAs, this biomarker was included in the new RA classification criteria released based on collaborative efforts between the ACR and the European League Against Rheumatism (EULAR) **(*Aletaha et al., 2010*)**.

The discovery of anti-citrullinated protein autoantibodies has led to the development of various new tests, such as anti-cyclic citrullinated peptide (anti-CCP) antibodies, and anti-mutated citrullinated vimentin (anti-MCV) antibodies, to diagnose RA and to distinguish between RA and other causes of arthritis **(*Al-Shukaili et al., 2012*)**.

Autoantibody production

Many autoantibodies are present in the sera of HCV infected patients including mixed cryoglobulins (60-90%), RF (70%), antinuclear (20-40%), anticardiolipin (15%), antithyroid (12%) and anti-smooth muscle antibodies (7%). These autoantibodies are not associated with manifestations of a connective tissue disease except for mixed cryoglobulins. The underlying mechanism for formation of these autoantibodies includes HCV-induced activation and proliferation of B-lymphocytes **(*Cacoub et al., 2016*)**.

Review of literature

Chapter (3)

Rheumatoid Arthritis

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease characterized by symmetrical peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and primarily affects the synovial joints resulting in joint damage and physical disability. RA is characterized by an inflammatory process that leads to proliferation of the synovial cells in joints with subsequent pannus formation which may lead to underlying cartilage destruction and bony erosions. Overproduction of pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-6, drives the destructive process. Extra-articular features occur in 8-12% of individuals with RA and cause significant morbidity and increased mortality **(*Firestein et al., 2017*)**.

Epidemiology

RA affects approximately 0.5–1% of the adult population worldwide and its prevalence varies by geographic location. It affects all ethnic groups with the lowest prevalence in black Africans and Chinese (0.2-0.4%) and the highest in Pima Indians (up to 7%). In Caucasians, the prevalence is about 0.8-1% with a female to male ratio of 3:1 and peak age of onset between 35-45 years **(*Cross et al., 2014*)**.

Aetiology and risk factors:

Like many autoimmune diseases, the etiology of RA is multifactorial. Genetic, environmental, hormonal, and infectious factors may play significant roles. Socioeconomic, psychological and lifestyle factors (e.g. tobacco use) may influence the disease outcome **(*Firestein et al., 2017*)**.

Genetic factors account for 50% of the risk for developing RA. About 60% of RA patients in the United States carry a shared epitope of the human leukocyte antigen HLA-DRB1 **(*Barton and Worthington, 2009*)**.

Many infectious agents have been suggested as a potential cause of RA, including Mycoplasma, Epstein-Barr virus (EBV), and Rubella virus. Periodontal disease and oral pathogens have been also implicated **(*Routsias et al., 2011*)**.

Sex hormones may play a role in RA, as evidenced by increased prevalence in females, amelioration during pregnancy, recurrence in the early postpartum period, and reduced incidence in women using oral contraceptives **(*Firestein et al., 2017*)**.

Many studies have demonstrated that smoking increases the risk for developing RA. Women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after

smoking cessation. Smoking is related to RF and anti-CCP positive disease; however, smoking cessation does not improve the disease activity **(*Sugiyama et al., 2010*)**.

Pathogenesis

RA is characterized by infiltration of the synovial membrane with lymphocytes, plasma cells, dendritic cells and macrophages leading to formation of lymphoid follicles. T lymphocytes, including Th1 cells and Th17 cells, play a central role in the process. T-cell–B-cell interactions lead B-cells to produce cytokines and autoantibodies, including RF and Anti-CCP **(*Ralston and McInnes, 2014*)**.

Synovial macrophages are activated to produce pro-inflammatory cytokines, including TNF, IL-1, IL-6 and IL-15. These cytokines stimulate synovial fibroblasts, osteoclasts and chondrocytes leading to destruction of soft tissues, bone and cartilage. The granulation tissue (pannus) formed by the above sequence of events spreads over and under the articular cartilage, which is progressively eroded and destroyed **(*Firestein et al., 2017*)**.

TNF plays an important role by regulating production of other cytokines, and by activating the endothelium. IL-6 plays a role within the joint and also in regulating the systemic effects of RA by inducing the acute phase response, anaemia of chronic disease,

fatigue and reduced cognitive function. New biologic disease modifying antirheumatic drugs (DMARDs) have been developed to target these cytokines **(*Ralston and McInnes, 2014*) (Figure 6)**.

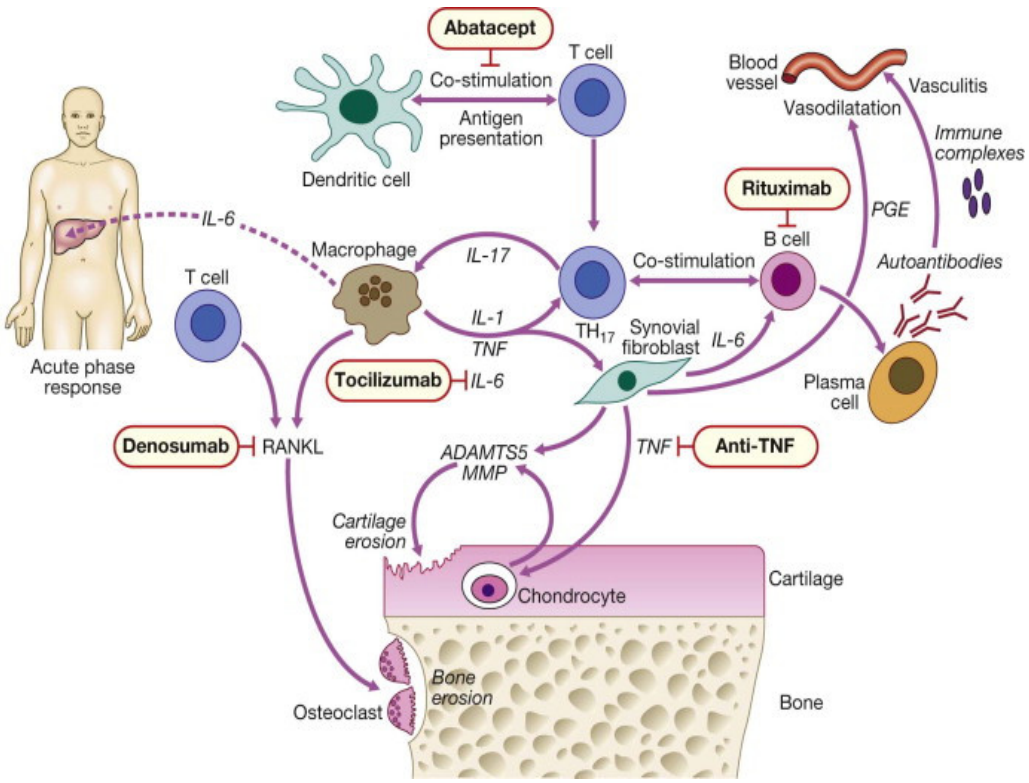


Figure (6): Pathophysiology of rheumatoid arthritis (*Ralston and McInnes, 2014*). *(ADAMTS5 = aggrecanase; IL = interleukin; MMP = matrix metalloproteinases; PGE = prostaglandin E; TNF = tumour necrosis factor)*

Clinical manifestations of rheumatoid arthritis

RA usually has an insidious onset with symptoms including morning stiffness, joint pain, swelling and limitation of movement, muscle weakness and fatigue **(*Smolen et al., 2016*)**.

Articular manifestations:

The articular manifestations of RA are the result of proliferation of synovial tissue leading to formation of pannus, an early event in the course of the disease before destruction of cartilage and bone. Morning stiffness is a common feature of synovial inflammation in RA. It usually lasts more than one hour and improves with physical activity **(*Erickson et al., 2017*)**.

RA mainly affects the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of hands, the wrists and the metatarsophalangeal (MTP) joints of the toes early in the disease. Other synovial joints of the upper and lower limbs, such as the elbows, shoulders, ankles and knees, can be also affected. Distal interphalangeal (DIP) joints involvement may occur in RA, but it is usually a manifestation of coexistent osteoarthritis **(*Conway, 2012*)**.

Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and "trigger" fingers. Progressive destruction of the joints and soft

tissues may lead to chronic, irreversible deformities which include (***Smolen et al., 2016***) **(Figure 7)**:

- Ulnar deviation: results from subluxation of the MCP joints, with deviation of the proximal phalanx to the ulnar side of the hand.
- Swan neck deformity: hyperextension of the PIP joint with flexion of the DIP joint.
- Boutonnière deformity: flexion of the PIP joint with hyperextension of the DIP joint.
- Z deformity of the thumb: subluxation of the first MCP joint with hyperextension of the first interphalangeal joint.
- Piano-key movement of the ulnar styloid: due to tenosynovitis of the extensor carpi ulnaris and subluxation of the distal ulna.
- Flat foot: due to chronic inflammation of the ankle and midtarsal regions.

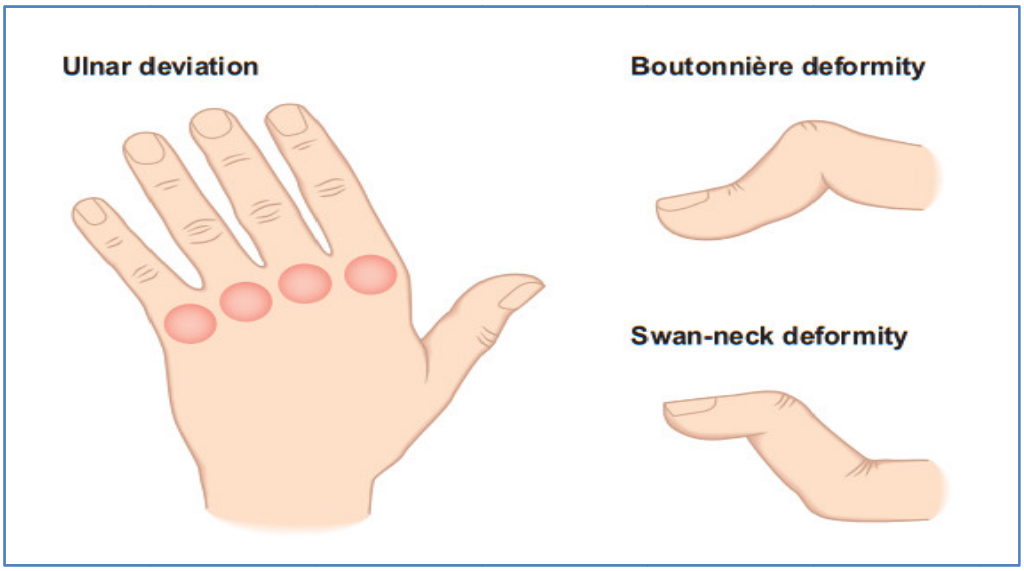


Figure (7): Hand deformities in RA (*Conway, 2012*).

Atlantoaxial involvement of the cervical spine is clinically important because of its potential to cause compressive myelopathy and neurologic dysfunction. Atlantoaxial subluxation has been declining in recent years, and occurs now in less than 10% of patients. RA rarely affects the thoracic and lumbar spines. Radiographic abnormalities of the temporomandibular joint occur commonly in patients with RA without significant symptoms or functional impairment **(*Conway, 2012*)**.

Extra-articular manifestations:

Rheumatoid arthritis is a systemic disease with many extra-articular manifestations that may develop even prior to the onset of arthritis. Patients who have a history of smoking, early onset of physical disability and positive RF test are more likely to develop extra-articular disease **(*Scott et al., 2010*)**.

Constitutional symptoms:

These manifestations include weight loss, fever, fatigue, malaise and depression. They reflect a high degree of inflammation and may precede the onset of joint symptoms. Fever more than 38.3°C may be due to systemic vasculitis or infection **(*Ralston and McInnes, 2014*)**.

Cutaneous manifestations:

Subcutaneous nodules occur in 30–40% of patients and more common in those with high disease activity, positive RF test, and radiographic evidence of joint erosions. The nodules are generally firm, non tender and adherent to periosteum, tendons, or bursae. It develops in areas with repeated trauma such as the forearm, sacrum, and Achilles tendon **(Figure 8)**. They may also occur in the lungs, pleura, pericardium, and peritoneum. Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene. Other less common skin manifestations include erythema elevatum diutinum, erythema nodosum, Gottron's papules, yaws, pinta, leprosy, and amyloid **(*Sayah and English, 2005*)**.

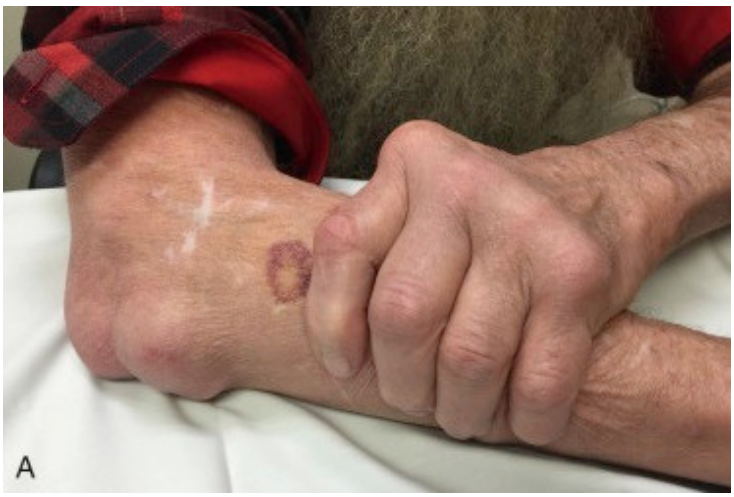


Figure (8): Rheumatoid nodule on the extensor surface of the forearm (*Erickson et al., 2017*)

Vasculitis:

Rheumatoid vasculitis occurs in patients with long-standing disease, positive RF test and hypocomplementemia. Its incidence has decreased significantly in the last 10 years to be less than 1% of patients. The cutaneous signs vary and include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases lower extremity ulcerations **(*Bartels et al., 2009*)**.

Ocular manifestations:

It includes keratoconjunctivitis sicca, episcleritis and scleritis. Episcleritis typically presents as a painless red eye without vision loss and engorged blood vessels. Scleritis is characterized by scleral injection, pain and areas of dusky discoloration. Episcleritis can be managed with topical anti-inflammatory agents, but scleritis requires systemic therapy. The sclera can become thinned and lead to scleromalacia **(*Erickson et al., 2017*)**.

Sjogren's syndrome:

Approximately 10% of patients with RA have secondary Sjögren's syndrome which is characterized by the presence of either keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) **(*Conway, 2012*)**.

Hematologic:

The most common hematologic abnormality is normocytic anemia. Platelet counts may also be elevated as an acute-phase reactant. Immune-mediated thrombocytopenia is rare in RA. Felty's syndrome is characterized by a clinical triad of neutropenia, splenomegaly, and rheumatoid nodules and is seen in less than 1% of patients **(*Erickson et al., 2017*)**.

Lymphoma:

Patient with RA have a two to four fold increased risk of developing lymphoma compared to the general population and the risk increases in patients with high levels of disease activity or Felty's syndrome. The most common histopathologic type is diffuse large B cell lymphoma **(*Smitten et al., 2008*)**.

Pulmonary:

Pleuritis is the most common pulmonary manifestation of RA. Pleural effusion can develop and is exudative in nature with increased number of neutrophils. Interstitial lung disease (ILD) may also occur in patients with RA. ILD can be associated with smoking and is generally found in patients with higher disease activity, although it may be diagnosed in up to 3.5% of patients prior to the onset of joint symptoms **(*Kelly et al., 2014*)**.

Cardiac:

Pericarditis is the most common cardiac manifestation of RA and may be detected in 50% of the patients by echocardiogram. However, clinical manifestations of pericarditis occur in less than 10% of patients. Cardiomyopathy is another manifestation of RA that may result from myocarditis, coronary artery disease, or diastolic dysfunction. It is usually subclinical and only detected by echocardiography or cardiac MRI. Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid. Mitral regurgitation is the most common valvular affection in RA **(*Solomon et al., 2006*)**.

Associated conditions:

In addition to the extra-articular manifestations, several conditions are associated with RA.

Cardiovascular Disease:

It is the most common cause of death in patients with RA. The incidence of coronary artery disease, carotid atherosclerosis and congestive heart failure is higher in patients with RA than in the general population. This may be attributed to elevated serum inflammatory markers **(*Avina-Zubieta et al., 2008*)**.

Osteoporosis:

Osteoporosis is common in patients with RA, with prevalence rates of 20–30%. This may be due to osteoclast activation by inflammatory mediators, chronic use of glucocorticoids, and physical immobility. Hip fractures are more common in patients with RA **(*Schett and Teitelbaum, 2009*)**.

Hypoandrogenism:

Men and postmenopausal women with RA have lower mean serum testosterone, luteinizing hormone (LH), and dehydro-epiandrosterone (DHEA) levels than control populations as a result of the chronic inflammatory response. In addition, patients receiving chronic glucocorticoid therapy may develop hypoandrogenism due to inhibition of LH and FSH secretion from the pituitary gland **(*Shah and Clair, 2015*)**.

Table (8): Extra-articular manifestations of rheumatoid arthritis (*Ralston and McInnes, 2014*):

Organ/System	*Manifestations*	
Constitutional	▪ Fever ▪ Fatigue	▪ Weight loss
Musculoskeletal	▪ Muscle wasting ▪ Tenosynovitis	▪ Bursitis ▪ Osteoporosis
Hematologic	▪ Anemia ▪ Thrombocytosis ▪ Eosinophilia	▪ Felty's syndrome ▪ Leukemia ▪ Lymphoma
Ocular	▪ Episcleritis ▪ Scleritis	▪ Scleromalacia ▪ Keratoconjunctivitis sicca
Dermatologic	▪ Rheumatoid nodules ▪ Purpura ▪ Skin ulcers	▪ Digital infarcts ▪ Pyoderma gangrenosum
Cardiac	▪ Pericarditis ▪ Myocarditis ▪ Endocarditis	▪ Conduction defects ▪ Coronary vasculitis ▪ Granulomatous aortitis
Pulmonary	▪ Pleuritis ▪ Pleural effusion ▪ Inetstitial lung disease (ILD)	▪ Bronchiolitis ▪ Nodules ▪ Caplan's syndrome
Neurological	▪ Cervical cord compression	▪ Peripheral Neuropathy ▪ Mononeuritis multiplex

Classification Criteria of RA

To establish the diagnosis of RA, thorough medical history, physical examination, laboratory and/or radiological tests are needed **(*Amy and Wasserman, 2011*)**.

The 1987 American College of Rheumatology (ACR) criteria for classification of RA requires that objective evidence of synovitis must be present for at least 6 weeks because many transient forms of synovitis are observed in primary care settings **(Table 9)**. To prevent irreversible joint damage, the diagnosis of RA should be confirmed or ruled out within two months after the onset of synovitis **(*Arnett et al., 1988*)**.

Classification criteria were revised in 2010 by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). The new criteria represent an effort to diagnose RA earlier in patients who may not meet the 1987 criteria **(Table 10)**. The 2010 criteria do not include presence of rheumatoid nodules or radiographic erosive changes which are less likely in early RA. Symmetric arthritis is also not required in the 2010 criteria, allowing the detection of early asymmetric presentation **(*Aletaha et al., 2010*)**.

Table (9): The 1987 revised American College of Rheumatology criteria for classification of RA (*Arnett et al., 1988*):

Criterion	*Definition*
Morning Stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement
Arthritis of ≥ 3 joint areas	At least 3 joint areas simultaneously having soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician (the 14 possible joint areas are [right or left] PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
Arthritis of hand joints	At least 1 joint area swollen as above in wrist, MCP, or PIP joint
Symmetric arthritis	Simultaneous involvement of the same joint areas (as in criterion 2) on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, as observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method that has been positive
Radiographic changes	Changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to involved joints (osteoarthritis changes alone do not qualify)
For classification purposes, a patient is said to have RA if he or she has satisfied at least four of the seven criteria. Criteria 1 through 4 must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded.	

Table (10): The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA (*Aletaha et al., 2010*):

Item	*Score*
A. Joint involvement	**(0-5)**
▪ One large joint	0
▪ Two to 10 large joints	1
▪ One to three small joints (with or without involvement of large joints)	2
▪ Four to 10 small joints (with or without involvement of large joints)	3
▪ > 10 joints (at least one small joint)	5
B. Serology (at least one test result is needed for classification)	**(0-3)**
▪ Negative RF and negative ACPA	0
▪ Low positive RF or low positive ACPA	2
▪ High positive RF or high positive ACPA	3
C. Acute phase reactants (at least one test result is needed)	**(0-1)**
▪ Normal CRP and normal ESR	0
▪ Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	**(0-1)**
▪ < six weeks	0
▪ ≥ six weeks	1
Target population (who should be tested?): patients who: ▪ have at least one joint with definite clinical synovitis (swelling) ▪ with the synovitis not better explained by another disease Classification criteria for RA (score-based algorithm: add score of categories A through D; A score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA).	

Laboratory tests:

Hematologic:

Common hematologic abnormalities associated with RA include anemia, thrombocytosis, and mild leukocytosis. Neutropenia can be present in Felty's syndrome **(*Conway, 2012*)**.

Autoantibodies:

About 75 to 80% of patients with RA test positive for RF, Anti-CCP or both. RF lacks diagnostic specificity and it may be found in association with other connective tissue diseases, such as primary Sjögren's syndrome, SLE, and mixed cryoglobulinemia, as well as chronic infections such as subacute bacterial endocarditis and hepatitis B and C. RF may also be detected in 1–5% of the general population. Anti-CCP antibodies have the same sensitivity as RF, but its specificity approaches 95% **(*Nishimura et al., 2007*)**.

Acute phase reactants:

Acute phase reactants such as ESR and CRP are usually elevated in patients with active disease and the degree of elevation correlates with disease activity **(*Conway, 2012*)**.

Synovial Fluid Analysis:

Synovial fluid from patients with RA reflects an inflammatory process with WBC counts ranging between 5000 and

50,000 WBC/μL, mostly neutrophils. It is useful for excluding infection or crystal-induced arthritis; such as gout or pseudogout. Other synovial fluid testing such as RF, ACPA, lactate, and glucose are not indicated **(*Shah and Clair, 2015*)**.

Joint Imaging:

Patients with RA develop joint space narrowing and bony erosions, which can be detected by plain X-ray of the hands and feet. These features may be present when first seen by a clinician but more usually develop over time with ongoing synovitis. The evaluation of any patient with RA should begin with the convential radiograph **(*Amy and Wasserman, 2011*)**.

Plain X-ray:

Plain x-rays are often normal early in the disease and may show only soft tissue swelling and periarticular osteopenia. Erosions in the MCP and PIP joints can be identified by plain x-rays in 15 to 30% of patients in the first year of the disease **(Figure 9)**. Other changes include periarticular osteopenia, and joint space narrowing. Joint deformities may occur with an active disease course **(*Koh et al., 2015*)**.

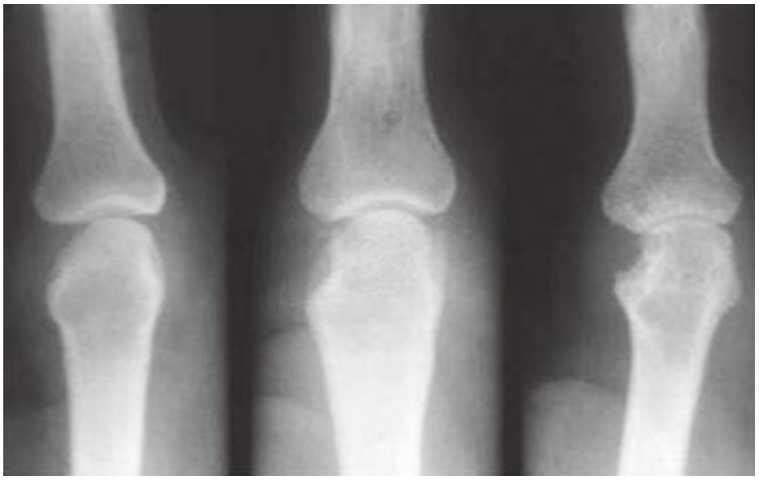


Figure (9): X-ray showing erosions in the PIP joints (*Shah and Clair, 2015*).

Magnetic resonance imaging (MRI)

MRI is more sensitive than plain x-rays for detecting bone erosions. When radiography and MRI were compared in a group of 55 patients with early arthritis, MRI identified seven times as many erosions in the MCP and PIP joints than plain radiography. MRI can also detect bone erosions earlier in the course of the disease than with plain films. It is also possible to identify and estimate the quantity of hypertrophic synovial tissue using MRI **(*Cohen et al., 2011*)**.

Ultrasonography:

Ultrasonography is another sensitive imaging technique for estimating the degree of joint inflammation. Comparison of color Doppler ultrasonography and contrast-enhanced MRI in one study

of 29 patients showed agreement, regarding the presence or absence of inflammation, between the two techniques in 75 % of the joints of the hands and wrists **(*Terslev et al., 2003*)**.

Both imaging techniques detected features of inflammation in joints that were neither tender nor swollen on physical examination. Ultrasonography can also be used to assess the MTP joints, which may become affected early in the course of disease **(*Szkudlarek et al., 2004*)**.

Disease activity measurements:

Patients with RA should be treated early and with a target of low disease activity or remission; however, no single examination finding or laboratory test satisfactorily measures disease activity in those patients **(*O'Dell, 2017*)**.

A lot of measures have been developed for this purpose. These measures use parameters derived from joint examination, patient and physician assessment of disease activity, and laboratory tests (ESR or CRP levels). Recently, the American College of Rheumatology (ACR) has endorsed a list of disease activity measures that have been shown to correlate with outcomes **(Table 11) (*Anderson et al., 2012*)**.

Some of these measures rely only on data from the patient, require complete joint examination, or require laboratory tests. This process is time consuming; therefore measures that simplify this process (DAS28, CDAI, RAPID) are more applicable. A high correlation exists among these measures, so it is more important to measure the disease activity than which measure to use **(*O'Dell, 2017*)**.

A new definition of remission for use in clinical trials has been developed by a joint ACR and EULAR effort **(Table 12)**. This definition has been rigorously tested and therefore is a huge progress for reporting and comparing results in clinical trials **(*Felson et al., 2011*)**.

Table (11): Commonly used disease activity measures (*O'Dell, 2017*):

Instrument	***Range***	***Thresholds of Disease Activity***			
		Remission	**Low**	**Moderate**	**High**
Disease Activity Score in 28 joints (DAS28)	0-9.4	≤2.6	≤3.2	3.2 - 5.1	>5.1
Simplified Disease Activity Index (SDAI)	0-86	≤3.3	≤11	11 - 26	>26
Clinical Disease Activity Index (CDAI)	0-76	≤2.8	≤10	10 - 22	>22
Rheumatoid Arthritis Disease Activity Index (RADAI)	0-10	≤1.4	<2.2	2.2 - 4.9	>4.9
Patient Activity Scale (PAS or PASII)	0-10	≤1.25	<1.9	1.9 - 5.3	>5.3
Routine Assessment Patient Index Data (RAPID)	0-30	≤1	<6	6 - 12	>12

Table (12): ACR/EULAR definition of remission (*Felson et al., 2011*):

Boolean-Based Definition
At any time point, the patient must satisfy all of the following: Tender joint count ≤ 1 Swollen joint count ≤ 1 C-reactive protein ≤ 1 mg/dL Patient global assessment ≤ 1 (on a 0-10 scale)
Index-Based Definition
At any time point, the patient must have a Simplified Disease Activity Index score of ≤ 3.3.

Treatment of rheumatoid arthritis

After RA has been diagnosed and an initial evaluation performed, treatment should begin. Treatment options for RA have changed dramatically over the last decade. Goals of therapy include minimizing joint pain and swelling, preventing deformity and radiographic damage, maintaining quality of life, and controlling extra-articular manifestations **(*Singh et al., 2016*)**.

Disease Modifying Anti-rheumatic Drugs (DMARDs):

DMARDs are drugs which alter or halt disease progression and joint damage and are the mainstay of RA therapy. They are more effective when introduced as early as possible once diagnosis has been confirmed. The conventional DMARDs have a delayed onset of action of approximately 6–12 weeks and include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine **(*Amy and Wasserman, 2011*) (Table 13)**.

Methotrexate is the drug of first choice for the treatment of RA and is the baseline for most combination therapies. Methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. Its side effects include hepatotoxicity, myelosuppression, infection, and interstitial pneumonitis and follow up by CBC and liver functions is required **(*Verstappen et al., 2007*)**.

Leflunomide is an inhibitor of pyrimidine synthesis with clinical efficacy similar to that of methotrexate. It is effective for the treatment of RA as monotherapy or in combination with methotrexate and other DMARDs **(*Amy and Wasserman, 2011*)**.

Hydroxychloroquine does not delay the radiographic progression of disease. It is generally used for treatment of early, mild disease or in combination with other DMARDs. It can cause irreversible retinal damage, thus fundus examination should be done every year **(*McInnes and O'Dell, 2010*)**.

Sulfasalazine has been shown to reduce radiographic progression of the disease. It can cause granulocytopenia, so follow up by CBC is required. Minocycline, gold salts, penicillamine, azathioprine, and cyclosporine have all been used for the treatment of RA, but they are rarely used now due to their unfavorable toxicity profile **(*Ralston and McInnes, 2014*)**.

A combination of DMARDs therapy is superior to monotherapy and newly diagnosed individuals with active RA should be treated with combination of DMARDs (including methotrexate and at least one other DMARD) plus short-term glucocorticoids. Once effective disease control is achieved, the dosage of the combination therapy should be 'stepped down' to the lowest effective level **(*De Jong et al., 2013*)**.

Biological DMARDs (Biologics):

Biologics are a class of drugs which are genetically engineered, and have been shown to slow the destruction of joints and reduce inflammation more effectively than the conventional DMARDs. They can be used alone, or in combination with traditional DMARDs, particularly methotrexate **(*Smolen et al., 2016*)**.

Tumor necrosis factor alpha (TNFα) inhibitors are the first line biologic therapy. Currently, five agents that inhibit TNF-α are approved for the treatment of RA; infliximab, adalimumab, etanercept, certolizumab and golimumab **(Table 14)**. All of the TNF inhibitors have been shown to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs are typically used in combination with methotrexate. Etanercept, adalimumab, certolizumab, and golimumab have also been approved for use as monotherapy **(*Singh et al., 2016*)**.

The major side effect associated with these drugs is the increased risk for infection, including serious bacterial infections, opportunistic fungal infection, and reactivation of latent tuberculosis (TB). All patients should be screened for latent TB by tuberculin skin test before starting anti-TNF therapy **(*O'Dell, 2017*)**.

Other biologic and synthetic DMARDs include rituximab, abatacept, anakinra, tocilizumab, tofacitinib **(Table 15)**.

NSAIDS and Corticosteroids:

Drug therapy for RA may involve NSAIDs and oral, intramuscular or intra-articular corticosteroids for controlling pain and inflammation **(*McInnes and O'Dell, 2010*)**. Short-term glucocorticoids should be considered when initiating or changing DMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible **(*Smolen et al., 2017*)**.

Exercise and physical therapy:

Physical exercise improves quality of life and muscle strength in patients with RA. Exercise training programs have not been shown to have deleterious effects on RA disease activity, pain scores or radiographic joint damage **(*Hurkmans et al., 2009*)**.

Joint replacement:

Joint replacement is indicated when there is severe joint damage with good outcomes; only 4 to 13 percent of large joint replacements require revision within 10 years. The hip and knee are the most commonly replaced joints **(*Shourt et al., 2010*)**.

Table (13): Commonly used conventional DMARDs (*Ralston and McInnes, 2014*):

Drug	*Mechanism of action*	*Dose*	*Main side effects*	*Monitoring*
Methotrexate	Inhibits DNA synthesis and cell division	5–25 mg/wk	GI upset, stomatitis, rash, alopecia, hepatotoxicity, acute pneumonitis	CBC, LFTs Initially monthly, then every 3 months
Leflunomide	Blocks T-cell division	10–20 mg/day	Nausea, GI upset, rash, alopecia, hepatitis, hypertension	CBC, LFTs, BP Monthly
Hydroxy-chloroquine	Unknown	200– 400 mg/day	Rash, nausea, diarrhea, headache, corneal deposits, retinopathy (rare)	Visual acuity, fundoscopy Every year
Sulfasalazine	Unknown	2–4 g/day	Nausea, GI upset, rash, hepatitis, neutropenia, pancytopenia (rare)	CBC, LFTs Monthly for 3 months, then every 3 months

Table (14): TNFa Inhibitors (*Shah and Clair, 2015*):

Drug	*Mechanism of action*	*Dose*	*Main side effects*	*Monitoring*
Infliximab (*Remicade*®)	Inhibits TNFa	3 mg/kg IV at weeks 0-2-6, then every 8 weeks May increase dose up to 10 mg/kg every 4 weeks	▪ ↑ Risk bacterial, fungal infections ▪ Reactivation of latent TB ▪ ↑ Lymphoma risk (controversial) ▪ Drug-induced lupus ▪ Neurologic deficits	PPD skin test LFTs periodically
Adalimumab (*Humira*®)	Inhibits TNFa	40 mg SC / 2 weeks		PPD skin test
Etanercept (*Enbrel*®)	Inhibits TNFa	50 mg SC / week		PPD skin test
Certolizumab (*Cimzia*®)	Inhibits TNFa	400 mg SC at weeks 0-2-4 then 200 mg SC / 2 weeks		PPD skin test
Golimumab (*Simponi*®)	Inhibits TNFa	50 mg SC / month		PPD skin test

Table (15): Other Biologic and synthetic DMARDs (*Shah and Clair, 2015*):

Drug	*Mechanism of action*	*Dose*	*Main side effects*	*Monitoring*
Abatacept (*Orencia*®)	Inhibits co-stimulation of T cells by blocking CD28-CD80 interactions	125 mg SC / week	↑ Risk of infections	PPD skin test
Anakinra (*Kineret*®)	Interleukin 1 receptor antagonist	100 mg SC / daily	↑ Risk of infections Reactivation of latent TB Neutropenia	PPD skin test CBC
Rituximab (*Mabthera*®)	Monoclonal antibody against B-cells (CD20)	1000 mg IV weeks 0-2 May repeat course / 6 months	↑ Risk of infections Hepatitis B reactivation Cytopenias	CBC Viral hepatitis markers
Tocilizumab (*Actemra*®)	Interleukin 6 receptor antagonist	4-8 mg/kg / month	↑ Risk of infections Elevated LFTs Cytopenias, dyslipidemia	PPD skin test CBC, LFTs
Tofacitinib (*Xeljanz*®)	Inhibits JAK1 and JAK3	5 mg orally BID	↑ Risk of infections Elevated LFTs Neutropenia, dyslipidemia	PPD skin test CBC, LFTs

Table (16): The 2016 EULAR updated recommendations for management of rheumatoid arthritis (*Smolen et al., 2017*):

Overarching principles	
A	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
B	Treatment decisions are based on disease activity and other patient factors, such as progression of structural damage, comorbidities and safety issues.
C	Rheumatologists are the specialists who should primarily care for patients with RA.
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.
Recommendations	
1	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.
2	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.
3	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.
4	MTX should be part of the first treatment strategy.
5	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.

Table (16) (*continue*): The 2016 EULAR updated recommendations for management of rheumatoid arthritis (*Smolen et al., 2017*):

6	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.
7	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors, other csDMARDs should be considered.
8	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD or a tsDMARD should be considered; current practice would be to start a bDMARD.
9	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.
10	If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action.
11	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD.
12	If a patient is in persistent remission, tapering the csDMARD could be considered.

(*csDMARDs: conventional synthetic, bDMARDs: biologic, tsDMARD: targeted synthetic*)

Patients and Methods

Patients and Methods

This study was an observational cross sectional study including three hundred Egyptian patients (≥ 18 years old) diagnosed with rheumatoid arthritis (RA) according to the ACR/EULAR 2010 classification criteria (***Aletaha et al., 2010***). Patients were enrolled into the study from the rheumatology outpatient clinics at Ain Shams University Hospitals and Ahmed Maher Teaching Hospital, Cairo, Egypt, during the period from June 2015 till February 2017. A study done by ***El-Zanaty and Way in 2009*** on 11,126 apparently normal individuals was used to compare our results with the general population.

Exclusion Criteria:

- Patients younger than 18 years old.
- Patients with end stage renal disease on dialysis.
- Patients with other connective tissue diseases.

After approval of the ethical committee of the Faculty of Medicine, Ain Shams University, an informed written consent was obtained from each participant. Then, all participants were subjected to the following:

A) Medical History:

Full medical history was obtained from all participants including demographic data, risk factors for HCV transmission, duration and clinical manifestations of RA, current medications, and history of other diseases.

B) Clinical Examination:

Thorough clinical examination was performed with special emphasis on manifestations of rheumatoid arthritis and chronic liver diseases.

C) Assessment of RA disease activity:

Patients' disease activity was estimated using the Disease Activity Score (DAS28) **(*Prevoo et al., 1995*)**. The examined joints included; small joints of both hands (MCP and PIP joints), both wrists, elbows, shoulders and knees. Number of tender and swollen joints was calculated. The patients' global health was evaluated by the patient himself with a score ranging from 0 to 100 (0 means the best condition, while 100 means the worst). ESR was used. The score was calculated using the following formula:

$$(0.56 \times \sqrt{T}) + (0.28 \times \sqrt{S}) + (0.70 \times \ln ESR) + (0.014 \times PGH)$$

Interpretation of the DAS28 Score:

Score	Disease activity
≤ 2.6	Remission
> 2.6 – ≤ 3.2	Low
> 3.2 – ≤ 5.1	Moderate
> 5.1	High

D) Laboratory investigations:

- Complete blood count (CBC) by Beckman Coulter Counter.
- Erythrocyte sedimentation rate (ESR) by Westergren method.
- C - reactive protein (CRP) by Immunophelometry.
- Alanine aminotransferase (ALT).
- Aspartate aminotransferase (AST).
- Rheumatoid factor (IgM RF) by Immunophelometry.
- Anti-cyclic citrullinated peptide (Anti-CCP) when needed.

E) HCV Testing:

Sample collection and storage:

Approximately 7 ml of venous blood was collected from each participant into an EDTA tube. Each blood sample was centrifuged for 20 minutes at 800-1600 x g within 6 hours and plasma was separated into three labeled microvials and stored under (- 20 °C) till the time of testing.

Anti-HCV antibodies testing:

A third generation enzyme-linked immunosorbent assay (ELISA) (Enzygnost® Anti-HCV 4, Siemens, Germany) was used to detect antibodies to hepatitis C virus according to the manufacturer's protocol as follows:

Test Procedure:

Sample buffer, control, and tested samples were pipetted into the corresponding wells of the test plate. Then, the test plate was placed into the BEP® III automated test processing system. The following steps were performed automatically by the system:

- The plate was incubated for 30 minutes at 37 °C, and then all wells were aspirated. Each well was filled with approximately

0.3 mL diluted Washing Solution POD, and then the plate was aspirated. The wash cycle was repeated three times.

- 100 µL of Conjugate Working Solution was pipetted into each well, then the test plate was incubated for 30 minutes at 37 °C, and then washing was done as above.
- 75 µL of Chromogen Working Solution was pipetted into each well, and then the test plate was incubated at 18-25 °C for 30 minutes.
- 75 µL Stopping Solution POD was added to each well and kept for 30 minutes.
- The test plate was read at 450 nm within one hour. The recommended reference wavelength was 650 nm.
- Test results ≥ cut-off value, were considered reactive. All reactive test samples were tested again for confirmation.

HCV RNA Testing:

All samples positive for anti-HCV antibodies by ELISA were tested to detect the presence of HCV RNA by Real Time PCR (Artus HCV QS-RGQ assay, Qiagen®, Germany) **(*Paba et al., 2012*)**.

Step (1): Nucleic acid purification:

Nucleic acid purification was done using QIAsymphony SP, Qiagen®. A magnetic rod protected by a rod cover enters a well

containing the sample and attracts the magnetic particles. The magnetic rod cover is positioned above another well and the magnetic particles are released.

Test Procedure:

Test samples were prepared, placed into the sample carrier and loaded into the sample drawer of the machine. Information about the sample and the required test was entered into the machine software. Once the run started, all steps were fully-automated and it took about 2 hours for the process to complete. The Elute containing the purified nucleic acid was retrieved and stored.

Step (2): Nucleic acid amplification and detection:

Nucleic acid amplification and detection was done by Real-Time PCR (Rotor-Gene Q, Qiagen ®, Germany). The lower limit of detection of the Artus HCV QS-RGQ is 36 IU/ml.

Test Procedure:

30 µL of elute obtained from the previous step was transferred to the PCR tube and 30 µL of the master mix solution containing the primer was added. Then, the tube was placed in the Rotor-Gene Q cycler and the run was started. After the run was completed (in about 3.5 hours), the results were interpreted using the special software provided by the manufacturer.

Recombinant Immunoblot Assay (RIBA) testing:

Patients positive for anti-HCV antibodies by ELISA and negative for HCV RNA were tested again for anti-HCV antibodies by Recombinant Immunoblot Assay (RIBA) using commercial kits to exclude those with false positive ELISA **(*Janot and Courouce, 1990*)**.

Test Procedure:

The test is a three-stage test. In the first stage, the specimen was diluted and incubated with the strip. Antibodies specific to HCV, if present, would bind to the recombinant antigen and/or synthetic peptide bands on the strip. Removal of unbound plasma components was accomplished by aspiration and washing.

In the second stage, the strip was incubated in the presence of a peroxidase-labeled goat antihuman IgG conjugate. The conjugate should bind to the human IgG portion of the antigen-antibody complexes if present. Removal of unbound conjugate was accomplished by washing.

In the third stage, a colorimetric enzyme detection system was added. If bound conjugate was present, the enzymatic reaction would produce a black color. The visual band patterns were then interpreted.

Statistical Analysis

The collected data was entered into Microsoft Excel® and subjected to statistical analysis using EpiInfo® (Version 7.2, CDC, USA).

- Qualitative data were represented as frequencies and percentages.
- Chi-square test was used to calculate difference between qualitative variables in different groups.

$$\chi^2 = \sum \frac{(O-E)^2}{E}$$

(Σ = sum; O= observed value; E= expected value)

- Quantitative data were expressed as range and mean ± standard deviation.

I- Arithmetic Mean:

$$\bar{x} = \frac{\sum x}{n}$$

(Σx = sum of individual data; n = number of individual data)

II- Standard deviation (SD):

$$SD = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$$

(Σx = sum of data; Σx2 = sum of squares of data; n = number of data)

- Independent student's *t-test* was used to calculate difference between quantitative variables in normally distributed data.

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

($\bar{x1}$ = Mean of first set of values; $\bar{x2}$ = Mean of second set of values; S1 = Standard deviation of first set of values; S2 = Standard deviation of second set of values; n1 = Total number of values in first set; n2 = Total number of values in second set)

- The significance level for all the above mentioned statistical tests was done using *P-value*. *P-value* > 0.05 indicates non-significant results, while *P-value* ≤ 0.05 indicates significant results. *P-value* ≤ 0.001 indicates highly significant results.

Results

Results

The current study included 300 patients with RA, 268 females (89.3%) and 32 males (10.7%). Their age ranged between 18 to 89 years with a mean of 42.7±12 years. Disease duration ranged between less than 1 to 45 years with a mean of 6.2±7.4 years. 126 patients (42%) have been diagnosed with RA for 1 to 5 years, 36 patients (12%) for less than 1 year, and 22 patients (7.3%) for more than 20 years **(Table 17)**.

Most of the study participants were females (89.3%) and were living in urban areas (80% compared to 20% living in rural areas). The age group with the highest number of participants was the (40-49 y) group (29.3%); while there was only 1 participant aged below 20 years old **(Table 17)**.

As regard RA manifestations; the number of tender joints ranged between 0 and 28 with a mean of 10.8±8.2. The number of swollen joints ranged between 0 and 28 with a mean of 10.4±8.1 **(Table 18)**.

Table (17): Demographic characteristics of the studied RA patients:

		No. of patients (n=300)	*Percent*
Sex	**Female**	268	89.3%
	Male	32	10.7%
Age (years)	**Mean ± SD**	42.7 ± 12	
	Range	18 - 89	
	18-19	1	0.3%
	20-29	43	14.3%
	30-39	83	27.7%
	40-49	88	29.3%
	50-59	61	20.3%
	≥ 60	24	8%
RA disease duration (years)	**Mean ± SD**	6.2 ± 7.4	
	Range	1 - 45	
	<1	36	12%
	1-4	126	42%
	5-9	78	26%
	10-14	20	6.7%
	15-19	18	6%
	≥ 20	22	7.3%
Residence	**Urban**	240	80%
	Rural	60	20%

Table (18): Descriptive analysis of the commonest musculoskeletal manifestations among our studied RA patients (*n=300*):

	Range	*Mean ± SD*
Tender joints	0 – 28	10.8 ± 8.2
Swollen joints	0 – 28	10.4 ± 8.1

As for history of hepatic manifestations; only 8 patients (2.7%) had a history of jaundice, but none of the study participants had a history of ascites, hematemesis, or hepatic coma **(Table 19, Figure 10)**.

Table (19): History of hepatic manifestations among the studied RA patients (*n=300*):

	No. of patients	*Percent*
Jaundice	8	2.7%
Ascites	0	0%
Hematemesis	0	0%
Hepatic Coma	0	0%

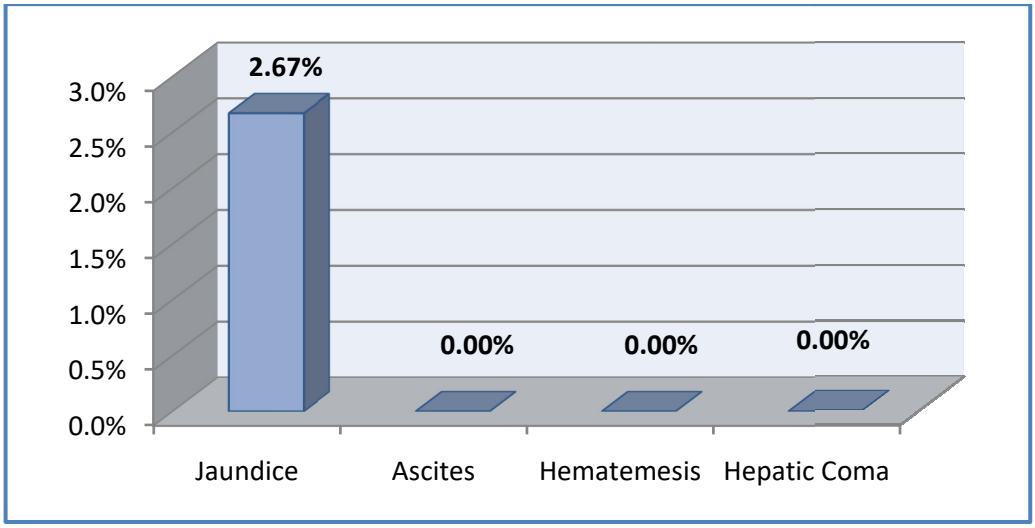


Figure (10): History of hepatic manifestations among the studied RA patients (*n=300*).

Thirty patients (10%) had diabetes mellitus, 38 patients (12.7%) had hypertension, 22 patients (7.3%) had cardiac diseases (ischemic heart disease, rheumatic heart disease or heart failure), 22 patients (7.3%) had lung diseases (interstitial lung disease or bronchial asthma)), 6 patients (2%) had renal diseases (renal stones, renal impairment, or UTI), and 4 patients (1.3%) had neurologic disease (stroke, transient ischemic attacks) **(Table 20, Figure 11)**.

Table (20): Associated diseases among the studied RA patients (*n=300*):

	No. of patients	*Percent*
Diabetes	30	10%
Hypertension	38	12.7%
Cardiac diseases	22	7.3%
Lung diseases	22	7.3%
Renal diseases	6	2%
Neurologic diseases	4	1.3%

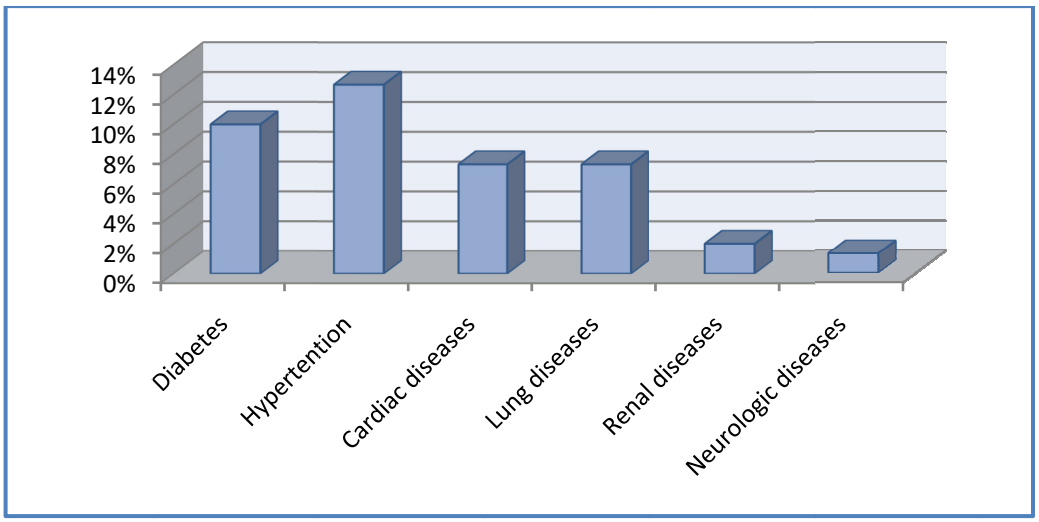


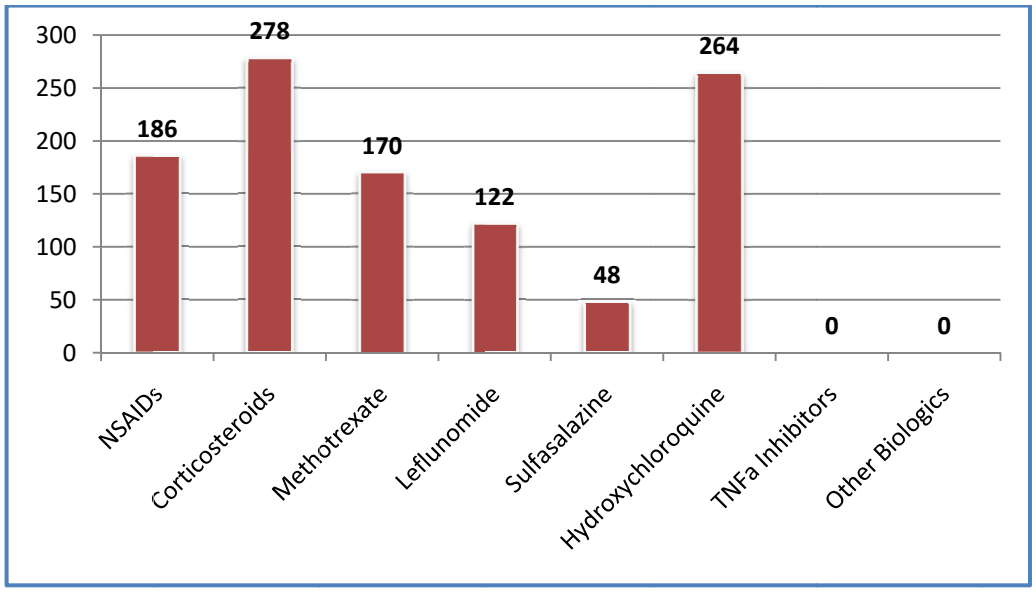
Figure (11): Other associated diseases in the studied RA patients.

Corticosteroids were the most commonly used medications by our studied population; used by 278 patients (92.7%). Hydroxychloroquine was the most commonly used DMARD (88% of patients), followed by methotrexate and leflunomide (56.7% and 40.7% of patients, respectively). None of the studied patients used TNFα Inhibitors or other biologic DMARDs before **(Table 21, Figure 12)**.

Table (21): Drugs used for treatment of RA among the studied patients (*n=300*):

Drugs	*No. of patients*	*Percent*
NSAIDs	186	62%
Corticosteroids	278	92.7%
Methotrexate	170	56.7%
Leflunomide	122	40.7%
Sulfasalazine	48	16%
Hydroxychloroquine	264	88%
TNFα Inhibitors	0	0%
Other Biologics	0	0%

(NSAIDs: Non-steroidal anti-inflammatory drugs, TNF: Tumor necrosis factor)



(NSAIDs: Non-steroidal anti-inflammatory drugs, TNF: Tumor necrosis factor)

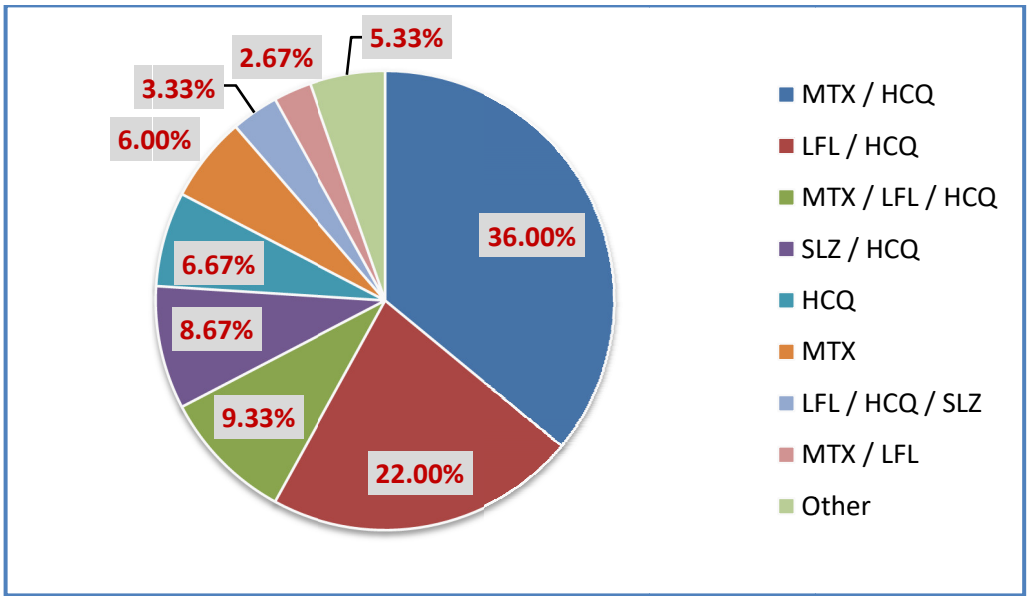
Figure (12): Drugs used for treatment of RA among the studied patients (*n=300*).

While the majority of our studied patients used a combination of different DMARDs, a few number (42/300) used a single drug (14% of patients). The most common combination was methotrexate and hydroxychloroquine, used by 108 patients (36%), followed by leflunomide and hydroxychloroquine, used by 66 patients (22%). Other combinations were used by 16 patients (5.3%) and included (Leflunomide alone, Leflunomide/Sulfasalazine, Methotrexate/Sulfasalazine, Methotrexate/Hydroxychloroquine/ Sulfasalazine, and Methotrexate/Leflunomide/Hydroxychloroquine/ Sulfasalazine) **(Table 22, Figure 13)**.

Table (22): The most common DMARDs combinations used by the studied population (*n=300*):

DMARDs combinations	*No. of patients*	*Percent*
Methotrexate / Hydroxychloroquine	108	36%
Leflunomide / Hydroxychloroquine	66	22%
Methotrexate/ Leflunomide / Hydroxychloroquine	28	9.3%
Sulfasalazine / Hydroxychloroquine	26	8.7%
Hydroxychloroquine	20	6.7%
Methotrexate	18	6%
Leflunomide / Hydroxychloroquine / Sulfasalazine	10	3.3%
Methotrexate/ Leflunomide	8	2.7%
Other	16	5.3%

(DMARDs: Disease modifying anti-rheumatic drugs)



(*MTX: Methotrexate, HCQ: Hydroxychloroquine, LFL: Leflunomide, SLZ: Sulfasalazine*)

Figure (13): The most common DMARDs combinations used by the studied population (*n=300*).

According to the DAS28 score; only 33 patients (11%) were in remission, 16 and 63 patients (5.3% and 21%) had low and moderate disease activity, respectively. The majority of patients (62.7%) had high disease activity. The total DAS28 Score ranged between 0.97 and 9.27 with a mean of 5.6±2 **(Table 23, Figure 14)**.

Table (23): RA disease activity as assessed by DAS28 Score among the studied RA patients (*n=300*):

Disease activity Score	*Mean ± SD*	*No.*	*Percent*
Remission (≤2.6)	1.92 ± 0.47	33	11%
Low disease activity (>2.6 - ≤3.2)	2.86 ± 0.12	16	5.3%
Moderate disease activity (>3.2 - ≤5.1)	4.25 ± 0.5	63	21%
High disease activity (>5.1)	6.98 ± 0.96	188	62.7%
	Mean ± SD	***Range***	
Total DAS28 Score	5.6 ± 2	0.97 – 9.27	

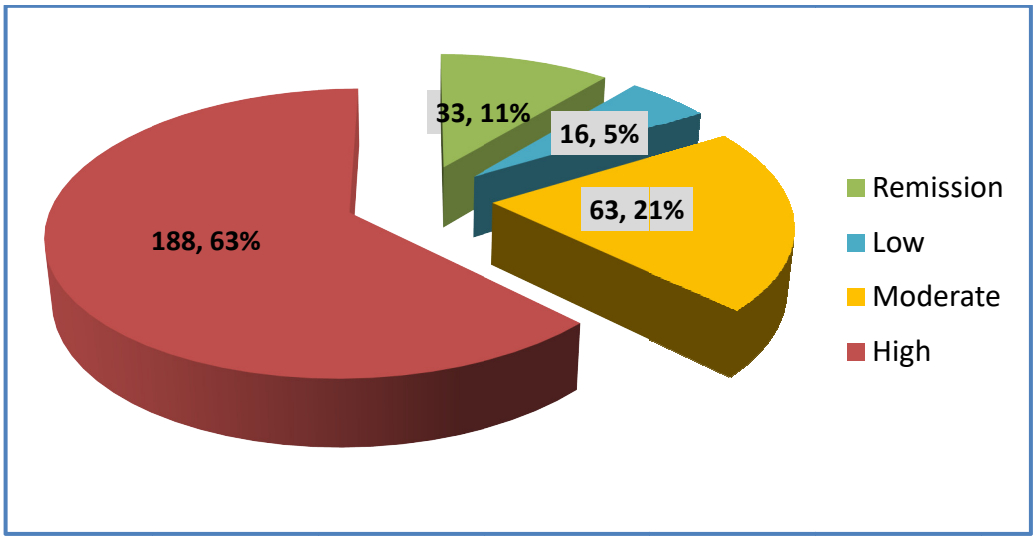


Figure (14): Assessment of patients' disease activity by DAS28 Score.

All patients included in our study were tested for RF, of which 59.3% were positive (178/300); while only 128 patients were tested for anti-CCP, of which 58 patients (45.3%) were positive **(Table 24)**.

Table (24): Results of Rheumatoid Factor and anti-CCP tests among the studied RA patients:

	No. of patients	***Percent***
Rheumatoid Factor *(n=300)*		
Negative	122	40.7%
Positive	178	59.3%
Anti-CCP *(n=128)*		
Negative	70	54.7%
Positive	58	45.3%

(Anti-CCP: Anti-cyclic citrullinated peptide)

Laboratory tests among our studied RA patients showed that Hemoglobin level ranged between 7 and 16 gm/dl with a mean of (12 ± 1.5). Platelets ranged between 112 and 649 $x10^3$ cells/mm^3 with a mean of (301 ± 92). ESR ranged between 4 and 145 with a mean of (46±26) **(Table 25)**. 26 patients (8.7%) had elevated ALT and 31 patients (10.3%) had elevated AST. ESR was elevated in 206 patients (68.7%). 47 patients (15.7%) had microcytic anemia, while 18 patients (6%) had normocytic anemia. Thrombocytosis was found in 126 patients (42%) **(Table 26)**.

Table (25): Results of routine laboratory tests among the studied RA patients:

	Normal range	*Range*	*Mean ± SD*
Hemoglobin (gm/dl)	Men: 13.5 – 17.5 Women: 12 – 15.5	7 – 15.9	12 ± 1.5
WBCs ($x10^3$ cells/mm^3)	4 – 11	3.3 – 20.3	7.1 ± 2.44
Platelets ($x\ 10^3$ cells/mm^3)	150 – 300	112 – 649	301 ± 91.76
ESR 1st hour (mm/hour)	Men: 0 – 22 Women: 0 – 29	4 – 145	45.8 ± 25.55
ALT (IU/ml)	< 32	6 – 80	21.1 ± 10
AST (IU/ml)	< 32	6 – 75	21.2 ± 9.3

(WBCs: White blood cells, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase)

Table (26): Abnormalities found in the routine laboratory tests (*n=300*):

	No. of patients	*Percent*
Elevated ALT	26	8.7%
Elevated AST	31	10.3%
Elevated ESR	206	68.7%
Microcytic Anemia	47	15. 7%
Normocytic Anemia	18	6%
Macrocytic Anemia	1	0.3%
Leukocytosis	15	5%
Leukopenia	7	2.3%
Thrombocytosis	126	42%
Thrombocytopenia	4	1.3%

(ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase)

All patients included in our study were tested for HCV antibodies by ELISA, of which 15% were positive (45/300). Patients positive for HCV antibodies were tested for HCV RNA by Real-Time PCR, of which 80% were positive (36/45). Patients positive for anti-HCV antibodies, but negative for HCV RNA (n=9) were tested again to confirm the presence of HCV antibodies by RIBA and all the 9 patients (100%) were positive. This means that 20% of the infected patients (9/45) cleared the virus spontaneously **(Table 27)**.

Table (27): Hepatitis C testing results of the studied RA patients:

	No. of patients	***Percent***
Results of anti-HCV antibodies testing by ELISA *(n=300)*		
Negative	255	85%
Positive	45	15%
Results of HCV RNA testing by Real-Time PCR*(n=45)*		
Negative	9	20%
Positive	36	80%
Results of anti-HCV antibodies testing by RIBA *(n= 9)*		
Negative	0	0%
Positive	9	100%

(ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction; RIBA: Recombinant immunoblot assay)

Of the 300 RA patients tested, 45 patients (15%) were positive for HCV antibodies, while 36 patients (12%) were positive for HCV RNA. Prevalence of HCV antibodies in females was 15.3%, while it was 12.5% in males. Patients who live in rural areas had a prevalence of HCV antibodies of 16.7%, while it was 14.6% in those living in urban areas. It also increased gradually with age to reach 50% in patients older than 60 years **(Table 28)**.

Table (28): Hepatitis C testing results of the studied RA patients according to their demographic characteristics (*n=300*):

	No. of patients	*HCV Abs +ve*		*HCV RNA +ve*	
		No. of pts	*Percent*	*No. of pts*	*Percent*
Total	300	45	15%	36	12%
Distribution by Sex					
Females	268	41	15.3%	32	11.9%
Males	32	4	12.5%	4	12.5%
Distribution by Age groups					
18-19	1	0	0%	0	0%
20-29	43	2	4.7%	2	4.7%
30-39	83	6	7.2%	5	6%
40-49	88	13	14.8%	11	12.5%
50-59	61	12	19.7%	8	13.1%
≥ 60	24	12	50%	10	41.7%
Distribution by Urban/Rural					
Urban	240	35	14.6%	28	11.7%
Rural	60	10	16.7%	8	13.3%

As regard risk factors for HCV transmission, blood transfusion, surgery, and dental procedures had statistically highly significant association ($p<0.001$) with HCV prevalence. Repeated injection also had a statistically significant association ($p<0.05$) with HCV prevalence **(Table 29)**.

Table (29): History of exposure to risk factors for HCV transmission by chi-square test:

Risk Factor		HCV Abs		HCV Abs Prevalence	χ^2	*P*	*Sig.*
		-ve	*+ve*				
Blood Transfusion	No	221	35	13.7%	89.7	**0.0000**	**HS**
	Yes	34	10	22.7%			
Surgery	No	175	27	13.4%	13.7	**0.0002**	**HS**
	Yes	80	18	18.4%			
Dental Procedure	No	219	23	9.5%	33.1	**0.0000**	**HS**
	Yes	36	22	37.9%			
Repeated injections	No	192	26	11.9%	5.91	**0.015**	**SIG**
	Yes	63	19	23.2%			
PAT	No	253	45	15.1%	0.36	0.55	NS
	Yes	2	0	0%			
Household contact	No	201	37	15.6%	0.27	0.60	NS
	Yes	54	8	12.9%			
Healthcare worker	No	253	45	15.1%	0.36	0.55	NS
	Yes	2	0	0%			

(Abs: antibodies, IV: Intravenous, PAT: Parentral antischistosomal therapy, χ^2: Chi-square, HS: highly significant (p-value ≤0.001), SIG: significant (p-value ≤0.05), NS: non-significant (p-value >0.05))

Comparison between the results of the current study and the Egyptian Demographic Health Survey 2008 (EDHS 2008) **(*El-Zanaty and Way, 2009*)** showed that there was no statistically significant difference (*p>0.05*) in the total prevalence of HCV antibodies (15% vs. 14.7%). When we compared the prevalence in the 20 – 59 years age group, it was significantly higher (*p<0.05*) in EDHS 2008 (17% vs. 12%) **(Table 30)**.

HCV prevalence was higher in females than males in the current study (15.3% vs. 12.5%), while it was higher in males in EDHS 2008 (17.4% vs. 12.2%), but the difference was not statistically significant (*p>0.05*) **(Table 30, Figure 15)**.

In both studies, HCV prevalence was higher in patients living in rural areas than urban areas (16.7% vs. 14.6% and 18% vs. 10.3%), but prevalence in urban areas was significantly higher (*p<0.05*) in the current study than the prevalence in urban areas in EDHS 2008 **(Table 30, Figure 16)**.

In both studies, HCV prevalence increased sharply with age, but it was significantly higher (*p<0.05*) in those aged between 40 and 60 years in EDHS 2008 **(Table 30, Figure 17)**.

Table (30): Comparison between HCV antibodies prevalence in the current study and EDHS 2008 by chi-square test:

	Current Study			*EDHS 2008*			χ^2	*P*
	Number tested	*HCV Abs +ve*		*Number tested*	*HCV Abs +ve*			
		No.	*%*		*No.*	*%*		
Total	300	45	15%	11,126	1,636	14.7%	0.02	0.89
Distribution by Sex								
Females	268	41	15.3%	5,828	711	12.2%	2.48	0.12
Males	32	4	12.5%	5,298	922	17.4%	0.53	0.47
Distribution by Age groups								
15-19	1	0	0%	1,995	82	4.1%		
20-29	43	2	4.7%	3,339	182	5.5%	0.05	0.82
30-39	83	6	7.2%	2,365	301	12.7%	2.21	0.14
40-49	88	13	14.8%	2,009	515	25.6%	5.28	**0.022**
50-59	61	12	19.7%	1,418	550	38.8%	9.07	**0.003**
≥ 60	24	12	50%					
20-59	275	33	12%	9,131	1,548	17%	4.68	**0.03**
Distribution by Urban/Rural								
Urban	240	35	14.6%	4,799	494	10.3%	4.48	**0.034**
Rural	60	10	16.7%	6,327	1,139	18%	0.07	0.79

(χ^2: Chi-square; EDHS: Egyptian Demographic and Health Survey)

Comparison between results of the current study and the Egyptian Health Issues Survey 2015 (EHIS 2015) **(*El-Zanaty and associates, 2015*)** showed that the total HCV antibodies prevalence was significantly higher ($p<0.05$) in the current study (15% vs. 10%). When we compared the prevalence in the 20 – 59 years age group, there was no statistically significant difference ($p>0.05$) between both studies (12% vs. 11.7%) **(Table 31)**.

HCV prevalence was higher in females than males in the current study (15.3% vs. 12.5%), while it was higher in males in EHIS 2015 (12.4% vs. 8.1%) with a statistically highly significant difference ($p<0.001$) **(Table 31, Figure 15)**.

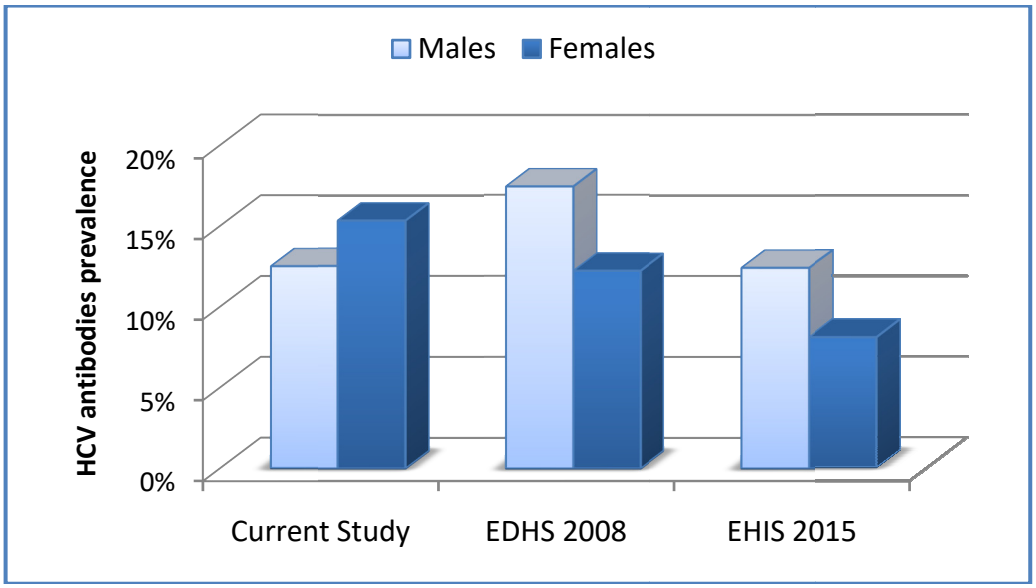
In both studies, HCV prevalence was higher in patients living in rural areas than urban areas (16.7% vs. 14.6% and 11.7% vs. 7.1%), but prevalence in urban areas was higher in the current study than the prevalence in urban areas in EHIS 2015 with a statistically highly significant difference ($p<0.001$) **(Table 31, Figure 16)**.

In both studies, HCV prevalence increased sharply with age, without any statistically significant difference ($p>0.05$) between both groups **(Table 31, Figure 17)**.

Table (31): Comparison between HCV antibodies prevalence in the current study and EHIS 2015 by chi-square test:

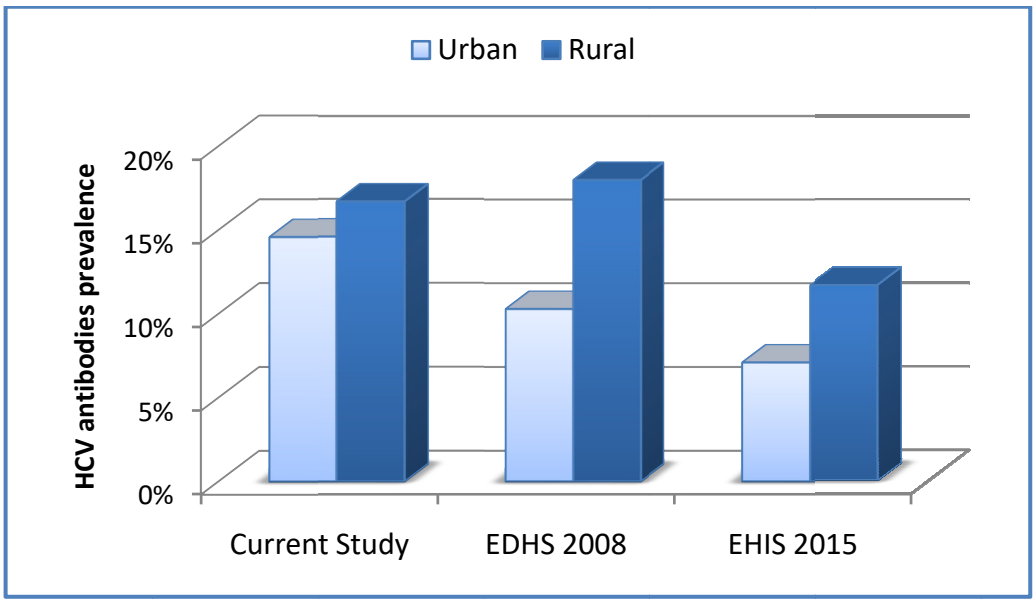
	Current Study			EHIS 2015			χ^2	P
	Number tested	HCV Abs +ve		Number tested	HCV Abs +ve			
		No.	%		No.	%		
Total	300	45	15%	16,003	1,600	10%	8.12	**0.004**
Distribution by Sex								
Females	268	41	15.3%	8,838	716	8.1%	17.7	**0.000**
Males	32	4	12.5%	7,165	888	12.4%	0.00	0.99
Distribution by Age groups								
15-19	1	0	0%	2,600	26	1%		
20-29	43	2	4.7%	4,301	166	3.9%	0.07	0.79
30-39	83	6	7.2%	3,888	296	7.6%	0.02	0.9
40-49	88	13	14.8%	2,873	399	13.9%	0.06	0.81
50-59	61	12	19.7%	2,341	713	30.5%	3.28	0.07
≥ 60	24	12	50%					
20-59	275	33	12%	13,403	1,574	11.7%	0.02	0.9
Distribution by Urban/Rural								
Urban	240	35	14.6%	5,958	423	7.1%	18.9	**0.000**
Rural	60	10	16.7%	10,045	1,175	11.7%	1.42	0.23

(χ^2: Chi-square; EHIS: Egyptian Health Issues Survey)



(EDHS: Egyptian Demographic and Health Survey, EHIS: Egyptian Health Issues Survey)

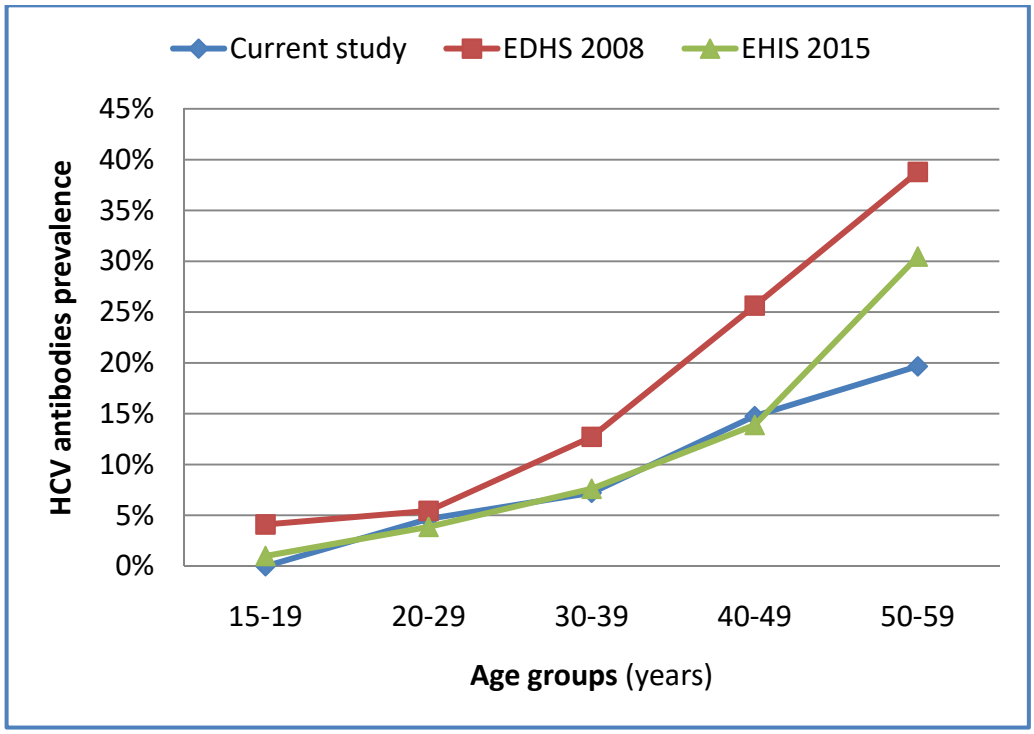
Figure (15): Comparison between HCV antibodies prevalence in the current study, EDHS 2008 and EHIS 2015 by sex.



(EDHS: Egyptian Demographic and Health Survey, EHIS: Egyptian Health Issues Survey)

Figure (16): Comparison between HCV antibodies prevalence in the current study, EDHS 2008 and EHIS 2015 by residence (rural / urban).

When comparing HCV antibodies prevalence in different age groups in the current study, EDHS 2008 and EHIS 2015, prevalence increased sharply with age. In the current study, HCV antibodies prevalence was remarkably high in patients above 60 years as it reached 50%. We couldn't compare this finding with EDHS 2008 or EHIS 2015 as they didn't include patients above 60 years (**Figure 8)**.



(EDHS: Egyptian Demographic and Health Survey, EHIS: Egyptian Health Issues Survey)

Figure (17): Comparison between HCV antibodies prevalence in the current study, EDHS 2008 and EHIS 2015 by age groups.

There was a statistically highly significant difference ($p<0.001$) in the mean age and disease duration in the HCV antibodies positive group (51.1 vs. 41.2 and 11.7 vs. 5.2 years, respectively **(Table 32)**. On the other hand, no statistically significant difference ($p>0.05$) was found regarding sex and residence (urban/rural) between both groups **(Table 33, Figure 18)**.

Table (32): Comparison between HCV antibodies negative and positive RA patients according to demographic characteristics by student's *t* test:

		HCV Abs -ve *(n= 255)*	***HCV Abs +ve*** *(n= 45)*	***T***	***P***	***Sig.***
Age *(years)*	*Range*	18 – 89	24–72	5.27	**<0.0001**	**HS**
	Mean ± SD	41.2 ± 11.5	51.1 ± 12.6			
Disease duration *(years)*	*Range*	0 – 25	0 – 45	5.74	**<0.0001**	**HS**
	Mean ± SD	5.2 ± 5.5	11.7 ± 12.8			

Table (33): Comparison between HCV antibodies negative and positive RA patients according to demographic characteristics by chi-square test:

		HCV Abs -ve *(n= 255)*		***HCV Abs +ve*** *(n= 45)*		χ^2	***P***	***Sig.***
		No.	***%***	***No.***	***%***			
Sex	*Male*	28	11.0%	4	8.9%	0.18	0.68	NS
	Female	227	89.0%	41	91.1%			
Residence	*Urban*	205	80.4%	35	77.8%	0.16	0.69	NS
	Rural	50	19.6%	10	22.2%			

(T: t-test, χ^2: Chi-square, P: p-value, Sig.: significance)

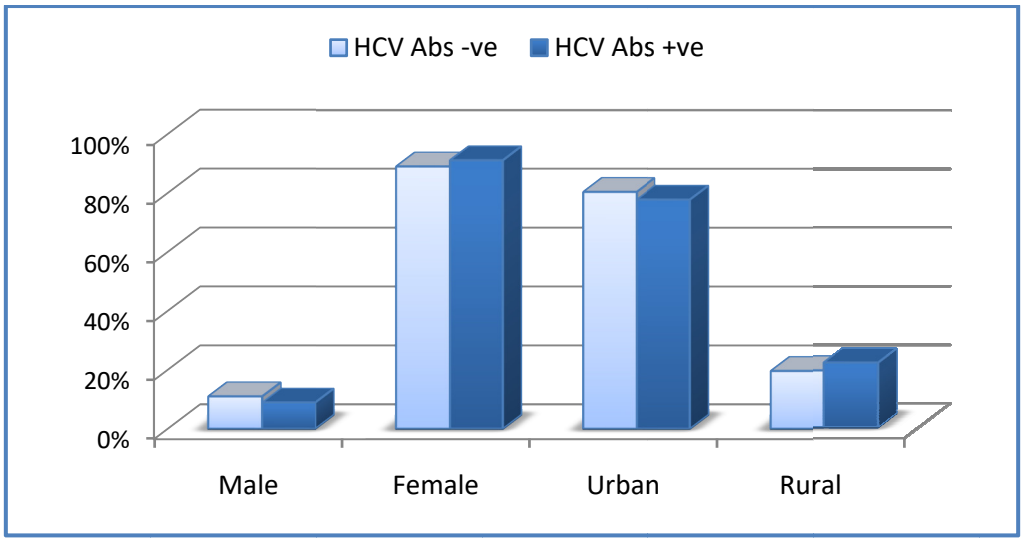


Figure (18): Comparison between RA patients with negative and positive HCV antibodies as regard some demographic characteristics.

Comparison between RA patients with negative and positive HCV antibodies according to the mean DAS28 Score and grade of disease activity showed no statistically significant difference (*p>0.05*) **(Table 34, Figure 19)**.

Table (34): Comparison between RA patients with negative and positive HCV antibodies as regard disease activity assessed by DAS28 Score by student's *t* test:

		HCV Ab -ve (n= 255)		HCV Ab +ve (n= 45)		*T*	*P*	*Sig.*
DAS28 Score	*Range*	0.97 - 9.27		1.85 - 8.96		1.12	0.26	NS
	Mean ± SD	5.7 ± 2		5.3 ± 2.2				
Disease Activity		***No.***	***%***	***No.***	***%***			
	Remission	26	10.2%	7	15.6%	1.43	0.15	NS
	Low activity	12	4.7%	4	8.9%			
	Moderate activity	54	21.2%	9	20.0%			
	High activity	163	63.9%	25	55.6%			

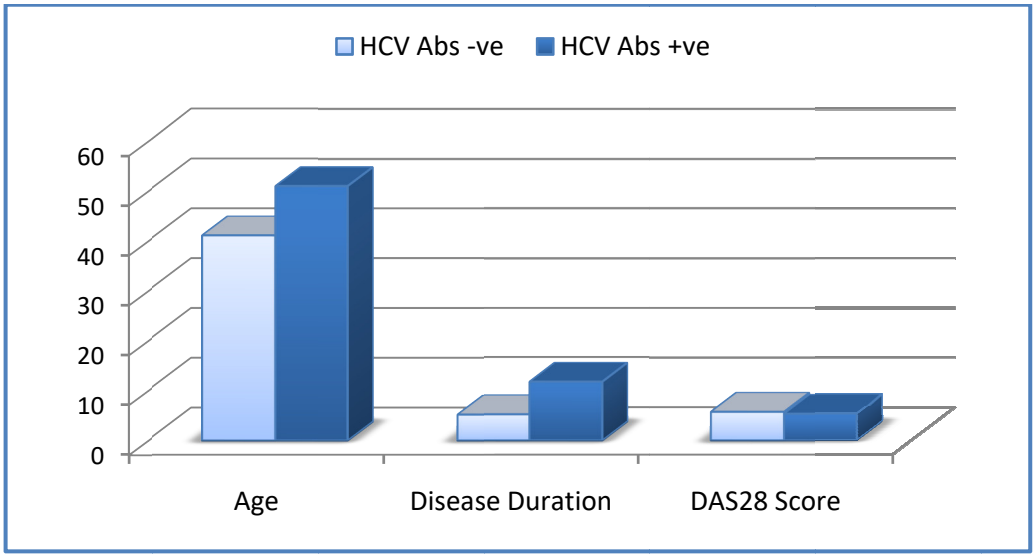


Figure (19): Comparison between RA patients with negative and positive HCV antibodies by the mean age, RA disease duration, and DAS28 Score.

There was no statistically significant difference ($p>0.05$) between both groups as regard to history of jaundice **(Table 35, Figure 20)**.

There was a statistically highly significant difference ($p<0.001$) in the prevalence of lung diseases among patients positive for HCV antibodies (24.4% vs. 4.3%), however, the difference was not statistically significant ($p>0.05$) between both groups as regard the prevalence of diabetes, hypertension, cardiac and renal diseases **(Table 35, Figure 20)**.

Table (35): Comparison between RA patients with negative and positive HCV antibodies as regard history of hepatic manifestations and associated diseases by chi-square test:

Variable	*HCV Abs -ve (n= 255)*		*HCV Abs +ve (n= 45)*		χ^2	*P*	*Sig.*
	No.	*%*	*No.*	*%*			
Jaundice	6	2.4%	2	4.4%	0.64	0.43	NS
Diabetes	24	9.4%	6	13.3%	0.65	0.42	NS
Hypertension	30	11.8%	8	17.8%	1.25	0.26	NS
Cardiac diseases	20	7.8%	2	4.4%	0.65	0.42	NS
Lung diseases	11	4.3%	11	24.4%	22.8	**0.0000**	**HS**
Renal diseases	4	1.6%	2	4.4%	1.61	0.20	NS
Neurologic diseases	4	1.6%	0	0.0%	0.72	0.40	NS

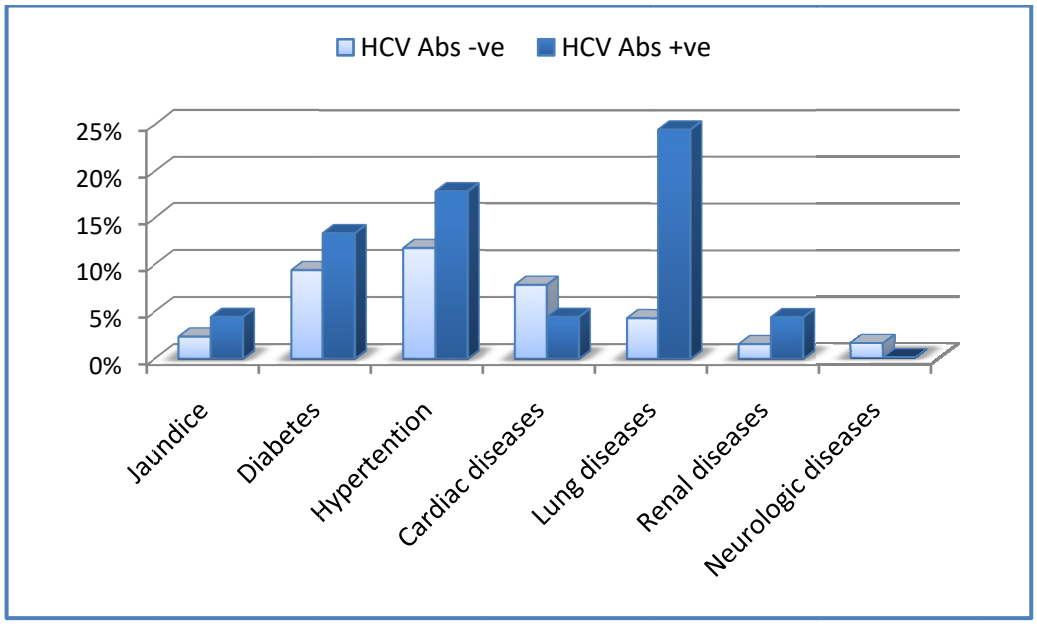


Figure (20): Comparison between RA patients with negative and positive HCV antibodies as regard history of hepatic manifestations and other associated diseases.

As regard the medications used for treatment of RA among our study population, there was a statistically highly significant ($p<0.001$) decrease in the use of NSAIDs and methotrexate, while there was a statistically highly significant ($p<0.001$) increase in the use of sulfasalazine in patients with positive HCV antibodies. Moreover, there was no statistically significant difference ($p>0.05$) in the use of steroids, leflunomide and hydroxychloroquine between both groups **(Table 36, Figure 21)**.

Table (36): Comparison between RA patients with negative and positive HCV antibodies as regard drug therapy for RA by chi-square test:

Drugs	*HCV Ab -ve (n= 255)*		*HCV Ab +ve (n= 45)*		χ^2	*P*	*Sig.*
	No.	*%*	*No.*	*%*			
NSAIDs	173	67.8%	13	28.9%	24.6	**0.0000**	**HS**
Corticosteroids	235	92.2%	43	95.6%	0.65	0.42	NS
Methotrexate	156	61.2%	14	31.1%	14.1	**0.0002**	**HS**
Leflunomide	103	40.4%	19	42.2%	0.05	0.82	NS
Sulfasalazine	30	11.8%	18	40.0%	22.7	**0.0000**	**HS**
Hydroxy-chloroquine	222	87.1%	42	93.3%	1.43	0.23	NS

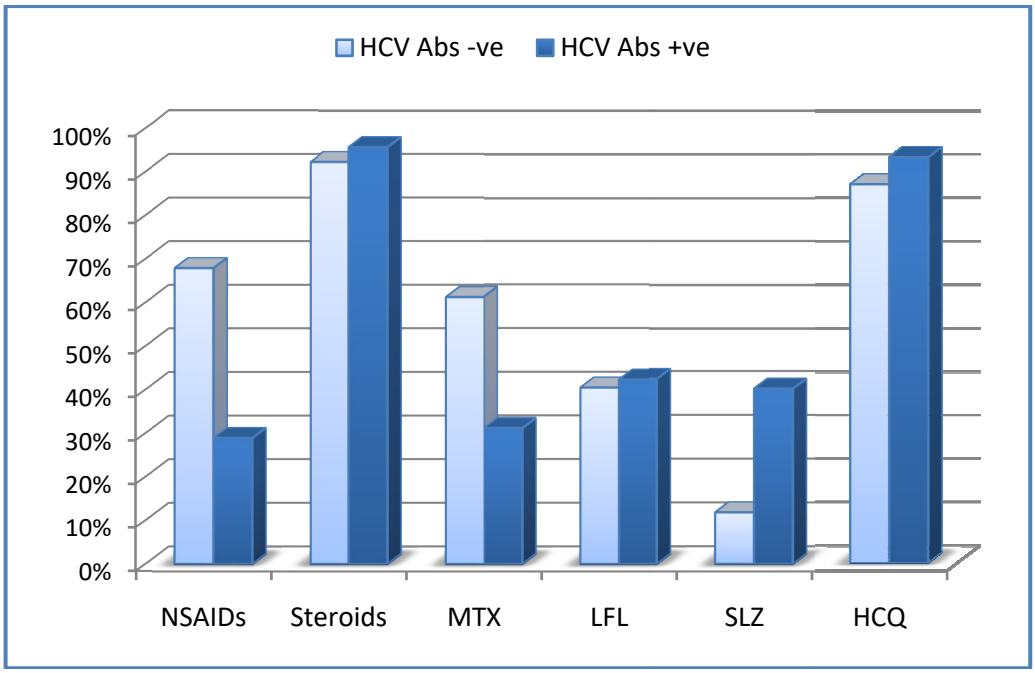


Figure (21): Comparison between RA patients with negative and positive HCV antibodies as regard drug therapy for RA.

Rheumatoid factor positivity was much higher with a statistically highly significant difference ($p<0.001$) in patients positive for HCV antibodies (82.2% vs. 55.3%). On the other hand, there was no statistically significant difference ($p>0.05$) as regard anti-CCP results between both groups **(Table 37, Figure 22)**.

Table (37): Comparison between RA patients with negative and positive HCV antibodies as regard RF and anti-CCP by chi-square test:

		HCV Abs -ve (n= 255)		*HCV Abs +ve (n= 45)*		χ^2	*P*	*Sig.*
		No.	*%*	*No.*	*%*			
Rheumatoid Factor	*Negative*	114	44.7%	8	17.8%	11.5	**0.0007**	**HS**
	Positive	141	55.3%	37	82.2%			
Anti-CCP	*Negative*	58	54.2%	12	57.1%	0.06	0.80	NS
	Positive	49	45.8%	9	42.9%			

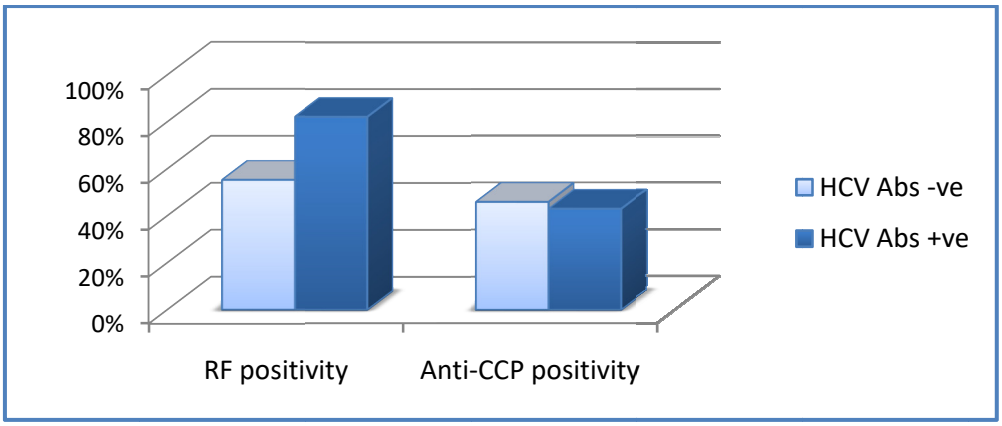


Figure (22): Comparison between RA patients with negative and positive HCV antibodies as regard RF and anti-CCP.

Patients positive for HCV antibodies had a statistically highly significant increase ($p<0.001$) in ALT and AST levels and a significant increase ($p<0.05$) in hemoglobin level. There was no statistically significant difference ($p>0.05$) as regard other laboratory test results between both groups **(Table 38)**.

Table (38): Comparison between RA patients with negative and positive HCV antibodies as regard some laboratory data by student's *t* test:

	HCV Abs -ve *(n= 255)*		***HCV Abs +ve*** *(n= 45)*		***T***	***P***	***Sig.***
	Range	***Mean ± SD***	***Range***	***Mean ± SD***			
Hb *(gm/dl)*	7 - 15.9	11.9 ± 1.5	8.9 - 15.9	12.5 ± 1.6	2.45	**0.015**	**SIG**
WBCs $x10^3$ *(cells/mm^3)*	3.3 - 20.3	7.1 ± 2.5	4 - 14.1	7.6 ± 2.2	1.31	0.19	NS
PLT $x10^3$ *(cells/mm^3)*	112 - 641	302 ± 88	129 - 649	293 ± 111	0.62	0.54	NS
ESR 1st hour *(mm/hour)*	4 - 145	45.8 ± 25.8	10 - 105	45.8 ± 24.4	0.01	0.99	NS
ALT *(IU/ml)*	8 - 51	20 ± 7.5	6 – 80	27.2 ± 17.7	4.61	**<0.0001**	**HS**
AST *(IU/ml)*	6 - 38	19.9 ± 6.6	10 – 75	29 ± 16.2	6.45	**<0.0001**	**HS**

(Hb: Hemoglobin, WBCs: White blood cells, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase)

The mean disease duration was higher in the HCV RNA negative group, who succeeded to clear the virus, than the positive group (16 vs. 10.7 years), but the difference was not statistically significant ($p>0.05$). Moreover, there was no statistically significant difference ($p>0.05$) as regard age, sex and residence (urban/rural) between both groups **(Table 39, Table 40)**.

Table (39): Comparison between RA patients with negative and positive HCV RNA according to demographic characteristics by student's *t* test:

		HCV RNA -ve *(n= 9)*	***HCV RNA +ve*** *(n= 36)*	***T***	***P***	***Sig.***
Age *(years)*	*Range*	36 - 70	24 - 72	0.44	0.66	NS
	Mean ± SD	52.8 ± 11.3	50.7 ± 13.1			
Disease duration	*Range*	0 - 45	0 - 45	0.16	0.88	NS
	Mean ± SD	16 ± 14.2	10.7 ± 12.4			

Table (40): Comparison between RA patients with negative and positive HCV RNA according to demographic characteristics by chi-square test:

		HCV RNA -ve *(n= 9)*		***HCV RNA +ve*** *(n= 36)*		χ^2	**P**	**Sig.**
		No.	***%***	***No.***	***%***			
Sex	*Male*	0	0.0%	4	11.1%	1.08	0.29	NS
	Female	9	100.0%	32	88.9%			
Residence	*Urban*	7	77.8%	28	77.8%	0	1	NS
	Rural	2	22.2%	8	22.2%			

Comparison between HCV RNA negative and positive patients as regards RA disease activity showed that there was no statistically significant difference (p>0.05) between both groups **(Table 41)**.

Table (41): Comparison between RA patients with negative and positive HCV RNA as regard RA disease activity by student's *t* test:

		HCV RNA -ve *(n= 9)*		***HCV RNA +ve*** *(n= 36)*		***T***	***P***	***Sig.***
DAS28 Score	*Range*	2.38 - 8.62		1.85 - 8.96		0.14	0.89	NS
	Mean ± SD	5.2 ± 2.4		5.3 ± 2.1				
Disease Activity		***No.***	***%***	***No.***	***%***			
	Remission	2	22.2%	5	13.9%	0.46	0.65	NS
	Low activity	1	11.1%	3	8.3%			
	Moderate activity	1	11.1%	8	22.2%			
	High activity	5	55.6%	20	55.6%			

Jaundice was the only manifestation of hepatic affection found in our studied patients and it was slightly higher in patients positive for HCV RNA, but the difference was not statistically significant (*p>0.05*) **(Table 42)**.

There was no statistically significant difference (*p>0.05*) as regard prevalence of diabetes, hypertension, cardiac, lung, and renal diseases between both groups **(Table 42)**.

Table (42): Comparison between RA patients with negative and positive HCV RNA as regard history of hepatic manifestations and other associated diseases by chi-square test:

	HCV RNA -ve *(n= 9)*		***HCV RNA +ve*** *(n= 36)*		χ^2	***P***	***Sig.***
	No.	***%***	***No.***	***%***			
Jaundice	0	0.0%	2	5.6%	0.52	0.47	NS
Diabetes	1	11.1%	5	13.9%	0.05	0.83	NS
Hypertension	2	22.2%	6	16.7%	0.15	0.70	NS
Cardiac diseases	1	11.1%	1	2.8%	1.18	0.28	NS
Lung diseases	3	33.3%	8	22.2%	0.48	0.49	NS
Renal diseases	1	11.1%	1	2.8%	1.18	0.28	NS

As regard the medications used for treatment of RA, there was no statistically significant difference (*p>0.05*) in the use of these medications between both groups **(Table 43)**.

Table (43): Comparison between RA patients with negative and positive HCV RNA as regard drug therapy for RA by chi-square test:

Drugs	*HCV RNA -ve (n= 9)*		*HCV RNA +ve (n= 36)*		χ^2	*P*	*Sig.*
	No.	*%*	*No.*	*%*			
NSAIDs	4	44.4%	9	25.0%	1.33	0.25	NS
Corticosteroids	9	100%	34	94.4%	0.52	0.47	NS
Methotrexate	5	55.6%	9	25.0%	3.14	0.08	NS
Leflunomide	3	33.3%	16	44.4%	0.36	0.55	NS
Sulfasalazine	3	33.3%	15	41.7%	0.21	0.65	NS
Hydroxychloroquine	8	88.9%	34	94.4%	0.36	0.55	NS

There was no statistically significant difference ($p>0.05$) in the results of rheumatoid factor and anti-CCP tests between both groups. Three patients in the HCV RNA negative group were tested for Anti-CCP and all of them were negative; in contrast, 18 patients in the positive group were tested and 50% were positive **(Table 44, Figure 23)**.

Table (44): Comparison between RA patients with negative and positive HCV RNA as regard RF and anti-CCP results by chi-square test:

		HCV RNA -ve		HCV RNA +ve		χ^2	P	Sig.
		No.	%	No.	%			
Rheumatoid Factor (n= 45)	Negative	2	22.2%	6	16.7%	0.15	0.7	NS
	Positive	7	77.8%	30	83.3%			
Anti-CCP (n= 21)	Negative	3	100.0%	9	50.0%	2.63	0.11	NS
	Positive	0	0.0%	9	50.0%			

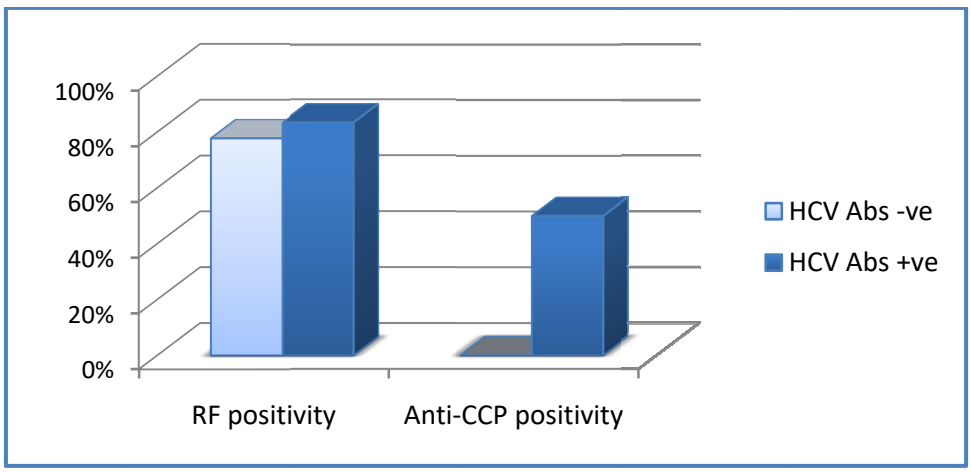


Figure (23): Comparison between RA patients with negative and positive HCV RNA as regard RF and anti-CCP results.

Comparison between HCV RNA negative and positive RA patients as regards results of routine laboratory tests showed that there was no statistically significant difference ($p>0.05$) in test results between both groups **(Table 45)**.

Table (45): Comparison between RA patients with negative and positive HCV RNA as regard results of routine laboratory tests by student's *t* test:

	HCV RNA -ve *(n= 9)*		***HCV RNA +ve*** *(n= 36)*		***T***	***P***	***Sig.***
	Range	***Mean ± SD***	***Range***	***Mean ± SD***			
Hb *(gm/dl)*	10.1 - 15	12 ± 1.6	8.9 - 15.9	12.6 ± 1.6	1.03	0.31	NS
WBCs $x10^3$ *(cells/mm^3)*	4.8 - 13.3	8.2 ± 2.4	4 - 14.1	7.4 ± 2.2	0.92	0.36	NS
PLT $x10^3$ *(cells/mm^3)*	161 - 433	287 ± 88	129 - 649	295 ± 117	0.18	0.86	NS
ESR 1^{st} hour *(mm/hour)*	18 - 103	48.6 ± 29.7	10 - 105	45.1 ± 23.3	0.38	0.70	NS
ALT *(IU/ml)*	6 - 80	27.4 ± 22.2	9 - 77	27.1 ± 16.8	0.46	0.96	NS
AST *(IU/ml)*	10 - 48	28.6 ± 15.2	10 - 75	29.1 ± 16.7	0.86	0.93	NS

(Hb: Hemoglobin, WBCs: White blood cells, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase)

Discussion

Discussion

HCV is one of the main problems facing the Egyptian healthcare system. Egypt has the highest HCV prevalence in the world, estimated to be 15% in some studies. This Egyptian HCV epidemic has historic causes; as many studies blame PAT campaigns, carried out by the health authorities in the sixties and seventies, to be the cause **(*Frank et al., 2000*)**. In these campaigns, intravenous injection of tartar emetic was used to treat schistosomiasis. Glass syringes were reused and improperly sterilized between patients, which caused mass transmission of hepatitis C. However, this epidemic has not come to its end, as many studies reported that there is still ongoing transmission **(*Miller & Abu-Raddad, 2010*)**.

Many studies were done to study the epidemiology of HCV in Egypt, including HCV prevalence, incidence and risk factors associated with its transmission. These studies estimated the prevalence of HCV in the general population, populations at high or intermediate risk of exposure, and among special clinical populations. All these studied showed an exceptionally high HCV prevalence in Egypt when compared to other countries **(*Mohamoud et al., 2013*)**.

Despite this unique HCV epidemic, few studies were done to estimate the prevalence of HCV in patients with RA in Egypt. Patients with RA are more exposed to healthcare services and invasive procedures as repeated injections and intra-articular injections, which are a major risk for HCV transmission if the proper antiseptic measures are not followed **(*El Garf et al., 2012*)**.

Moreover, there is a complex relationship between RA and HCV. ***Su and colleagues in 2014*** reported that chronic HCV infection alone was significantly associated with an increased risk for RA. ***Cacopardo et al. in 2013*** published a case report presenting a patient who developed RA 9 weeks after treatment of hepatitis C with Peg-IFN and ribavirin.

The prevalence of HCV antibodies in our studied RA patients was 15%. This high prevalence may be explained by increased exposure to HCV transmission, especially through the iatrogenic route, in RA patients. This prevalence is nearly equal to HCV prevalence in the Egyptian general population reported by ***El-Zanaty and Way in 2009*** (14.7%) in EDHS 2008, but it is higher than the prevalence estimated by ***El-Zanaty and associates in 2015*** (10%) in EHIS 2015.

In the current study, EDHS 2008, and EHIS 2015, HCV prevalence increased sharply with age. This supports the theory of an epidemic HCV transmission that took place in the sixties and seventies due to PAT campaigns and other iatrogenic exposures (***Mohamoud et al., 2013***). The difference in HCV prevalence between the 3 studies may be due to the different age of patients included in these studies. While our study included patients with ages ranging between 18 and 89 years, EDHS 2008 and EHIS 2015 included patients aged 15-59 years. When we compared HCV prevalence in the 20-59 years age group in the 3 studies, it was 12% in the current study, 17% in EDHS 2008, and 11.7% in EHIS 2015. In this case, the prevalence in the current study is nearly similar to EHIS 2015 and lower than EDHS 2008.

The prevalence of HCV antibodies was higher in females than males in our study (15.3% vs. 12.5%), while it was higher in males in EDHS 2008 and EHIS 2015 (17.4% vs. 12.2% and 12.4 vs. 8.1). This may be attributed to the relatively small number of male patients included in our study as RA is more prevalent in females (9:1) (***El-Zorkany et al., 2016***).

In the current study, EDHS 2008, and EHIS 2015, HCV antibodies prevalence was higher in patients living in rural areas than those living in urban areas (16.7% vs. 14.6%, 18% vs. 10.3%, and 11.7% vs. 7.1% , respectively). This is nearly a constant finding

in all epidemiologic studies done on HCV in Egypt. Schistosomiasis was more prevalent among farmers living in rural areas and PAT campaigns were performed mainly in rural areas and may have caused this large reservoir of HCV infection. Low standard of healthcare services and other traditional practices may be another factor **(*Frank et al., 2000*)**.

Many risk factors are associated with HCV transmission. Blood transfusion was a major risk factor in Egypt till 1994, when screening of blood donations for HCV was started **(*Moftah, 2002*)**. IV drug use is another important risk factor, but its role in Egypt is limited **(*Miller et al., 2015*)**. Many reports point to iatrogenic transmission as the main cause of this high HCV prevalence in Egypt **(*Paez et al., 2010*)**. The role of sexual and intra-familial transmission is controversial **(*Magder et al., 2005; Mohamed et al., 2005*)**.

In the present study, HCV antibodies prevalence was significantly higher ($p<0.001$) in those who had a history of previous blood transfusion (22.7% vs. 13.7%). Iatrogenic exposures like surgery, dental procedures and repeated injections also had a significant association ($p<0.05$) with increased HCV prevalence. Household contact was not associated with higher HCV prevalence ($p>0.05$). None of our studied patients had a history of IV drug use, and only 2 patients had a history of PAT.

After reviewing other Egyptian studies that estimated the prevalence of HCV antibodies in patients with RA, we found the same high prevalence as the current study. In a study published by ***El Garf et al. in 2012***, 157 patients admitted to rheumatology department were tested for HCV antibodies. Only 17 of those patients had RA and 3 of them (17.6%) were positive for HCV antibodies.

In another Egyptian study done by ***Mahmoud et al. in 2011***, 110 RA patients were tested for HCV antibodies, of which, 22 patients (20%) were positive. HCV antibodies prevalence increased sharply with age and the highest prevalence was found in patients older than 60 years (36.4%), which is consistent with findings in the current study.

A cross sectional, multi-center, international study (COMORA), done by ***Dougados et al. in 2014***, included 3920 patients with RA from 17 countries to study the prevalence of co-morbidities associated with RA. The study included 308 Egyptian RA patients, in which HCV prevalence was much higher than patients from other countries (6.8% vs. 1.7%) **(*El-Zorkany et al., 2016*)**.

On reviewing studies that estimated HCV prevalence in patients with RA in other countries, a much lower prevalence was

reported. ***Skinner-Taylor et al. in 2016*** evaluated the records of 960 RA patients in an area non-endemic for HCV in Mexico. 275 patients (28.6%) were tested before for HCV, of which only one patient (0.36%) was positive.

In study published by ***Agmon-Levin et al. in 2009***, sera from 1322 patients with 18 different autoimmune diseases (AID) and from 236 healthy matched controls were collected from referral centers in Europe and Latin America and tested for HCV antibodies. HCV antibodies were detected in 115/1322 (8.7%) of patients with AID and 0.4% of the controls. Only 95 patients had RA, none of them (0%) tested positive for HCV antibodies.

In France, ***Maillefert and colleagues in 2002*** evaluated 309 patients with RA for the prevalence of HCV infection and found that only two patients (0.65%) were positive for HCV antibodies and one for HCV RNA. Similarly, ***Guennoc and colleagues in 2009*** evaluated the prevalence of HCV and HBV in patients with recent-onset polyarthritis suggestive of RA and stated that the prevalence of HCV antibodies was 0.86% (7/813).

Furthermore, a study done by ***Barbosa and colleagues in 2005***, including 367 patients with rheumatic diseases from Brazil, reported that the overall HCV antibodies prevalence was 1.9% (7/367), while the prevalence in patients with RA was 3.4% (3/89).

All the seven patients, positive for HCV antibodies, were also positive for HCV RNA.

In addition, ***Yilmaz and colleagues in 2014*** evaluated 1517 RA patients in Turkey and HCV antibodies prevalence was 1.1% (17/1517), while the prevalence in the general population was 0.95% according to a nationwide study.

Spontaneous Clearance of HCV occurs in around 15-30% of acute infections. Several host, viral and environmental factors are determinants of spontaneous clearance **(*Kong et al., 2014*)**. Female gender, young age at the time of infection, aboriginal ethnicity and a history of icteric hepatitis are reported to be associated with increased spontaneous clearance, while African-American ethnicity, excess alcohol and illicit drug use are associated with low viral clearance rates **(*Grebely et al., 2014*)**. Many host genetic factors are associated with spontaneous clearance of HCV. The most important genetic factor is single-nucleotide polymorphisms (SNPs) around IL28B gene **(*Balagopal et al., 2010*)**.

In our study, HCV RNA prevalence was 12%, compared to 9.8% in the EDHS 2008 **(*El-Zanaty and Way, 2009*)** and 7% in the EHIS 2015 **(*El-Zanaty and associates, 2015*)**. This means that HCV clearance occurred in 20% of the cases in our study, 33.3% in the EDHS 2008, and 30% in the EHIS 2015. A strong host immune

response (innate and adaptive) is important for spontaneous HCV clearance. The lower rate of HCV clearance in our studied patients may be explained by the immune suppression caused by the disease itself, or by medications **(*Diepolder, 2009*)**. Interestingly, 92.7% of our studied patients (278/300) used corticosteroids for management of their RA disease.

Most of our studied RA patients had disease duration longer than one year (88%). The mean disease duration was 6.2±7.4 years and it was significantly longer ($p<0.001$) in patients positive for HCV antibodies (11.7±12.8 vs. 5.2±5.5 years). The same finding was reported in a study published by ***Mahmoud and colleagues in 2011***. This could be explained by the fact that the longer the disease duration, the more the risk for iatrogenic exposure to HCV infection **(*Miller et al., 2015*)**.

Most of the studied RA patients (63%) in the current study had high disease activity and only 11% were in remission by DAS28 score. The mean DAS28 score was 5.6±2. This goes with the results of the COMORA study, published by ***El-Zorkany and colleagues in 2016***, in which the mean DAS28 score was 5.2±1.4 in Egyptian RA patients compared to 3.6±1.4 in non-Egyptian patients. ***El-Zorkany et al.*** attributed this high disease activity to financial issues, as most of the Egyptian RA patients cannot afford the high costs of biologic DMARDs. Another cause is that patients

usually seek medical advice when they have a flare of disease activity.

In the current study, there was no significant difference (*p>0.05*) as regard disease activity between patients with positive and negative HCV antibodies and RNA. This goes in concordance with an Egyptian study done by ***Mahmoud and colleagues in 2011***. In this study, disease activity was nearly equal in RA patients positive and negative for HCV antibodies (mean DAS28 score: 5.85 vs. 5.12, respectively). Similarly, a study done by ***Hussein and colleagues in 2016***, including 90 patients with RA alone and 90 patients with RA and concomitant HCV, found that there was also no significant difference in disease activity between both groups.

HCV is known to be a hepatotropic and lymphotropic virus that does not affect the liver only, but has many extrahepatic manifestations (EHMs). Articular involvement is one of these manifestations and HCV-related arthropathy varies widely in its clinical presentation. It can presents as polyarthralgia, monoarticular or oligoarticular intermittent arthritis, or symmetric chronic arthritis **(*Cacoub et al., 2016*)**.

Polyarticular symmetrical arthritis associated with HCV can be very close in clinical picture to recent onset RA, in which articular damage and deformities have not yet occurred, making it

very difficult to distinguish between both diseases **(*Palazzi et al., 2014*)**. Detection of serologic markers of RA could be helpful in differentiating between both disorders; however, HCV is known to be associated with production of many auto-antibodies as one of its extra-hepatic manifestations. About 70% of HCV positive patients have a positive RF test, so it can't be used to differentiate between RA and HCV related arthropathy **(*Palazzi et al., 2012*)**.

In the current study, 59.3% of RA patients (178/300) were positive for rheumatoid factor. RF positivity was significantly higher ($p<0.001$) in RA patients with positive HCV antibodies (82.2% vs. 55.3%). This goes with the results of two Egyptian studies done by ***Mahmoud et al. in 2011*** and ***Hussein et al. in 2016***. Both studies stated that RF positivity was higher in RA patients positive for HCV antibodies than negative patients (77.3% vs. 69.3% and 83.3% vs. 66.6%, respectively). There was no significant difference ($p>0.05$) in RF positivity between HCV RNA positive and negative patients in the current study (83.3% vs. 77.8%, respectively).

Anti-CCP is a more specific test for RA, with a specificity >94% and a sensitivity >70%. It is very useful in confirming the diagnosis of RA especially in the early stages of the disease, and carries a prognostic value for disease progression and joint damage. In a study done by ***Bombardieri et al. in 2004*** to evaluate the utility

of anti-CCP in differentiating between RA and HCV-related arthropathy, it was detected in 76.6% of patients with RA but not in patients with chronic HCV, whether articular involvement was present or not.

In a similar study done by ***Sene and colleagues in 2006***, Anti-CCP was detected in 78% of patients with RA, 5.7% of patients with HCV and arthralgia, and 0% of patients with HCV without arthralgia. The same findings were reported in an Egyptian study done by ***Ezzat and colleagues in 2011***, in which Anti-CCP was positive in 83.3% of patients with RA and 4.5% of patients with HCV and polyarthropathy, while RF was positive in 90% of RA patients and 81.1% of patients with HCV and polyarthropathy.

In the present study, anti-CCP was done in selected cases if the diagnosis of RA couldn't be confirmed according to the ACR/EULAR 2010 classification criteria. Only 128 patients were tested for anti-CCP, of which 58 were positive (45.3%). There was no significant difference ($p>0.05$) in anti-CCP test results between patients with positive and negative HCV antibodies (42.9% vs. 45.8%) since both groups have established RA. This goes with the results of the study done by ***Mahmoud and colleagues in 2011***, in which anti-CCP positivity was equal (72.7%) in RA patients with positive and negative HCV antibodies. It also agrees with the results of ***Hussein et al. in 2016*** who reported in their study that anti-CCP

was detected in 72.2% of patients with RA alone, 71.1% of RA patients with concomitant HCV, and 0% of patients with HCV related arthropathy.

Treatment of RA patients with concomitant HCV infection represents a huge challenge to rheumatologists as many DMARDs are hepatotoxic. NSAIDs can be used with caution because of the potential for hepatotoxicity or variceal bleeding. Although steroids can increase the viral load, they are considered safe in low doses **(*Palazzi et al., 2014*)**. As regard the use of conventional DMARDs, methotrexate and leflunomide should be avoided in all Child classes. Hydroxychloroquine is safe in patients with Child class A or B, but should be avoided in Child class C. Sulfasalazine can be used in Child class A only. Cyclosporine A has antiviral activity against HCV, so its use can be beneficial **(*Joseph, 2012*)**.

TNFα inhibitors are safe in HCV positive patients, but they should be avoided in patients with Child classes B and C. Screening for viral hepatitis is recommended before starting the treatment. Reactivation of HCV was reported in some studies after the use of TNFα inhibitors, so they should be avoided in patient successfully treated from HCV **(*Joseph, 2012*)**.

In the present work, corticosteroids and NSAIDs were used by 92.7% and 62% of the studied RA patients, respectively. ***El-***

Zorkany et al. in 2016 reported in the COMORA study a lower use of corticosteroids (58.4% and 54%) and a similar use of NSAIDs (65.9% and 54.2%) in Egyptian and non-Egyptian RA patients, respectively. Methotrexate was used by 56.7% of our studied RA patients; in contrast, its use was higher in the COMORA study (94.5% and 88.1% in Egyptian and non-Egyptian RA patients, respectively). None of our studied patients used biologics before. This goes with the findings of ***El-Zorkany et al. in 2016*** who reported the use of biologics in 7.1% of Egyptian RA patients, compared to 41.6% of non-Egyptian patients. The cause for this lower use of biologics was explained earlier in the discussion.

When comparing the medications used for treatment of RA in HCV antibodies positive and negative patients in the current study, there was a statistically highly significant decrease ($p<0.001$) in the use of NSAIDs and methotrexate in patients with positive HCV antibodies, while there was a statistically highly significant increase ($p<0.001$) in the use of sulfasalazine. Moreover, there was no statistically significant difference ($p>0.05$) in the use of steroids, leflunomide and hydroxychloroquine between both groups. In addition, there was no statistically significant difference ($p>0.05$) in the use of RA medications between HCV RNA positive and negative patients.

In a study published by ***Patel and colleagues in 2015*** to assess treatment patterns in RA patients with co-morbid hepatitis C virus infection, the use of methotrexate was significantly lower in patients positive for HCV antibodies, while the use of sulfasalazine was significantly higher. This goes in concordance with our findings.

Summary

Summary

HCV is one of the main problems facing the Egyptian healthcare system. Egypt probably has the highest HCV prevalence in the world, estimated to be 15% in some studies. The 2008 Egyptian Demographic Health Survey (EDHS 2008) estimated that the prevalence of HCV antibodies was 14.7%. In 2015, The Egyptian Health Issues Survey (EHIS 2015) was done to re-estimate the prevalence of HCV infection in Egypt. The prevalence of HCV antibodies in the 15-59 years age group dropped to 10%.

Despite this unique HCV epidemic, few studies were done to estimate the prevalence of HCV in patients with RA in Egypt. The aim of the current study was to estimate this prevalence. Three hundred patients (older than 18 years) diagnosed with RA according to the ACR/EULAR 2010 criteria were tested for HCV antibodies by ELISA, and those with positive results were tested for HCV RNA by RT-PCR.

The prevalence of HCV antibodies in our studied RA patients was 15%. This high prevalence may be explained by increased exposure to HCV transmission, especially through the iatrogenic route. This prevalence is nearly equal to HCV prevalence in the Egyptian general population estimated in EDHS 2008 (14.7%), but it is higher than the prevalence in the EHIS 2015 (10%).

When we compared HCV prevalence in the 20-59 years age group in the 3 studies, it was 12% in the current study, 17% in EDHS 2008, and 11.7% in EHIS 2015. In this case, the prevalence in the current study is nearly similar to EHIS 2015 and lower than EDHS 2008.

The prevalence of HCV antibodies was higher in females than males in our study (15.3% vs. 12.5%), while it was higher in males in EDHS 2008 and EHIS 2015(17.4% vs. 12.2% and 12.4 vs. 8.1). In the 3 studies, HCV antibodies prevalence was higher in patients living in rural areas than those living in urban areas (16.7% vs. 14.6%, 18% vs. 10.3%, and 11.7% vs. 7.1%, respectively) and it usually increased sharply with age.

In our study, HCV antibodies prevalence was significantly higher ($p<0.001$) in those who had a history of previous blood transfusion (22.7% vs. 13.7%). Other iatrogenic exposures like surgery, dental procedures and repeated injections also had a significant association ($p<0.05$) with increased HCV prevalence.

After reviewing other Egyptian studies that estimated the prevalence of HCV antibodies in patients with RA, we found the same high prevalence as the current study (17.6% and 20%). On reviewing studies that estimated HCV prevalence in patients with

RA in other countries, a much lower prevalence was reported, ranging from 0% to 8.7%.

Spontaneous Clearance of HCV occurred in 20% of the cases in our study, 33.3% in the EDHS 2008, and 30% in the EHIS 2015. The lower rate of HCV clearance in our studied patients may be explained by the immune suppression caused by the disease itself, or by medications.

The mean disease duration was significantly longer ($p<0.001$) in patients positive for HCV antibodies (11.7±12.8 vs. 5.2±5.5 years). Most of the studied RA patients had high disease activity (63%). There was no significant difference ($p>0.05$) as regard disease activity between patients with positive and negative HCV antibodies and RNA. This was confirmed in other similar studies.

In the current study, RF positivity was significantly higher ($p<0.001$) in RA patients with positive HCV antibodies (82.2% vs. 55.3%). Anti-CCP is a more specific test for RA which is very useful in differentiating between RA and HCV-related arthropathy.

Corticosteroids and NSAIDs were used by 92.7% and 62% of the studied RA patients, respectively, while methotrexate was used by 56.7% of the patients. None of our studied patients used biologics before.

When comparing the medications used for treatment of RA in HCV antibodies positive and negative patients in the current study, there was a statistically highly significant decrease ($p<0.001$) in the use of NSAIDs and methotrexate in patients with positive HCV antibodies, while there was a statistically highly significant increase ($p<0.001$) in the use of sulfasalazine. Moreover, there was no statistically significant difference ($p>0.05$) in the use of steroids, leflunomide and hydroxychloroquine between both groups. In addition, there was no statistically significant difference ($p>0.05$) in the use of RA medications between HCV RNA positive and negative patients.

Conclusion

Conclusion

HCV represents a major public health problem to Egypt, the country with the highest HCV prevalence in the world. In this study, we estimated that the prevalence of HCV antibodies in patients with RA is 15%, which is higher than any other country in the world. This prevalence is higher than the prevalence in the general population in EHIS 2015 (10%) as RA patients are more exposed to HCV transmission through iatrogenic exposure.

HCV antibodies prevalence was higher in patients living in rural than urban areas (16.7% vs. 14.6%) and increased sharply with age. It was also higher in patients with longer RA disease duration. History of blood transfusion, surgery, dental procedures, or repeated injections was associated with increased prevalence.

Spontaneous clearance of HCV was lower in our studied RA patients when compared to that in EDHS 2008 and EHIS 2015 (20%, 33.3%, and 30% respectively). This may be due to the immune suppression caused by the disease or medications used to treat it.

Although most of the studied RA patients (63%) had high disease activity, there was no significant difference ($p>0.05$) between HCV antibodies positive and negative patients.

Recommendations

Recommendations

Given the exceptionally high prevalence of HCV in Egypt in general and in RA patients in particular, the similar presentation of early RA and some variants of HCV related arthropathy, and the safety concerns of RA medications in patients with HCV infection, we recommend screening of all RA patients for hepatitis C at diagnosis and before starting treatment.

Further national surveys to estimate HCV prevalence should include individuals older than 60 years, as this age group probably has the highest prevalence of HCV, acting as a reservoir for infection.

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Arabic Summary

المقدمة

تم اكتشاف فيروس سى لاول مرة عام 1989 و يشكل فيروس سى مشكلة كبيرة للصحة العامة عالميا حيث يبلغ معدل انتشار المرض 2-3% من سكان العالم اى انه يوجد حوالى 130-150 مليون شخص مصابون بالمرض، وتعد مصر من اعلى دول العالم من حيث معدل انتشار العدوى بفيروس سى والذى يبلغ حوالى 14.7%، وتم ارجاع هذا المعدل المرتفع الى حملات العلاج من مرض البلهارسيا عن طريق الحقن والتى تمت فى الستينيات حتى اوائل الثمانينيات من القرن الماضى.

تنتقل العدوى بفيروس الالتهاب الكبدى سى عن طريق التعرض للدم الملوث بالفيروس، وقد مثل نقل الدم ومشتقاته مصدرا كبيرا لانتقال العدوى حتى عام 1994 عندما تم تعميم برنامج قومى لفحص الدم فى مصر للتاكد من خلوه من فيروس سى، وتشمل العوامل الاخرى لانتقال العدوى ما يلى: التعرض المهنى لمقدمى الخدمة الصحية عن طريق وخز الابر، تعاطى المخدرات عن طريق الحقن، انتقال العدوى من الام المصابة للجنين، ممارسة العلاقة الجنسية مع شخص مصاب بالمرض أو مشاركة ادواته الشخصية مثل فرش الاسنان وامواس الحلاقة، ويعتبر التعرض الطبى عن طريق الحقن والجراحات واجراءات الاسنان احد اهم العوامل فى استمرار انتقال العدوى حاليا فى مصر.

معظم حالات الالتهاب الكبدى الفيروسى سى الحاد ليس لها اعراض وتمر دون ملاحظة، نحو 15-30% من الحالات يتخلصون من العدوى تلقائيا والنسبة الباقية اى 70-85% تتطور الى عدوى مزمنة، 20% من مرضى الالتهاب الكبدى الفيروسى سى المزمن يصابون بتليف كبدى خلال 10-20 عام، و حوالى 2-5% من هؤلاء يصابون بورم كبدى.

وقد اوضحت دراسة مصرية ان معدل انتشار العدوى بفيروس الالتهاب الكبدى سى بين مرضى القسم الداخلى للروماتيزم حوالى 18.5% وهو ما يزيد عن معدل الانتشار العام بين

السكان، ولا يوجد بيانات كافية حاليا عن معدل انتشار العدوى بين مرضى التهاب المفاصل الروماتويدى فى مصر، هؤلاء المرضى اكثر عرضة للاصابة بالعدوى نتيجة ضعف الجهاز المناعى اما بسبب المرض نفسه او بسبب الادوية التى يتعاطونها لعلاج هذا المرض، هذا بالاضافة الى تعرضهم للعديد من الاجراءات الطبية الاجتياحية.

الهدف من الدراسة

الهدف من الدراسة الحالية هو تقدير معدل انتشار العدوى بفيروس الالتهاب الكبدى سى فى مجموعة من مرضى التهاب المفاصل الروماتويدى فى مصر.

الاشخاص والطرق

هذه الدراسة شملت 300 مريض مصرى مصابون بالتهاب المفاصل الروماتويدى ممن تتجاوز اعمارهم 18 عام واستوفوا خصائص التصنيف الصادرة عن الكلية الامريكية للروماتيزم والرابطة الاوروبية ضد الروماتيزم لعام 2010، تم اختيار المشاركين بالدراسة من العيادات الخارجية للروماتيزم بمستشفيات جامعة عين شمس ومستشفى احمد ماهر التعليمى بالقاهرة فى الفترة من يونيو 2015 الى فبراير 2017، وتم استبعاد المرضى اللذين تقل اعمارهم عن 18 عام، و مرضى الفشل الكلوى المزمن اللذين يخضعون لجلسات الغسيل الكلوى، و المرضى المصابون بامراض الانسجة الضامة الاخرى.

بعد موافقة لجنة اخلاقيات البحث العلمى بكلية الطب بجامعة عين شمس، تم الحصول على موافقة مستنيرة مكتوبة من كل المشاركين بالدراسة، وتم الحصول على تاريخ مرضى كامل واجراء فحص سريرى دقيق لجميع المشاركين واجراء الفحوصات المعملية الآتية (صورة دم كاملة، سرعة الترسيب، عامل الروماتويد، انزيمات الكبد، الاجسام المضادة لفيروس الالتهاب الكبدى سى عن طريق مقايسة الممتز المناعى المرتبط بالانزيم)، المرضى ذوى النتائج الايجابية

للاجسام المضادة لفيروس الالتهاب الكبدى سى خضعوا الى القياس الكمى للحمض النووى الريبوزى لفيروس الالتهاب الكبدى سى باستخدام تفاعل البلمرة المتسلسل.

النتائج

اثبتت الدراسة ارتفاع نسبة الاصابة بفيروس الالتهاب الكبدى الفيروسى سى بين مرضى الروماتويد المفصلى المشاركين بالدراسة حيث بلغت نسبة الاصابة 15%، وهذه النسبة مرتفعة اذا ما قورنت بالدراسات التى اجريت على المصابين بنفس المرض فى دول اخرى، ومتقاربة مع نتائج الدراسات الاخرى التى اجريت فى مصر.

وعند مقارنة هذه النتائج مع نتائج المسح السكانى الذى اجرى على الاشخاص العاديين فى مصر نجد ان النسبة متقاربة مع نتائج المسح السكانى لعام 2008 (14.7%)، ولكنها اعلى من نتائج المسح السكانى لعام 2015 (10%)، وقد اثبتت الدراسة ان نسبة الاصابة بفيروس سى تزداد مع زيادة السن وبين المرضى اللذين يعيشون فى مناطق ريفية، كما تزداد ايضا كلما طالت مدة الاصابة بمرض الروماتويد المفصلى.

وقد لوحظ ان نسبة نشاط التهاب المفاصل الروماتويدى بين المرضى المشاركين بالدراسة عالية، ويرجع هذا الى ضعف استخدام الادوية البيولوجية الحديثة لعلاج المرض فى مصر بسبب ارتفاع اسعارها، كما ان المرضى فى مصر غالبا ما يلجأون للطبيب فى فترات زيادة نشاط المرض، ووجد ايضا ان نسبة نشاط التهاب المفاصل لا تختلف بين المرضى المصابين وغير المصابين بفيروس سى.

وتوصى الدراسة بضرورة اجراء فحصوصات فيروس سى للمرضى المصابين بالتهاب المفاصل الروماتويدى عند التشخيص وقبل بدء العلاج.

معـــدل انتشـــــار العـدوى بفـيروس الالتهـاب الكـبدى سى فى مجموعة من مرضى التهاب المفاصل الروماتويدى فى مصر

دراسة مقدمة من

الطبيب/ محمود صلاح الزلبانى

بكالوريوس الطب والجراحة - كلية الطب - جامعة المنصورة

توطئة للحصول على درجة

الماجيستير فى الامراض الباطنة العامة

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كلية الطب

جامعة عين شمس

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