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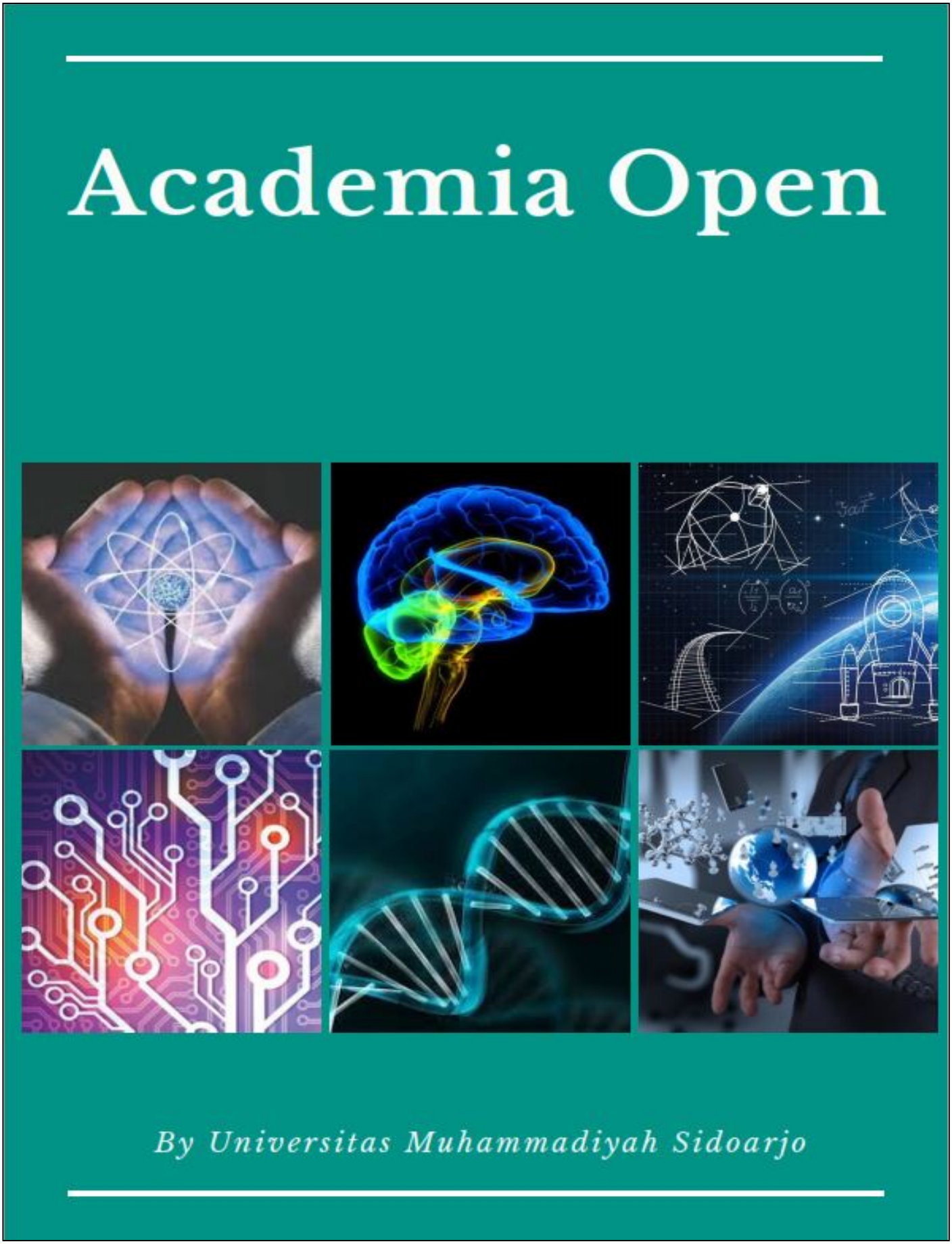

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Sero Positivity of Hepatitis C among Patients with ?-Thalassemia Major in Karbala Center

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Abstract

Background: Hepatitis C virus is a major cause of post-transfusion hepatitis infection and remains a significant global health problem. Patients with thalassemia major are at high risk of HCV due to frequent blood transfusions from infected donors. **Objective**: To evaluate the sero positivity of HCV infection among patients aged 3 to 18 years with β-thalassemia major. **Methods**: A retrospective study was conducted on 254 patients (131 females, 123 males) attending the Thalassemia Center at Karbala Children's Hospital from August 2014 to March 2015. Ages ranged from 3 to 18 years. Serological viral markers for anti-HCV antibody were tested using enzyme linked immune sorbent assay. **Results**: Out of 254 patients, 123 (48.4%) were male and 131 (51.6%) were female. Seventeen (6.7%) were seropositive for HCV. Among patients <6 years, 1 (2.3%) was positive; in ages 6-12 years, 7 (5.3%) were positive; and above 12 years, 9 (11.5%) were infected. Blood transfusion frequency showed that 1 (2.2%) of 45 patients receiving <100 transfusions was positive, 6 (5.4%) of 111 receiving 101-200 transfusions, 6 (9.8%) of 61 receiving 201-300 transfusions, and 4 (10.8%) of 37 receiving >300 transfusions were positive. None of the 10 patients who had undergone splenectomy were infected, while 17 (7%) without splenectomy were infected. Among 59,886 volunteer blood donors in Karbala from 2012 to 2014, 54 (0.1%) were anti-HCV positive. **Conclusion**: Higher rates of HCV infection in older thalassemia patients with more transfusions highlight the importance of accurate blood screening techniques like PCR to prevent infections in thalassemia patients.

Highlights:

- HCV infection increases with patient age and number of transfusions.
- Older thalassemia patients show higher seropositivity rates.
- Emphasizes the need for PCR screening to ensure safer transfusions.

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Introduction

Hepatitis C virus is the major cause of post-transfusion hepatitis infection and still a major health problem worldwide. WHO studies show that, 170-200 million of people are infected by HCV in the world. Patients with thalassemia major are at high risk of hepatitis C due to the blood transfusion from donors infected by HCV which might lead to disabling symptoms, cirrhosis and hepatocellular carcinoma. It is said that from 2010–2019, HCV may cause to the loss of 1.83 million years of life among people less than 65 years of age [1].

It became apparent after the discovery of the hepatitis A and B viruses in the late 1960s and early 1970s that a large proportion of cases of acute and chronic hepatitis could not be explained by either of these agents. Another viral agent was suspected, and patients infected with this suspected agent were said to have non-A, non-B hepatitis. The agent was finally identified in 1989 when the genome of the virus was cloned and the agent was designated the hepatitis C virus (HCV) [2]. HCV is closely related to flaviviruses and pestiviruses. Its genetic organization and protein products classify it in the Flaviviridae family, although its diversity is great enough for it to be classified as a separate genus. The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides. There are highly conserved 5' and 3' untranslated regions flanking an approximately 9000 nucleotide single open reading frame which encodes a large polyprotein of about 3000 amino acids [3].The polymerase enzyme of RNA viruses such as HCV lacks proofreading ability and is therefore unable to correct copying errors made during viral replication. This leads to heterogeneity that is extremely important in the diagnosis of infection, pathogenesis of disease, and the response to treatment [4].Over decades and centuries, the degree of HCV diversity has evolved into several distinct genotypes of the virus [5].Sequence homology between genotypes is less than 80 percent.

There are Six major genotypes of HCV have been defined [6]. More than 50 subtypes have also been described; the most common subtypes are 1a, 1b, 2a, and 2b [7].The evolution of genotypes has probably been influenced by several factors, including immune selection, infection patterns, replication efficiency, and population migration. Thus, there is a distinct geographic distribution of HCV genotypes [8], [9].

The clinical significance of viral genotypes is not entirely clear, but they have a significant effect upon the response to interferon-based therapy [10], [11].

The proportion of children who are HCV antibody-positive who are also HCV RNA positive is not known precisely; based upon studies in adults, it is estimated to be approximately 75 to 80 percent [12], [13].

The introduction of anti-HCV screening has reduced the transmission by up to almost 100% [14]. The prevalence is much higher (50 to 95 percent) in individuals who received blood products for conditions such as thalassemia or hemophilia before 1992 [12], [13]. Seroprevalence rates of 10 to 20 percent have been reported among children with a variety of other potential exposures such as malignancy, hemodialysis, extracorporeal membrane oxygenation, or surgery for congenital heart disease[15], [16]. Areas of higher prevalence include countries in the Far East, Mediterranean countries and certain areas in Africa and eastern Europe [13], [17]. Prevalence rates in Egypt were low in the 1990s among children without a history of exposure to blood products[18], but a more recent series reported HCV rates of 2 percent [19].Mean intervals between the onset of acute post-transfusion hepatitis infection and detection of chronic active hepatitis (10 years), cirrhosis (20 years) and Hepatocellular carcinoma (30 years) [20], [21].Factors that may affect the natural history of HCV infection: Various cofactors such as presence of HBV and alcohol intake appear to promote disease progression [20].consistently normal ALT levels are associated with slower fibrosis progression [21], [22], [23].Disease expression is related to viral expression: low levels of circulating HCV RNA are generally found in asymptomatic patients with normal ALT levels [12].Transmission occurs by percutaneous exposure to contaminated blood and plasma derivatives. Contaminated needles and syringes are most important vehicles of spread, especially among injecting drug users[24], [25]. Because the virus possesses a lipid-containing envelope, exposure of virus to bile and secretion from the liver through the biliary tract to the gut would result in rapid loss of virus infectivity [14].Transmission by household contact and sexual activity appears to be low [14], [24], [25].Uncommon but occasional is the transmission at birth from mother to child. About 5 out of every 100 infants born to HCV infected women become infected at the time of birth. Unfortunately, no treatment can prevent this from happening [26], [27].Perinatal transmission

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explains only a small proportion of chronic HCV infections. This contrasts with HBV infection, in which most adult chronic carriers acquired infection in the newborn period [14], [24], [25].The presence of HCV RNA in serum indicates the presence of active infection and a potential for transmission of the infection and/or the development of chronic liver disease [25].There is no such thing as safe blood since there is still the risk of having antibody-negative and PCR-negative blood units that can transmit disease [28], [29].

Acute hepatitis typically develops 2 to 26 weeks after exposure to hepatitis C virus (HCV), with a mean onset of 7 to 8 weeks [30]. The majority of patients with acute HCV are asymptomatic some develop symptoms of acute hepatitis [31].Jaundice is a common symptom reported among patients presenting with symptomatic acute HCV. In a study that included 51 patients with symptomatic acute HCV, patients reported jaundice (68 percent), dark urine and white stool (39 percent), nausea (34 percent), and abdominal pain (25 percent, predominantly right upper quadrant pain) [32].Additional symptoms reported in other studies include fatigue, low-grade fever and chills, loss of appetite, pruritus, muscle aches, mood disturbances, joint pain, dyspepsia, and confusion [33]. Chronic hepatitis C has been described as a mild disease in children, but viremia persists up to adult life in more than 80% of cases, fibrosis is slowly progressing throughout adolescence and youth, and early appearance of end stage liver disease has been recently documented. These findings, and the efficacy of current therapeutic strategies in adults, support the potential benefits of early treatment in children with chronic hepatitis C [34].Chronic infection with HCV has been associated with hepatocellular carcinoma, which occurs almost exclusively in individuals with cirrhosis [35].

Diagnostic tests for hepatitis C virus (HCV) can be divided into two broad categories:

Serologic assays that detect antibodies to hepatitis C [36].

Molecular assays that detect or quantify HCV RNA

Other investigations such as genotype testing, serum fibrosis panels and liver biopsy may help to predict the response to treatment and prognosis. [36], [37], [38].

The commonly available screening test for anti-HCV is an enzyme immunoassay (EIA, also called enzyme-linked immunosorbent assay or ELISA) that detects HCV antibodies. A third version of the anti-HCV screening test (EIA-3) has been approved for screening blood products in the United States and has been introduced into the diagnostic setting at some institutions. EIA-3 adds an additional antigen from the nonstructural region (NS5). EIA-3 appears to have increased sensitivity in the high prevalence setting[39].and slightly better specificity in the blood donor population [40]. In addition, the mean time to detection of seroconversion is shortened by two to three weeks [41].For immunocompromised individuals, including those with HIV infection, patients on dialysis, and transplant recipients, anti-HCV may not be detectable despite the presence of HCV infection. For patients at risk for HCV infection or in whom HCV is suspected (such as those with an elevated serum ALT level), HCV RNA testing should be considered even if anti-HCV tests are negative [42], [43].

HCV RNA tests are used to confirm the presence or absence of infection and to quantify the amount of HCV RNA present at specific time points during therapy to guide decisions regarding duration of treatment.

All HCV RNA assays are calibrated using the World Health Organization HCV international unit standard to provide better accuracy and comparability of results across different assays. The standard is based upon the quantitative analysis of HCV RNA genotype 1. Results can vary between assays, especially for some non-1 HCV genotype specimens [44], [45].

As a result, serial measurements of HCV RNA during treatment are ideally performed using the same assay throughout. For detection of HCV RNA have been traditionally divided into two categories: qualitative and quantitative assays.

Qualitative tests**:** provide results as positive or negative and must have a lower limit of detection of <50 international units/mL HCV RNA. Examples of qualitative HCV RNA assays are Amplicor PCR assay (Roche Diagnostics) and Versant TMA assay (Siemens Healthcare Diagnostics). These tests are capable of detecting low levels of HCV RNA and are used for confirming the diagnosis of HCV infection and assessing sustained virologic responses (SVR) to antiviral therapy.

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Quantitative assays assess the quantity of HCV RNA in international units/mL and vary in their limits of detection and dynamic range. In the past, these assays were less sensitive than qualitative assays and were therefore not used for detection of infection or confirmation of viral clearance. More recently, real-time PCR methods have become commercially available. These assays are more sensitive than prior quantitative assays (limits of detection of approximately 10 to 15 international units /mL. Thus, the real-time PCR assays offer the combined diagnostic capabilities of qualitative and quantitative assays. PCR-based methods use target amplification and DNA methods use signal amplification.

Quantitative assays are used before treatment to measure baseline HCV viral load and during treatment to assess on-treatment response and to guide therapy (e.g., stopping therapy in a patient who does not have an appropriate decline in HCV RNA during treatment) [46].

A liver biopsy is not necessary for the diagnosis of hepatitis C virus (HCV) infection. However, many patients undergo liver biopsy prior to treatment of chronic HCV infection [47], [48].

Acute HCV infection is uncommonly recognized in children except in rare outbreaks [49]. Fulminant hepatitis is rare. There are no data regarding treatment of acute HCV infection in children. We generally observe such patients for six to eight weeks to determine whether there is spontaneous clearance, treating those who continue to have HCV viremia.

In chronic infection, treatment of HCV in children was initially guided by experience in adults, but now includes multicenter trials in pediatric populations.

Pegylated interferon, in combination with ribavirin, is the treatment of choice for most adults and children with chronic HCV infection who are considered to be appropriate candidates for therapy[50].In adults, response rates are higher among patients treated with combination therapy using pegylated interferon as compared to those treated combination therapy using standard interferon [51], [52].

Combination therapy with interferon-alfa and ribavirin was the first established treatment for HCV infection in children[53].For most children and adults, pegylated interferon is now preferred.

Treatment for children with chronic HCV are similar to those for adults[54].our course of action depends on the HCV genotype: For those with genotype 2 or 3 (in whom response rates are highest), we proceed to treatment. We do not generally recommend a liver biopsy before treatment in such patients since the response rates are high. Exceptions are children whose parents want to know the stage of disease in considering treatment, and those with comorbid diseases in whom the results of a biopsy might influence the decision to treat [54].For those with genotype 1, we also encourage proceeding to treatment, but the child's age, presence of comorbid diseases, and family's preference are important components of the decision. We encourage treatment more strongly in children with perinatally acquired HCV who are older than 10 years, and in those with a comorbid disease or other features that raise concern for rapid progression; for these groups we recommend a liver biopsy primarily for prognostic purposes rather than as part of a treatment decision [54].Pegylated interferon alfa-2b has been approved by the FDA for use in children three years and older (60 mcg/m 2 once weekly, maximum dose 1.5 micrograms/kg) in combination with ribavirin (15 mg/kg/day in two divided doses). Pegylated interferon alfa-2a (180 micrograms/1.73 m 2 weekly, maximum dose 180 micrograms) can also be used in combination with ribavirin in children five years and older. The treatment duration varies by genotype, as it does for adults [54].

This study was conducted to detect to detect the sero positivity and risk factors of HCV in thalassemic patients in thalassemia center at Karbala teaching hospital.

Method

A retrospective analytic study design was done on group of 254 patients with beta thalassemia major diagnosed by hemoglobin electrophoresis registered in thalassemia center in Karbala Teaching Hospital with regard to the hepatitis C infection . Those patients with β-thalassemia major attending thalassemic center in Karbala Teaching Hospital , were studied during the period from from 1st of August 2014 to the 1st of March 2015 . Their ages were between (3-18) years, 131 patients were females and 123 were males.

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Patients were evaluated for hepatitis C twice in a year, unless develop complications. All patients had been on a regular transfusion program (every 10–25 days) with the aim of maintaining pre-transfusion hemoglobin levels above 9 g/dL. All thalassemic patients, subjected to an iron chelating program with subcutaneous deferoxamine, were active and self-dependent after enrollment. The majority of them had shifted recently to an oral chelator (Exjade).

The subject's medical history was documented by a review of previous medical records. The subject interview questionnaire included items on demographics, medical and surgical history (e.g. splenectomy). A medical record review was conducted by the researcher, which included documentation of transfusion and chelating therapy and recent laboratory values of liver enzymes.

1. Data collection

A special questionnaire had been designed to collect data about the following and include: Name,age,sex,weight,adress(rural, urban), age of first blood transfusion, frequency of blood transfusion per month, type of chelating agent, type (Exjad or Desferal), and previous surgical history including splenectomy.The information's were taken from patient files at the hospital as each patient has it is own file that contain information's mentioned above in addition to the previous and recent investigation regarding (serum ferritin,hepatic, renal) .

Data for three years (2012-2014) of the volunteer blood donors were retrospectively reviewed to serve as guess of disease prevalence in population.

In this study we exclude other types of haemoglobinopathy rather than β-Thalassemia major , age above 18 years and patients who received less than 15 units blood.

2. Investigations

S.ferritin

Material was used: mini VIDAS is compact multi-parametric immunoanalyzer .

Morning blood samples were collected in a plain red venipuncture tube without additives or anticoagulant. Blood then allowed clotting for centrifugation to separate the serum. The value is expressed in ng/ml.

Liver enzymes: which include alanine transaminase (ALT) and aspartate transaminase (AST) measured by Spectrophotometer.

Alkaline phosphatase (ALP) .

Total serum bilirubin (TSB) .

HCV antibodies were tested by (ELx800 READER) Automated microtiter plate ELISA reader and EIA KIT. enzyme immunoassay EIA (3 rd generation) A Sample of 5ml of fresh blood was drawn from individual and collected in a sterile plastic tube, left to clot at room temperature then centrifuged at 2000 rpm for 10 minutes, then serum was collected in sterile tube and examined by ELISA Assay to detect anti HCV.

3. Statistical Analysis

All Statistical analysis was done using SPSS program version 20.0 Quantitative data are summarized as median or mean ± standard deviation and categorical data as percentage. P-values less than 0.05 were considered as statistically significant.

Results and Discussion

A. Results

A total of 254 thalassemic patients enrolled in this study, their general characteristics are explained in the following tables, figures and paragraphs.

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1. Age and gender

As it shown in table 1, the mean age of the studied group was 10.2 ± 4.3 (range: 3 -18) , furthermore, the distribution of age groups revealed that 44 (17.3%) patients aged < 6 years, 52% of the patients aged 6-12 years and 30.7% aged > 12 years (Fig 1).

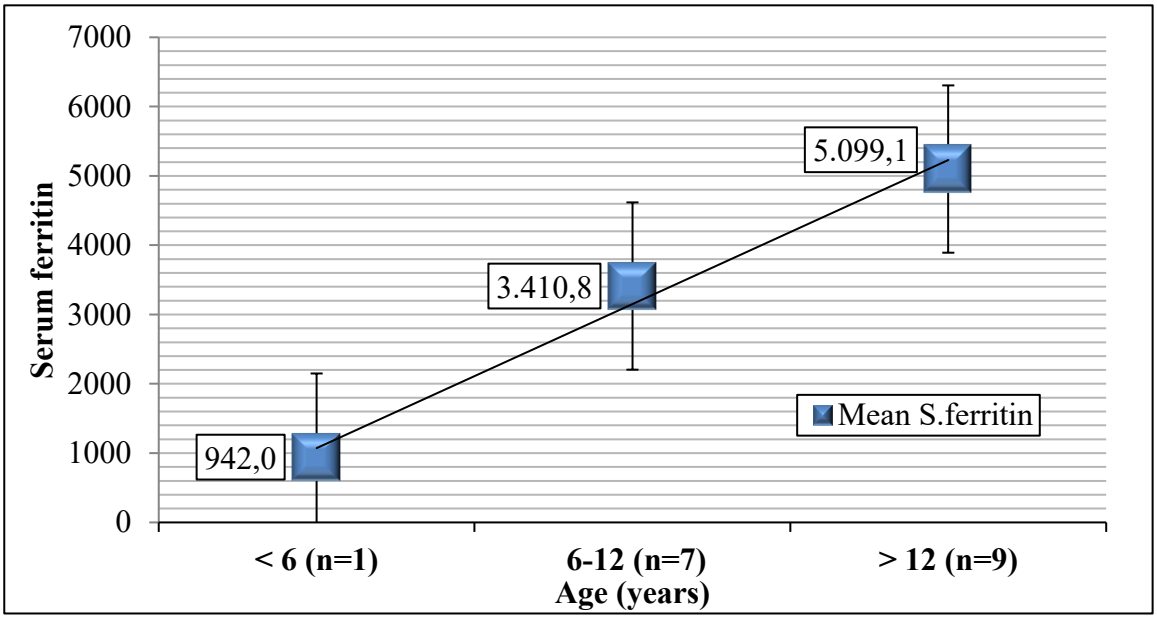

Figure 1. Distribution of patients according to the number of transfusion received

Regarding the gender distribution, males relatively less than females, 123 (48.4%) and 131 (51.6%), respectively with a female to male ratio of 1.07 to 1, (Fig 2).

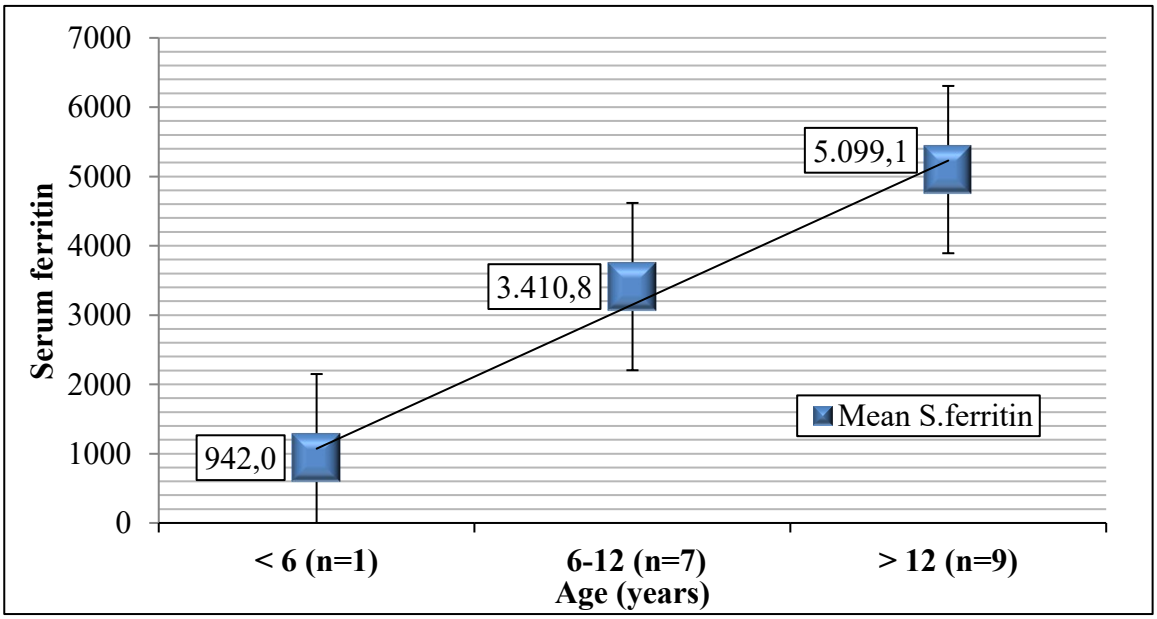

Figure 2. The direct association between the age and serum ferritin in HCV positive thalassemic patients (N=17)

Splenectomy was reported in only 10 patients (3.9%). The median number of transfusion the patient did received was 185, ranged 40-370 transfusions. Further distribution of the number of transfusion is shown in figure 3.

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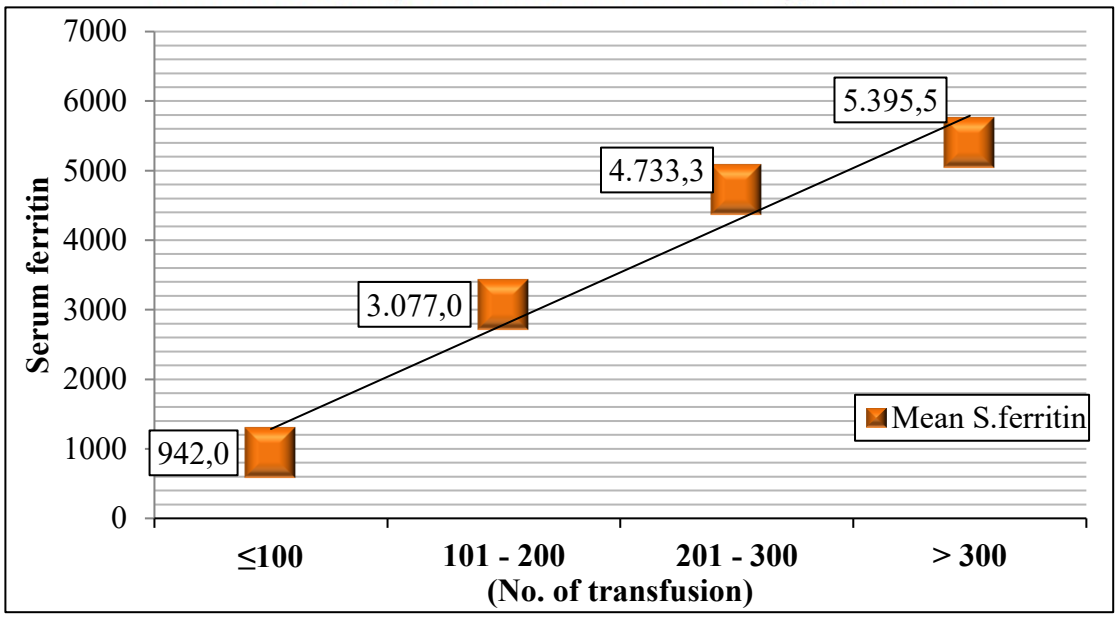

Figure 3. The direct (positive) association between S. ferritin and frequency of transfusion in HCV positive thalassemic patients (N=17)

Variable	
Age (years)	**No. (%)**
> 6	44 (17.3)
6 – 12	132 (52.0)
12-18	78 (30.7)
Mean ± SD	10.2 ± 4.3
Range	3 – 18
Gender	
Male	123 (48.4)
Female	131 (51.6)
Splenectomized	10 (3.9)
Number of transfusions/patient	
Median	185
Range	40 - 370

Table 1. Age and gender distribution of the studied group (N=254)

The seropositivity rate of 0.10% indicates a relatively low prevalence of HCV among the volunteer blood donors over this three-year period.

2. Laboratory findings

The mean values (and standard deviation (SD)) of the liver enzymes and other laboratory parameters are shown in table 2.

Parameter	**Mean ±**	**SD**
Serum ferritin (ng/ml)	3156.0	1885.5

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TSB (mg/dl)	1.4	0.9
ALT (u/l)	12.0	4.9
AST (u/l)	14.9	9.2
Alkaline phosphatase (u/l)	146.7	51.2

Table 2. Laboratory findings of the liver enzymes and other laboratory parameters

Table 2 The table summarizes the laboratory findings comparing liver enzymes and serum ferritin levels between HCV positive and HCV negative patients. Here are the key points:**Serum Ferritin (ng/ml)**:**HCV Positive**: Mean = 4159.4, indicating significant iron overload.**HCV Negative**: Mean = 3083.7, also elevated but lower than HCV positive patients.**P-Value**: 0.036 (Statistically significant), indicating a meaningful difference in ferritin levels between the two groups.**Total Serum Bilirubin (TSB) (mg/dl)**:**HCV Positive**: Mean = 1.7.**HCV Negative**: Mean = 1.4.**P-Value**: 0.28 (Not statistically significant), suggesting similar bilirubin levels in both groups.**Aspartate Transaminase (AST) (u/l)**:**HCV Positive**: Mean = 14.3.,**HCV Negative**: Mean = 11.8.**P-Value**: 0.15 (Not statistically significant), indicating similar levels of liver inflammation or damage.Alanine Transaminase (ALT) (u/l):HCV Positive: Mean = 20.1.HCV Negative: Mean = 14.5.P-Value: 0.16 (Not statistically significant), showing similar ALT levels between the groups.Alkaline Phosphatase (u/l):HCV Positive: Mean = 153.9.HCV Negative: Mean = 146.3.P-Value: 0.30 (Not statistically significant).

3. Prevalence of Hepatitis C viral infection

Data for three years (2012-2014) of the volunteer blood donors were retrospectively reviewed, according to these data, the overall prevalence among those subjects was 0.10% for HCV and 0.29 for HBV, table 3.with no statistically significant differences between these years regarding the rates of infection, Table 3.

Year	**No. of volunteers**	**HCV positive**
2012	20452	19
2013	19734	16
2014	19700	19
Total	59886	54
Seropositivity		**0.10%**

Table 3. Prevalence of HCV infection among volunteer blood donors for the period 2012-2014.

Among the 254 thalassemic patients 17 had positive HCV infection and 237 were negative, this give a prevalence of 6.7% among thalassemic patients which was much higher than the volunteer donors. (Table 4 and fig. 4)

HCV	**No. of patients**	**%**
Positive	17	6.70
Negative	237	93.3
Total	254	100.0

Table 4. Seropositivity of HCV infection among the 254 Thalassemic patients.

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4. Relationship between HCV infection and other risk factors:

Table 5 shows the cross-tabulation between the HCV and other variables, as it shown in this table prevalence of HCV infection was significantly increased with the advancing age of the patients (P=0.043), moreover, the mean age of the HCV positive group was significantly higher than HCV negative, 12.5±3.8 vs. 10.1 ± 4.2 years. , respectively, (P=0.022)

Other variables, including gender and splenectomy showed no statistically significant association with the prevalence of HCV.

Demographic variable		HCV positive		HCV negative		P.value
		No.	%	No.	%	
Age group (years)	< 6	1	2.3	43	97.7	0.043
	6 – 12	7	5.3	125	94.7	
	> 12	9	11.5	69	88.5	
Mean± SD		12.5± 3.8		10.1± 4.2		0.022
Gender	Male	7	5.7	116	94.3	0.62
	Female	10	7.6	121	92.4	
Splenectomy	Yes	0	0.0	10	100.0	0.49
	No	17	7.0	227	93.0	

Table 5. Correlation between HCV infection and demographic variable:

There was a statistically significant association between the higher number of transfusion that the patients did received and the higher prevalence of HCV infection (P = 0.043), when the number of transfusion compared as a mean the differences were statistically significant (P=0.022); it had been significantly found that HCV positive patients had significantly higher number of transfusion (P=0.011) and there was a statistically significant association between the number of transfusion and the prevalence of HCV, (P=0.040), (Table 6).

Transfusion	HCV positive		HCV negative		P
	No.	%	No.	%	
≤ 100	1	2.2	44	97.8	**0.040**
101 – 200	6	5.4	105	94.6	
201 – 300	6	9.8	55	90.2	
> 300	4	10.8	33	89.2	
Mean ± SD	243 ± 85		189 ± 92		**0.011**

Table 6. Correlation between number of blood transfusion and HCV infection

Regarding the Laboratory findings, only serum ferritin showed a statistically significant association with the HCV infection; HCV positive group had significant higher serum ferritin level than HCV negative, (P=0.036), the mean S. ferritin was 4159.4± 1900.5 and 3083.7 ± 1867.6, respectively) Table 7.

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Table 6. Correlation between number of blood transfusion and HCV infection The data clearly demonstrates a significant increase in HCV positivity with the number of blood transfusions received. .The mean number of transfusions for HCV positive patients is 243 (± 85), whereas for HCV negative patients it is 189 (± 92). The P-value of 0.011 indicates this difference is statistically significant.

Table 7 Laboratory findings of the patients The significant finding is higher serum ferritin levels in HCV positive patients, indicating more severe iron overload. Other parameters show trends but are not statistically significant.

Laboratory findings	HCV positive		HCV negative		P
	Mean	± SD	Mean	± SD	
Serum ferritin	4159.4	1900.5	3083.7	1867.6	**0.036**
TSB	1.7	1.3	1.4	0.9	0.28
AST	14.3	6.6	11.8	4.8	0.15
ALT	20.1	15.6	14.5	8.5	0.16
Alkaline phosphatase	153.9	35.7	146.3	52.0	0.30

Table 7. Laboratory findings of the patients

Further analysis to assess the association of S. ferritin with the age in HCV positive and HCV negative groups , it had been found that s.ferritin increased significantly (p=0.033) with the age in HCV positive group but not significant in HCV negative (P>0.05), table 8, which indicated a direct association between these two variables, figure 5.

HCV	**Age (years)**	**N**	**Mean s. ferritin**	**Std. Deviation**	**P.value**
HCV positive	3- 6	1	942.0	-.	**0.033**
	6 – 12	7	3410.8	1920.1	
	12-18	9	5099.1	1296.4	
	Total	17	4159.4	1900.5	
HCV negative	3-6	44	2938.6	2332.5	0.081
	6 - 12	124	2898.4	1662.5	
	12-18	69	3506.9	1853.7	
	Total	237	3083.7	1867.6	

Table 8. Association between S. ferritin and age

The table shows that serum ferritin levels, indicative of iron overload, significantly increase with age in patients with HCV infection

Figure 5. The direct association between the age and serum ferritin in HCV positive thalassemic patients (N=17)

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A direct (positive) association had been found between S. ferritin and the number of transfusion, patients with higher number of transfusion had the higher mean S. ferritin than those who received less frequent transfusion, however the association was statistically significant in HCV positive patients (P=0.031), Figure 6., and not in those HCV negative.

HCV	No. of transfusion	N	Mean s. ferritin	Std. Deviation	P.value
Positive	≤100	1	942.0	.	**0.031**
	101 - 200	6	3077.0	1867.7	
	201 - 300	6	4733.3	1805.8	
	> 300	4	5395.5	734.9	
	Total	17	4159.4	1900.5	
Negative	≤100	44	2953.4	2307.4	0.061
	101 - 200	104	2792.6	1657.1	
	201 - 300	55	3269.9	1717.9	
	> 300	33	3626.7	1858.7	
	Total	236	3083.7	1867.6	

Table 9. Association between S. Ferritin and frequency of blood transfusion

The table show in HCV positive patients, there is a significant increase in serum ferritin levels with the number of transfusions, indicating a higher iron overload. The correlation in HCV negative patients is less pronounced, but still present.

Figure 6. The direct (positive) association between S. ferritin and frequency of transfusion in HCV positive thalassemic patients (N=17). The figure shows higher serum ferritin levels in HCV positive patients, indicating more severe iron overload Other parameters show trends but are not statistically significant

B. Discussion

The current study conducted in the Thalassemia center in Karbala Teaching Hospital/ middle of Iraq aimed to detect the prevalence and risk factors of HCV in thalassemic patients. The studied group consisted of 254 thalassemic patients who attended this center during the study period. The mean age of the studied group was (10.2 ± 4.3), ranged 3-18 years. Females were relatively more than males, 51.6% and 48.4%, respectively.

Among the 254 thalassemic patients , Anti HCV was positive in 17 patients giving a prevalence of 6.7% , the prevalence of HCV reported in the current study was lower than that reported in a previous Iraqi study was conducted by Imran A**.** in 2011 [55]. who reported a prevalence of (12.5%). Other previous Iraqi studies on beta-thalassemic patients reported a wide range of 15-67.3% for HCV prevalence; Rahman et al[56]. in 2000 reported a prevalence of 26.4% in Diyala, Majeed, in 2002 [57].found aprevalence of 15% in Najaf**,** Al-Kubaisy et al [58]. reported a prevalence of 67.3% among 559 Iraqi children with thalassaemia in 2006**.** Abed B [59].in 2008 reported a prevalence of 46% in Baghdad (Ibn-Albalady hospital).

In comparison with previous Iraqi studies our study that reports prevalence of 6.7% indicates a significant reduction in the prevalence of HCV than the last years.

On the other hand, prevalence reported in the present study was lower than that reported in an Iranian study; in which Ataei et al [1].found a prevalence of 8% among 466 Iranian patients with major thalassemia during the period 1996-2011, additionally a retrospective cross-sectional Iranian study[60]. was conducted on 206 thalassemia patients during 2006-2007 reported an overall prevalence of anti-HCV of 28.1%.

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Other studies from some countries reported that HCV infection rate widely varies in different countries; Daw MA and Dau AA [61].mentioned in a review article that the prevalence of HCV infection in thalassemia patients was 42.4% in Morocco, and 40% in Saudi Arabia, moreover, prevalence studies from other countries revealed wide range in the prevalence of HCV infection among thalassemia patients; an Indian study [62].reported a prevalence of 18% , another study involving 104 thalassemic patients in Thailand [63]. showed that prevalence of HCV infection among Thai thalassemic patients was 20.2% . In Jordan Al-Sweedan et al in 2008 [64]. found a prevalence of 32.8%. Therefore, the rate we found in this study does not appear to be very high, however, it had been widely postulated that the countries with a higher HCV prevalence in general population had a higher prevalence rate among thalassemia patients, too. For instance, a study in Egypt in 2010 [65].reported that prevalence of anti-HCV positive was 40.5% by ELISA considering the fact that the prevalence in their controls (general population) was 3%. However, the virus is distributed worldwide with a prevalence varying in different countries from 0.2% up to 40% [66], [67]., moreover , HCV was found to be remarkably high among thalassemia patients who received repeated blood transfusion [61].

It is worth mentioning, that the HCV infection rate reported in our study much higher than that reported among the volunteers blood donors during the period 2012- 2014, where overall sero positivity of HCV for the three years was 0.1%, these indicated the higher risk of HCV infection among thalassemic patients, compared to the general population. This higher prevalence might attributed to the fact that thalassemic patients were frequently exposed to blood transfusion process and more liable to get the infection.

Regarding the risk factors for HCV infection in thalassemic patients in the current study, the mean age was significantly ($p=0.022$) higher in patients with positive HCV (12.5 ± 3.8) compared to negative subjects (10.1 ± 4.2). on the other hand the sero positivity appears to be significantly ($p=0.043$) increased with the advancing age . The current study shows lower sero positivity (2.3%) among those aged less than 6 years compared to 5.3% among those aged 6-12 years and the higher prevalence among those aged more than 12 years. The higher rate of HCV infection in advancing age patients, reflecting increase frequency of transfusion ($p<0.01$) and revealed the importance of providing safe blood to reduce the incidence of HCV infection in thalassemic population. these findings agreed that reported by Boroujerdnia et al [62].in Iran in 2012, also in an Egyptian study, Mansour et al in 2010 [65]. found that the mean age of HCV patients was significantly higher than HCV negative group and concluded that older age was significantly associated with a higher prevalence of HCV. Similar findings were also consistent with that reported in earlier studies[1], [59], [61].

In the current study, the sero positivity of HCV infection was relatively lower in male patients (5.7%) than females (7.6%), however, the difference between both genders was statistically insignificant indicated no significant association between the prevalence of HCV infection and gender, these findings were compatible with other earlier studies [59], [1]. , (Abed B, Ataei), these findings were also supported by that reported by Ansari et al [68]. in 2008 who found the prevalence of this infection among males and females was 12.8 and 16%, respectively with no significant difference was seen between males and females regarding prevalence of hepatitis C.

Despite splenectomy is associated with high incidence of complications in thalassemic patients [69]., the current study found no significant association between splenectomy and HCV infection, where all the 10 patients with splenectomy were HCV negative, this finding in agreement with a previous Iraqi study was conducted by Easa Z in Karbala in 2009. Also these finding agreed that of Ansari et al in 2007 [68].and Mahdaviani et al [70].in 2004.

In contrast different studies found that splenectomized patients were significantly more likely to have HCV infection than non-splenectomized; a strong association had been reported between splenectomy and higher prevalence of HCV infection in earlier studies [1]. Triantos et al [71].found a significant association between splenectomy and higher sero postivity of HCV infection in 144 Greece thalassemic patients in 2013, another study from Australia was conducted by Yapp et al [72].revealed a higher prevalence of HCV infection among splenectomized thalassemic patients than non-splenectomized.

Splenectomy has been a common management strategy for reducing regular transfusion requirements, iron overload, and extramedullary hematopoiesis in patients with hemoglobinopathies [72] ; however, the use of

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splenectomy in thalassemia has declined in recent years. This is partly due to a decreased prevalence of hypersplenism in adequately transfused patients. There is also an increased appreciation of the adverse effects of splenectomy on blood coagulation. In general, splenectomy should be avoided unless absolutely indicated [73].

The current study revealed that higher number of transfusion significantly associated with higher sero positivity of HCV infection ; the mean number of transfusion was significantly higher in HCV positive patients than HCV negative , on the other hand, the lower prevalence (2.2%) was found in patients who received 100 transfusion or less while the higher prevalence (10.8%) among those received > 300, this was expected, as the mainstay of management of thalassemia major is lifelong blood transfusions which increase the risk of transfusion transmitted HCV infection. This finding supported that reported by Ataei et al during 1996 -2011 [1]. Who found that the higher number of units transfused per month, number of transfusions per month and duration of transfusion had significant association with HCV seropositivity, that HCV is the major cause of post-transfusion hepatitis infection (PTH), and patients with thalassemia major are at high risk of hepatitis C due to the blood transfusion from donors infected by HCV. These findings are also in agreement with some earlier studies, found a high prevalence of HCV (20%) in multiply transfused thalassemia major patients. [60], [74], [75] , from other point of view, A three-years prospective study from India by Choudhury *et al* [75], observed that anti-HCV prevalence in the same number of thalassemia major patients during three years was 23%, 30.7%, and 35.9% each year, respectively.

Introduction of tests for screening of blood donors after 1995 has markedly reduced the risk of HCV transmission through blood product transfusion [1]. This result clearly indicates high incidence of transfusion transmitted hepatitis in thalassemic patients and much higher incidence of HCV infection compare to donor population is a matter of concern and research [76]. Other study from Colombia [73]suggested that having received more than 48 units of blood components is a main risk factor associated with infection by HCV [77]

The findings of Ocak et al [78] indicated that patients who were anti-HCV positive had a significantly higher mean number of blood transfusions and peak serum alanine transaminase level than anti-HCV-negative patients. Wanachiwanawin et al [79]showed that there was no significant relationship between the presence of anti-HCV antibodies and the number and frequency of blood transfusions.

Our findings highlighted blood transfusion as the main risk factors for HCV infection among beta-thalassemic patients. The higher rate of HCV infection in older patients, as well as patients with more number of units transfused, more number of transfusions per month and longer duration of transfusion display the importance of providing safe blood to decrease the incidence of HCV infection in thalassemia population and confirm the important role of blood donors screening in the prevention of viral transmission.

The present study demonstrated a significant higher mean serum ferritin (4159.4±1900) ng/dl in HCV positive than HCV negative patients (3083.7±1867.6). These findings are in accordance with that of Anwar et al study [80], who found the mean serum ferritin was lower and degree of hepatic fibrosis was less in hepatitis C negative patients of thalassemia major. The higher rate of HCV infection in patients with thalassemia who had higher serum ferritin level reflecting transfusion of more units of blood and revealed the importance of providing safe blood to reduce the incidence of HCV infection in thalassemia patients. From other point of view, the current study found that older patients and higher number of transfusion were significantly associated with higher serum ferritin levels among HCV positive patients but not significant in HCV negative, these findings reflecting indirect relationship between HCV infection and higher serum ferritin, as the older patients and multiple transfusion were significantly associated with higher prevalence of HCV infection and also associated with higher serum ferritin that lead to higher serum ferritin in HCV positive group. These findings consistent with previous studies concerned with this subject which referred that older thalassemic patients and multiple transfusion both associated with higher levels of serum ferritin and higher prevalence of HCV infection [80], [81], Moreover Riaz et al [81] mentioned that, the mean serum Ferritin levels are approximately ten times higher than the normal recommended levels for normal individuals and use of iron chelation therapy and titrating the dose of according to the need can significantly lower the iron load reducing the risk of iron-overload related complications leading to a better quality of life and improving survival in beta thalassemia major patients [81].

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The mean levels of total TSB, ALT, AST and ALP were higher in HCV positive group than HCV negative; nonetheless, the differences in these parameters were statistically insignificant [82]. Found no correlation with liver function tests (alanine aminotransferase and aspartate aminotransferase: ALT and AST), but a significant correlation was observed in respect to the duration of dialysis and the number of units transfused. Consequently, it still seems that blood transfusion is the main factor for increasing the incidence of HCV in thalassemia sufferers and haemodialysis patients. Findings of the current study regarding these parameters disagreed, in part; Alvai et al [83]. who demonstrated that Anti-HCV positive subjects have significantly higher ALT level conducted that reported in previous study

Wu et al [84] study suggested that increased ALT's levels occurred more frequently in hepatitis C positive thalassemia major patients. Chang et al [85] showed that the prevalence of raised ALT and AST in the HCV-positive group was more significant than in the negative group. Wang et al[86] showed a strong positive correlation between the prevalence of an elevated ALT level and anti-HCV positivity, earlier study by the same authors, Wang et al[87], showed that subjects with elevated ALT levels were more likely to be seropositive for anti-HCV. The serum level of alanine aminotransferase was found to be significantly altered between the two groups of HCV-infected and non-infected thalassemic patients in Chakravarti and Verma's [88]study. The prevalence of hepatitis viruses and raised ALT levels are found to be significantly associated with the increasing age and number of blood units transfused to them that was shown in Jaiswal's et al [89]study.

The observations of the current study strongly indicated that blood transfusion and older age are the main risk factor for HCV infection acquisition among thalassemic patients[90], from other point of view, the higher rates of HCV infection in older thalassemia patients, patients who had higher number of transfusion and those with higher serum ferritin level- all reflecting transfusion of more units of blood and revealed the importance of providing safe blood to reduce the incidence of HCV infection in thalassemia patients[91].

Conclusion

The seropositivity of hepatitis C infection among patients with thalassemia major in Karbala was lower than that reported in other Iraqi provinces and the neighborhood countries.

There was a significant reduction in the prevalence of HCV infection in thalassemic patients compared to the last years.

The seropositivity of HCV infection was much higher in Thalassemic major patients compared to volunteer donors.

Advancing age was significant risk factor to get HCV infection in Thalassemia major patients in Karbala.

Multiple transfusion and higher number of blood units transferred were major risk factors related to higher seropositivity of HCV infection among the studied group.

The prevention of HCV transfusion transmission represented a challenge for transfusion medicine.

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