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# Factors Affecting the Transmission of Hepatitis C Among the Thalassemic Patients in Holy Najaf

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**Abstract**

On a global scale, thalassemia is the most frequent genetic condition. The reason that has made thalassemia so widespread are unknown, but they are thought to be related to malaria's geographic distribution. Children with thalassemia have shorter red cell lives, fetal hemoglobin in their red cells longer than normal, and more susceptible red cells to oxidative stress. In humans, thalassemia major is a prevalent hemoglobinopathy. Because thalassemia patients require multiple blood transfusions which is a common transmission vector for hepatitis C virus (HCV), numerous studies have found varying prevalence of hepatitis C among thalassemia major patients. As a result, this study was carried out to discover anti-HCV in thalassemia patients in our location. The main aim of this study is to find out the factors that increase the chance of getting HCV infection in thalassemia patients via a clinical and serological investigation of those patients in Holy Najaf. This is a descriptive analytic study carried out at The Hematology Center in al–Zahraa Teaching Hospital for Maternity and Children in Holy Najaf from October 2019 to October 2020. A total number of 550 patients, 330 males and 220 females, who registered in thalassemic center were surveyed; among them, 48 thalassemic patients were found to have HCV infection when their medical records were analyzed. A detailed clinical account was made for every patient by using a proforma, taking into account information like name, age, sex, residency, age at starting blood transfusion, frequency of blood transfusion per month, splenectomized or not, blood group, HCV antibodies test, and liver function test. The total infected donors with HCV were 43 (0.17%) and 62 (0.30%) at 2019 and 2020 respectively. The study group comprised 48 thalassemic patients, 33 (68.75%) males and 15 (31.25%) females. The mean ± SD age was 18.4 ± 7.57months ranging from 2 to 35 years old. There was a direct association between age and seropositivity to anti-HCV as the latter was significantly associated with older ages ($P \leq 0.01$). However, there was no association between gender and anti-HCV seropositivity as there were no significant differences ($P= 0.653$). Out of 48 patients, 26 (54.14%) live in urban while 22 (45.17%) live in rural areas. In regard to residency, however, there was no direct relationship ($P \leq 0.01$) between the residency and the seropositivity to anti-HCV. Yet, there is a high significant relationship ($P \leq 0.01$) between frequency of blood transfusion per month and seropositivity to anti-HCV. HCV seropositivity was significantly associated with the longer duration of the disease ($P \leq 0.01$). Besides, patients of O+ blood group represented a higher ($P \leq 0.01$) seropositivity to anti-HCV than in patients with other blood groups; meanwhile, patients with Rh- showed a lower degree of seropositivity to anti-HCV. In addition, the study showed a highly significant ($P\leq 0.01$) relationship between splenectomy and seropositivity to anti-HCV.

**Key words:** β- thalassemia; Hepatitis C; Seropositivity.

## INTRODUCTION

Thalassemia syndromes are inherited hemoglobin synthesis abnormalities in which one or more globin chains are produced insufficiently or not at all. Alpha-thalassemia and beta-thalassemia are the two most frequent kinds of thalassemia, in which one of the two chains is formed in insufficient amounts [1].

Beta-thalassemia major is said to be prevalent predominantly in the Mediterranean and Middle Eastern region, including Italy, Greece, and Turkey, and Iran, Pakistan, India, and China, respectively. In these countries, the frequency of the thalassemia gene ranges between 5 and 25%. In the Far East, notably Thailand, alpha-thalassemia is common, with about one-fourth of the population carrying the gene for one of the two types of thalassemia[2].

The name of the globin whose production is affected is used to classify thalassemia genetically. There is an excess of alpha chain synthesis compared to beta chain synthesis in beta-thalassemia disorders. The abnormalities are expressed in both heterozygous and homozygous individuals, and the inheritance mechanism is autosomal. Beta thalassemia is divided into two kinds, each with further subclasses. Thalassemia minor, or trait, refers to heterozygous state, whereas thalassemia major, or Cooley's anemia, refers to homozygous state. A multitude of factors, including race and interaction with other inherited erythrocytic illnesses, determine the severity of certain kinds of thalassemia[3]

HCV infection is seen all over the world and according to World Health Organization (WHO) estimates, up to 3% of the world's population (170 million) is infected with HCV[4]. Children with thalassemia who undergo repeated blood transfusions are at an increased risk of contracting the HCV[5]. Infection rates in healthy blood donors range from 0.01 to 0.02% in northern Europe, 1 to 1.5% in southern Europe, and 6.5% in portions of equatorial Africa[6]. In Egypt, prevalence rates have been reported to be as high as 20%. Because of this disparity, alternative preventive techniques, community intervenetions, and even therapy procedures must be chosen based on economic and social factors [7].

Only 15-25% of sick people appear to have totally recovered from their infection and are no longer contagious. This implies the rest develop chronic infection and may become contagious as soon as one to two weeks after exposure, and they will remain infectious (carrier) for the rest of their lives. Approximately 30% of chronically infected people just have persistent infection and do not develop liver disease, refed them as "healthy carriers"; 50% have no symptoms but have elevated liver enzymes, and 20% have clinical liver disease [8]. A chronic liver disease may progress to cirrhosis in between 10 to 38% within approximately 20 years while a hepatocellular carcinoma develops within approximately 10 years after appearance of cirrhosis, with a prevalence of at least 20% [9].

*Diagnosis*

1. Serological tests for HCV specific antibodies: An anti-HCV antibody is not protective; it does not confer immunity, and is usually present simultaneously with viruses [10].

(a) Enzyme Immuno Assay (EIA)

HCV is usually positive for approximately 6-8 week after the patient's exposure to it, whether or not having symptoms. Mean-while, the sensitivity of EIA is at least 95% after window period.

(b) Recombinant Immuno Blot Assay (RIBA)

RIBA procedures are carried out on a cellulose strip, where four HCV antigens are blotted and reacted with the serum of the patient. In 85% of HCV-infected patients who have reactivity in at least two bands (RIBA-2), results are observed to be positive.[11]

2. Direct demonstration of HCV RNA by PCR: A reverse transcriptase converts viral RNA from whole blood, serum, plasma, and fixed tissues to complementary DNA (cDNA), which is then amplified by polymerase chain reaction (PCR). This is a confirmatory test that is both sensitive and specific and is particularly useful for monitoring the efficacy of interferon therapy.[8] False negative, but not false positive, results do exist.

3. Quantification of HCF RNA: The test results may be used to distinguish between treatment responders and nonresponders[9].

4. Determination of HCV genotypes: The diagnosis of HCV genotypes will also aid in determining the infection's severity, potential prognosis, and management. Type Ib appears to be more aggressive, poorly reacting to interferon therapy, and necessitating more liver transplants, whereas type 2 appears to be more benign and responds well to interferon therapy[12,13].

*Treatment*

For six months, a three-time a week interferon Alfa-2b (Intron A) 3 million U sub-cutaneously is the conventional treatment. This therapy produces an initial response in 40% of patients, however, only half or less of these individuals have a longterm maintained response. In this therapy, what influences the response of chronic hepatitis C is the viral genotype, Ib type with poor response, level of viremia, severity of liver disease, and hepatic iron content, or high serum ferritin level mien poor response [14].

This study aims to show the possible risk factors of getting infection with HCV in thalassemic patients in Holy Najaf.

**Materials and Methods**

This study was carried out at the hematology center in al-Zahraa Teaching Hospital for Maternity and Children in Holy Najaf from October 2019 to October 2020 where a total of 550 patients registered in the Thalassemic Center were surveyed and the medical records of 48 thalassemic patients infected with HCV were analyzed.

The data collected from each medical record includes:

1- Name, age, sex and residence.
2- Age at starting blood transfusion.
3- Frequency of blood transfusion per month
4- Splenectomies or not.

The total number of blood donors and the patients infected with HCV during 2019-2020 in Holy Najaf were collected from the Public Health Department, CDC Section, in Najaf Health Directorate. Then, in a test for HCV antibodies, a second-generation ELISA kit was used for identifying HCV antibodies. The instrument used was Biotech, manufactured in China and the procedure for detecting HCV was made by Foresight method.

As for the liver function tests, 5 ml of blood sample were collected from each patient; 200 micro serums were analyzed.

The three enzymes of ALT, AST and ALP were assessed on the Chemistry autoanalyzer (bt. 35i), manufactured in Turkey.

All of the analyses were statistical carried out with software (SPSS version 21). The Chi squared (X2) test was used to look for the significant differences in nonparametric data (tables 2–8). Besides, the paired sample t-test was used to evaluate the continuous variables in Table 9 (enzymes assay). At 1% and 5%, P-values of 0.05 and 0.01 were considered statistically significant and highly significant, respectively.

## Results

Table (1) above shows that the total infected donors with HCV were 43 (0.17%) and 62 (0.30%) at 2019 and 2020 respectively. The total number of thalassemic patients was 550. The study group comprised 48 anti-HCV seropositive thalassemic patients (33 [68.75%] males and 15 [31.25%] females). The mean ± SD age in months was 18.4 ± 7.57 (range: 2 – 35 months).

Table (2) below shows the association between age and seropositivity to anti-HCV; there is a direct association between the age and the seropositivity to anti –HCV where HCV seropositivity was significantly associated with an older age ($P \leq 0.01$).

However, Table (3) below demonstrates no association between gender and seropositivity to anti –HCV where there are no significant differences ($P = 0.653$).

**Table 1:** Total number of blood donors and percentage of HCV infections among them during 2019-2020 in Holy Najaf

| Month | 2010 | | | 2011 | | |
|---|---|---|---|---|---|---|
| | No. of Blood donors | Infected | | No. of Blood donors | Infected | |
| | | No. | % | | No. | % |
| Jan. | 1786 | - | 0 | 2210 | 11 | 0.50 |
| Feb. | 1780 | 8 | 0.45 | 1486 | 11 | 0.74 |
| Mar. | 2122 | 5 | 0.24 | 2148 | 2 | 0.09 |
| Apr. | 2025 | 4 | 0.20 | 1918 | - | 0 |
| May. | 2991 | 5 | 0.17 | 2113 | 2 | 0.09 |
| Jun. | 2235 | 2 | 0.09 | 2153 | 13 | 0.60 |
| Jul. | 1996 | 14 | 0.70 | 2408 | 17 | 0.71 |
| Aug. | 2075 | - | 0 | 1657 | 1 | 0.06 |
| Sep. | 1613 | - | 0 | 1280 | 3 | 0.23 |
| Oct. | 1929 | 2 | 0.10 | 2029 | 1 | 0.05 |
| Nov. | 1789 | 1 | 0.06 | 2879 | 1 | 0.03 |
| Dec. | 2175 | 2 | 0.09 | 2133 | 11 | 0.52 |
| **Total** | 24516 | 43 | 0.17 | 24414 | 62 | 0.30 |

**Table 2:** Association between age and seropositivity to anti -HCV

| Age in year | No. | (%) | P-value |
|---|---|---|---|
| < 5 | 7 | 14.58 | |
| ≥ 5 – 10 | 8 | 16.67 | |
| > 10 – 15 | 10 | 20.83 | 0.000** |
| >15 – 20 | 12 | 25.00 | |
| >20 | 11 | 22.92 | |
| **Total** | 48 | 100 | |

** *Significant at P* ≤ 0.01, Chi squared ($X^2$) test

**Table 3:** Association between gender and seropositivity to anti -HCV

| Gender | No. | % | P-value |
|---|---|---|---|
| Male | 25 | 52.08 | 0.653 NS |
| Female | 23 | 47.92 | |
| **Total** | 48 | 100 | |

*NS=no significant at P* ≤ 0.05, Chi squared ($X^2$) test

Table (4) below demonstrates that out of 48 patients, 26 (54.14%) live in urban, 22 (45.17%) in rural area. In regard to residency, there is no direct association (*P* ≥ 0.05) between the residency and the seropositivity to anti-HCV.

According to Table (5) below, there is a significant correlation between blood transfusion per month and that making blood transfusion more than once a month was highly affecting (62.5%) than that of once a month in the other group.

Table (6), on its turn, shows that there is a direct relationship between duration of the disease and the seropositivity to anti-HCV, where HCV seropositivity was significantly associated with the longer duration of the disease (*P* ≤ 0.01).

Patients of O+ blood group represented the higher (*P* ≤ 0.01) seropositivity to anti-HCV than those of other blood groups, *cf*. Figure 4. However, patients with Rh-ve showed lower seropositivity to anti-HCV, as shown in Table (7) below.

Table (8) shows that there is a highly significant (*P* ≤ 0.01) associa-tion between splenectomy and the seropositivity to anti-HCV, 28 (58.33%) patients with splenectomy had positive hepatitis while 20 (41.67%) non-splenectomized patients were hepatitis positive.

Table (9) shows the liver enzymes in previous and recent periods of infection, the titer of all liver enzymes was higher in recent (*P* ≤0.05) than previous periods.

**Table 4:** Association between residence and seropositivity to anti -HCV

| Residence | No. | % | P-value |
|---|---|---|---|
| Urban | 26 | 54.17 | 0.092 NS |
| Rural | 22 | 45.83 | |
| **Total** | 48 | 100 | |

*NS=no significant at P* ≤ 0.05, Chi squared ($X^2$) test

**Table 5:** Association between blood transfusion per month and seropositivity to anti-HCV

| No of Blood Transfusion | No. | % | P-value |
|---|---|---|---|
| Once per month | 18 | 37.5 | 0.000** |
| More than once per month | 30 | 62.5 | |
| **Total** | 48 | 100 | |

** *significant at P* ≤ 0.01, Chi squared ($X^2$) test.

**Table (6).** Association between duration of disease and seropositivity to anti-HCV

| Duration of disease | No. | % | P-value |
|---|---|---|---|
| <1 yr | 5 | 10.42 | |
| 1 – 5 | 16 | 33.33 | 0.006** |
| >5 | 27 | 56.25 | |
| **Total** | 48 | 100 | |

** *significant at P* ≤ 0.01, Chi squared ($X^2$) test.

**Table 7:** The Association between blood groups and seropositivity to anti-HCV

| Blood groups | No. | % | P-value |
|---|---|---|---|
| A+ | 10 | 20.83 | |
| A- | 1 | 2.08 | |
| B+ | 10 | 20.83 | |
| B- | 1 | 2.08 | |
| AB+ | 8 | 16.67 | 0.001** |
| O+ | 16 | 33.33 | |
| O- | 2 | 4.16 | |
| **Total** | 48 | 100 | |

** *Significant at P* ≤ 0.01, Chi squared ($X^2$) test

**Table 8:** The Association between splenectomy and seropositivity to anti-HCV

| Splenectomy | No. | % | P-value |
|---|---|---|---|
| Splenectomized patients | 28 | 58.33 | |
| Non-splenectomized patients | 20 | 41.67 | 0.000** |
| **Total** | 48 | 100 | |

** *significant at P* ≤ 0.01, Chi squared ($X^2$) test

**Table (9)** Liver enzymes in previous (six months) and recent period of infection

| Liver enzymes | previous | recent | P-value |
|---|---|---|---|
| SGpT(ALT) | 44.74±3.49 | 49.87±4.86 | 0.034* |
| SGoT(AST) | 32.40±3.75 | 39.25±4.32 | 0.032* |
| **ALP** | 84.62±11.69 | 110.22±13.860 | 0.013* |

* *Significant at P* ≤ 0.05, t-student test.

**Discussion:**

The risk of hepatitis infection among thalassemic patients is related to many factors that have important effects on the prevalence of hepatitis infection. These factors include age, gender, residence, frequency of blood trans-fusion per month, blood group, duration of thalassemia and splenictomy [15].

The present study has shown that in Najaf hematology center, the total donors infected with HCV were 43 (0.17%) and 43 (0.30%) in 2019 and 2020 respectively. By contrast, other studies showed that infection rates among healthy blood donors range from 0.01-0.02% in northern Europe, 1-1.5% in Southern Europe, and 6.5% in portions of Equatorial Africa [16].

This study has revealed that 8.73% of thalassemic patients were infected with HCV. However, another study Mosul Province (Iraq) reported that 26.20% of thalassemic patients were infected with HCV[17]. A higher infection rate (18%) was reported in Iran [15]. The other studies from some neighboring Arabic countries reported an HCV infection rate of 33% in Kuwait in1998 (sample size 129 patients) [18] and 40% in Bahrain in 1995 (sample size 242 patients) [19] and in Jordan in 2001(sample size 143 patients) [20].

A study by Allavian et al. (2010) compiled all available data on epidemiological characteristics and risk factors affecting HCV infection in thalassemia patients in Eastern Mediterranean countries. They came to the conclusion that the results of the available study in this area are highly disparate, and the prevalence of HCV infection among the individuals living in this area is still unknown. [15] On the contrary, the present study has shown that the prevalence of hepatitis C was significantly higher among the older age group because this group usually has a longer duration and frequency of transfusion. Similarly, HCV infection was found to be highly prevalent in the older age groups of Taiwan thalassemic patients [21].

In this study, gender and residency were not risk factors for HCV. However, Abdul Nasir [22] statistically found in the region of

Southern Punjab there was significant evidence of gender survival that male patients of Thalassemia are at a higher risk than female patients. Besides, for Ali et al, males had a higher prevalence (17.30%) of HCV than that (12.68%) in females and that males are more likely to have HCV since they are exposed to more risk factors [23].

Furthermore, the present study has shown an evident association between the frequency of blood transfusion and prevalence of hepatitis C. It has been found that 37.5% of thalassemic patients who transfused once per month are hepatitis positive while 62.5% of those who received transfusion more than once per month were positive for hepatitis C. Yet, for Angelucci and Pilo (2008) [24], the prevalence of HCV infection was demonstrated to be related to the number of units of blood received among thalassemic patients transfused before the 1990s, and surpassed 80% in adult patients.

The rate of new infections in thalassemia patients has decreased significantly in recent years in nations with a high Human Development Index, but this has not been the case in countries with a low-medium Human Development Index. This was proved by unpublished data from an Androulla Eleftheriou survey done on behalf of the Thalassemia International Federation (TIF) from 2005 to 2007. HCV infection is a significant problem for patients with thalassemia major because the vast majority of continuously transfused patients live in underdeveloped or developing countries.

Shahram Mirmomen [25], followed the commencement of blood donor screening in Iran in 1995, demonstrated that the prevalence of HCV infection reduced considerably from 22.8% to 2.6%. Furthermore, patients who received unscreened blood were exposed to HCV infection six times more than those who received blood after the screening program began. The rigorous screening of blood donors is likely to eliminate the incidence of HCV infection among thalassemic patients in Iran in the future. He stated that these findings strongly suggested that blood transfusion was the most common cause of HCV infection in thalassemic patients, and that donor screening was extremely effective in preventing or mitigating viral transmission. The efficiency of blood donor screening has also been established in cohort studies from Italy [26] and the United States [27].

The higher rate of HCV infection in older patients, patients with thalassemia major, and subjects with higher serum ferritin levels indicating that more units of blood were transfused, highlighted the importance of providing safe blood to reduce the incidence of HCV infection in the thalassemic population [27].

In addition, the present study has shown that there is a direct association between the duration of the disease and the seropositivity to anti-HCV as HCV seropositivity was significantly associated with the longer duration of the disease ($P \leq 0.01$). This goes in agreement with other studies [27].

The prevalence of hepatitis C among the patients with O blood group was more than the other patients; this is maybe due to blood group O is higher than other group, therefore, it seems that they are at higher risk of infection than other patients.

This data is consistent with those of Ansari (28), who found that patients with the O blood type had the highest prevalence of hepatitis C (20.6%), implying that this blood group is more susceptible to contamination than other blood groups. As a result, proper screening of this blood type is much more critical.

Liver enzymes showed that Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP) levels significantly increased in recent reading of patients as compared to their previous levels. Touran S. [29] observed that a link was discovered between HCV RNA PCR and abnormal liver testing. The findings were in line with a recent study in Tonekabon thalassemic patients, which found a link between increased ALT and iron overload, transfusion index, age, and anti-HCV positive. Even in the absence of HCV infection, aminotrans-ferase flares are common in thalassemic patients, according to long-term follow-up of these patients. The levels of AST, ALT, and ferritin dramatically changed in patients, according to Touran S. [29] who hypothesized that there was a correlation between ALT and AST, ferritin and age, and ALT and ferritin.

Asma, et al [30] stated that serum ALT and AST more significantly raised in HCV positive patients in comparison to other thalassemic. Shekhar, et al [31] found that the Alanine aminotransferase Aspartate aminotransferase and Alkaline phosphatase levels significantly increased in posttrans-fused patients as compared to their pre-transfused levels.

Anti-HCV antibody has been linked to a number of risk factors. Anti-HCV positive was linked to the number of blood transfusion units, splenectomy, and thal-assemia duration in thalassemic patients [32].

In the present study, 50% of Splenectomized patients had positive hepatitis while 25% of the non-splenectomized patients were hepatitis positive. Splenectomy acts as an important risk factor. This is because many of Splenectomized patients are older than non-splenectomized patients (i.e., additional risk factor), and splenic-tomy done mostly in thalassemic patient because of hypersplen-ism which in turn increase the number of blood trans-fusion and the risk of hepatitis. So, early splenectomy (after 4 years and before 15 years) with good preoperative management can decrease the risk of hepatitis infection by decreasing the need for blood transfusion, with no significant increase in the rate of postoperative morbidity and mortality [33].

## CONCLUSION

1- The percent of HCV among thalassemic patients in Holy Najaf is lower than previous Iraqi studies.
2- Seropositivity is significantly related to age, frequency of blood transfusion per month, duration of the disease, and splenectomy.
3- Gender and residency show no associa-tion with the prevalence of HCV.
4- Patients of O+ blood group represented the higher seropositivity to anti-HCV than patients with other blood groups.

## RECOMMENDATIONS

1- In thalassemia patients with HCV chronic hepatitis or cirrhosis who have contraindica-tions to antiviral medication or have previously failed antiviral therapy, clinical surveillance of liver disease is required.
2- Effective screening program should be applied to all the donor of blood and blood product. It should have more than one screening available to increase its sensitivity as much as possible; so, further ensuring of the safety of donated blood, like use of PCR in screening program, is needed.
3- HCV infected donor should be followed; their families especially their partners should be followed as well by screening.

4- Further studies are necessary to prove if there is factual relationship between blood group & hepatitis C in thalassemic patients.
5- Patients who have been infected with HCV for a long time need to be counseled on how to avoid transmitting the virus to others.

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