INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 16 June 2026
Revised: 23 July 2026
Accepted: 09 Aug 2026
Published: 17 Aug 2026

Volume 12 Issue 08, 2026
Page No - 121-128
DOI - 10.55640/ijmsdh-12-08-14

Article Citation: Al-Kaif , L. A. I. K., Hameed, O. R., Merza, M. A., & Kazem, K. M. (2026). Association of Tumor Necrosis Factor-Alpha (TNF-α) With Hepatitis C Virus Infection: A Case-Control Study. International Journal of Medical Science and Dental Health, 12(08), 121-128. https://doi.org/10.55640/ijmsdh-12-08-14

Association of Tumor Necrosis Factor-Alpha (TNF-α) With Hepatitis C Virus Infection: A Case-Control Study

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Abstract

Background: Although apparent antiviral medications have greatly increased the likelihood of eradication, hepatitis C virus (HCV) infection is still a major host threat to liver infection and disease development because chronic contamination can result in persistent liver insufficiency, fibrosis, cirrhosis, and hepatocellular carcinoma. One important perceived inflammatory cytokine implicated in innate adaptive immune responses and chronic HCV is tumour necrosis factor-alpha (TNF-α). The purpose of this study was to assess the possible status of TNF-α as a marker of the pro-inflammatory immune response linked to HCV infection and to compare serum TNF-α concentrations in patients with HCV infection with those of seemingly healthy controls.

Materials and Methods: A quantitative sandwich enzyme-linked immunosorbent assay (ELISA) was used to assess blood TNF-α concentrations in a case-management study of 80 volunteers, comprising 40 patients with HCV infection and 40 trustworthy healthy controls. Anthropometric and demographic traits have also been evaluated.

Results: Compared to healthy controls, individuals with HCV had substantially higher serum TNF-α values. The HCV group's adjusted serum TNF-α consciousness was 59.14 ± 31.27 pg/mL, whereas the management populations was 18.15 ± 6,81 pg/mL. It was shown that differences between businesses were statistically

significant (P < 0.001). In conclusion, a substantial increase in serum TNF-α was shown to be correlated with HCV infection. TNF-α may also have potential as an immune marker of HCV contamination inflammation because elevated TNF-α awareness may also reflect more desirable pro-inflammatory immune activation in HCV-infected subjects and contribute to the inflammatory environment associated with liver injury. However, large-scale studies involving viral load, liver biochemical index, fibrous phase.

Keywords: Hepatitis C Virus, Tnf- A, ELISA, BMI.

1. Introduction

Despite the development of relatively strong external direct effects of HCV infection on a single curable viral disease, hepatitis C virus (HCV) infection continues to be a major global public fitness disorder due to its ability to progress from chronic viral infection to persistent hepatitis, cirrhosis, hepatocellular carcinoma (HCC), and liver-related death. However, there are still significant gaps in diagnosis, treatment access, and prevention. According to the World Health Organization's (WHO) hypothesis, HCV is responsible for a significant portion of viral hepatitis-related fatalities worldwide. Epidemiological monitoring highlights the ongoing need for early identification and the search for host factors linked to disease progression.

The dynamic interaction between viral replication and host immune responses determines the scientific outcomes of HCV infection. After infection, innate immunity triggers intracellular anti-viral pathways, interferon-mediated signalling, interferon-induced gene expression, and the formation of so-called adaptive immune responses. Thru targeted alterations in virus-specific T cells, immunological fatigue, and viral breakout mechanisms, chronic HCV infection allows viral tolerance despite ongoing immune activation, even tho effective viral clearance is not always attained [2, 3]. In the early phases of HCV infection, the innate immune response is very crucial. Intracellular pattern prestige receptors, signalling pathways that control type I and III interference, and different inflammatory mediators can help detect viral RNA. Hepatocytes, Kupffer cells, natural killer (NK) cells, and dendritic cells all contribute to immune activation and inflammation with intercellular limiliu antiviral defence, but they can become pathological when inflammatory activation is prolonged [2, 4].

The immune characteristics of hepatocytes and the hepatic microenvironment can be changed by HCV infection. Interacting with both resident and recruited immune cells, infected hepatocytes have the ability to control the expression of immunoregulatory, antiviral, and inflammatory pathways. While viral replication is comparatively less significant, prolonged infection may be redundant, which makes this ongoing modification of the liver tissue environment crucial. [3] Therefore, it is impossible to completely evaluate the immunological effects of HCV contamination in terms of viral load; On the other hand, another physiologically relevant aspect of HCV-associated illness is the host inflammatory response [5].

With activated macrophages, monocytes, NK immune cells, and T non-immune cell populations, tumour necrosis element-alpha (TNF-α) is a multifunctional pro-inflammatory cytokine that plays significant roles in innate immunity, leukocyte activation, inflammatory signalling, apoptosis, cellular stress response, and tissue repair. TNF receptors and downstream signalling pathways, including nuclear factor kappa-B (NF-κB), mitogen-activated protein kinases, and pathways related to cell survival or death, often mediate its organic interest [6].

TNF-α may have a dual biological function in the removal of HCV. On the one hand, via trafficking inflammatory and antiviral responses, TNF-α enhances host defence. On the other hand, hepatocellular damage and prolonged liver infection may be caused by persistent or unmediated TNF-α signalling. According to experimental research, HCV contamination can influence NF-κB-dependent signalling and control the cellular response to TNF-α, which provides a molecular explanation for the increased sensitivity of infected livers[7].

From a biological perspective, the union of TNF-α and liver fibroblasts is equally valid. As much as it can aid in development, chronic liver infarction stimulates the activation of hepatic stellate cells, which eventually develop a myofibroblast-like phenotype and contribute to extracellular matrix deposition and consequently persistent inflammatory signalling via cytokines, chemokines, macrophages, and various immune mediators [8,9]. At TNF-α-konsentratiónirnar kunnu broytast, kliniskar kanningar hava givið prīv fyri, meðan •haldandi HCV-smitta er. Early research on patients with persistent HCV infection showed much higher levels of circulating TNF-α compared to healthy controls and a corresponding rise in soluble TNF receptors, which supported systemic activation of the TNF-α pathway throughout persistent contamination, as seen in patients with chronic diseases TNF-α and suggests biochemical signs of liver dysfunction[10]. However, the lack of a strong correlation between TNF-α and HCV viral load suggested that TNF-α may also reflect the host's inflammatory activity rather than the quantity of circulating virus [11]. Prior to longitudinal observations confirming improved TNF-α concentrations in patients with advanced HCV-related liver disease, including cirrhosis and HCC in subjects with less dysfunction, additional evidence suggests that circulating cytokine profiles may correlate with the degree and severity of HCV-related liver disease [12]. Additionally, studies comparing

cytokine pairs revealed correlations between TNF-α and histology fibroblasts, which may help date the relationship between structural liver damage and inflammatory cytokine leaking [13]. Even after the virus has been eradicated, the immunological effects of HCV infection may not be entirely reversed. The majority of patients treated with DAA experienced a durable virological response, and the therapeutic outcomes of fast reduction of HCV replication are exceptional. Nevertheless, several adjuncts for immune modulation may continue following therapy. Significant alterations in T cell morphologies, innate immune signalling, cytokine production, and inflammatory biomarkers have been seen in studies analysing immunological responses after DAA therapy [2, 14, 15]. Moist DAA therapies may not be able to completely restore HCV immunity immunological disorders, according to a new evaluation. [3].

TNF-α translation is especially affected by changes in cytokine profiles following HCV elimination. Before and after DAA-mediated viral eradication, a prospective study combining several cytokines and growth factors looked at persisting variance in many inflammatory mediators, including TNF-α, compared to healthy people [14]. The fact that the difficulties were not fully recovered [15] raises the possibility that HCV-related inflammatory pathways might lead to reinfection. Cytokine alterations may have long-term effects on liver outcomes. Long-term changes in many cytokines were linked to the development of HCC in individuals with superior fibrosis who had viral eradication. In a unique way, changes in TNF-α following antiviral therapy were found to be unquestionably valuable in predicting HCC improvement of biomarkers, which was on record illuminating earlier questions [16]. These findings, however, should not be taken as proof that circulating TNF-α is a reliable biomarker for diagnosis or prognosis because a variety of host and environmental variables might affect its concentration.

TNF-α is a nonspecific inflammatory mediator that can be stimulated by age, obesity, metabolic abnormalities, concurrent infections, autoimmune diseases, and liver diseases. Despite the biological significance of TNF-α in infection, many aspects of its association with HCV infection remain incompletely characterised. The variance in TNF-α concentrations reported throughout research may be attributed to demographic observations, illness phases, antiviral therapy prestige, and sample processing.

In order to determine whether circulating TNF-α is linked to inhibition of the inflammatory response in the acute phase HCV immunum, it may also be possible to obtain additional information on the systemic inflammatory response associated with HCV contamination, expressed as pg/mL, by comparing serum TNF-α concentrations in HCV-infected subjects to seemingly healthy controls [8,15,16].

2. Methods

2.1 Study and participants

About 80 participants, comprising 40 patients with HCV infection and 40 trustworthy healthy controls, participated in a case-manipulation study. Those with HCV infection who met the Cooperative Medical Center's diagnostic criteria were included in the patient cohort. The cohort's seemingly healthy individuals had either clinically visible liver disease or externally detected HCV contamination. Anthropometric data, such as body mass index (BMI), and demographic traits, such as age and sex, were noted if available.

2.2 Important methodological requirement

Since anti-HCV positive cannot differentiate between ongoing infection and previously cleared infection, the final paper should clarify precisely how HCV infection was verified, such as by anti-HCV serology followed by HCV RNA detection.

2.3 Blood collection and serum preparation

A clever phlebotomy technique was used to get venous blood samples from the subjects. To extract serum, blood samples might be clotted and then centrifuged using a typical laboratory procedure. For biochemical immunoanalysis, serum samples were kept in suitable conditions.

2.4 Measurement of TNF-α

A quantitative sandwich enzyme-linked immunosorbent test (ELISA) was used to evaluate changes in serum TNF-α awareness. The assay was adjusted to finish in accordance with the manufacturer's instructions. The unit of measurement for TNF-α was pg/mL. The author of the final publication, u. S.S., contributed base, catalogue number, analytical sensitivity/detection variation, and version of the TNF-α ELISA package both within and across assays. Particularly for international publications, this information is crucial for repeatability.

2.5 Statistical analysis

IBM SPSS Statistics version 26.0 was utilised for statistical analysis. Frequencies and probabilities were used to express categorical statistics. Means ± standard deviation (SD) are used to display continuous variables. Categorical variables were compared between institutions using the chi-square test, while continuous variables were examined using the Independent Samples t-test, with a P value of less than 0.05 being regarded as full size. The most conclusive statistical estimate should also provide 95% confidence ranges and effect sizes, particularly for the variations in TNF-α concentrations, for a more potent worldwide script.

3. Results

3.1 Characteristics of the study population

Forty instances of HCV contamination and forty controls who appeared to be in good condition were observed. Within the available data set, there were no significant differences in the distribution of orgasm between the groups. Table (1), summarises anthropometric and demographic features.

Table 1. demographic and anthropometric characteristics of HCV and patients and healthy controls

Parameter	HCV patients (n=40)	Controls (n=40)	P value
Male, n (%)	31 (77.5%)	25 (62.5%)	0.143
Female, n (%)	9 (22.5%)	15 (37.5%)	
Age (years), Mean ± SD	53.78 ± 12.32	39.86 ± 20.21	<0.001
BMI (kg/m²), Mean ± SD	17.34 ± 5.22	19.98 ± 6.13	0.041

Chi-square test was used for sex and independent samples t-test for age and BMI. P <0.05 was considered statistically significant.

3.2 Serum TNF-A Concentrations

Serum TNF-α concentrations were found to differ significantly between HCV-infected patients and healthy controls. HCV-infected individuals had a mean serum TNF-α level of 59.14 ± 31.27 pg/mL, whereas healthy controls had a similar value of 18.15 ± 6.81 pg/mL. There was a statistically significant difference between the two populations (P <0.001).

Table 2. serum TNF-α concentrations in HCV patients and healthy controls

Parameter	HCV patients (n=40) Mean ± SD	Controls (n=40) Mean ± SD	P value
TNF-α (pg/mL)	**59.14 ± 31.27**	**18.15 ± 6.81**	**<0.001**

Independent sample t-test, P< 0.05 was considered statistically significant.

4. Discussion

Serum TNF-α awareness is 59.14 ± 31.27 pg/mL in HCV-infected patients compared to 188 pg/mL in dependably healthy controls, according to the current case manipulation observation. difference (P < 0.001) in systemic TNF-α-related inflammation; these results provide an intriguing comparison of the two groups. The altitude is biologically plausible given the known relationship between HCV and host immune mechanisms. In terms of interferons, cytokines, chemokines, and intracellular antiviral signalling pathways, HCV infection stimulates innate immune systems. While concurrent immune fatigue and viral immune evasion mechanisms promote prolonged infection, continuous antigen stimulation can also sustain the activation of innate adaptive immunological populations when viral clearance fails [2,3]. One element of this inflammatory network is TNF-α. Under inflammatory circumstances, activated macrophages, monocytes, NK cells, and other immune groups may contribute to the generation of TNF-α. Therefore, rather than the immediate aspect of viral replication itself, the elevated circulating TNF-α in the current HCV treatment may also represent the systemic activation of inflammatory pathways linked to persistent viral contamination.

Our results align with preclinical evidence of increased circulating TNF-α in chronic HCV infection. Nine serum TNF-α values were found in a conventional research of 53 individuals with chronic HCV [10]. The association of circulating HCV contaminants is often used, despite the fact that the absolute amounts range significantly from those found in the present, perhaps reflecting change in demographics, symptoms, testing procedures, and pre-analytical status: TNF-α.

Ren et al. reported that chronic HCV patients have higher serum TNF-α than healthy people. Crucially, whereas high-quality relationships were found with biochemical indicators of liver damage, TNF-α is no longer substantially linked with HCV virus load [11]. Because it implies that circulating TNF-α is linked to or may be linked to liver disease, this statement is very pertinent to understanding the current findings.

The current results can also be seen in light of earlier long-term studies on liver damage linked to HCV. It has been shown that the development of chronic hepatitis approaching cirrhosis and HCC increases cytokine concentrations, such as TNF-α, suggesting that systemic inflammatory activation may also grow to further differentiate with advanced liver disease [12]. Examining another, there was a substantial fibrotic correlation between serum TNF-α and C113. When taken as a whole, these findings offer an organic framework in which increased TNF-α may also contribute to the inflammatory milieu linked to chronic liver damage and fibrogenesis. Because chronic inflammatory signalling can produce hepatic stellate cells and promote extracellular matrix deposition, dating between TNF-α and fibrosis is physiologically crucial. Inflammatory cytokines from immune cells and damaged plaques are activated by activated stellate cells, which are significant effector cells in hepatic fibrogenesis. follow an inflammatory environment that can promote increased TNF-α fibroblast reworking in HCV, but the status rise can no longer be considered as proof that TNF-α alone predicts the severity of fibrosis since fibrosis status was not evaluated right away in donation analysis.

A possible harmful connection between HCV and TNF-α signalling is also supported by experimental data. HCV infection can increase vulnerability to inflammatory cytokine-mediated cell damage and modify NF-κB-established mobile responses to TNF-α. [7] These pathways offer a potential explanation for how cytokines that typically aid in host defence may also cause tissue damage when inflammatory activity persists. The TNF-α variations discovered in the current observation are significant. However, because serum cytokine measurements are highly dependent on assay characteristics, measurements, detection limits, modelling approaches, storage conditions, and biological variation, the significance of cytokine concentrations should be interpreted cautiously. As a result, independent of particular research, TNF-α concentrations may not be directly comparable to external estimates.

During the course of DAA treatment, gift effects are also significant. Modern DAA therapy directly targets viral proteins, in contrast to treatment mostly based on older interferon, and can provide a persistent virologic response in patients receiving maximum treatment. In many cases, hepatitis and fibrosis improve when viruses are eliminated, although immunopathologies discovered in states that are not affected [1]. Analysing cytokine growth curve profiles before to and during DAA administration revealed consistent variations in a number of cytokines, including TNF-α, when compared to healthy controls [14]. These findings support the idea that viral eradication, host rash country Furthermore, entire generalisations are not always interchangeable.

This conclusion is further supported by data from a number of recent immunological research. Normalisation or development of certain innate adaptive immune characteristics, such as TLR signalling and T-mobile cytokine responses, is linked to successful DAA therapy [17]. While other research has looked at inflammatory mediator remission following viral suppression, substance abuse has demonstrated immune activation with a persistent observational virologic response [18]. Immune changes linked to HCV may also have a longer biological route.

It is equally important to look at the relationship between long-term effectiveness and cytokine dynamics during therapy. Lu et al. assessed the cytokine profile of individuals with superior fibrosis following HCV eradication and noted that alterations in TNF-α during antiviral treatment were linked to an increased risk of HCC [16] 2.

Previous research highlights the potential significance of longitudinal evaluation of inflammatory and immunological markers rather than relying exclusively on unweighted baseline measures, even tho the current observation did not look at treatment response or the progression of hepatocellular carcinoma (HCC). In addition to normalising T cell production of interleukin-2 and interferon-γ and restoring TLR8 expression and activity in peripheral blood mononuclear cells, successful DAA therapies are linked to notable alterations in host immunological responses [17].

The idea that viral treatment no longer always results in immediate and complete normalisation of the host immune environment prior to TNF treatment may also help determine whether folded TNF-α indicates energetic viral contamination, persistent immune activation, or residual hepatitis. Additionally, studies evaluating victims with chronic HCV contamination following DAA treatment demonstrated that additional immune changes can persist after viral eradication.

The requirement for long-term evaluation is further supported by possible timing between inflammatory cytokines and liver fibrosis. Prior research has demonstrated that effective DAA treatment can ameliorate liver fibrosis and is associated with a decrease in profibrogenic biomarkers, such as alterations in the MMP-9/TIMP-1 axis [19], as well as following DAA-mediated

HCV eradication by histological and laboratory confirmation and first has The strong relationship between infection and fibrogenesis provides a biological justification for looking for inflammatory mediators, such as TNF-α, with rising indicators of fibrosis and liver damage[20]. Additionally, hepatic stellate cell activation and extracellular matrix disintegration are facilitated by chronic inflammatory signalling, but the breakdown of protein infections can decrease [21].

The fact that TNF-α is not always specific for HCV infection is a crucial factor to take into account. Additionally, circulating TNF-α concentrations that can independently confirm HCV contamination may be accommodated by systemic inflammations linked to weight disorders, metabolic syndrome, bacterial or viral coinfections, autoimmune disorders, tissue injury, and other chronic inflammatory diseases. Future research should incorporate relevant metabolic, infectious, hepatic, and inflammatory variables when assessing independent HCV infection and circulating TNF-α because ascites and fibrosis are correlated but nonspecific organic techniques that arise in many chronic liver diseases [21]. Examine organisations Another potential confusing factor is the age gap in skill levels. Ageing may have an impact on baseline inflammatory cytokine production and is linked to contemporary alterations in innate and adaptive immune disorders. Therefore, the link between HCV contamination and serum TNF-α concentrations may be strengthened by age matching or multivariate statistical correction. In a similar vein, variations in body mass index (BMI) and metabolic status should be taken into account because adipose tissue serves as an energetic source of inflammatory mediators, and weight disorders and metabolic dysfunction may also cause systemic cytokine elevations that are not related to HCV infection [23]. Therefore, it is preferable to interpret TNF-α concentrations in conjunction with hepatic, metabolic, and demographic characteristics to affect confounders and lower capacity.

Study strength and limitations

One of its main advantages is the statistically significant difference (P <0.001) between HCV-infected and seemingly healthy controls as established by a quantitative ELISA-based method. Additionally, an immunological marker with a physiologically plausible date for liver damage and chronic viral infection is the subject of this work.

First, statistical power and generalizability are sometimes limited by the small sample size. Important HCV-specific clinical characteristics, such as HCV RNA viral load, genotype, ALT, AST, bilirubin, platelet count, degree of fibrosis, illness duration, antiviral treatment status, or length of virology response, were not included in the available dataset. Third, it is unable to demonstrate causation or ascertain if elevated TNF-α predicts the emergence of later liver disease using the go-sectional case-manipulated design. Fourth, combination or multivariate statistical adjustment should be used to handle possible visit factors like age and BMI.

5. Conclusion

In comparison to seemingly healthy controls, this case-manipulated scenario demonstrated a comparatively significant increase in serum TNF-α in HCV infection patients. Superior pro-inflammatory immune activation linked to HCV infection and the inflammatory milieu driving ParNF staining may also be reflected in elevated TNF-α concentrations. Larger, better-characterized longitudinal studies, including sustained virologic response, are necessary to ascertain whether TNF-α can provide clinically meaningful facts about the concerns and evolution of HCV. Despite significant differences between HCV patients and controls, the current findings are insufficient to establish TNF-α as an independent diagnostic or prognostic biomarker HCV RNA staging, liver biochemical parameters, fibrotic assessment, and antiviral treatment.

Ethics Statement:

The Declaration of Helsinki's ethical guidelines were followed when conducting the observation. The Institutional Ethics Committee of Babylon University and Hammurabi Medical College, Babylon, Iraq, have evaluated and approved the study protocol, player assessment form, and informed consent form. Prior to the model series, all participants were required to provide written informed permission. Every observation process has been carried out in compliance with institutional norms and approved ethical indicators.

Funding:

No funding received.

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