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# ChemiluminescenceMicroparticle Immunoassay in the Diagnosis of Hepatitis C Virus among Patients on Hemodialysis: A Comparative Study

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chemiluminescence hepatitis C virus; HCV; ELISA; hemodialysis.

## ABSTRACT

**Background:**The goal of the study was to assess the effectiveness of two screening procedures for the detection of anti-HCV in hemodialysis patients: the enzyme-linked immunoassay method (ELISA) and the chemiluminescencemicroparticle immunoassay (CMIA).

**Materials and Methods:**The sera from 80 patients with renal failure (RF) were isolated for the qualitative determination of IgG HCV-antibody. Each serum was tested by ELISA and CMIA.

**Results:**The positive anti-HCV Abs were from (57.5%) males, and (42.5%) females aged>25 years. Hypertension was the most common cause (34/80) of RF, followed by kidney agenesis (12/80). Four systemic diseases were found to be closely related to RF, including hypertension, hyperglycemia, large doses of analgesia, and rheumatoid arthritis. The gender differences revealed the contribution of all causes among males, while four causes were not recorded in females: rheumatoid arthritis, nephrotic syndrome, and IgA nephropathy. Complications were more prevalent in males (90%) as hypertension alone (52.5%) or hypertension and diabetes mellitus (31.25%). There were no statistically significant differences between the two techniques, and only two samples were false-positive by ELISA.

**Conclusion:**Improving the screening method for HCV infection by using at least two serological tests is exceedingly suggested to restrict the spread of such viral infection among patients on hemodialysis and to prevent improper treatment or enhance the treatment for early diagnosis

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## INTRODUCTION

HCV is a member of the Flaviviridae family of viruses. It is recognized as a virus with a global distribution and is a member of the genus Hepacivirus [1]. It is a tiny, enveloped, positive-sense single-stranded RNA virus that causes several fatal conditions, including lymphomas and hepatocellular carcinoma[2].

A high prevalence is usually recorded with patients suffering from chronic kidney disease (CKD) in comparison to the general population, with a high tendency for morbidity and mortality if they are not treated [3]. Moreover, the development of HCV infection is determined by the virus, host-related factors (the immune system), and risk factors such as the surgical process, blood transfusion, and infected partner, making it a serious disease [4, 5].Studies in Iraq on the occurrence of HCV and HBV infections among patients on hemodialysis and the general population found that HCV was far more frequent than HBV [6, 7]. A new study showed that an improvement in the detection and diagnosis of HCV characterizes an opportunity to decrease the burden of HCV [8]. In addition, primary screening of the high-risk group of people like patients on hemodialysis using highly sensitive tests is vital to treat infected patients and avoid distribution among the population [2]The anti-HCV enzyme-linked immunosorbent assay (ELISA) is widely used to find antibodies against HCV infection. Usually, confirmation is done by recombinant, costly techniques like immunoblotting assays (RIBA) or HCV RT-PCR [9]. Thus, a need for a cost-effective, rapid, and advanced serological diagnostic technique is critical. To determine the quality of the anti-hepatitis C virus, a sensitive, selective, and automated chemiluminescent assay was created [2, 10].

In this study, we tried to evaluate the two screening tests for the detection of anti-HCV antibodies in a patient's serum on hemodialysis using chemiluminescencemicroparticle immunoassay (CMIA) and compare them with the enzyme-linked immunoassay method (ELISA). Subsequently, giving an impression of the accuracy of the screening test results used in hemodialysis centers in Baghdad, Iraq, and may provide a recommendation for the people in charge on the best test to be used.

## MATERIAL

A cross-sectional prospective study was designed to collect blood samples from 80 patients attending the Iraqi Center for Dialysis at Baghdad Teaching Hospital in The Medical City, Baghdad, Iraq. The samples were collected in the period from the 1st of Feb. to the 1st of March 2022. When the patients signed the informed consent form, the researchers guaranteed that all information in this study would not be disclosed to anyone without the patient's consent, except to the patient's physician, and the medical staff of this center. In addition, their information was treated anonymously.

Tubes with no anticoagulant material were used. After one hour at room temperature, the coagulated serum was centrifuged at approximately 1000 × g for 15 min. Each collected serum was stored (≤1 month) in two different tubes at -20 °C for the subsequent analysis.

The IgG HCV-antibody in human serum was determined qualitatively using a human anti-HCV (Hepatitis C

Virus antibody) ELISA kit (Catalogue number: EH3774, Wuhan Fine Biotech Co., Ltd., Wuhan, Hubei, China). The kit was developed using 96-well plates that were pre-coated with recombined HCV antigen using an indirect enzyme-linked immune-sorbent assay technique. The blood serum was examined according to the manufacturer's recommendations. There were two positive and negative control wells. There was one well designated as blank. Except for the blank well, 100 L of sample dilution buffer was added to each well.

The wells were filled with ten microliters for each of the samples, negative control, and positive control before the plate was gently tapped to ensure good mixing. The plate was then covered and incubated for 60 minutes at 37 °C. The cover was taken off, and the plate was washed with wash buffer five times for one to two minutes each time. With wash buffer, the conjugates that were not bound were removed. Horse Radish Peroxidase (HRP) conjugated anti-human IgG Antibody (100 L/well) and HCV-Antibody would combine to form a complex in all but the blank well (no HRP was added). Once more, the plate was covered and incubated at 37°C for 30 min. The washing process was then repeated as previously mentioned.

To see the HRP enzymatic response, TMB (3, 3', 5, 5'-tetramethylbenzidine) substrates were utilized. TMB is a chromogen that, when activated by HRP, produces a blue color. 50 l of TMB substrate A and 50 l of TMB substrate B were added to each well, and the plate was gently tapped to ensure that everything was thoroughly mixed. The plate was covered and incubated at 37°C in the dark for 30 min. While the negative control wells showed no discernible color, the positive controls showed various degrees of blue. After adding 50 l of acidic stop solution to each well and properly combining, the product's original blue hue changed to yellow. The color immediately turns yellow. Immediately following the addition of the stop solution, the optical density of the produced color is measured at 450 nm in a microplate reader. The blank well was used to set zero.

The Architect Anti-HCV Reagent Kit, a two-step chemiluminescent microparticle immunoassay (CMIA), was employed (Catalogue number: 6C37, Abbott, Wiesbaden, Germany). Anti-HCV antibodies are qualitatively found in human serum. The Architect i2000 system and Cobas e411 analyzer were used to test the samples, respectively.

The Architect system made use of a fusion protein called HCr43, which was created by E. coli and contained the HCV genomic coding area core and NS3 (Architect-CMIA). Moreover, a yeast-produced NS4 protein of c100-3 was included in the Architect anti-HCV assay. When loading the reagent kit onto the ARCHITECT system, make sure to invert the microparticle vial numerous times to resuspend the microparticle.

Ensure that all required reagents are available, and check that each reagent bottle has a septum. Within three hours of the system's application, the test was run on the patient samples, calibrator, and controls simultaneously. The minimum sample volume for each anti-HCV test on the ARCHITECT system is 150 l, plus 20 l for each additional replicate from the same sample. In case the minimum sample volume is 70 µl for the first Anti-HCV test, a volume of 20 µl can be added for each additional replicate.

***Data Analysis***

The ELISA kit's cutoff value (C.O.) was derived as (C.O.) = NCx2.8. When NCx is less than 0.05, 0.05 is assumed to be the default value. NCx is the mean absorbance of the negative control. Samples are deemed to be negative for HCV-antibody when the absorbance ratio S/C.O. is less than 1. Whereas samples with an absorbance value of S/C.O. 1 are thought to contain HCV antibodies. It shall be regarded as invalid and retested if the mean absorbance of the positive control is less than 0.5 or the mean absorbance of the negative control is greater than 0.08.

The ARCHITECT Anti-HCV assay calculates a result based on S/CO. The Anti-HCV Calibrator 1 mean chemiluminescent signal is calculated by the ARCHITECT system using three Calibrator 1 replicates, and the result is stored. To determine the cutoff value, multiply the calibrationator1 mean relative light units (RLU) value by 0.074. S/CO is calculated using the formula Sample RLU/Cutoff RLU.In this case, no further testing is necessary if S/CO is less than 1.00. S/CO less than 1.00 is regarded as reactive and should be retested twice. The material is regarded as nonreactive or negative for anti-HCV if both results are negative. If one or both results are positive, the specimen is deemed repeatedly positive for anti-HCV according to the ARCHITECT Anti-HCV criteria.

The Mann-Whitney U test was used to assess nonparametric data. When two quantitative variables are correlated, the correlation coefficient, or R, is determined. To examine the relationship between nominally categorized variables, utilize the Chi-square Z test.$P<0.05$ is considered significant.

**RESULTS**

As they matched the inclusion criteria, a total of 80 patients with renal failure (RF) and known HCV infection were eligible to participate in this study. There were 46 (57.5%) men and 34 (42.5%) women, ranging in age from 25 to 83 years for men and 26 to 70 years for women. Males had an average and median age of 52 while females had values of 50.2 and 49, respectively. For males, the age mode was (50, 57, 52, each appeared twice) and for females, it was (58, 48, each appeared twice). All of the RF patients who tested positive for anti-HCV Abs were older than 25years.

The duration since first diagnosis as HCV Abs positive was wide in range (8 months to 7 years) for males. Unlikely, the duration of the first diagnosis was (6 months-7 years) for females. The median duration of infection was equal to 2 years for each gender group, while the mean was (26.3 months) for males and (28.6 months) for females.

The mean duration of RF diagnosis among the studied population was 5.4 years, and since the diagnosis for females was equal to 4.647 years and for males was (6.13) years, the range of diagnosis was 12 years (1–13 years) for both genders.

Hypertension was the most common cause (34/80) of RF among the study group, followed by kidney agenesis (KA) (12/80). Four causes of systemic diseases include hypertension, hyperglycemia, large doses of analgesia, and rheumatoid arthritis (unilateral RA and bilateral RA); there were five renal causes of RF among the study population, these are: kidney agenesis (KA), nephrotic syndrome, hereditary nephrolithiasis, polycystic kidney disease, and IgA nephropathy. The

gender differences revealed the contribution of all causes among males while four causes were not recorded in females, these are: RA and unilateral RA, nephrotic syndrome, and IgA nephropathy, these results are illustrated in Figure (1).

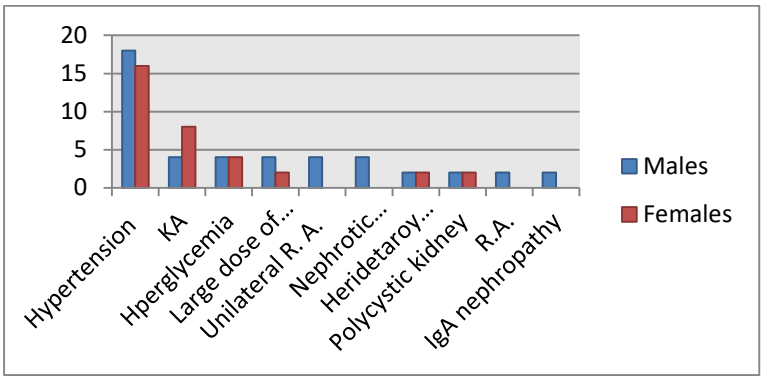


**Figure (1):** The etiology of RF among the study population

The complications of RF were present in 72 patients (90%) of the study group, while 8 patients (10%) didn't have obvious complications and all of them were males. Hypertension alone was the most frequent complication [n=41 (52.5%)], followed by a combination of hypertension and diabetes mellitus in 25 (31.25%); the other complications, which were uncommon, involved hyperglycemia, hyperlipidemia, and a combination of hypertension and hyperlipidemia, Figure (2).

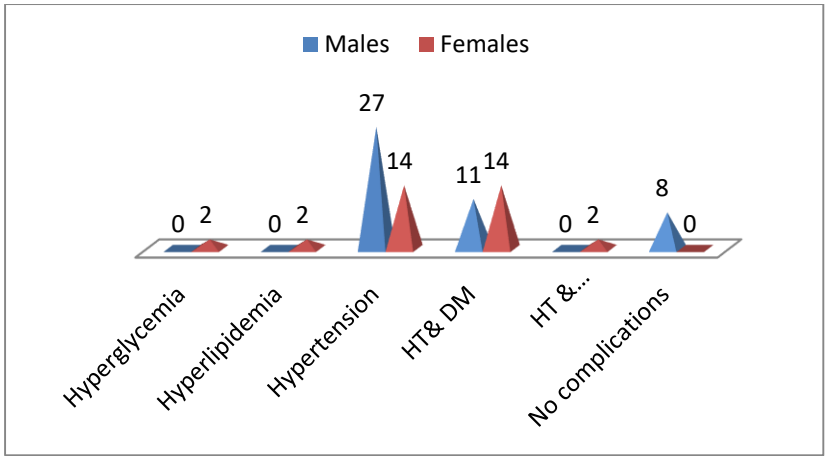


**Figure (2):** The types of complications among RF patients. HT: hypertension. DM: diabetes mellitus

The 80 RF patients were positive for anti-HCV Abs by ELISA screening technique, after that we tested these sera samples again for detection of anti-HCV Abs by Chemiluminescent Immunoassay (CIA) to compare the performance of both techniques. The CIA and ELISA were positive for 78/80 samples (97.5%) and 80/80 (100%), respectively. However, the results were not

statistically significant (P > 0.05) between the two techniques. The titers of positive anti-HCV Abs in sera by CIA technique (n=78) were ranging (1.75 to 20.17) with mean and median equal to 12.1 and 13.14 signal-to-cutoff (S/C), respectively.

There was a non-significant very small negative relationship (R = -0.1104) between the patients' ages and anti-HCV Abs titers measured by the CIA technique, Figure (3).

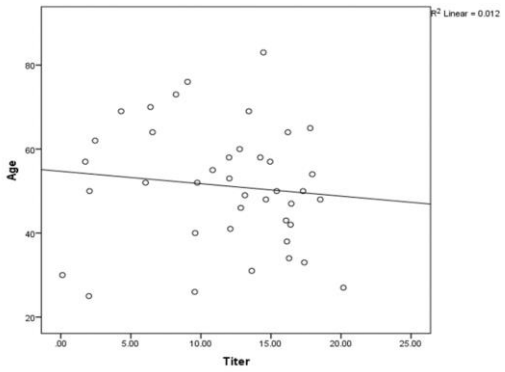


**Figure (3):** Correlation between patients' ages and anti-HCV Ab titers (R= -0.1104)

The duration of HCV infection since the first diagnosis as HCV positive cases has a non-significant weak negative correlation with HCV Abs titers (R= -0.0731), Figure (4).

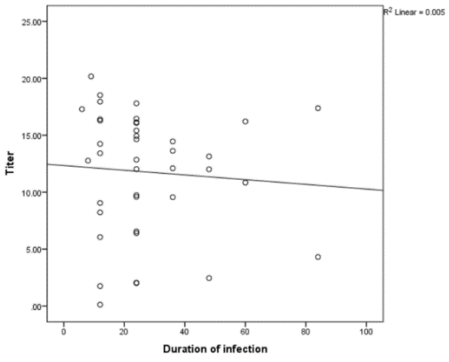


**Figure (4):** Correlation between duration of HCV infection and anti-HCV Ab titers (R= -0.0731)

Moreover, the correlation between the duration of RF infection and anti-HCV Abs titers was a weak negative correlation (R= -0.238), Figure (5).

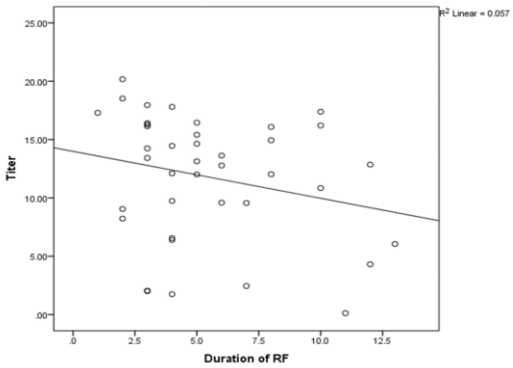


**Figure (5):** Correlation between duration of RF and anti-HCV Ab titers (R=--0.238)

We calculated the relation between the gender of RF patients and the anti-HCV Abs titers using the Mann-Whitney U Test Calculator. 106 is the U-value. U's crucial value at p .05 is equal to 81. -1.06265 is the z-score. 0.28914 is the p-value. As a result, at p 0.05, the outcome is not significant.Anti-HCV Abs titers were evaluated to determine their relationship to the causes of RF in the study group; the U-value is 94.5.

At p 0.05, U has a critical value of 81. As a result, the outcome is not significant at p 0.05. -1.4769 is the z-score. That is 0.13888 for the p-value. At p 0.05, the outcome is unremarkable.

The kind of complication among the HCV-infected RF patients did not affect their anti-HCV Abs titers. At p .05, U has a critical value of 13. Nonetheless, the U-value is 28. Z-score = 0.367577. 0.71138, or p, is the value. At p 0.05, the outcome is unremarkable.

## DISCUSSION

Patients with chronic renal failure have a higher occurrence of hepatitis C virus (HCV) infection compared to the overall population. HCV infection affects their survival if they are not treated. Many diagnostic tests for HCV infection permit a one-stop easy way to test and cure [3, 8]. Dependently, comparing the used tests for HCV infection diagnosis in important centers like dialysis centers is very important to manipulate the spread of this infection among patients and for infection management.

According to the study's findings, men (57.5%) were more likely than women (42.5%) to have HCV infections, and the mean age was 52 for men and 50.2 for women. Moreover, all of the renal failure (RF) patients who had anti-HCV Abs positive were older than 25 years old. These findings deviate from those of earlier studies conducted in Iraq, which revealed that HCV infections declined with age and were more prevalent in females than males [11, 12]. Moreover, the studies found that hemodialysis was the most risk factor prone for HCV infection and this infection is most common among hemodialysis patients[11, 12]. Conversely, the findings of other studies are in agreement with the current study results. These studies investigated the incidence rate of HCV in different Iraqi governorates and found that the prevalence of HCV infections was higher in males than females with a high incidence among the age group 15 to 45 years and low in age group 1 to 4 years [5, 6].

A study conducted in Iraq by Nasir and Abdilazeem in 2019 came to the results that HCV infection was related to the higher number of longer duration of renal failure and longer duration of hemodialysis [13]. The participants in this study with a 5.4-year mean duration of RF diagnosis in which 4. 647 years were for females and 6.13 years were for males, respectively. The results coordinated the previously mentioned studies' results that hemodialysis is considered an important risk factor for HCV infection and the infection is higher among patients with chronic renal failure disease than normal individuals [14, 15].

Subsequently, most of the participants were first diagnosed as positive HCV Abs in a wide range (6 months- 7 years). For males, it was 8 months-7 years while for females the range was 6 months-7 years with the median duration of infection equal to 2 years for each gender group. This proved the fact that a longer time on dialysis is associated with HCV seroconversion [15].

The collected data found that hypertension was the most common cause (34/80) of RF among the studied group followed by kidney agenesis (KA) (12/80). The study findings can be explained by the fact that hypertension pathogenesis is related to the severity of the renal damage. The collapse in the renal auto-regulatory mechanisms is associated with preventing the blood pressure elevation from being transmitted to the renal microvasculature. Damage in these protective mechanisms in patients with diabetic and non-diabetic chronic kidney disease was expected for their increased susceptibility to gradual renal damage with even moderate hypertension. Moreover, renal damage can act as an initiator for a hypertension vicious cycle that is difficult to control [16].

Four systemic diseases were found to be closely related to RF in the studied group, including hypertension, hyperglycemia, large doses of analgesia, and rheumatoid arthritis (unilateral RA and bilateral RA). Furthermore, five nephropathy syndromes were recorded among the studied population, these are: kidney agenesis (KA), nephrotic syndrome, hereditary nephrolithiasis, polycystic kidney disease, and IgA nephropathy. The gender differences revealed the contribution of all causes among males while four causes were not recorded in females, these are: rheumatoid arthritis and unilateral RA, nephrotic syndrome, and IgA nephropathy. Besides, complications were more predominant in males (90%) of the studied group, while(10%) of the patients didn't show obvious complications. Hypertension alone was the most frequent complication (52.5%), followed by a combination of hypertension and diabetes mellitus (31.25%). The other complications, which were uncommon complications involved hyperglycemia, hyperlipidemia, and a combination of hypertension and hyperlipidemia.The findings of the current study are compatible with other studies that demonstrated that HCV infection with the presence of genetic factors, hypertension, diabetes mellitus, and the use of drug-induced nephrotoxicity all contribute to an increased risk of renal disease[17, 18]. Likely, HCV infection increases the risk of developing cardiovascular disease, diabetes mellitus, atherosclerosis in renal vasculature, and other less common renal diseases including IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, fibrillary and immunotactoidglomerulopathy in comparison to individuals without HCV[14, 15, 19].

The collected sera from patients with RF were shown to be anti-HCV Abs positive by ELISA screening technique. Later, these sera samples were tested for the detection of anti-HCV Abs by Chemiluminescent Immunoassay (CIA) to compare the performance of both techniques. The ELISA test was positive for all 80 samples, while the CIA was positive for 78/80 samples (97.5%). Between the two methods, there were no statistically significant differences. The findings support that the Food and Drug Administration has not yet approved any new anti-HCV confirmatory assays. The recommendation recommends performing a second anti-HCV screening assay on first-round anti-HCV-positive samples for anti-HCV confirmation. As a result, the FDA advises following such a protocol in HCV prevalence investigations to distinguish between cured HCV infection and false positive anti-HCV results. This is because incorrect biological results should not occur with two distinct assays[20].

The data analysis revealed a non-significant relationship between the anti-HCV Abs titers measured by the CIA technique and the patients' ages and gender, the first diagnosis as HCV positive, the duration of RF infection, and the causes of RF among the studied group. As well, the titers of anti-HCV Abs among the HCV-infected RF patients were not affected by the type of complication among the RF patients. These results concur with the circumstance that Architect anti-HCV chemiluminescence immunoassay can be applied as a screening assay due to the large number of specimens that can be tested at a short processing time, in

addition to its high sensitivity [21].The benefit of the anti-HCV screening test is due to its ability to identify anti-HCV antibodies at low levels in the blood. Hence, such a condition may reflect an existing HCV infection or remaining antibody activity after a resolved and past infection [22]. Therefore, the current study recommends using the CIA technique as the test of choice for confirmation of free HCV sera from patients on hemodialysis.

The study faced limitations in the number of available samples for screening. The ELSA test used to be done in the Hemodialysis center routinely, while CLIA was done in the private sector. A large number of samples need to be applied in the future. However, we recommend using the automated chemiluminescenceimmunoassay (CLIA) analyzers in high-volume laboratories and as a first-line assay to screen for anti-HCV. Further, analysis by ELISA could be followed for confirmation.

## CONCLUSION

It is recognized that Hepatitis C virus infection continues to be a frequent problem in patients on renal substitute therapy. The infection has a potential influence on patients' morbidity and mortality with chronic hemodialysis.Thus, early diagnosis and follow-up of HCV infection in those patients are critical for their survival and their life quality. Using at least two serological tests is highly recommended to control and diagnose such viral infections among patients on hemodialysis in order not to spread the infection to other patients in the same dialysis center or to help them improve their health by taking the proper treatment early before the complications of such infection.

## CONFLICT OF INTEREST

The authors declare no competing interest.

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