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Role of Programmed Cell Death-1 and Programmed Cell Death Ligand-1 immune checkpoint biomarkers among chronic Hepatitis C virus patients under Hemodialysis

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Abstract:

Background: Hepatitis C virus (HCV) infection is one of the most common infections associated with chronic kidney disease (CKD) patients undergoing hemodialysis (HD) in Iraq.

Aim of the study: To determine the prognostic factor value of Programmed Cell Death-1 (PD-1) and Programmed Cell Death Ligand-1 (PD-L1) immune checkpoint biomarkers among CKD patients with HCV infection under HD.

Methodology: ELISA technique was used for the measurement of the above-mentioned biomarkers in the serum of 90 Iraqi patients. The participants were divided into three groups; Group I included 30 patients infected with HCV without antiviral treatment, group II included 30 patients infected with HCV with recent/previous antiviral treatment, and Group III included 30 patients without viral infection (control group).

Results: Serum levels of the measured biomarkers were elevated among all the participants, and highly statistically significant differences were found between patients with no treatment. The area under the curve (AUC) of PD-1 was 99% and for PD-L1 was 96%.

Conclusions: The PD-1 and PD-L1 immune checkpoint biomarkers have excellent prognostic factor value as predictors for patients with CKD on HD infected with HCV.

Keywords: HCV in HD; PD-1/PD-L1 and HD; Immune checkpoint biomarkers; Immune biomarkers in CKD with/out HCV.

Introduction:

Hepatitis C virus infection is considered the most common bloodborne infection [1]. The infection has two phases; acute and chronic [2]. The most common method of virus spread is exposure to blood and blood products [3]. Infection with HCV is a major problem among HD patients in developing countries, ranging from 6-60%, and is related to high mortality rates [4]. The main reasons behind this prevalence are the duration of HD, the need for transfusions, lack of standard infection precautions, insufficient disinfection of HD machines, tools, and equipment, and the need for vascular access to perform the HD [5, 6]. Immune checkpoints are immunity regulators. They play a crucial role in self-tolerance, preventing the immune system from attacking cells randomly, in addition to blocking autoimmune reactions to self-proteins [7]. The most common important and studied biomarkers, Programmed death-1 (PD-1) and Programmed death-ligand-1 (PD-L1), which are termed clusters of differentiation (CD279 and CD274), respectively [8]. Their expression aid in controlling T–cell proliferation, restoring immune function in tumor micro-environment as well as regulating responses to self-proteins [9]. Recent clinical data demonstrate that these biomarkers have been implicated in many medical conditions, including melanoma [10], sepsis [11], and viral infections [12, 13]. In Iraq, however, there were no clinical data to demonstrate the role of these biomarkers as predictors for HCV infection. Thus, this study aimed to determine the prognostic factor value of PD-1 and PD-L1 immune checkpoint biomarkers for CKD patients with HCV infection under HD.

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Patients and Methods

Study Design and Population: A case-control study was carried out at the Department of Microbiology, College of Medicine, University of Baghdad and the Iraqi Center of Hemodialysis at Baghdad Teaching Hospital from the 3rd of October to the end of December 2021, and included 90 patients, group

one(30)patients infected with HCV not take antiviral treatment, group two (30) patients take antiviral treatment, and group three non-infected with HCV.. Data (age, sex, HD duration, route of vascular access and existence of chronic diseases) were collected by direct interview with all the participants.

Inclusion and Exclusion Criteria: Patients with CKD on HD with/without HCV infection only clear from any other microbial infection and/or other medical diseases/conditions were included in this study.

Laboratory Analysis: Blood specimens were collected from 90 patients with CKD undergoing HD, and were divided into three groups group one(30)patients infected with HCV not take antiviral treatment, group two (30) patients take antiviral treatment, and group three non-infected with HCV. The serum was transferred to the wells of the microtitration plate and after serial adding and washing the concertation was read by the ELISA reader at a specific wavelength.

Statistical analysis: The SPSS version 16.0.0, Microsoft Excel 2010, and Graphpad Prism version 7.04 were used for data analysis. Descriptive and inferential analysis approaches were used to investigate/ predict relationships between variables, and a *P* value < 0.05 was considered to be statistically significant.

Results: There were 48 males (53%) and 42 females (47%). Age ranged from (19-69) years, with a mean age of (51.12 ± 14.72) years. A total of 79 (88%) patients were using the A.V fistula as a method of vascular access, while 11 (12%) patients are using the dual lumen catheter. The relationship with the existence of other chronic diseases was also determined; data reveals that 78 (87%) patients had hypertension, with non-significant differences in the distribution between the three study groups. The results are shown in Table 1.

Table (1): Quantitative parameters and clinical profile of the studied groups

Parameters		Clinical groups			*P* value
		Control No. (%)	Without treatment No. (%)	With treatment No. (%)	
Gender	Male	15 (50)	16 (53)	17 (57)	0.964
	Female	15 (50)	14 (47)	13 (43)	
Route of HD	A.V fistula	29 (97)	27 (90)	23 (77)	0.203
	Dual lumen	1 (3)	3 (10)	7 (23)	
Hypertension	Yes	26 (87)	26 (87)	26 (87)	1
	No	4 (13)	4 (13)	4 (13)	

Analysis using Pearson's chi-square test with application of Fisher's correction whenever applicable
HD: Hemodialysis; A.V fistula: Arteriovenous fistula

Data analysis shows that the mean duration of HD of the participants was (4.3±2.4) years, which was significantly different between the control and the patients' groups, (5.0±2.3) and (3.0±2.1) years, respectively, (control havea longer duration of HD). The results are shown in Table 2.

Table (2) Characteristics of study groups

Parameter	Study Groups			*P* value
	HCV - Ve	HCV + Ve Without treatment	HCV + Ve With treatment	
	Mean (Range) ± SD	Mean (Range) ± SD	Mean (Range) ± SD	
Age (years)	53.80 ± 13.18 (16-74)	49.00 ± 15.63(19-80)	50.53 ± 15.45(20-75)	0.442
HCV Duration (years)	-	3.37 ± 2.34 (0.67-11)	3.38 ± 2.10 (0.67-9)	0.768
HD duration (years)	2.99 ± 2.18 (0.42-12)	4.90 ± 2.53 (1-12)	5.06 ± 2.13 (2-10)	0.001[ɬ]

[ɬ] Significant difference in parameters between study groups using one-way ANOVA test at 0.05 level

Three immune checkpoint biomarkers were measured for all the participants in this study. Data analysis revealed that the mean level of PD-1, PD-L1 and were (41.4±12.61), (134.5±42.6), respectively, with highly significant differences in their concentration between the controls and the study groups. The results are shown in Table 3.

Table (3): Serum levels of the studied immune checkpoint biomarkers

Immune checkpoint biomarkers	Study groups			*P* value
	HCV - Ve	HCV +Ve Without treatment	HCV +Ve With treatment	
	Mean (Range) ± SD	Mean (Range) ± SD	Mean (Range) ± SD	
PD-1	30.73 ± 3.68 (21-37)	39.10 ± 4.99 (33-52)	54.43 ± 12.27 (40-79)	< 0.001[ɬ]
PD-L1	92.03 ± 15.43 (64-133)	132.83 ± 23.80 (65-170)	178.57 ± 29.81 (111-299)	< 0.001[ɬ]
CTLA4	444.13 ± 80.12 (325-590)	604.53 ±116.39 (296-910)	893.83 ± 108.123 (749-1275)	< 0.001[ɬ]

[ɬ] Significant difference between HCV +ve and -ve patients using one-way ANOVA test at 0.05 level

The receiver operating characteristic (ROC) analysis was used to assess the prognostic factor value of the studied biomarkers among patients with HCV infection on HD. The values of the area under the curve (AUC) for PD-1, PD-L1, and biomarkers were (99%), (96%), respectively. These findings, however, indicate the excellent predictive power of these biomarkers. The results are shown in Table 4.

Table (4): Results of receiver operating characteristic analysis for the studied immune checkpoint biomarkers

Biomarker	Cut-off value	Sensitivity	Specificity	AUC
PD-1	≥ 20.0	100%	0%	99%
	≥ 32.5	100%	56.7%	
	≥ 34.5	95.0%	96.7%	
	≥ 37.5	76.7%	100%	
PD-L1	≥ 63.0	100%	0%	96%
	≥ 64.5	100%	3.3%	
	≥ 90.5	96.7%	50.0%	
	≥ 109.0	93.3%	93.3%	
	≥ 133.5	78.3%	100%	

Discussion

The current study is the first in Iraq to detect the serum levels of three immune checkpoint biomarkers in patients with CKD on HD infected with HCV. The main goal was to demonstrate the prognostic factor value of these biomarkers among those patients, in addition to identifying any possible association between the demographic data and the measured markers. In this study, high rate of infection was recorded among men than women. These findings were in accordance with the results of other studies which demonstrated that the prevalence of HCV infection appears to be higher among men than women [3, 14]. The sex factor influences both infection rate and response to treatment [15]. People from the sixth decade, however, are predisposed to different types of harm over time, which can lead to a decrease in physiological and mental abilities, making them vulnerable to different medical conditions and their complications [16, 17]. A study conducted in Italy in 2007 revealed that the prevalence of HCV infection seems to be higher among women than men [18], which disagrees with our findings and the facts that the HCV clearance rate was significantly higher in women (women are more likely to clear the virus spontaneously), and they have slower rates of disease-progression if they become chronically infected [19]. The predominance of patients using the A.V fistula in the current study agrees with other studies which revealed that this type of HD access represents the first choice, is the most common and best vascular access for longevity in patients with HD [20, 21]. The National kidney foundation declared that A.V. fistula should be considered the gold standard preferred access for HD, because it lasts longer and has fewer problems such as infections and thrombotic complications [22]. In the current study, hypertension was highly prevalent (87%) with non-significant associations between all groups. This result was in agreement with studies from Canada and Brazil which showed that hypertension among CKD patients was poorly controlled, difficult to manage, and associated with other co-morbidities [23, 24]. Increased arterial stiffness due to volume overload/ sodium retention, sleep apnea, and using of recombinant human erythropoietin are factors that predispose these patients to the risk of hypertension [25, 26].

The current study found a significant difference between patients and controls regarding the duration of HD. A study done in Italy in 2012 and later supported by a CDC observation in 2018 reported that > 50% of HCV outbreaks from 2008-2015 appeared in HD settings [27, 28]. This observation, however, confirms the fact that the risk of HCV infection increased as patients stayed longer in HD units, which supports our findings concerning the mean duration of HD. The diagnosis of HCV infection in patients with CKD seems not to be made on time due to many reasons, including the presence of nonspecific signs and symptoms, fluctuating levels of liver enzymes, the lower sensitivity of detection tests, and lower viremia seen among those patients [29, 30]. Immune checkpoint molecules are regulators of the immune system. Via self-tolerance, they prohibit autoimmune reactions and the immune system from randomly attacking cells [31]. The current study demonstrated that there were highly statistically significant differences between the serum levels of the studied biomarkers and the three groups of participants. The significant use of these biomarkers was proved to be efficient not only among End Stage Renal Disease patients [32] and HCV-infected patients [8, 33], but also to other diseases/ medical conditions, including melanoma [10], sepsis [11] and viral infections including COVID-19 [12, 13].

It has been revealed that immune checkpoints were utilized in the immune escape of HCV by causing dysfunction of T-cells, and the expression of these molecules on suppressor cells will influence its secretion, and that was the reason beyond difficulties in excluding such infections [34]. A comparative analysis of infection outcomes with PD-1 levels during the acute phase of infection exhibited that PD-1 expression in HCV-specific T-cells differs and varies highly through the acute stage of infection, suggesting that it is one of the independent determinants of outcomes, hence, we could conclude that upregulating PD-1 in the acute stage of infection was associated with fighting the infection [35], whereas, in the chronic stage, it was associated with an impaired T-cells function, resulting in viral infection of a persistent type, a conclusion that shows relevance to intervention with blocking-antibodies [36]. The findings of the current study were not compatible with those of a molecular study done in the USA in 2015 which showed that PD-1 levels were lowered regardless of continual high HCV-RNA levels [37]. Inconsistencies of results might be due to differences in study design, geographic differences, patient populations, the assay used, and certain conditions related to such diseases since the participants enrolled in this study were CKD patients on regular HD. These results, however, provide evidence that immune evasion mechanisms permitting HCV to persist either include epitope escape or signals maintaining higher expression of checkpoint receptors on virus-specific T-cells [38].

Conclusion

Based on these results we can conclude that PD-1 and PD-L1 immune checkpoint biomarkers have an excellent prognostic factor value as predictors for CKD patients on HD with HCV infection.

Authors' declaration:-

Conflicts of Interest: None

We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given permission for re-publication attached with the manuscript.-Authors sign on ethical consideration's approval-Ethical Clearance: The project was approved by the local ethical committee in the College of Medicine/ University of Baghdad according to **the code number 1439.6.11.2021).**

Authors' contributions:

Ryiam S. Jouda: MSc students

Basim M. Ibrahim: first supervisor

Ahmed F. Al-Khafagi: second supervisor

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دور المؤشرات الحيوية لنقاط الفحص المناعي بين مرضى غسل الكلى المصابين بألتهاب الكبد الوبائي المزمن

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الخلاصة:
خلفية البحث: عدوى فيروس التهاب الكبد الوبائي (ج) هي واحدة من أكثر أنواع العدوى شيوعًا المرتبطة بأمراض الكلى المزمنة (CKD) الذين يخضعون لغسيل الكلى (HD) في العراق.
الأهداف: لتحديد قيمة عامل التكهن للمؤشرات الحيوية لنقاط التفتيش المناعية بروتين موت الخلية المبرمج وبروتين موت الخلية المبرمج المرتبط بين المرضى المصابين بعدوى التهاب الكبد الفيروسي تحت الغسيل الدموي.
المنهجية: تم استخدام تقنية ELISA لقياس المؤشرات الحيوية المذكورة أعلاه في مصل 90 مريضا عراقيا. تم تقسيم المشاركين إلى ثلاث مجموعات؛ تضم المجموعة الأولى 30 مريضًا مصابًا بفيروس التهاب الكبد الوبائي بدون أي علاج مضاد للفيروسات، والمجموعة الثانية تضم 30 مريضًا مصابًا بفيروس التهاب الكبد الوبائي بأدوية مضادة للفيروسات حديثة / سابقة. المجموعة الثالثة تضم 30 مريضاً بدون أي عدوى فيروسية (مجموعة المراقبة).
النتائج: تم رفع مستويات المصل من المؤشرات الحيوية المقاسة بين جميع المشاركين، وشوهد فرق دلالة إحصائية عالية في مجموعة المرضى دون علاج. كانت المنطقة الواقعة تحت المنحنى (PD-1 (AUC و 99) PD-L1٪) و (96٪) على التوالي.
الاستنتاجات: المؤشرات الحيوية لنقطة التفتيش المناعية التي تم فحصها لها قيمة عامل تنبؤية ممتازة كمؤشرات للمرضى الذين يعانون من مرض الكلى المزمن على HD والمصابين بفيروس التهاب الكبد الوبائي.
الكلمات المفتاحية: التهاب الكبد الفيروسي نوع ج في الغسيل الدموي للكلى؛ بروتين الموت المبرمج الخلوي ١، وبروتين موت المبرمج الخلوي المرتبط ١، المؤشرات الحيوية لنقاط التفتيش المناعية؛ المؤشرات الحيوية المناعية في الغسل الكلوي المزمن.