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Evaluate microbial profile and IL-17 level in transmission transfusion infection patients

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***Abstract*---**Transfusion-transmitted infections (TTIs) an important causes of morbidity and mortality among recipients of blood /blood products since it among the essential vehicles for infectious agents that lead to disability or death. So this study aimed to evaluate the important causative agents and the role of IL-17 in progressive disease. A Case-control study was performed to 100 patients with Transfusion blood attended to AL-Sadder teaching hospital with group of 30 healthy individual as control. Blood sample was collected from all patients and control. IL-17 level were measured by enzyme-linked immunosorbent assay (ELISA). The result shown that Hemodialysis patients 54 (54%) patient from which 40(74%) suffering from TTI, HCV were most common causative agents with 42 % and the male recorded 63%. While 46(46%) patients with thalassemia from which 32(70%) were TTI and HCV a most common pathogen with 19(41 %), the male higher than female with frequency (65%). In conclusion: This result explain that HCV infected more than non-infected HD patients and the serum IL-17 level increased significantly in HD patients with HCV, then patients without HCV infection in comparison with healthy control group.

***Keywords*---**transmission, transfusion, infection, IL-17, HCV.

Introduction

Blood transfusion (BT) an essential lifesaving treatment that saves millions of lives every year around the world which would otherwise have died because of various natural diseases and disasters ,it's an integral part of the World Health Organization (WHO) list of essential medicines , unsafe blood remains a threat to the spread of infections **(**Ehsan *et al.*,2020). Different outcomes may follow unsafe

transfusion, as it can cause an acute clinical sickness; it can persist in the receiver as a carrier or cause asymptomatic infection, These infections include viral, bacterial, parasites and prions. The most prominent among these are, Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus HCV (CDC., 2018). Blood and blood products that gave to vulnerable patient cohorts such as a naemic, cancer , hemodialysis , acute trauma, hemorrhage or post-operative patients, these blood products can result in significant adverse events including immunologic reactions, infections, inefficacy, and others which can sometimes result in death and severe disability (Fong ,2020). Pro inflammatory cytokines also accumulate in blood products may cause Transfusion-Associated Adverse Reactions (TAARs) and transfusion-induced systemic inflammation (Meekers, 2021). Cytokines modulate the immune response to infection or inflammation and regulate inflammation itself via a complex network of interactions, However, excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes, organ failure, and ultimately death also dysregulation of these cytokines activity is associated with inflammatory, autoimmune, and metabolic diseases, and cancer (Chen *etal.*,2018).

Method

Patients and control characterization

A case –control study was conducted during October 2021-febreuary 2022 in AL-Saddar medical city and AL. Zahra teaching hospital in AL-Najaf provenances on 100 blood transfusion patients suffering from thalassemia 46 patients and 54 hemodialysis since different causes. In addition to 30 randomly healthy persons (20 male and 10 female) with age range between (1-60) years.

Collection of sample

Five ml of blood specimens were collected from all subjects, 3ml collected in EDTA tube and centrifuged to separate plasma for viral RNA for HCV identification extraction Kite(Norgen, China) and HBsAg (Norgen , China) while 2 ml collected in gel tube to separate serum then stored at -20°C until used for measuring IL-17 according to (Elabscience, USA). While urine used to isolate bacterial species that were inoculated on general and differential media.

The following samples were excluded

samples from individuals who had received antibiotic therapy; patient not fill all information or correct sample and sample from patients suffering from DM type 1.

Ethical committee

This study was approved by the Ethics Committee of the Faculty of Science, Kufa University (N0 1798) and Medical Ethics Committee of the Ministry of Health in Iraq.

Statistics

Analysis of data was performed by using Statistical Package for Social Science (SPSS) system/ version 20. Results expressed as mean ±S.D.

Results and Discussion

Distribution of study subjects according to type of disease, age and sex

A total of 100 patients with blood transfusion infection that are divided into two main group, First: 54 (54%) patient with hemodialysis from which 40(74 %) suffering from TTI, HCV were most common causative agents with 42.1% and the male recorded 63%. Second group: 46(46%) patients with thalassemia from which 32(70%) were TTI and HCV a most common pathogen with 19(41 %), the male higher than female with frequency (65%). In addition to 30 apparently healthy subjects as controls group as shown in table 1.

Table 1: Distribution of study subjects according to type of disease, age and sex

Gender	Blood transfusion infection		Healthy group
	Hemodialysis N=54	Thalassemia N=46	
Male	34(62.9)	30 (65.2)	20 (66.7)
Female	20(37.1)	16 (34.8)	10 (33.3)
Age Mean ± SE	48 .93± 11.42	18.60 ± 4.10	21.87±6.36
Age range	12-60	1-39	1-60
1-9	-	15(32.6)	2(6.6)
10-19	4 (7.4)	12 (26)	10 (33.3)
20-29	5 (9.2)	8 (17.3)	5 (16.5)
30-39	15 (27.7)	1 (2.1)	4 (13.3)
40-49	20 (37)	-	6 (20)
50<	10 (18.7)	-	3 (10)
HCV+	23(42)	19(41.3)	-
HBV+	6(11)	4(8.6)	-
Bacterial infection	11(20.4)	9(19.5)	-
Non-infected patients	14(26)	14(30)	

This study confirmed that male outnumber than female, this in line with (Al Hroob *et al* .,2020) observed that male represent high number than female in transfusion transmission infection and found that HBV and HCV most prevalence in infected patients . In local study , Baghdad provenance (Mousa *et al.,*2022) they demonstrated that male comprise about 55% of HD patients with mean age of patients was 51.2 ± 14.5 years, approximately 20% of them were illiterate,. Hypertension and diabetes were the most common etiologies of ESRD (38.7% and 32.8%, respectively).In Iraq, (Mohsen *etal* 2020) demonstrated that renal failure occurs in male more than female and the mean age is 49.5 ± 5.91 years respectively. Bahat and Parmaksız (2022) found that hemodialysis patients recorded 75 (58%) male and 55 (42%) female with mean age was 54.8 ± 14.7

years also observed that most common comorbidities were HT (80 patients, 62%) and DM (43 patients, 33%). In this regard (Ahmadi *et al.*,2022) appear that male recorded 51% among hemodialysis patients with mean age of patients was (62.7 ± 16.6) years.

According to thalassemia: the result observed that male comprise 30 (65.2) and the age range 1-59 years with high frequency in age between 1-9 years 15(32.6). This result agree with (Ali and Abdulla., 2020) who found that male recorded 94(54%) and 81(46%) were females with a ratio 1.2: 1and mean age of patients were (10.5 ±5.8 years) , the range age of patients from 5 months to 34 years and found that more than half (55%) between aged 1 - 10 years. In study by Amin *et al* confirmed that male more susceptible to *β*-thalassemia disease with frequency 56.6% males and 43.4% females, with ratio male : female ratio of 1.3 : 1. The patients' ages ranged between 1.4 - 54 years with a median of 15 yrs. (Amin *et al.*,2020).

According to HCV infection. In study by (Ngilibuma *et al.*,2021) shows a high frequency of HCV infection in patients on chronic hemodialysis and explain that the risk factors associated with HCV infection were the number of blood transfusions, the absence of EPO treatment, the time on HD as well as the characteristics of the centers. The results of this study show 41.3% of thalassemia patients were anti HCV sera-positive .This in line with local study by (ALbakaa *et al,*2020) observed that male more than female with frequency 53.57 , their ages range from (2-34) years and HCV PCR positive were (57.14 %). While (Surhan *et al.*,2018) founded that 36.6% of thalassmeic patients sera was confirmed positive for anti- HCV- antibodies. In Iran (Aminianfar.,2017)reported that 0.7% of thalassemia patients were positive for HBV and 60 10.2% were positive for HCV.

Dawood *et al.*,(2020) in the province of Mosul explain that Iraq is one of the countries in the Middle East that has had an increased incidence of Hepatitis C infections over the past few years, and the increasing incidence can be observed in hemodialysis and thalassemia patients, due to the lack of health awareness among individuals, the failure of follow-up of new cases, and the deficiency of appropriate treatment in addition to the failure invention suitable vaccine .

Classification patients according to type of kidney injury

The results explain that acute kidney injure represent 6(11 %) while chronic kidney failure represent 48(89%) with significant difference at P≤ 0.05 .As show in figure 1.

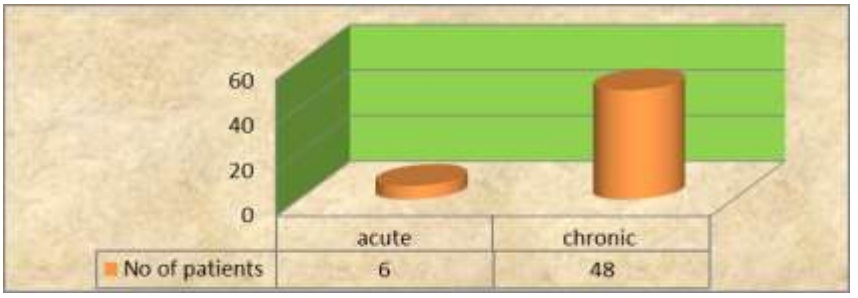

Figure 1: Distribution of patients according to type of kidney injury

Acute kidney injury (AKI) a rapid loss of kidney function results in renal damage caused by nephro-toxins, radiocontrast agents, surgery, sepsis, and antibiotics that associated with significant morbidity and mortality and surviving patients are at increased risk of developing CKD and ESRD (Webster *et al.*,2017). Also (James *et al.*,2010) indicated that hospital dialysis during AKI was associated with an increased risk of chronic dialysis . Dialysis- requiring acute renal failure was independently associated with a 28- fold increase in the risk of developing stage 4 or 5 CKD (Lo .,2009).

Distribution patients according to common cause of hemodialysis

The results appear common causes of hemodialysis in this study was lupus nephrites 20(37) % followed by chronic disease (Diabetic mellitus and hypertension) with 17 (31.4)% and cancer treatment 12(22.3) % were more common in HD while genetic disease 5 (9.3%) were less common (Figure 2).

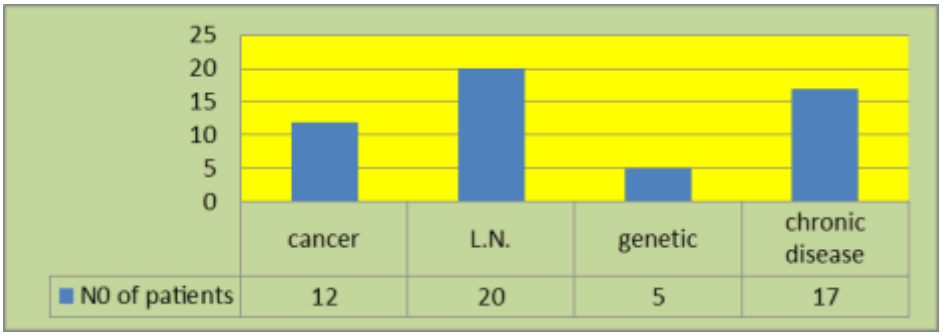

Figure 2: distribution of hemodialysis patients according to causes of disease

Chronic kidney disease (CKD), cancer and hematological diseases share areas of reciprocal influence, Cancer can affect the kidney either as glomerular lesions or as a result of the toxic effects of medication or radiation with acute (thrombotic microangiopathy, acute kidney injury, interstitial nephropathies among others) or chronic processes worsening of CKD after nephrectomy due to renal cancer, interstitial fibrosis, hydro electrolytic disorders (Francisco *et al.*,2019). (Moore *et al.*,2022) confirmed that metabolism of many chemotherapeutic agents dependent on adequate renal function which makes management challenging for patients with significant renal dysfunction requiring HD. Rossing and Zeeuw ,(2011) mention that Diabetic nephropathy one type of CKDs are a serious

public health problem that record 20%–40% of patients with diabetes developed nephropathy and lead to hemodialysis treatment . (Umebayashi *et al.*,2022) observed that the main risk factors for developing CKD are diabetes mellitus, high blood pressure, cardiovascular disease, and a family history of kidney disease and explain that diabetic nephropathy is the most common cause of CKD. The result agreement with result of (Timofte *et al.*,2020) found that an increase the risk of HCV infection in the HD patients compared to general population and the patients on chronic hemodialysis are at a high risk of contracting HCV.

Evaluation of IL-17 serum level in hemodialysis patients and healthy group

The results appear that serum IL-17 level was significantly increased in hemodialysis patients (189.26 ± 36.28) in compare to healthy control group (18.84 ± 3.06). According to type of infection, chronic patients record 213.56 ±34.61 while acute patients record 165.93 ± 24.80 pg/ml (Figure 3).

Figure 3: IL-17 serum level in hemodialysis patients, Acute , chronic state and healthy

Orejudo *et al.*,(2019) confirmed that IL-17A deficiency in angiotensin II-induced hypertension models significantly reduces the pressure and inflammation in target organs and demonstrated that increased IL-17A levels increased blood pressure by induction of arterial remodeling and stiffness . Also, Orejudo *et al.* (2020) observed an associating the Th17/IL-17 axis with primary hypertension and renal inflammation. (Abbas, *et al.*,2020) found that means of IL-17 elevated in nephropathy DM patients 368.45pg/ml compare to healthy group 128.50 pg/ml and concluded that L-17 play a significant role as a risk factor for the development of nephropathy DM**.** In study by Mohamed, *et al.*,(2016) confirmed that low-dose IL-17A administration to Type 1 and type-2 diabetic mice prevented diabetic nephropathy as a promising therapeutic approach in diabetic kidney disease while high dose of IL-17 developed more severe nephropathy. (Kuo *et al.*,2018) revealed that IL-17A was significantly upregulated in DN patient tissues (102.4 ±12.8 pg/μg total protein) compared with normal control patient tissues (21.4 ±6.6 pg/μg total protein; $P < 0.005$).

IL-17 concentration in hemodialysis patients according to cause of disease

The present study observed that IL-17 concentration was significant increase in HD patients with SLE followed by tumor patients then patients with chronic disease and genetic causes (218.67 ±45.80 ; 188.43 ± 43.71 ; 169.52 ± 29.76 ; 148.89 ± 41.07) in compare to healthy control subjects (18.84 ± 3.06) (Figure 4).

Figure 4: Illustrate IL-17 serum level in hemodialysis patients according to cause of disease

Radwan *etal.*,(2021)show that serum levels of IL-17 were significantly higher among patients with SLE as compared to healthy controls with a median 138 pg/nl versus 8.6 pg/nl respectively (p=0.001).**(**Galil *et al.* 2015) found that mean serum levels of IL-17 in SLE patients were significantly higher (19.54 pg/ml) at ($p < 0.001$) in relation to Healthy control group(10.78 pg/ml)and observed that patients with LN had lower levels of IL-17 during periods of remission with mean (13.18 pg/ml) than in active disease. Parhi *et al.*,(2019) reported that the levels of IL 17 (normal level ≤ 10 pg/ml) was found to be increased in DM (mean = 25.06 pg/ml) which is higher than in non-diabetic controls (mean = 5.232 ± 2.867 pg/ml) . Kuen *et al* .,(2020) noted that Th17 frequency is higher in the tumor cell than in healthy tissues or PBMCs,tumor cells and demonstrated elevated IL-17 production associated with persistence inflammation. (Wang *et al.*,2016) found the Serum level of IL 17 is higher in hemodialysis patients with hypertension risk than those in the control group and observed that easy-to-control hypertension group was 10.88±1.41 pg/ml and refractory hypertension group was 14.51±1.43 pg/ml found that increased IL 17 was associated with the risk of refractory hypertension in hemodialysis patients ,considering the significant association between blood pressure level and IL-17 pro-inflammatory cytokine secreted from Th17 cells.

IL-17 serum level in hemodialysis patients according to infected with HCV

The level of IL-17 was significantly elevated in hemodialysis patient infected with HCV (182.59 ± 25.46) in compare to patients none infected with HCV (114.73 ± 19.46) P≤ 0.05 (Figure 5).

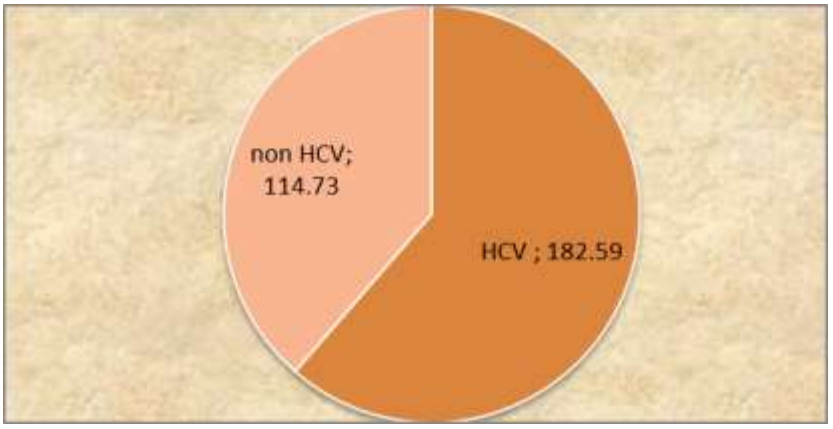

Figure 5: illustrate IL-17 level in hemodialysis patients according to infection with HCV

Abou El-Khier *et al*, (2018) found elevated serum levels of IL-17 in HCV infection patients 46.2 pg/ml while control subjects showed 18.4 pg/ml (P<0.0001) and observed that HCV infection closely associated with the extent of tissue inflammation. (Gomaa *et al.*, 2019) reported the serum level of IL.17 were higher in chronic HCV patients 52.9±32.6pg/ml than 17.1±10.4pg/ml in the control group and was correlated to viral load and proposed IL-17A to be a better biomarker in HCV infection. Also, Turner *et al.* (2010) observed that circulating IL-17A was elevated in hemodialysis patients especially among hepatitis C virus infected patients. In similarity (Hetta *etal.*,2017) observed that serum IL-17A levels were higher in diabetic patients infected with HCV (52.26±10.94 pg/ml) than in non-diabetic patients infected with HCV (28.77±11.84 pg/ml) and controls 1.65±1.14 pg/ml at P=0.0005.

Estimation the level of IL-17 in thalassemia patients according to HCV infection

The results revealed that mean serum level of IL-17 highly increased in thalassemia patients infected with HCV more than thalassemia patients non infected with HCV in compare with healthy group (73.66 ± 25.39 ; 48.81± 16.30 , 12.84 ±1.97 pg/ml respectively) and the maximum value were 122.4 , 59.8 and 19.3 respectively while the minimum were 54.6 , 27.0 and 18.5 pg/ml) (Figure 6).

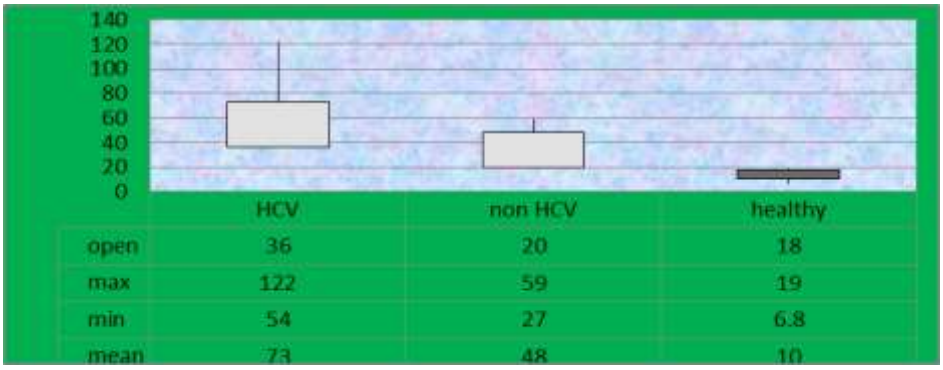

Figure 6: Level of IL-17 in thalsemic patients with HCV infection

This result is in line with a study done by Gomaa *etal.*,(2019) they demonstrated the serum values of IL17A were higher in patients with chronic HCV than the other group with the mean values being 52.9±32.6 pg/ml in the patient group and 17.1±10.4 pg/ml in the control group.and this suggests its pivotal role in the formation of chronic HCV infection, so, it can be used as a new marker for disease progression due to its positive correlation with the severity of liver injury. In consistence with results of this study Elbanan *et al.*, (2020) explain that the IL-17 serum concentration in HCV patients were signicantly higher (5.56 ± 4.860 pg/ml) compared to the control group(1.14 ± .218 pg/ml).

Evaluation IL-17 serum level in thallasemia patients according to splenectomy

This result explain that thallasemia patients appear highly increased after splenectomy than non-splenectomy patients (83.2± 27.1, 40.9 ± 22.4, 12.84 ±1.97 pg/ml) respectively (Figure 7).

Figure 7: IL-17 serum level of thalassemia patients according to splenectomy

This result covenant with result by Baharlou *et al*,.(2016) that found Serum levels of IL-17 among thalassemic patients were significantly increased compared to the controls (25.76 ± 4.15 vs. 19.91 ± 2.79 pg/mL; P = 0.005) ,and noted significant differences in the serum levels of IL-17 in peripheral blood of patients with low ferritin (less than 4500 ng/mL) and splenectomized and nonsplenectomized patients compared to the healthy controls (28.21 ± 5.17, 30.94 ± 13.38, and 22.79 ± 3.69 vs. 19.91 ± 2.79 pg/mL; P = 0.004, 0.04, and 0.01, respectively. Other study by Yiannikourides and Latunde-Dada.,(2019) suggest that the increased production of IL-17 contribute to abnormalities in iron metabolism and it is probably due to overstimulation of IL.17, iron deposition in the reticuloendothelial system such as macrophages and epithelial cells may influence the regulation of IL.17 responses in thalassemia patients and result in higher levels of its cytokines in the circulation, on the other hand, multiple blood transfusions may cause the immune system in β-thalassemia patients to be under constant alloantigen stimulation, despite the suppressed immune responses due to iron overload.

Conclusion

This result explain that HCV infected more than non-infected HD patients and the serum IL-17 level increased significantly in HD patients with HCV, then patients without HCV infection in comparison with healthy control group.

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