Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 5 Issue 4 April 2022

Research Article

Need of Improving the Diagnostics of Viral Hepatitis C in Patients with Chronic Kidney Disease, Receiving Hemo dialysis

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Received: February 18, 2022

Published: March 11, 2022

Abstract

This article presents a retrospective analysis of laboratory parameters in patients with end-stage chronic renal failure receiving lifelong hemodialysis and having a positive test for viral hepatitis C. The indicators of the complete blood count (red blood cell count, leukocyte count, platelet count, hemoglobin concentration, hematocrit and ESR) were analyzed, biochemical studies for glucose, total protein, albumin, renal functional tests (glomerular filtration rate - GFR, creatine and urea), liver function tests (ALT and AST), iron examination (concentration of serum iron and ferritin), C-reactive protein. For the diagnosis of viral hepatitis C, only the test for the determination of antibodies against viral hepatitis anti-HCV (Hepatitis C virus) was used. A statistical analysis of the obtained data was carried out - the number and percentage, the arithmetic average, the level of significance P at ≤ 0.05. Assessment of the terminal stage of chronic renal failure in terms of sexual dimorphism in a comprehensive study of the diagnosis of hepatitis C in patients receiving hemodialysis was made for the first time. Fluctuations in individual diagnostic and prognostic indicators of laboratory tests, suggesting the involvement of sex factors in the combined development of viral hepatitis C and chronic renal failure were identified with an unfavorable prognosis. An important conclusion was made that, in order to improve diagnosis, it is necessary to follow the algorithm for early diagnosis of viral hepatitis C in patients with chronic kidney disease, who are shown to undergo dialysis, according to the guidelines of KDIGO (Kidney disease: Improving Global Outcomes, 2018). First of all, it is necessary to include a test for determining the nucleic acids of the causative agent of viral hepatitis C - the RNA test.

Keywords: Glomerular Filtration Rate; Albuminuria; Liver Enzymes; RNA Test

Introduction

Patients in the end-stage of CKD (chronic renal failure) and receiving hemodialysis may be at risk for HCV infection (viral hepatitis C). The main risk factors for hepatitis C in patients on hemodialysis units are infusion therapy, frequent blood transfusions, duration of hemodialysis treatment, and contact with artificial kidney machines, which can be a source of HCV infection. In addition, patients can be admitted to hemodialysis units both at the end of the incubation (seronegative) period and in the pre-icteric (pre-icteric) period, which causes viral (viral) contamination [1-3].

The risk of infection in hemodialysis patients is directly proportional to the duration of this treatment method and the frequency of treatment methods. In hemodialysis units, antibodies to HCV are detected in 25% of patients. Antibodies in the blood to HCV are found in 17.4% of patients on program hemodialysis for up to 1 year, and in 40.6% with a treatment duration of 5 years or more [4].

Patients on program hemodialysis in the terminal stage of CRF have a tendency to chronic HCV in 79-92% of cases. Early serological diagnosis of HCV is difficult because HCV Ag (Hepatitis C virus antigen) appears in the phase of the established (established) infection after a seronegative period that varies greatly in duration. The time from disease onset to the appearance of antibodies varies from 4 to 35 weeks (mean 15 weeks), and in some cases seroconversion occurs a year or more after infection. In addition, hemodialysis patients produce antibodies at an extremely low titer.

With the interaction of such rather severe pathological conditions as HCV and CRF-5 (chronic renal failure of the terminal stage 5), a pronounced suppression of immunity occurs. In a third of patients with HCV, and according to some data - in 80% of cases, against the background of the presence of HCV RNA (ribonucleic acid) in the blood serum, normal liver transaminases are noted. Due to immunosuppression, approximately 15% of all HCV-infected hemodialysis patients are able to respond with an increase in aminotransferase activity.

The KDIGO (kidney disease: Improving Global Outcomes) Practice Guidelines for the Prevention, Diagnosis, Evaluation and Treatment of Hepatitis C in Patients with CKD (Chronic Kidney Disease) Revised 2018 contains recommendations based on the latest information available at the time of publication. It is intended to assist in the clinical decision-making process. This guideline is not a recognized standard in clinical practice and should not be used as such. Also, it should not be considered the only correct tactic for managing patients.

In clinical practice, differences in the methods of managing patients inevitably occur. This is based on the availability of a wide variety of clinical cases, resources for diagnosis and treatment, accepted standards of therapy in this medical institution. It is the responsibility of the physician using this guide to critically evaluate these recommendations and make a decision based on the particular clinical situation (Figure 1).

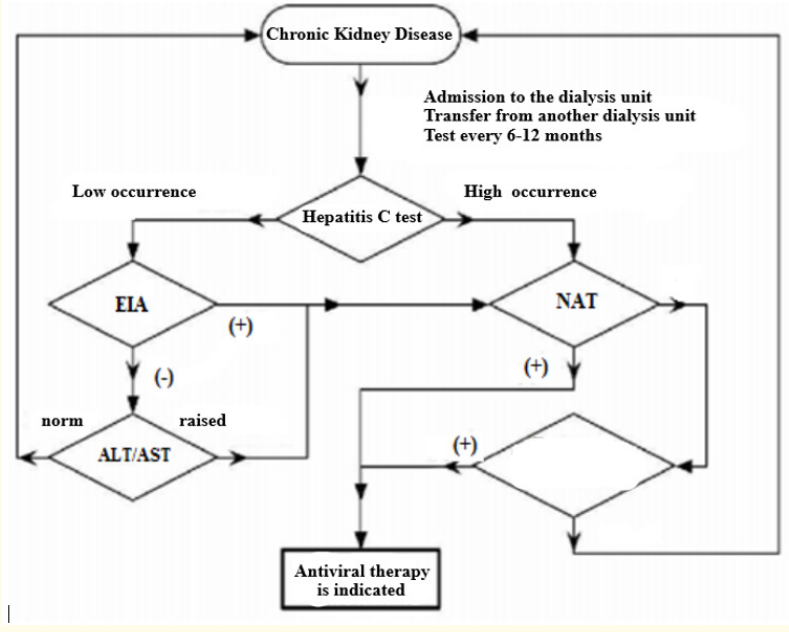

Figure 1: Algorithm of testing for viral hepatitis C in patients with end-stage chronic renal failure receiving hemodialysis. ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; EIA: Enzyme Immunoassay; NAT: Nucleic Acid Testing

The prevalence of HCV among patients with hepatitis varies worldwide from 1% to 85%. and is the main cause of increased morbidity and mortality in patients with end-stage renal disease [5-8]. Factors such as blood transfusion and frequent parenteral interventions have been shown to be associated with an increased risk of this HCV infection [9]. The duration of hemodialysis treatment and the possibility of nosocomial transmission of HCV have also been suggested as additional factors contributing to the occurrence of this infection. There are 11 known HCV genotypes and more than 80 subtypes. In clinical practice, 6 genotypes are distinguished, of which the main ones are 1a, 1c, 2a, 2c, 3a. For most European countries, outbreaks of AVHC (acute viral hepatitis C) in hemodialysis units are associated with HCV subtype lb. However, there are indications that the number of HCV-infected patients in hemodialysis centers can reach 20%, and HCV induced by genotype 2a is predominantly detected [12-15].

In contrast to hepatitis A and hepatitis B viruses, the diagnosis of acute infection of which is based on the detection of antibodies to IgM (immunoglobulin M), there is no serological marker in acute HCV infection [16]. Screening tests for chronic HCV infection are Enzyme Linked Immunosorbent Assay (EIA) or Chemical Immunosorbent Assay (CIA) for anti-HCV, as well as verification by an additional, more specific method - for example, nucleic acid analysis for HCV RNA\NAT (Figure 1).

The aim of this study is to retrospectively study the state of diagnosis of hepatitis C in patients with CKD-5 on hemodialysis in accordance with the recommendations of KDIGO 2018 using the example of the hemodialysis department of the City Clinical Hospital No. 7 in Almaty.

Materials and Research Methods

A retrospective study was carried out in the hemodialysis department and the clinical diagnostic laboratory of the city clinical hospital No. 7 in collaboration with the Department of Clinical Laboratory Diagnostics of NMU JSC and the Department of Biophysics and Biomedicine of Al-Farabi Kazakh National University (for the period from September 2019 to February 2020). The study protocol was approved by the Ethics Committee of "As fendiyarov Kazakh National Medical University" (No. 6 (83) dated by May 29, 2019). (Close the space) A total of 65 case histories were studied in patients with end-stage chronic renal failure - CKD-5 (G5) for the period 2017-2018. All patients underwent regular dialysis according to the appointment of specialists from the hemodialysis department of the City Clinical Hospital No. 7 according to the standard for the treatment of chronic kidney disease (CKD) established by the Ministry of Health of the Republic of Kazakhstan. Blood samples were taken from patients with their informed consent in 2017-2018. Following all necessary standard precautions, 10 ml of venous whole blood was taken from a patient with and without HCV who received hemodialysis under strict aseptic conditions. All blood samples were delivered to the clinical laboratory for hematological, biochemical and immunological studies on automatic analyzers with digital analysis in compliance with biosafety rules and quality control. Routine laboratory tests included complete blood counts (erythrocyte, leukocyte, platelet count, hemoglobin concentration, hematocrit and ESR), biochemical tests for glucose, total protein, albumin, renal function tests (glomerular filtration rate - GFR, creatinine and urea), liver function tests (ALT and AST), iron testing (serum iron and ferritin concentrations), C-reactive protein. In our study, only anti-HCV was taken as a criterion for diagnosing HCV infection. PCR test is necessary if patients are prescribed antiviral therapy. Thus, while there is a limit to the use of a single anti-HCV test across all factors, it is still the test of choice for screening for HCV as recommended by the CDC USA (Centers for Disease Control and Prevention - Centers for Disease Control and Prevention USA).

Statistical analyzes and plots were built using Microsoft Excel software. The following statistical tests were used: number and percentage, arithmetic mean, significance level P at ≤ 0.05.

The following results were obtained

The maximum number of cases of viral hepatitis in our study was in the age group from 41 to 60 years (86.14), and the smallest number of cases was in the age group of 21-30 years (5.4%) with an equal number of men and women (Table 1).

Age	Gender		Total	As a percentage of the total %
	Men	Women	In sum	Both genders
21-30	1	1	2	5.4
31-40	1	2	3	8.1
41-50	5	3	8	21.6
51-60	4	4	8	21.6
over 60	7	9	16	43.2
Total	18	19	37	37 (100%)

Table 1: Age and sex indicators of patients with viral hepatitis C receiving hemodialysis.

In 65 patients screened for hepatitis C, 37 tested positive for anti-HCV antibodies, with an incidence rate of 56.9%. The majority of seropositive cases belonged to the age group 41-60 years and older than 60 years (Table 1).

The glomerular filtration rate (GFR) averaged 10.39 ± 1.1 ml/min/1.73 m^2 for patients with HCV, while it did not differ statistically significantly ($p \leq 0.05$) in men and women (Table 2). Albuminuria exceeded the level for A3 and was high, it did not particularly depend on the gender of the patients (Table 2). Mean glomerular filtration rates confirm the end stage of chronic renal failure in patients with HCV [17]

The dynamics of creatinine and urea clearance before and after hemodialysis are presented in table 3.

GFR			Gender (GFR)		Albuminuria (≥ 30 mg)		
G5	Renal failure in the terminal stage	GFR (ml\minute, 1,73 м^2)	Men	Women	Total	Men	Women
+	+	10.39 ± 1,1	9.4 ± 0.98	11.5 ± 0.87	35,3 ± 2,4	34,7 ± 2,3	36.4 ± 1,9

Table 2: Indicators of glomerular filtration rate (GFR) and albuminuria.

№	Gender	GFR(ml/minute)	Creatinine before dialysis (µmol/l)	Creatinine after dialysis (µmol/l)	Urea before dialysis (mmol/l)	Urea After dialysis (mmol/l)
1	men	9.4 ± 0.98	819.55 ± 11,2	318,17 ± 4,3	20.84 ± 1,1	8.74 ± 0,78
2	women	11.5 ± 0.87	782.42 ± 6.4	292,01 ± 3,3	25.2 ± 1,4	8.79 ± 0,67
	P	≥ 0.05	≥ 0.05	≥ 0.05	≥ 0.05	≥ 0.05

Table 3: Indicators of glomerular filtration rate (GFR), creatinine and urea clearance.

From the data in table 3 it follows from that the nitrogen excretion capacity of the kidneys in patients with hepatitis C decreases and does not reach the degree of reliability between groups of patients of different genders (Table 3), i.e., we do not find problems of sexual dimorphism in kidney function in hepatitis C in patients with CPB at the terminal stage.

Indicators of the dynamics of the general blood test are shown for men and women separately in table 4.

The study showed that in hemodialysis patients with HCV of different sexes, hemoglobin (Hb) values were higher in women (89.7 + 5.3) than in men (80.2 + 2.2), respectively, but without significant statistical differences. While hematocrit (HCT) HCT) did not have a significant statistical difference between male and female groups. The remaining indicators of the number of leukocytes, platelets and erythrocyte sedimentation rate did not have a significant statistically significant difference between the studied groups (p ≥ 0.05).

№	Gender	RBC *10^{12}/ul	Hb г/л	Ht %	WBC *10^9/ul	PLT *10^9/ul	ESR mm/h
1	men	3.61 ± 0,75	80.2 ± 2.2	30.5 ± 1.9	6.3 ± 2.3	190,6 ± 4,4	36.4 ± 1,9
2	women	3.82 ± 0,7	89.7 ± 5.3	33.6 ± 1,9	5.9 ± 3.1	197.8 ± 4.9	29.5 ± 1,5
3	P	≥ 0,05	≥ 0,05	≥ 0,05	≥ 0,05	≥ 0,05	≥ 0,05

Table 4: Parameters of peripheral blood.

Biochemical examination of patients' peripheral blood showed that there were no significant statistical differences in the distribution of total protein and albumin, while serum iron and ferritin levels were lower in men than in women. The level of C-reactive protein was statistically significantly higher (19.4 ± 1.1 mg/ml) in men compared to the same indicator (6.5 ± 0.7) in women.

№	Gender	Glucose (mmol/l)	Total protein (g/l)	Albumen (g/l)	Ferritin (ng/ml)	Serum iron (mmol/l)	CRP (mg/ml)
1	men	4.46 ± 0,4	69.9 ± 2.3	34.7 ± 2,3	12.9 ± 1,1	8,9 ± 0,4	19,4 ± 1.1
2	women	6.2 ± 0,3	70.0 ± 3.2	36.4 ± 1,9	16.3 ± 1,2	14.3 ± 1.1	6.5 ± 0.7
3	P	≥ 0,05	≥ 0,05	≥ 0,05	≥ 0,05	≥ 0,05	≤ 0,05*

Table 5: Some biochemical parameters of serum.

Note: * - differences are statistically significant P ≤ 0,05.

In assessing the prognosis of the development of both HCV and CPD, liver tests play an important supporting role associated with determining the nature of hepatocyte damage when studying the level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes. Below is a table of liver enzymes and the de R it is coefficient.

Mean ALT levels were significantly high in HCV-positive male patients (P < 0.05). The level of alanine aminotransferase (ALT) and AST in the peripheral blood of patients was 1.5 times higher than the reference intervals and was higher than ALT and AST in women. The average value of AST in the group of hemodialysis patients with viral hepatitis in men was 55.1 ± 3.1 U/l and was higher

№	Gender	ALT (U/l)	AST (U/l)	De Ritis coefficient	HCV	RNA/NAT
1	men	66. 5 ± 2.8	55,1 ± 3.1	0.89	+	––
2	women	38.4 ± 2.7	47,7 ± 2.5	1.25	+	––
	P	≤ 0.05	≥ 0.05			

Table 6: Parameters of alanine aminotransferase (ALT), aspartate aminotransferase (AST), de Ritis coefficient, tests for determination HCV and NAT (Nucleic acids test).

than in the female group (47.7 ± 2.5 U/l). This difference between the two groups was not statistically significant (P ≥ 0.05). According to the latest KDIGO-2018 recommendations, PCR (polymerase chain reaction) for RNA \ NAT - the test should be prescribed to patients on hemodialysis with elevated serum aminotransferase levels, unexplained by other reasons [1].

Discussion of the Obtained Results

Patients receiving hemodialysis have a high risk of infection with viral hepatitis C [18]. However, data on the prevalence of HCV infection in the Republic of Kazakhstan among patients receiving hemodialysis are not complete. The seroprevalence of anti-HCV (Is it anti-HBC or anti-HCV) is 13.3% in patients on hemodialysis at 1 year compared with 69.9% in patients at 10 years [10], indicating that the duration of hemodialysis is associated with the risk of HCV infection. In our study, 37 out of 65 patients screened for hepatitis C tested positive for anti-HCV antibodies, with an incidence rate of 56.9%. The majority of seropositive cases belong to the age group 41-60 years and older than 60 years.

The performance parameters of the testing method used have a direct impact on the detection of hepatitis C and therefore may lead to differences in HCV prevalence data. With the advent of molecular techniques, circulating virus can now be detected by measuring HCV RNA using a PCR test [16]. This testing is used for early detection (before seroconversion) and is also important for confirming active HCV infection and monitoring antiviral therapy. However, a limitation of this test is cost effectiveness and unavailability in most laboratories. The KDIGO-2018 practice guideline recommends RNA testing when there is a high incidence of nosocamial infection in hemodialysis units.

In our study, only the anti-HCV test was taken as a criterion for diagnosing viral hepatitis C. According to WHO recommendations from 2017, a PCR test should be performed before prescribing antiviral therapy. However, this was not the aim of the present study. Although there is a limit to the use of a single anti-HCV test taking into account all factors, it is still the test of choice for screening for HCV as recommended by the US Centers for Disease Control (CDC USA). Current CDC recommendations for HCV screening in hemodialysis patients included anti-HCV and serum alanine aminotransferase (ALT) testing at admission, ALT every month, and anti-HCV every six months. However, new enzyme immunoassays aimed at detecting HCV antigens may solve the problem of using an expensive and inaccessible PCR method [19,20].

The indicators of glomerular filtration rate (GFR) and albuminuria corresponded to the diagnostic laboratory criteria for CKD-5 and A3 and did not depend on gender. The decrease in creatinine and urea clearance before and after hemodialysis confirmed the therapeutic effect of hemodialysis.

Anemia is a common clinical problem in patients with chronic kidney disease and is associated with increased morbidity and mortality. Anemia affects 60% to 80% of patients with chronic kidney disease (CKD) and reduces their quality of life [21-23]. Another cause of anemia is iron deficiency. A patient on hemodialysis is in a state of constant iron loss due to gastrointestinal bleeding, blood draws and/or, most importantly, when receiving hemodialysis therapy [27,28,30]. In the present study, laboratory indicators of anemia were studied in patients of different sexes. The study

showed that in hemodialysis patients with HCV of different sexes, hemoglobin (Hb) values were higher in women (89.7 + 5.3) than in men (80.2 + 2.2), respectively, but without significant statistical differences. Whereas hematocrit (HCT) (HCT) did not have a significant statistical difference between male and female groups. The remaining indicators of the number of leukocytes, platelets and erythrocyte sedimentation rate did not have a significant statistically significant difference between the studied groups ($p \geq 0.05$).

Biochemical study of peripheral blood in patients on hemodialysis with viral hepatitis C showed that the level of C-reactive protein was statistically significantly higher (19.4 ± 1.1 mg/ml) in the group of men compared to the same indicator (6.5 ± 0.7) in the group of women. This fact is associated with other indicators of the functional state of the kidneys and serum seropositivity in patients with CKD-5 clearly indicates ongoing liver inflammation and damage to kidney tissue [24-28].

Several studies have shown that aminotransferases (AST, ALT) in patients on hemodialysis have low levels and this decrease seems to occur already in patients with advanced chronic kidney disease even before the start of renal replacement therapy [29,30].

Conclusions

For the first time in the Republic of Kazakhstan, in a comprehensive study of the diagnosis of hepatitis C in patients with hemodialysis, CKD-5 was assessed from the position of sexual dimorphism. The revealed differences in the fluctuations of individual diagnostic and prognostic indicators of laboratory tests suggest the involvement of gender factors in the development of two deadly diseases - viral hepatitis C and kidney failure. The fact of low levels of transferases during hemodialysis is confirmed only in women, mainly under 40 years of age. In men in the terminal stage of CKD against the background of viral hepatitis, a decrease in transferases is not observed. There is a lack of attention on the part of nephrologists to the effect of antiviral therapy on the dynamics of viral response rates and the functional state of the kidneys, noted in the new KDIGO-2018 practical guideline. In hemodialysis units, where the level of infection with viral hepatitis C is high, it is necessary for patients to conduct a PCR test for the determination of RNA (NAT - Nucleic acid test) before starting hemodialysis. It is recommended that in hemodialysis units with a high incidence of hepatitis C, immediately prescribe a test for the determination of RNA (NAT - Nucleic acid test). This statement is not clear. It is important to note that the PCR test for HCV RNA is used to rule out active hepatitis C infection from distant infection. In recovered and treated patients, the test for antibodies to HCV remains positive for life, so there is a limitation in its use in this category of patients. Testing for hepatitis C in patients with end-stage chronic kidney disease (CKD5) receiving hemodialysis should be mandatory. It is necessary to test for RNA content before hemodialysis and when transferring a patient from one hemodialysis department to another. The NAT test should be considered in dialysis patients with elevated serum aminotransferases and other unexplained causes. If a newly diagnosed hepatitis C infection is suspected of being nosocomial, a NAT test should be performed on all contact patients. It is possible to repeat the NAT test in patients in the next 2-12 weeks if the first test is negative. Thus, it is necessary to improve the diagnosis of viral hepatitis C for patients with chronic kidney disease receiving hemodialysis, according to the algorithm of the KDIGO-2018 practical guideline.

No Conflict of Interest Declared

Funding was not provided for the study of patient histories.

Bibliography

1. Borzanova MV. "Viral hepatitis B and C in patients with chronic renal failure undergoing treatment in programmed hemodialysis centers". *Moscow* (2005): 130.

2. Zemchenkov A., *et al*. "Anemia in patients with CKD 5: current trends in the world and the picture in St. Petersburg". *Nephrology and Dialysis* 19.3 (2017): 47-56.

3. "KDIGO Clinical Practice Guideline 2012 for Anemia in Chronic Kidney Disease". *Nephrology and Dialysis* 15.1 (2013): 14-53.

4. Practical guide to the prevention, diagnosis, evaluation and treatment of hepatitis C in patients with CKD. (2018): 19.

5. Stepanova EN., *et al*. "Immunity indices in patients with end-stage renal failure and the uremic toxin para-cresol (literature review and our own research)". *Experimental Clinical Urology* 1 (2016): 112-119.

6. Shvedov AK., *et al*. "Viral hepatitis in dialysis patients". *Manual for Physicians* (2003): 56.

7. Shilo V., *et al*. "Russian national guidelines for the diagnosis and treatment of anemia in chronic kidney disease". *Nephrology and Dialysis* 18.1 (2016): 19-34.

8. Akchurin OM and Kaskel F. "Update on Inflammation in Chronic Kidney Disease". *Blood Purifier* 39 (2015): 84-92.

9. Agrawal S., *et al*. "Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPS-stimulated cytokine production". *Nephrology Dialysis Transplantation* 25.3 (2010): 737-746.

10. Chen YC., *et al*. "Hepatitis C virus itself is a causal risk factor for chronic kidney disease beyond traditional risk factors: a 6-year nationwide cohort study across Taiwan". *BMC Nephrology* 14 (2013): 187-195.

11. Chigurupati P., *et al*. "Study of incidence of hepatitis C virus infection in hemodialysis patients". *Annals of Tropical Medicine and Public Health* 7 (2014): 167-170.

12. Collister D., *et al*. "Anemia management in chronic kidney disease and dialysis: a narrative review". *Current Opinion in Nephrology and Hypertension* 26.3 (2017): 214-218.

13. Fabrizi F., *et al*. "Hepatitis C virus increases the risk of kidney disease among HIV-positive patients: Systematic review and meta-analysis". *Journal of Medical Virology* 88.3 (2016): 487-497.

14. Gregory M Lucas. "Association between hepatitis C virus and chronic kidney disease: heterogeneity begets heterogeneity". *Kidney International* 92.3 (2017): 546-548.

15. Kang SS., *et al*. "Nutritional Status Predicts 10-Year Mortality in Patients with End-Stage Renal Disease on Hemodialysis". *Nutrients* 9.4 (2017): 99-104.

16. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease". *Kidney International Supplements* 2.4 (2012).

17. Lee JJ., *et al*. "Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis". *PLoS One* 9 (2014): e100790.

18. Li M., *et al*. "A systematic review and metaanalysis: Does hepatitis C virus infection predispose to the development of chronic kidney disease?" *Oncotarget* 8.6 (2017): 10692-10702.

19. Li WC., *et al*. "Age and gender differences in the relationship between hepatitis C infection and all stages of chronic kidney disease". *Journal of Viral Hepatitis* 21 (2014): 706-715.

20. Lui´s Henrique Bezerra Cavalcanti Sette and Edmundo Pessoa de Almeida Lopes. "Liver enzymes serum levels in patients with chronic kidney disease on hemodialysis: a comprehensive review". *CLINICS* 69.4 (2014): 271-278.

21. Liu B., *et al*. "Hepatitis C virus infection among hemodialysis patients in Asia: a meta-analysis". *European Review for Medical and Pharmacological Sciences* 18 (2014): 3174-3182.

22. Mai Nabil Elnaggar., *et al*. "Effect of HCV Infection Versus HBV Infection on the Response to Erythropoietin Therapy in The Treatment of Anemia in Prevalent Haemodialysis Patients". *The Egyptian Journal of Hospital Medicine* 70 (2018): 92-96.

23. Mohamed Fouad., *et al*. "Influence of Chronic Hepatitis B and C Infections on Anemia in Hemodialysis Patients". *Enliven Archive* 20 (2015): 1-6.

24. Molnar MZ., *et al*. "Association of hepatitis C virus infection with incidence and progression of chronic kidney disease in a largecohort of US veterans". *Hepatology* 61 (2015): 1495-1502.

25. Necati **Örmeci**. "Treatment of Patients with Hepatitis C Virus and Kidney Diseases". *International Journal of Gastroenterology Disorders and Therapy* 5 (2018): 138-145.

26. Nosratola D Vaziri., *et al*. "Effect of uremia on structure and function of immune system". *Journal of Renal Nutrition* 22.1 (2012): 149-156.

27. Obi Y., *et al*. "Latest consensus and update on protein-energy wasting in chronic kidney disease". *Current Opinion in Clinical Nutrition and Metabolic Care* 18.3 (2015): 254-262.

28. Perunicić-Peković G., *et al*. "Predictors of mortality in dialysis patients-association between malnutrition, inflammation and atherosclerosis (MIA syndrome)". *Medicinski Pregled* 57.3-4 (2004): 149-152.

29. Sabatino A., *et al*. "Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis". *Clinical Nutrition* 36.3 (2017): 663-671.

30. Yao Q., *et al*. "Systemic inflammation in dialysis patients with end-stage renal disease causes and consequences". *Minerva Urology and Nephrology* 56 (2004): 237-248.