Al-Azhar Med. J . (Medicine). *Vol. 52 (2), April, 2023, 675-686*
DOI: 10.21608/amj.2023.291687
https://amj.journals.ekb.eg/article_291687.html

INCIDENCE, CHARACTERISTICS, AND OUTCOME OF COVID-19 INFECTION IN HEMODIALYSIS PATIENTS AND ITS EFFECT ON ERYTHROPOITEIN RESPONSE

By

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ABSTRACT

Background: The COVID-19 (coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) pandemic has reached unknown dimensions and is overwhelming societies, politics, medical systems and, in particular, intensive care unit and ESRD patients undergoing hemodialysis.

Objective: To study the incidence, characteristics, and outcome of COVID-19 infection on MHD patients and its effect on Erythropoitein (ESA) response.

Patients and Methods: This study was done at Sayed Galal University Hospital during the period between January 2021 to April 2021. A total of 90 MHD patients were recruited for this survey. Their anthropometrics and laboratory data were collected. Twenty patients were infected by COVID-19, and 70 patients were free from covid-19 infection. EPO responsiveness was evaluated by the erythropoietin resistance index (ERI). Statistical analyses were conducted to evaluate the incidence, characteristics, and outcome of COVID-19 infection in hemodialysis patients and its effect on ESA response.

Results: Two patients had home isolation; 18 patients had been admitted to the Hospital. Of them, 14 patients had been admitted to ICU. The mortality rate (cause specific mortality rate) of COVID 19 infection among those hemodialysis patients was 20%.

Conclusion: COVID 19 infection among hemodialysis patients was correlated with higher hospital admission, ICU admission and higher mortality rate, and also higher erythropoietin resistance index (ERI) and lower erythropoietin responsiveness.

Keywords: Hemodialysis, COVID-19, and erythropoietin resistance index.

INTRODUCTION

Severe acute respiratory syndrome of COVID-19 patients involves pulmonary and systemic inflammation, leading to multi-organ dysfunction in patients at high risk. Acute respiratory distress syndrome, sepsis, and acute cardiac decompensation are the most common critical complications during exacerbation. Approximately 15–33% of COVID-19 patients have severe course requiring intensive care, of whom up to > 30% need mechanical ventilation *(Wu and McGoogan, 2020)*.

ESRD is defined as Kidney damage for ≥3 months by structural or functional

abnormalities of the kidney, with GFR<15 ml/min *(KDIGO, 2013)*.

The major cause of anemia is insufficient erythropoietin (EPO) levels in MHD patients *(Lau et al., 2015)*.

The administration of erythropoiesis stimulating agents (ESAs) in the treatment of anemia of ESRD has been the single most important aspect of anemia protocols for over three decades. However, current ESA dosing guidelines do not appear to provide information about optimal ESA therapies *(Chait et al., 2014)*.

Unfortunately, a considerable proportion of end-stage renal disease patients exhibit a suboptimal hematologic response to EPO, as evidenced by the persistence of anemia despite adequate dosing or by the need for high-dose EPO therapy to achieve the recommended hemoglobin target *(Ogawa et al. 2014)*.

The definition of EPO hyporesponsiveness has been introduced to identify the inability to achieve or maintain target hemoglobin levels despite higher than usual doses of EPO *(Bellinghieri et al. 2015)*. However, observational studies suggested that higher EPO doses were needed to achieve anemia correction associated with higher risks of all-cause mortality and cardiovascular events *(Bellinghieri et al. 2015)*.

Several risk factors for EPO hyporesponsiveness have been identified, including inadequate iron administration, inflammation, malnutrition, suboptimal dialysis, secondary hyperparathyroidism, and malignancy *(Kanbay et al. 2016)*.

The present work aimed to study the incidence, characteristics, and outcome of COVID-19 infection on MHD patients and its effect on Erythropoitein (ESA) response.

PATIENTS AND METHODS

This was an observational cohort study with retrospective data analysis including ninty (age and sex matched) patients with end stage renal disease. The study was conducted at Nephrology Unit of Bab El-Shaaria University Hospital during the period between January 2021 and April 2021.

Inclusion criteria: Patients aging 16 years or more, duration of dialysis > 3 months, and use of arteriovenous fistula in the patients.

Exclusion criteria: Age <16 years, active bleeding or pure red cell aplasia and nonuse of EPO, patients who have malignant diseases, and patients with hepatic impairment or infectious diseases in nearly a month.

At enrollment, all patients were subjected to the following: Full history taking from patients including sex, age, weight, primary kidney disease, EPO use, and iron treatments. Complete clinical examination. Basal laboratory work-up: (serum creatinine, Blood Urea, BUN pre, BUN post, CRP, iron profile, S. Albumin, CBC, iPTH). All patients were undergoing hemodialysis 3 times per week and 4 hours per dialysis. All patients were using standard dialysis fluids. The dialysate flow was 500 mL/min, and the blood flow rate was 200–350 mL/min, all patients have URR> 60%, and were taking recombinant human EPO injection. The EPO responsiveness was evaluated by the erythropoietin resistance index (ERI). The ERI was calculated by dividing the

weekly weight-adjusted (kg) dose of EPO (IU) by the hemoglobin level (g/dL).

Patients were divided into 2 groups according to COVID-19 infection. Quick COVID-19 Severity Index (qCSI) which Predicts 24-hr risk of critical respiratory illness applied to all positive patients. Chest computed tomography scan were done for all patients.

SARS-CoV-2 infection was defined as detection of SARS-CoV-2 RNA in a nasopharyngeal swab specimen with quantitative real-time RT-PCR or in case of negative RT-PCR, a chest CT scan with a high level of suspicion (COVID-19 Reporting and Data System [CO-RADS] score of greater than or equal to four) in combination with suggestive clinical signs (fever, new-onset respiratory symptoms). - Quick COVID-19 Severity Index included respiratory rate, pulse oximetry and oxygen flow rate.

Statistical Analyses:

The SPSS 17.0 statistics package for Windows was used for statistical analysis.

Data were presented as Mean + Standard deviation and P-value was considered significant at <0.05.

Different comparisons were done using the t-student test for independent two groups variables. Data were tested for satisfying assumptions of parametric tests, but results showed that variables followed a non-normal distribution pattern so the non-parametric protocol of analysis was used.

Ethics and patient consent:

All procedures followed Al-Azhar University ethical committee regulations, and all patients gave consents.

Financial support:

No financial support.

RESULTS

A total of 90 patients were involved in this study and were analyzed. The mean age was 63.11±8.19 years, 12/20 (60%) of the patients were males, and the mean dialysis vintage was 87 ± 41 months. There was no significant difference between the two groups as regard to number of patients and covid19 infection incidence of infection rate was 22.2% **(Table 1)**.

Table (1): Incidence of COVID 19 Infection of hemodialysis patients

Patients / Ratios	No.	percent
COVID 19 Infection	20	22.2 %
Free from COVID 19 Infection	70	77.8%
Total hemodialysis Patients	90	100.0%

Table (2): In pateints with covid -19 infection there were 8 females and 12 females, 6 smokers, mean age was 63.11±8.19and mean weight was 83.73±14.43 **(Table 2)**.

Basic Characteristics of hemodialysis Patients with COVID 19 Infection (n.20).

Patient / Variables	n.	%
Females	8	40
Males	12	60
Smokers	6	30
non smokers	14	70
Age Mean ±SD	63.11±8.19	
Weight/kg Mean ±SD		

Table (3): In patients, diabetic kidney 25%, HTN kidney (20%), HTN kidney& diabetic kidney 20%, kidneys stones (10%), Cardiorenal Syndrome. 10% and polycystic kidney 15 **(Table 3)**.

Primary kidney disease of hemodialysis Patients with COVID 19 Infection (n.20)

Patient / Cause of ESRD	n.	Percent%
diabetic kidney	5	25
HTN kidney	4	20
HTN kidney& diabetic kidney	4	20
kidneys stones	2	10
Cardiorenal S.	2	10
polycystic kidney	3	15

Table (4): In patients' creatinine 8.6±1.65, urea 164.14±42.9, D dimer 1.62±0.25, CRP 62.71±22.28, ferritin 396.70±112.28, LDH 642.03±255.19, lymphocyte 12.96±4.8, Hb% 8.49±1.28 and iPTH 323.22±34.28 **(Table 4)**.

Laboratory finding of hemodialysis Patients with COVID 19 Infection.

Variables	Mean ±SD
creat	8.6±1.65
urea	164.14±42.9
D dimer	1.62±0.25
CRP	62.71±22.28
ferritin	396.70±112.28
LDH	642.03±255.19
lymphocyte	12.96±4.8
Hb%	8.49±1.28
iPTH	323.22±34.28

Table (5): Both lungs show GGO (40%), lung patches + GGO (60%), coRADS3 (10%), coRADS4(30%) coRADS5 (60). Home isolation (10%), Hospitalization (90%), high oxygen therapy (75%), low oxygen therapy (15%), ICU (70%), Mechanical ventilation (40) and Weaned /ventilated cases (50%) **(Table 5)**.

Clinical and radiological characteristics of COVID 19 Infection of hemodialysis Patients (n.20).

Variables	n	Percent %
CT finding		
both lungs show GGO	8	40
lung patches + GGO	12	60
COVID19 severity score		
coRADS3	2	10
coRADS4	6	30
coRADS5	12	60
Home isolation	2	10
Hospitalization	18	90
high oxygen therapy	15	75
low oxygen therapy	3	15
ICU	14	70
Mechanical ventilation	8	40
Weaned /ventilated cases)	4	50

Table (6): the mortality rate was 20% in patients **(Table 6)**.

Mortality rate (cause specific mortality rate) of COVID 19 Infection among hemodialysis Patients.

Patients / Ratio	n.	percent
Deaths of COVID 19 Infection	4	20
Survival COVID 19 Infection	16	80

Table (7): There was a significant difference between the 2groups as regard serum Albumin, D-Dimer and CRP, however There was no significant difference between remaining laboratory parameters **(Table 7)**.

Relation between laboratory finding among COVID 19 Infection of hemodialysis Patients and their survival (n.20).

Patients / Parametars	Survivors n.4x16	Non-survivors n.16x4	P-value
Lymphocyte	14.2±4.26	15.5±3.86	0.22
Hb	9.1±1.82	8.2±1.24	0.245
Albumin	3.79±0.88	1.9±0.96	< 0.01
D dimer	0.59±0.46	1.5±0.58	< 0.01
CRP	28.84±4.86	84±12.14	< 0.01
Ferritin	368±24.81	362±23.81	0.67
LDH	522±34.22	624±31.11	< 0.001
iPTH	321±25.31	322±26.21	0.95

Table (8): There was significant difference between the two groups as regard lung patches and CORAD s ICU admition and mechanical ventilation., However, there was no significant difference between remaining radiological and clinical parameters **(Table 8)**.

Relation between pattern of COVID 19 Infection of hemodialysis Patients and their survival (n.20).

Variables	Survivors n.16	Non-survivors n.4	n.	p
CT finding	.			
both lung show GGO	7	1	8	< 0.619
lung patches + GGO	9	3	12	
COVID19 severity score				
coRADS3	2	0	2	< 0.01
coRADS4	6	0	6	
coRADS5	8	4	12	
Home isolation	2	0	2	1
Hospitalization	14	4	18	1
high oxygen therapy	12	3	15	1
low oxygen therapy	3	0	3	0.579
ICU	10	4	14	< 0.267
Mechanical ventilation	4	4	8	< 0.014

Table (9): There was significant difference between the two groups as regard serum Iron, and ERI, however There was no significant difference between remaining parameters **(Table 9)**.

Comparison between COVID 19 Infection patients and non-infected Patients as regard Hb%, Ferrokinetics and erythropoietin resistant index (n.20).

Patient / Hemoglobin	COVID 19 N=2	Non- COVID 19 N=2	P-value (Sig.)
Hb %	8.49±1.28	10.2±1.24	0.08
S.iron	28.84±4.86	26±12.14	< 0.01
Ferritin	368±24.81	312±23.81	0.67
TIBC	412±34.11	342±21.22	0.55
ERI	14.17±1.88	7.46±1.62	< 0.01

DISCUSSION

Erythropoietin is a hypoxia- inducible growth factor, named after its original discovery in hematopoiesis *(Krantz, 2012)*.

Over the last 30 years, it became more and more clear that EPO is expressed in many organs and tissues of the body, where it exerts multiple functions in the sense of a pleiotropic tissue-protective cytokine. EPO has not only successfully been used to treat or prevent anemia (the approved indication) but also for various other conditions, ranging from brain to different other organ diseases, in both human trials and numerous animal studies. Overall, in critically ill patients, EPO was safe and probably efficient, as summarized in recent meta-analyses *(Litton et al., 2019)*.

Pneumonia, lymphopenia, lymphocyte exhaustion markers and cytokine storm

characterize severe COVID19. CRP and D-dimer are abnormally high. Substantially elevated serum levels of proinflammatory cytokines, including IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF and others, contribute to shock and multi-organ damage as well as to extremely diminished numbers of CD4+ T cells, CD8+ T cells, B cells, natural killer cells, monocytes, eosinophils and basophils *(Clarke et al., 2020)*.

In addition, SARS-CoV-2 infection of T cells could potentially induce T cell apoptosis *(Wu et al., 2020)*.

At the end of 2019, a novel coronavirus (ie, SARS-CoV-2) was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China *(Wu et al., 2020)*.

By2020, it led to a pandemic that has spread throughout most countries of the world *(Flythe et al., 2020)*.

SARS-CoV-2 disease (COVID -19) primarily manifests as a lung infection with symptoms ranging from those of a mild upper respiratory infection to severe pneumonia, acute respiratory distress syndrome, and death *(Goicoechea et al., 2020)*. COVID-19 disproportionately affects patients with pre-existing comorbidities, such as patients with various types of kidney disease. All medical professionals, including nephrology clinicians, are tasked with rapidly adjusting their practice to curtail the spread of the virus, while providing life-sustaining care to *(Clark et al., 2020)*.

Patients receiving in-center hemodialysis typically present to an outpatient facility three times per week to undergo dialysis. This limits their ability to observe physical isolation for infection control, which likely contributes to a higher risk of infection in this population *(Valeri et al., 2020)*. This was demonstrated in one study from France, in which patients receiving in-center dialysis had an approximately twofold greater risk of infection compared with patients receiving home dialysis *(Couchoud et al., 2020)*. Dialysis patients may also have a different clinical presentation compared with patients without pre-existing kidney disease *(Burgner et al., 2020)*. As examples, dialysis patients are more likely to have altered mental status and gastrointestinal illness and less likely to have respiratory symptoms (eg, cough or shortness of breath) or fever *(Jager et al., 2020)*. Unfortunately, here in Egypt However, little is known about clinical characteristics of hemodialysis patients with COVID-19, which we going to investigate.

The ERI is a sensitive evaluation index of EPO responsiveness and can predict composite events (CVD, infection, hospitalization, or death) and all-cause mortality in regular hemodialysis patients *(Xiong et al., 2019)*.

The present work aimed to evaluate the relationship between COVID-19 and EPO resistance represented as EPO Resistance Index (ERI) in maintenance hemodialysis patients and also the incidence, characteristics, and outcome of COVID-19 infection in Hemodialysis patients.

Unfortunately, researches in the field of COVID-19 in the ESRD patients and its effect on EAS response is limited but up growing.

CONCLUSION

Dialysis patients may have a different clinical presentation compared with patients without pre-existing kidney disease to COVID-19 infection. There is highly significant difference between the two groups as regard EPO resistance represented as EPO Resistance Index (ERI) in maintenance hemodialysis patients.

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دراسة معدل الانتشاروالخصائص والمردود الإكلينيكي لعدويالفيروس التاجي- ١٩ في المرضى المعاشين على الإستصفاء الدموي المزمن وتأثيرها علي المقاومة لهرمون الإريثروبيوتين

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خلفيـــة البحـــث: انتشـــرت العـــدوي بفيـــروس كورونـــا المســـتجد -2019 عالميـــا بـــلا حـــدود، وأثـــرت علـــي كـــل المســـتويات والمجتمعـــات والسياســـات والأنظمـــة الطبيـــة وخاصـــة العنايـــات المركـــزة ومرضـــي الفشل الكلوي المعاشين علي الاستصفاء الدموي.

الهـــدف مـــن البحـــث: دراســـة معـــدل انتشـــار العـــدوي بفيـــروس كورونـــا المســـتجد-2019 وخصائصـــه ومـــردوده الإكلينيكـــي وعلاقتـــه بالاســـتجابة لعقـــار الإريثروبيـــوتين فـــي مرضـــى الاستصـــفاء الـــدموي المزمن.

المرضـــى وطـــرق البحـــث: أجريـــت هـــذه الدراســـة فـــي وحـــدة الكلـــى الصـــناعية بمستشـــفي بـــاب الشـــعرية الجـــامعي فـــي الفتـــرة مـــن ينـــاير 2021م وحتـــي أبريـــل 2021م. وضـــمت الدراســـة 90 مريضًـــا مـــن مرضـــي الغســـيل الـــدموي المـــزمن. وقـــد جُمعـــت بيانـــات القياســـات البشـــرية والمختبـــرات الخاصـــة بهـــم, تـــم تقيـــيم اســـتجابة الإريثروبيـــوتين عـــن طريـــق مؤشـــر مقاومـــة الإريثروبـــويتين (ERI). تـــم تقســـيم المرضـــى إلـــى مجمـــوعتين وفقـــا لثبـــوت الإصـــابة بفيـــروس كورونـــا المســـتجد. مجموعـــة تشـــمل المرضـــي المصـــابين وعـــددهم 20مريضـــا

والمجموعة الثانية الذين لم تثبت إصابتهم. وتم عمل الدراسات الإحصائية لتقييم معدل الإصابة وتأثيرها علي مرضي الغسيل الكلوي ومدي تأثيرالعدوي علي مقاومة الإريثروبيوتين.

نتائج البحث: لوحظ أن معدل انتشار الإصابة بفيروس كورونا المستجد يمثل تقريبا خمس عدد المرضي المعاشين على الاستصفاء الدموي، وتختلف استجابتهم للمرض عن المرضي غير المصابين بالقصور الكلوي، وللإصابة تأثير على معدل استجابة مرضي الكلي لعقار الإريثروبيوتين.

الاستنتاج: مرضي الاستصفاء الدموي المزمن يصابون بفيروس كورونا المستجدج-2019 وتظهر عليهم أعراض مشابهة للمرضي غير المصابين بالقصور الكلوي وأعراض أخري مختلفة ربما لاختلاف استجابة الجهاز المناعي للإصابة بالكوفيد في المرضى المعاشين على الاستصفاء الدموي. وقد تبين أن العدوي بالكوفيد يكون مرتبطا مع نقص استجابة المصاب لعقار الإريثروبيوتين.

الكلمات الدالة: الفيروس التاجى كوفيد 19، غسيل كلوي، الإستجابة لعقار الإريثروبيوتين، مؤشر مقاومة الإريثروبيوتين.