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Evaluation of the Impact of Local Protocol of King Salman Specialized Hospital-KSA of Management of Renal Disease patients requiring Immunosuppressive Therapy Afflicted by Acute COVID 19 Infection – an Observational Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author AFM gave research idea, performed study design, did data acquisition and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work. Authors DAAM and GES provided intellectual content of critical importance to the work described in the manuscript. Author OAAN did data analysis and interpretation. Author NSA supervised and mentored the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: We aimed to observe the effect of modification of the immunosuppressive regimen in response to the severity of COVID-19 infection on the outcome of renal disease patients and to study factors affecting their mortality.

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Methods and Materials: The study was conducted on 18 patients (13 males and 5 females) admitted to the King Salman Specialized hospital (KSSH), a COVID-19 isolation center, in Hail city in KSA; of them, 16 had kidney transplantation maintained on immunosuppression protocols, while 2 had immune-mediated nephritis maintained on immunosuppression. Locally agreed immunosuppressive protocol, the antivirals used as well as the used anticoagulant were followed without interference. Demographic data, associated comorbidities, baseline x-ray, routine laboratory data, and patients' outcomes were recorded.

Results: The ages of the studied patients ranged from 23 - 60 years. Nine patients were treated in the ward (group 1) and the other 9 patients needed admission to the ICU (group 2). Compared to group 1, group 2 patients had higher mortality, higher levels of TLC, CRP, and serum phosphorus as well as admission LDH and D-dimer. Furthermore, group 2 patients had lower serum albumin, and lower blood platelet and lymphocyte counts. All patients continued on corticosteroids and calcineurin inhibitors in case they had been maintained on them before the infection. Antiproliferative drugs (MMF or Azathioprine) were discontinued in all patients; 15 of them stopped it on the first admission day and 3 were reluctant to stop the drugs till a few days later when they were admitted to the ICU. Of the total observed patients 4 died; 3 of them were those who did not stop these drugs early in the course of the disease.

Conclusions: Appropriately early discontinuation of antiproliferative drugs in renal immunosuppressed patients and the use of higher doses of systemic steroids were associated with better prognosis of COVID-19 infection patients and did not cause deterioration of kidney function.

Keywords: COVID 19 infection; kidney transplant patients; immunosuppressed patients; antiproliferative drugs; isolated gastrointestinal symptoms.

1. INTRODUCTION

The new coronavirus disease 2019 (COVID-19) infection, which emerged in Wuhan city, China, in December 2019, has close genomic structural similarities with the severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the SARS pandemic in 2003 and the middle east respiratory syndrome coronavirus (MERS-CoV) that caused (MERS) epidemic in 2012 [1,2]. After that, it spread rapidly throughout the world, WHO declared this novel coronavirus a public health emergency of international concern [3]. At the time of data collection, on February 1, 2021, infections related to COVID-19 affected people from 210 countries were 103018643 reported cases worldwide and 368329 cases in KSA [4,5]. The risk factors related to the outcomes of SARS-CoV-2 infections included old age, male gender, obesity, and associated co-morbidities [6].

COVID-19 could be associated with high morbidity and mortality in kidney transplant recipients. However, risk factors for COVID-19 disease in patients with kidney transplants remain poorly defined. Solid organ transplant recipients may be at increased risk for COVID-19 as they are immunosuppressed and are less likely to have an effective immune response to vaccination [7]. According to the Scientific Registry of Transplant Recipients, currently 86% of renal transplant recipients receive MMF as part of their immunosuppressive regimen, most frequently in combinations with prednisone and tacrolimus [8]. MMF is an inhibitor of inosine-5-monophosphate and is able to preferentially inhibit B-cell and T-cell function [9]. Moreover, The Combined Immunosuppressive and Anti-inflammatory Effects of Dexamethasone were known [10].

Treatment of COVID-19 particularly in organ transplant recipients is empirical and debatable, exclusively the adjustment of the immunosuppressant drugs. However, there are limited studies available comparing this population with the general population when infected with COVID 19 regarding clinical symptoms, and laboratory data as well as disease severity and clinical outcomes.

2. METERIALS AND METHODS

The study was conducted on eighteen patients who were admitted to the King Salman Specialized hospital (KSSH), a COVID-19 isolation center, in Hail city in KSA during the period of February to October 2021. Of them, sixteen patients had kidney transplantation and were maintained on immunosuppressant protocol **(**OPTN/SRTR Annual Report, Immunosuppression use for maintenance by regimen prior to discharge, 1997–2006

Recipients with kidney transplants. 2007 [Accessed September 9, 2008]) including calcineurin inhibitors (tacrolimus or cyclosporine), antiproliferative agents (mycophenolate mofetil {MMF} or azathioprine), and a small dose of oral prednisolone [8]. The other two patients had immune-mediated nephritis maintained on immunosuppression. Locally agreed protocol, regarding immunosuppressive protocol, the antiviral used as well as the used anticoagulant, was planned between the treating team; Nephrology, Chest, and ICU consultants to be followed considering international guidelines for COVID 19 infection in immunosuppressed patients and Saudi MOH guidelines for the management of COVID 19 infection [11]. This management usually includes antiviral drugs, systemic steroids (dexamethasone 6-10 mg intravenously), anticoagulants, and antibiotics. Management of the studied patients was shared between nephrology, chest, and ICU consultants, according to the international guidelines for infection in immunosuppressed patients [12]. Soon after diagnosis, the immunosuppressive protocol was changed with strict instructions to discontinue the antiproliferative drugs, starting intravenous steroids by doses that were increased according to the severity of the chest condition or with an increased need for oxygen therapy, and continuing Tacrolimus with regular measurement of its trough level.

The antiviral therapy was used according to the severity of COVID 19 infection as follows: in mild cases with normal liver function, favipiravir 1800 mg twice for one day then 800 mg BID for 7-10 days, was given; while in severe and critical cases, a loading dose of Remdisivir 200 mg IV then 100 mg once daily for 5 days was used. Enoxaparin (LMWH)40 mg once daily was used as an anticoagulant in low-risk patients and 40 mg twice daily in high-risk patients. Unfractionated heparin (UFH) was used in cases with renal impairment. All the 18 cases were allowed to receive their routine medications for any associated comorbidities during their hospital stay unless contraindicated.

Demographic data, associated comorbidities, and routine laboratory data in addition to the D-dimer, serum ferritin, LDH as well as C-reactive protein of the studied patients were recorded. Imaging of the chest was done through baseline chest x-ray then follow up every 4-7 days and to be done urgently if there was any deterioration, while to be performed daily in cases admitted to ICU.CT chest was done in patients with a prolonged course to exclude post-COVID fibrosis. The protocol of management of every case was described. Patients 'outcomes; namely, ICU admission, length of hospital stay, and mortality were also noted. When serial laboratory data were available, the highest and the lowest values, in addition to those at admission and at discharge were selected for statistical analysis.

2.1 Statistical Analysis

After the collection of data, they were analyzed using the statistical package of social science (SPSS, IBM) software version 24. Categorical data were expressed as numbers and percentages and were analyzed by Fisher-exact tests. Scale data were expressed as means ±SD or medians (IQR) and minimum &maximum as appropriate. Normality was tested using the Shapiro Wilkinson test. Parametric data were analyzed using the independent sample T-test, while the Mann-Whitney test was used to analyze non-parametric data as appropriate. P value was considered significant if it was < 0.05.

3. RESULTS

The studied eighteen patients had ages ranging from 23 - 60 years. They were 13 males and 5 females. The studied patients were allocated into two groups; nine patients were admitted to the ward and did not need admission to ICU (group 1) and the other group comprised nine patients admitted to ICU (group 2). Days of hospital stay ranged from 6-48 days. The duration of transplantation of the studied sixteen transplanted patients ranged from 1.5 - 20 years. Descriptive data of the studied group were shown in Table 1 while, Tables 2-a, b, and c showed comparisons between cases with and without ICU admission. The four cases that received vaccination were not admitted to ICU. Days of hospital admission were statistically significantly lower in patients admitted to ICU and the frequency of mortality was much higher in the same group. The highest level of TLC, CRP, and serum phosphorus was higher in group 2, furthermore, the lowest blood hemoglobin, lowest platelet, and serum albumin levels were lower in the same group. Moreover, LDH at admission and the lowest D-dimer were higher in cases with ICU admission. Tables 3-a-b, showed comparisons between ICU cases in relation to fatality. Serum creatinine, blood urea nitrogen, and serum phosphorus were comparable on admission in all cases that admitted to ICU either passed away or were discharged alive. The

previous parameters were higher at discharge in the expired group. The highest and at-discharge levels of CRP and LDH were higher in the deceased group. In the reverse, the highest level of hemoglobin and serum albumin was higher in the surviving group. Moreover, the lymphocytic number was lower in the dead group. Tables 4-a, b, and c showed descriptive data, laboratory parameters, fate, and management, of every patient, individually.

Two of the sixteen transplanted patients (number eight and twelve) presented with isolated gastrointestinal symptoms; fever, abdominal pain, nausea, and diarrhea while, fourteen patients presented with COVID-19 pneumonia. The two cases admitted to the hospital showed COVID-19 swab positive. They had an oxygen saturation of more than 95% on room air and continued on their home medications with no intake of antiviral drugs, no change of immunosuppressive protocol, symptomatic management, and multivitamins with hospital stays 6 and 7 days respectively.

The less severe seven patients (cases 2, 4, 6, 13, 16, 17, 18) who were admitted to the ward, presented with cough, fever, and shortness of breath. Two of them (cases 2, and 6) were maintaining the required oxygen saturation on room air. Other cases were initially maintained on 2-4 L O2, most of them had a stationary course. However, for case 18, he was presented late with high O2 requirements. In all, a protocol for COVID-19 was started, and an adjustment of immunosuppressive therapy was done. They were not admitted to the intensive care unit and were discharged home after improvement. In all cases, Remdesivir and dexamethasone 10 mg intravenously were added. MMF and prednisolone were held, and tacrolimus was continued by measuring trough levels regularly.

Six males and three females were admitted to ICU because of deterioration of the chest condition while reaching to use an oxygen supply of up to 15 liters through a non-rebreathing face mask for the need to receive oxygen supply through high flow nasal cannula or non-invasive ventilation to be able to achieve the target oxygen saturation. Five of them (ICU survivors, cases 1, 5, 9, 11, and 15)' were admitted to ICU with a severe presentation; the first case (case 1);, 52 years old Saudi male patient who had hypertension, diabetes mellitus, chronic kidney disease, and renal transplantation three years ago. He presented to the emergency department with shortness of breath and fever and had been found with a COVID-19-positive swab. The patient was admitted directly to the ICU due to respiratory distress, high oxygen requirement, and a picture of ARDS clinically and radio-logically. Non-invasive ventilation was started alternating with a high-flow nasal cannula. While, Cases 5, and 9 were admitted first to the isolation ward as they were stable initially, after a few days, they were deteriorated with increased oxygen requirement and admitted to the intensive care unit to start non-invasive ventilation. Case 11; 51 y old female patient, known to be hypertensive, with a history of kidney transplant 8 years ago, was admitted with a history of fever, and cough for 2 days. The patient had a patch on her right lung in Chest x-ray, she was on room air; however, there was metabolic acidosis, with high creatinine 243 mmol / L. Also, there was electrolyte disturbance. After the correction of electrolytes, acidosis, and low blood pressure, and starting our COVID-19 protocol, the patient was discharged 7 days after admission. However, after one week, the patient was readmitted to the intensive care unit by extensive pneumonia, shortness of breath, tachypnea, and desaturation. Non-invasive ventilation was started; the COVID swab was repeated and was still positive. In all cases, dexamethasone 10 mg IV was added. Discontinuation of MMF, and prednisolone, tacrolimus was continued with measuring trough level regularly. When gradual weaning from non-invasive ventilation happened, oxygen supply through a non-rebreathing mask started. Additionally, a 53y old male patient (case 15)who was a known case of ANCA negative vasculitis, HTN, with a positive COVID swab, complaining of shortness of breath and cough, was admitted on 15 L O2 via non-rebreathing face mask; SPO2 was 89-90%. Non-invasive ventilation was initiated alternating with a high-flow nasal cannula. MRSA screen was positive for staph aureus, intravenous linezolid was started. Gradual weaning from O2 was done and the patient was discharged on 2 L O2. With the improvement of the patients, gradual weaning from oxygen was started, and discharged with the following immunosuppressive protocol; prednisolone 40 mg once daily with withdrawal by 5 mg weekly till 5 mg and restarted MMF when prednisolone 20 mg daily The case 15 patient was discharged on prednisolone 40 mg once daily with withdrawal by 5 mg weekly till 5 mg and restarted azathioprine 75 mg when prednisolone 20 mg daily.

Three patients of group 2(one male and two females) passed away in the intensive care unit. One patient (case 3) was admitted first to the ward for 2 days, and then shifted to ICU due to deterioration of chest condition, with tachypnea, hypoxia SPO2 on 15L non-rebreathing face mask 90 - 91%. The other 2 cases (cases 7, and 10) were admitted directly to the intensive care unit due to respiratory distress, refractory hypoxemia, and a picture suggesting adult respiratory distress syndrome on presentation. MMF was planned to be stopped in all cases but unfortunately, two of the three cases insisted to receive MMF from immunosuppressive home medications (prescribed and received from her primary transplant center) for 2-3 days still they became convened to stop it. Dexamethasone 10 mg intravenously was added. All three patients deteriorated with no response to non-rebreathing ventilation and a high-flow nasal cannula. So, the endotracheal tube was inserted with deterioration of the general condition of the three cases. Septic shock had complicated the course. Tacrolimus was discontinued after the Multidisciplinary meeting decision in the 3 cases; however. Kidney function tests deteriorated after the discontinuation of tacrolimus but not to the level necessitating renal replacement therapy. After a few days, the patients expired. The fourth ICU mortality case (number 14) was a lupus female patient maintained on MMF and 15 mg prednisolone. She insisted to receive MMF from her immunosuppressive home medications with an increased dose of steroid to 10 mg dexamethasone till deterioration happened, at that time she was convinced to discontinue MMF but further deterioration had happened, she was artificially ventilated, had deteriorated renal function, and started continuous renal replacement therapy (CRRT) for 72 hours and she received oral antiviral. Unfortunately, she passed away.

In summary; all patients continued on systemic steroids and calcineurin inhibitors in case they had been maintained on them before the infection. Antiproliferative drugs (MMF or Azathioprine) were discontinued in all patients; 15 of them stopped it on the first admission day and 3 were reluctant to stop the drugs till a few days later when they were admitted to the ICU. Of the total observed patients 4 died; 3 of them were those who did not stop these drugs early in the course of the disease. Dexamethasone was given to 8 survivor patients at the dose of 10 mg and to 3 survivors at the dose of 6 mg while hydrocortisone was given to one survivor. Isolated GI symptoms without the presence of respiratory symptoms have been observed in patients with COVID-19 and could be treated safely with symptomatic management.

Table 1-a. Descriptive data of the studied group

		n	%
Sex	**Female/ Male**	**5/13**	**27.8/72.2**
COVID 19 presentation	chest symptoms	16	88.9
	GIT symptoms	2	11.1
DM		8/18	44.4
HTN		13/18	72.2
IHD		2/18	11.1
Fate of the patient	Improved	14	77.8
	Died	4	22.2
Antiviral drugs used	no antiviral taken	4	22.2
	Oral antiviral	6	33.3
	IV antiviral	5	27.8
	oral and iv antiviral	3	16.7
Anticoagulant used	LMWH	16	88.9
	UFH	2	11.1
COVID 19 swab at discharge	Negative	11	61.1
	Positive	7	38.9
Transplantation/Nephritis		16/2	88.9/11.1
Previous COVID Vaccination	No	13	76.5
	One dose	3	17.6
	Two doses	1	5.9

Table 2-a. Comparison between cases with and without ICU admission

		ICU Admission				p
		Group 1		Group 2		
		n	%	n	%	
Sex	Female	2	22.2%	3	33.3%	1.000
	Male	7	77.8%	6	66.7%	
COVID-19 infection Presentation	Chest symptoms	7	77.8%	9	100.0%	0.471
	GIT symptoms	2	22.2%	0	0.0%	
DM	Yes	4/9	44.4%	4/9	44.4%	1.000
HTN	Yes	7/9	77.8%	6/9	66.7%	1.000
IHD	Yes	1/9	11.1%	1/9	11.1%	1.000
Kidney Transplantation	Yes	9/9	100.0%	7/9	77.8%	0.471
Fate of the Patient	Improved	9	100.0%	5	55.6%	0.082
	Died	0	0.0%	4	44.4%	
Renal function Deterioration	Stable	8	88.9%	5	55.6%	0.294
	Deterioration without need for RRT	1	11.1%	3	33.3%	
	Need for RRT	0	0.0%	1	11.1%	
Antiviral drugs used	No drug taken	2	22.2%	2	22.2%	0.389
	Oral	4	44.4%	2	22.2%	
	IV	3	33.3%	2	22.2%	
	Oral and iv	0	0.0%	3	33.3%	
Anticoagulant used	Heparin	1	11.1%	1	11.1%	1.000
	Clexan	8	88.9%	8	88.9%	
COVID 19 swab at Discharge	Negative	5	55.6%	6	66.7%	1.000
	Positive	4	44.4%	3	33.3%	
CKD	With kidney transplant	9	100.0%	7	77.8%	0.471
	With autoimmune disease.	0	0.0%	2	22.2%	
Vaccination	No dose	5	55.6%	9	100.0%	0.135
	One dose	3	33.3%	0	0.0%	
	Two doses	1	11.1%	0	0.0%	

**p value was measured using Fisher-Exact test*

Table 2-b. Comparison between cases with and without ICU admission

	n	Mean±SD	Median (Q1-Q3)	p
Duration of Kidney Transplantation	9	9.83±6.61	10.00 (3.0-16.0)	0.262
	7	8.71±7.06	7.0 (3.0-17.0)	
Days of hospital stay	9	10.67±4.00	11.00 (7.00-13.50)	0.010
	9	25.67±13.40	25.00 (15.00-37.00)	
Weight kg	9	85.17±19.02	82.00 (75.00-89.00)	0.605
	9	80.28±20.29	85.00 (62.50-95.50)	
BMI	9	30.23±8.19	29.73 (24.23-34.23)	0.648
	9	28.66±5.93	29.76 (22.96-32.76)	

**P value was computed using T test*

**First row represent group 1 *Second row represent group 2*

Table 2-c. Comparisons between with group1 and group 2

	n	Mean	SD	Median	IQ		p
					Q1	Q3	
Hemoglobin(Hb) at admission	8	13.04±2.3		12.5	11.67	15.57	0.963
	9	12.97±2.78		13.7	10	15.1	
Hb the lowest	8	10.78±3.15		11.55	8.77	13.6	0.021
	9	7.45±2.14		8.7	5.4	9.25	
TLC the highest	8	9.8±3.1		10.6	7.7	12.3	0.056
	9	16.3±8.4		17.4	8.9	22.6	
TLC the lowest	8	5.1±2.0		4.6	3.4	6.8	0.106
	9	3.7±1.4		3.7	2.4	4.8	
	9	173.0±66.4		174.0	132.5	212.0	
Platelet the highest	8	354.1±193.5		303.0	210.8	535.3	0.638
	9	319.3±94.6		298.0	218.0	423.0	
Platelet the lowest	8	222.8±159.7		188.5	123.8	223.8	0.08
	9	121.4±28.1		125.0	108.0	142.5	

	n	Mean	SD	Median	IQ		p
					Q1	Q3	
Lymph number at admission	9	0.6±0.3		0.5	0.4	0.9	0.986
	8	0.6±0.2		0.6	0.5	0.8	
Lymph number at discharge	8	0.6±0.4		0.5	0.4	0.6	0.536
	9	0.7±0.5		0.7	0.3	1.2	
Lymph number the highest	8	0.8±0.3		0.8	0.5	0.9	0.323
	9	1.0±0.4		1.1	0.6	1.3	
Lymph number the lowest	8	0.35±0.19		0.33	0.21	0.53	0.360
	9	0.28±0.24		0.18	0.14	0.46	
D-dimer at admission	7	0.9±0.8		0.4	0.2	1.6	0.9
	9	0.9±0.7		0.6	0.5	1.5	
D-dimer the highest	3	1.3±1.7		0.5	0.2		0.278
	9	13.0±17.1		6.6	1.8	19.9	
D-dimer the lowest	3	0.2±0.1		0.2	0.1		0.059
	9	0.7±0.4		0.6	0.4	1.0	
CRP at admission	5	3.1±2.9		1.9	1.1	5.6	0.194
	9	10.5±11.7		6.7	3.9	11.7	
CRP at discharge	2	3.2±2.9		3.2	1.1		0.291
	7	17.4±16.7		9.9	3.0	37.9	
CRP the highest	2	5.0±4.3		5.0	1.9		0.018
	7	24.8±14.5		18.6	11.3	39.7	
LDH at admission	2	158.5±71.4		158.5	108.0		0.054
	9	316.7±93.6		320.0	225.0	395.0	
S. ferritin	3	971.4±694.4		1002.0	262.3		0.382
at admission	5	602.0±435.8		376.2	303.5	1013.5	
INR the highest	8	1.6±1.1		1.2	1.1	1.4	0.258
	5	1.2±0.1		1.2	1.1	1.4	
Creatinine the highest	9	164.9±82.0		137.0	116.4	195.2	0.197
	9	271.4±222.6		210.6	119.5	315.0	
Creatinine the lowest	9	106.3±37.1		104.1	78.7	111.0	0.86
	9	101.7±68.4		81.0	61.1	125.1	
BUN the highest	9	14.5±6.8		16.5	7.5	17.8	0.136
	9	22.0±12.7		16.4	9.8	35.0	
BUN the lowest	9	8.5±4.8		6.5	4.8	12.8	0.982
	9	8.4±5.2		5.3	4.4	14.1	
Serum potassium the highest	9	5.4±1.1		5.2	4.5	6.1	0.885
	9	5.5±0.4		5.6	5.1	5.7	
Serum potassium the lowest	9	3.8±0.5		3.5	3.4	4.3	0.707
	9	4.0±1.2		4.0	3.1	4.2	
Phosphorus the highest	7	1.2±0.2		1.2	1.0	1.3	0.007
	9	1.8±0.6		2.0	1.3	2.3	
Phosphorus the lowest	7	0.8±0.2		0.8	0.6	0.9	0.736
	9	0.8±0.4		0.6	0.5	1.1	
Ca at admission	8	2.1±0.2		2.1	2.0	2.3	0.033
	9	2.0±0.1		2.0	1.9	2.1	
Ca at discharge	9	2.1±0.2		2.2	2.0	2.2	0.547
	9	2.1±0.2		2.1	2.0	2.2	
Ca the highest	8	2.0±0.2		2.0	1.8	2.1	0.092
	9	1.7±0.3		1.8	1.5	1.9	
Albumin the highest	8	32.1±7.6		29.4	25.6	41.2	0.975
	9	32.2±4.6		33.0	29.0	35.5	
Albumin the lowest	8	25.3±3.8		25.6	22.0	26.7	0.035
	9	21.9±2.2		22.4	20.0	23.5	

P value was measured using T test or Mann-Whitney test as appropriate.
**First row represent group 1 *Second row represent group 2*

Table 3-a. Comparisons between ICU cases according to fatality

		Outcome of the patients				P
		Survived		Died		
		n	%	N	%	
DM	No	3	60.0%	2	50.0%	1
	Yes	2	40.0%	2	50.0%	

		Outcome of the patients				P
		Survived		Died		
		n	%	N	%	
HTN	No	1	20.0%	2	50.0%	0.524
	Yes	4	80.0%	2	50.0%	
IHD	No	5	100.0%	3	75.0%	0.444
	Yes	0	0.0%	1	25.0%	
Mode of death	0	5	100.0%	0	0.0%	0.008
	With no indication to dialysis	0	0.0%	3	75.0%	
	With indication to dialysis	0	0.0%	1	25.0%	
State of kidney function	Stable	5	100.0%	1	25.0%	0.286
	With deteriorated kidney function	0	0%	2	50.0%	
	deterioration up to dialysis (Started CRRT)	0	0.0%	1	25.0%	
Antiviral drugs used	No drug taken	1	20.0%	1	25.0%	0.524
	Oral	0	0.0%	2	50.0%	
	IV	2	40.0%	0	0.0%	
	Oral and iv	2	40.0%	1	25.0%	
Anticoagulant used	Clexane	5	100.0%	3	75.0%	0.444
	Heparin	0	0.0%	1	25.0%	
Covid 19 swab at discharge	0	4	80.0%	2	50.0%	0.524
	1	1	20.0%	2	50.0%	
CKD with	Transplant	4	80.0%	3	75.0%	1
	autoimmune disease.	1	20.0%	1	25.0%	

P value was computed by Ficher-Exact tes

Table (3-b). Comparisons between ICU cases according to fatality

Fate of the patient		n			P
Age Mean±SD	Improved	5	43.6±12.8		0.232
	Died	4	53.3±7.9		
Duration of Kid	Improved	4	5.0±2.9		0.11
neyTransplantation Mean±SD	Died	3	13.7±8.5		
Days of hospital stay	Improved	5	31.6±15.5		0.147
Mean±SD	Died	4	18.3±5.3		
Days of ICU Admition	Improved	5	7.6±4.7		0.093
Mean±SD	Died	4	15.8±7.9		
weight/kg	Improved	5	77.7±26.8		0.696
Mean±SD	Died	4	83.5±10.7		
Hb at discharge	Improved	5	12.3±2.9		0.054
Mean±SD	Died	4	8.65±1.25		
Hb the lowest	Improved	5	6.9±2.4		0.624
Mean±SD	Died	4	8.1±1.95		
TLC the worest high	Improved	5	14.2±6.3		0.417
Mean±SD	Died	4	19.1±10.8		
TLC the worest low	Improved	5	3.9±0.9		0.660
Mean±SD	Died	4	3.4±2.0		
Platelet at admission	Improved	5	15.00 (127.5-271.0)	124.0-384.0	0.413
Median (Q1-Q3/ Min-Max	Died	4	144.0 (148.0-195.75)	140.0-202.00	
Platelet the lowest Mean±SD	Improved	5	130.8±19.6		0.294
	Died	4	109.8±35.6		
Lymph number at admission	Improved	4	0.7±0.3		0.651
Mean±SD	Died	4	0.6±0.1		
Lymph number at discharge	Improved	5	0.9±0.4		0.215
Mean±SD	Died	4	0.5±0.4		
Lymph number the highest	Improved	5	1.1±0.4		0.433
Mean±SD	Died	4	0.8±0.4		
Lymph number the lowest	Improved	5	0.4±0.3		0.128
Mean±SD	Died	4	0.1±0.1		
CRP at admission	Improved	5	12.1±16.0		0.681
Mean±SD	Died	4	8.5±3.8		
CRP at discharge	Improved	4	7.8±8.1		0.072
Mean±SD	Died	3	30.1±17.6		
CRP the highest	Improved	4	20.5±13.2		0.414
Mean±SD	Died	3	30.5±16.8		
LDH at admission	Improved	5	306.0±96.2		0.729
Mean±SD	Died	4	330.0±103.0		
LDH at discharge	Improved	5	241.4±46.1		0.01

Fate of the patient		n			P
Mean±SD	Died	3	465.0±127.5		
LDH the highest	Improved	5	321.6±75.0		0.036
Mean±SD	Died	3	572.7±193.3		
LDH the lowest	Improved	5	215.6±38.1		0.036
Mean±SD	Died	3	343.7±99.6		
S. ferritin at admission	Improved	2	1013.5±433.5		0.06
Mean±SD	Died	3	327.7±60.4		
S. ferritin at discharge	Improved	1	1116.9		0.801
Mean±SD	Died	3	901.6±650.6		
S. ferritin the highest	Improved	2	1087.5±328.8		0.97
Mean±SD	Died	3	1070.3±507.2		
S. ferritin the lowest	Improved	2	912.0±289.8		0.180
Mean±SD	Died	3	298.4±110.4		
INR the highest	Improved	5	1.5±0.3		0.474
Mean±SD	Died	3	2.3±1.7		
Creatinine at admission	Improved	5	151.4±74.9		0.954
Mean±SD	Died	4	147.7±81.3		
Creatinine at discharge	Improved	5	98.4±37.9		0.193
Mean±SD	Died	4	365.6±319.4		
Creatinine the highest	Improved	5	174.3±89.7		0.154
Mean±SD	Died	4	392.8±293.4		
Creatinine the lowest	Improved	5	9.89 (47.64-125.07)	41.03-159.48	0.462
Median (Q1-Q3)/ Min-Max	Died	4	70.9 (71.25-218.01)	68.0-261.07	
BUN at admission	Improved	5	7.6±3.5		0.981
Mean±SD	Died	4	7.7±5.2		
BUN at discharge	Improved	5	8.3±5.0		0.003
Mean±SD	Died	4	31.6±10.8		
BUN the highest	Improved	5	14.3±8.4		0.028
Mean±SD	Died	4	31.7±10.6		
BUN the lowest	Improved	5	84.91 (3.27-10.77)	2.58-16.47	0.190
Median (Q1-Q3)/ Min-Max	Died	4	4.92 (6.23-14.52)	5.25-14.91	
K the highest	Improved	5	5.5±0.5		0.959
Mean±SD	Died	4	5.5±0.3		
K the lowest	Improved	5	4.4±1.4		0.288
Mean±SD	Died	4	3.5±0.7		
K at discharge	Improved	5	4.09 (3.55-4.52)	3.42-4.70	0.063
Median (Q1-Q3)/ Min-Max	Died	4	5.59 (4.62-5.68)	4.30-5.70	
Mg at admission	Improved	5	0.7±0.2		0.355
Mean±SD	Died	4	0.6±0.1		
Mg at discharge	Improved	5	0.8±0.2		0.037
Mean±SD	Died	4	1.0±0.1		
Mg the worest high	Improved	5	0.98 (0.97-1.17)	0.95-1.31	0.413
Median (Q1-Q3)/ Min-Max	Died	4	1.11 (0.98-1.29)	0.95-1.33	
PO4 at admission	Improved	5	0.96 (0.84-1.38)	0.81-1.74	0.905
Median (Q1-Q3)/ Min-Max	Died	4	1.04 (0.74-1.38)	0.71-1.43	
PO4 the highest	Improved	5	1.5±0.4		0.01
Mean±SD	Died	4	2.3±0.3		
Phosphorus the lowest	Improved	5	0.8±0.3		0.799
Mean±SD	Died	4	0.8±0.4		
Ca the highest	Improved	5	2.3±0.1		0.17
Mean±SD	Died	4	2.1±0.1		
Ca the lowest	Improved	5	1.8±0.2		0.2
Mean±SD	Died	4	1.6±0.4		
Ca at discharge	Improved	5	2.16 (2.15-2.25)	2.13-2.26	0.016
Median (Q1-Q3)/ Min-Max	Died	4	2.01 (1.65-2.04)	1.54-2.04	
Albumin the highest	Improved	5	34.7±2.9		0.066
Mean±SD	Died	4	29.1±4.8		
Albumin the lowest	Improved	5	23.2±0.8		0.097
Mean±SD	Died	4	20.3±2.5		
BMI	Improved	5	26.8±6.5		0.311
Mean±SD	Died	4	31.0±4.9		

P value was measured using T-test as Mann-Whitney test as appropriate

Table 4-a. Clinical and the protocol of management of individual cases

	Gender	Age	Duration of Kid Tran	Total Length of stay	ICU	ICU Length of stay	Fate of the patient	Immunosuppressive protocol during	The antiviral used	BMI	anti-coagulant	Late presentation to the hospital
Case 1	Male	52	3.0	46	Yes	15	Improved	dexamethazone 6 mgthen 10 mg +tacrolimus	IV	34.29	Enoxaparin	
Case 2	Male	37	2.0	7	No		Improved	hydrocortisone 50mg/12 hours +tacrolimus	IV	26.12	Enoxaparin	After 2 days
Case 3	Female	51	17.0	14	Yes	12	Died	dexsmesathone 10 after 5 days of admission to icu hydrocortisone 80mg /12 hours +ltacrolimus stopped in the last 3 days	Oral + IV	37.50	Enoxaparin	After 5 days
Case 4	Female	40	10.0	14	No		Improved	hydrocortisone 50mg /6h then dexamethasone 6mg 3 days	IV	22.34	Enoxaparin	
Case 5	Male	39	7.0	11	Yes	6	Improved	dexamethazone 6mg +tacrolimus	IV	31.02	Enoxaparin	
Case 6	Male	50	6.0	13	No		Improved	dexamethazone 6mg +tacrolimus	oral	47.75	Enoxaparin	
Case 7	Male	59	4.0	17	Yes	15	Died	MMF for 3 days, dexamethazone 6mg then 10 mg then 6 mg +tacrolimus.	Oral	25.71	Enoxaparin	After 4 days
Case 8*	Male	51	4.0	6	No		Improved	No change in the immunosuppressive drugs	No	20.31	UFH	
Case 9	Male	23	2.0	25	Yes	3	Improved	dexamethazone 10 mg+tacrolimus	No	20.20	Enoxaparin	
Case 10	Male	60	20.0	26	Yes	27	Died	dexamethazone 6 for 2 day dexa 10 for 10 d ,hydrocortisone 50/6h +tacrolimus stopped in the last week	No	29.76	Enoxaparin	
Case 11	Female	51	8.0	48	Yes	5	Improved	dexamethazone 6mgthen 10 mg+ tacrolimus	Oral + IV	19.86	Enoxaparin	
Case 12*	Male	47	15.0	7	No		Improved	No o change in the	No	26.12	Enoxaparin	

	Gender	Age	Duration of Kid Tran	Total Length of stay	ICU	ICU Length of stay	Fate of the patient	Immunosuppressive protocol during	The antiviral used	BMI	anti-coagulant	Late presentation to the hospital
								immunosuppressive drugs				
Case 13	Male	41	18.0	18	No		Improved	dexa methazone 6mg then 10 mg+tacrolimus	Oral	35.25	Enoxaparin	
Case 14^	Female	43		16	Yes	9	Died	prednisolone 60mg, dexa 10, MMF for 3 days	1	31.22	UFH	After 5 days
Case 15^	Male	53		28	Yes	9	Improved	dexamesathone 10	Oral + IV	28.41	Enoxaparin	
Case 16	Male	38	16.0	8	No		Improved	dexamethazone 10mg +tacrolimus	Oral	31.25	Enoxaparin	
Case 17	Female	39	1.5	11	No		Improved	dexamethazone 10mg + tacrolimus	IV	33.20	Enoxaparin	
Case 18	Male	44	16.0	12	No		Improved	dexamethazone10mg +tacrolimus	Oral	29.73	Enoxaparin	

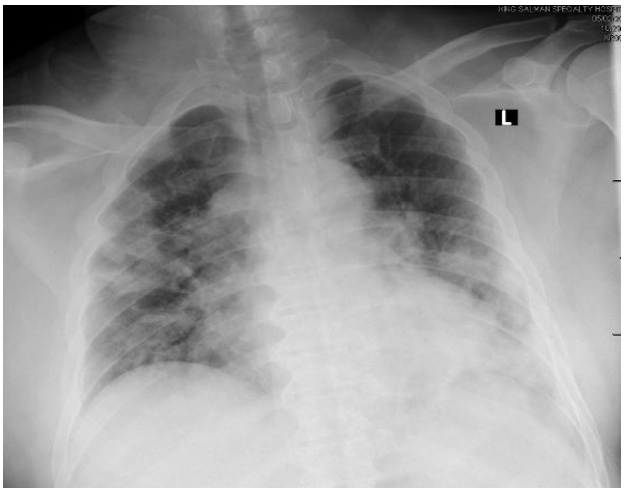
**Those cases are presented with GIT symptoms, ^ Cases with autoimmune disease*

Table 4-b. Laboratory data of selected individual cases

	D.dimer at admission	D.dimer The highest	CRP at admission	LDH at admission	HB on admission g/dl	TLC (the highest)	TLC the Lowest	PLT (the lowest)	Lymph count (the lowest)	D.Dimmer (the lowest)	INR (the highest)	Albumin (at admission)	LDH (the highest)	CRP (the highest)
Case-1	3.36	3.36	0.332	364	13.8	19.02	5.15	131	1.8	0.26	1.93	31	364	12.4
Case-2	0.22	.22	1.31		13.8					0.19	1.11	35.8		
Case-3	7.85	7.85	11.3	453	12.5	17.42	4.49	125	0.5	0.5	1.52	21.7	721	11.3
Case-4			8.05		14.8	12.77	4.52	193	3.1		1.27	27.5		8.05
Case-5	16.22	16.22	3.74	248	15.8	8.56	4.30	124	9.8	0.59	1.13	29	248	
Case-6			1.9		9.2	10.87	7.39	111	4.1		1.18	26		1.9
Case-7	23.6	23.60	4.01	320	12.1	22.71	5.59	114	0.7	0.084	1.2	30	354	37.9
Case-8					12.2	6.7	4.75	233	3.9		1.45	25		
Case-9	6.62	6.62	5.25	180	9.2	9.33	3.72	153	2.3	0.95	1.25	39	256	18.6
Case-10	54	54.00	12.1	345	14.9	30.9	1.44	59	0.4	1.06	4.27	23.5	643	42.4
Case-11	1.8	1.80	39.7	312	11.1	11.29	2.72	102	6	1.19	1.57	24	314	39.7
Case-12			3.24		15.9	3.85	3.60	196	17.3			34		
Case-13	3.19	3.19			12.3	12.85	5.01	184	1	0.088	1.16	24		
Case-14	1.8	1.80	6.66	202	8.9	5.22	2.06	141	5.4	0.84		27		
Case-15	1.7	1.70	11.3	426	14.6	22.56	3.61	144	1	0.61	1.5	22.4	426	11.3
Case-16					12.7	10.59	8.72	604	6.7			25.2		
Case-17	0.45	.45	0.807	209	14	10.57	3.34	117	2.7	0.33		40		
Case-18		3.36		108	14.6	10.57	3.34	144	3			32		

Table 4-c. Electrolyte presentation of the individual cases

	Creatinine		BUN		Ca		Po4		Mg		K	
	on admission	on discharge	on admission	on discharge	on admission	on discharge	on admission	on discharge	on admission	on discharge	on admission	on discharge
Case-1	106	73.13	5.69	4.27	2.01	2.16	1.02	1.11	0.7	0.72	4.58	4.7
Case-2	97.89	91.46	4.82	7.51	2.27	2.21	1.15	1.3	0.91	0.67	4.32	5.15
Case-3	135.23	198.29	7.32	36.13	1.88	1.98	0.71	1.62	0.66	1.17	4.22	4.3
Case-4	74.73	92.75	3.15	7.04	1.97	1.75	0.63	0.99	0.61	0.71	5.71	5.12
Case-5	93.91	79.14	4.13	6.45	2.09	2.26	0.96	0.89	0.63	0.56	4.36	4.09
Case-6	115	90	13.22	9.44	2.26	2.13	1.04	1.22	0.94	0.73	4.5	4.73
Case-7	126.55	105.69	6.1	15.95	2.12	2.03	1.24	1.38	0.66	1.09	5.3	5.6
Case-8	195.3	231.55	22.01	20.42	1.86	1.96	1.28	0.85	0.75	0.67	3.68	4.24
Case-9	222	159.48	9.99	16.47	1.95	2.24	1.74	1.31	0.89	0.98	4.57	4.34
Case-10	68	334.99	2.44	33.92	1.89	1.54	0.84	2.36	0.5	0.91	3.72	5.57
Case-11	243.71	69.22	12.59	4.92	2.03	2.13	0.81	0.73	0.55	0.78	3.54	3.42
Case-12	117.03	115	6.27	4.93		2.02			0.73		3.81	3.54
Case-13	231.84	104.12	18.15	14.26	2.03	2.21	1.24	1.34	0.82	0.82	7.56	4.25
Case-14	261.07	823.4	14.91	40.42	1.81	2.04	1.43	2.72	0.75	0.95	4.25	5.7
Case-15	91.62	110.78	5.7	9.14	1.9	2.16	0.87	1.09	0.89	0.87	3.65	3.68
Case-16	103.88	111.9	12.49	11.4	2.24	2.24			0.59	0.73	4.34	4.62
Case-17	106.19	114	6.46	17.2	2.08	2.15	0.5	0.71	0.61	0.71	3.35	4.41
Case-18	106.19	114	6.46	17.2	2.17	2.4	0.72	0.83	0.61	0.96	3.47	4.29



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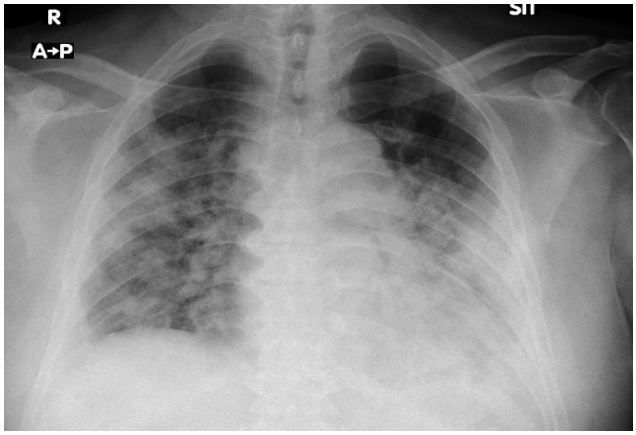

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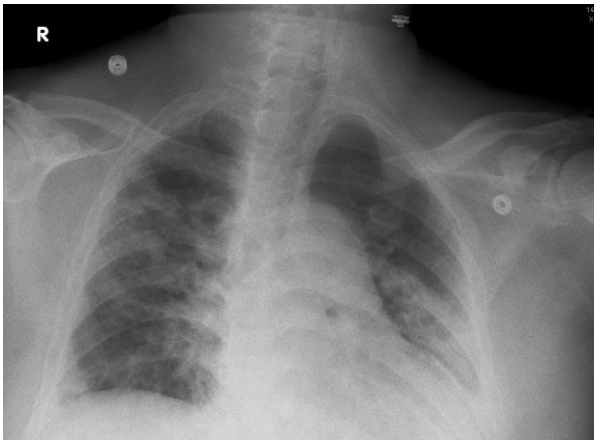
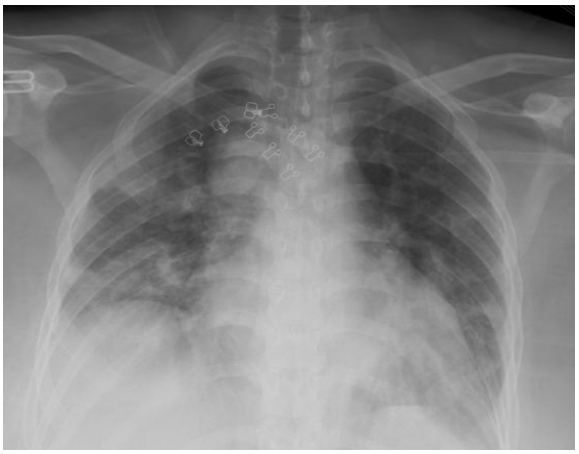


C

Case 1, an ICU survivor. A. CXR on admission shows bilateral infiltrates mainly in middle and lower lung zones. B. Ten days after admission; infiltrates increased on lt lower zone with consolidation. C. After 21 days of admission, CXR shows improvement with partial resolution of infiltrates



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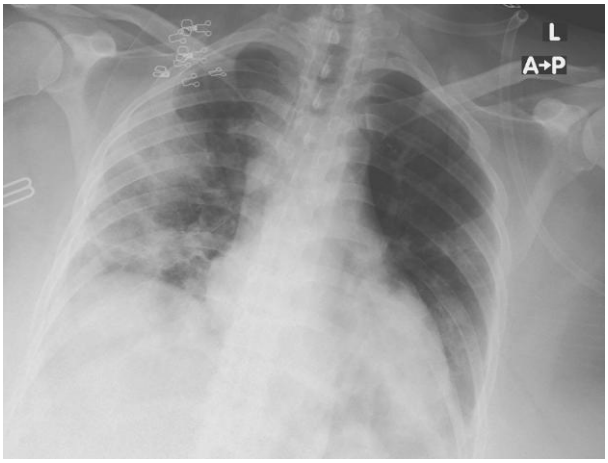

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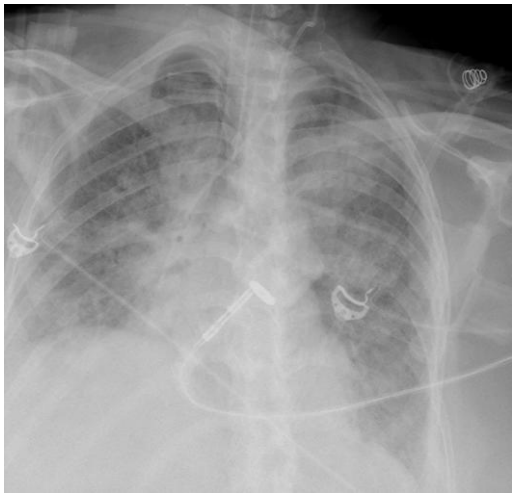
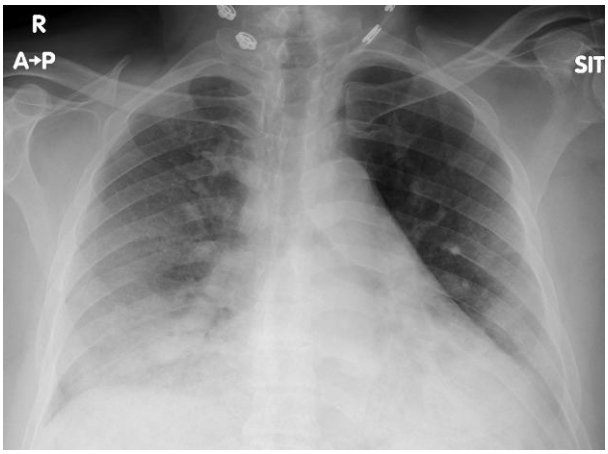


C

Case 3: Female ICU mortality. A. Chest X-Ray on admission shows minimal bilateral haziness. B. Two days later with increased opacity on right side. C. Chest X-Ray after one week with progressive worsening and extensive bilateral infiltrates (ARDS)



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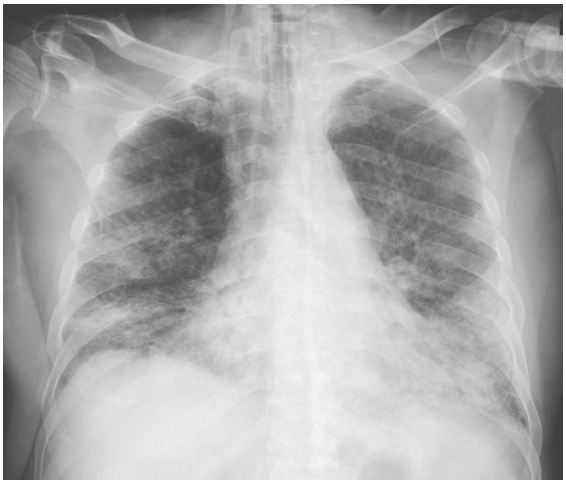

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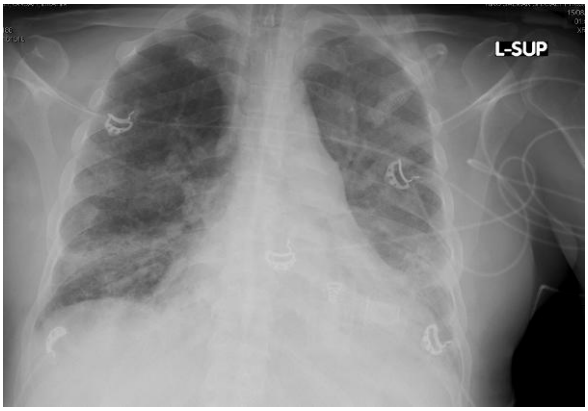
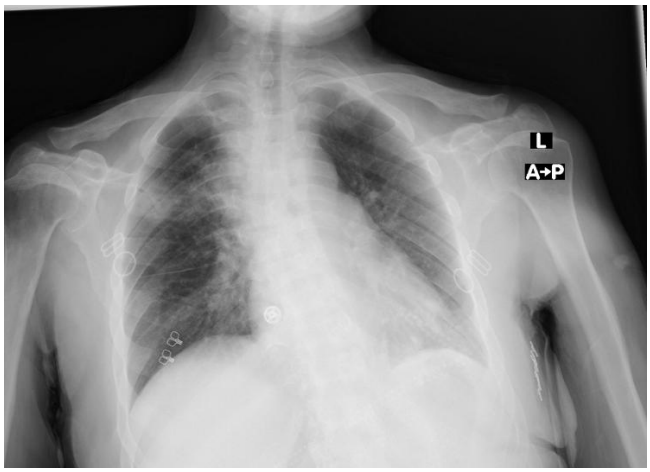


C

Case 10: Male ICU mortality. A. Chest X-Ray on admission with bilateral basal infiltrates more on right side. B. Two days later with increased infiltrates mainly on left side. C. Ten days later with stationary course regarding chest X Ray



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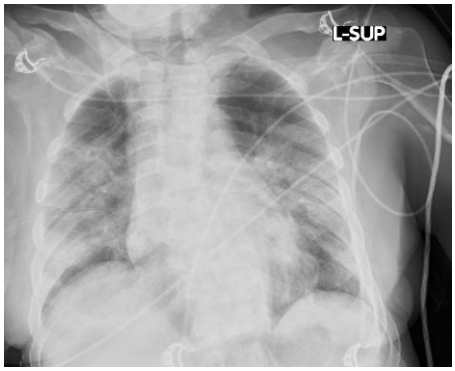

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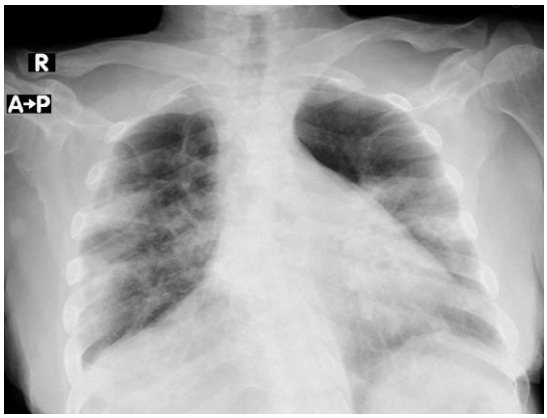
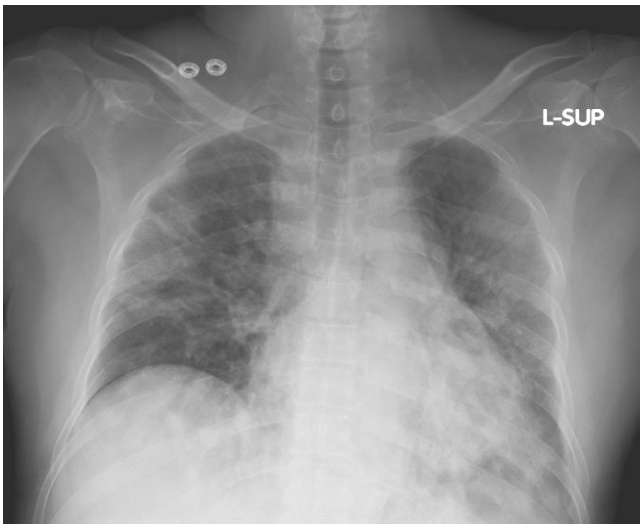


C

Case 11: Female ICU survivor. A. Chest X-Ray on admission; with minimal infiltrates on right upper zone. B. Chest X Ray ten days after admission with extensive bilateral infiltrates including all lung zones. C. Chest X-Ray before discharge with partial improvement



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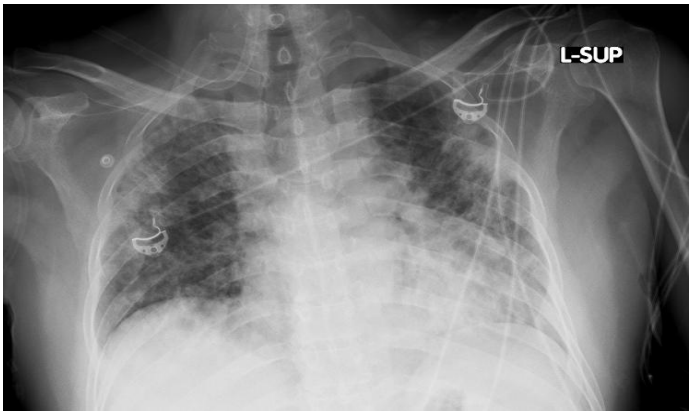

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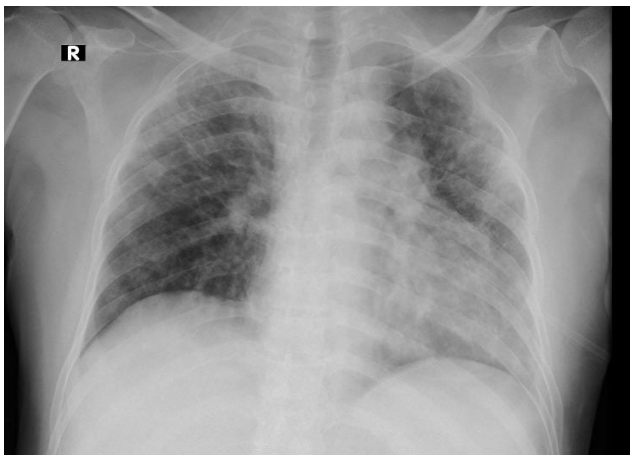
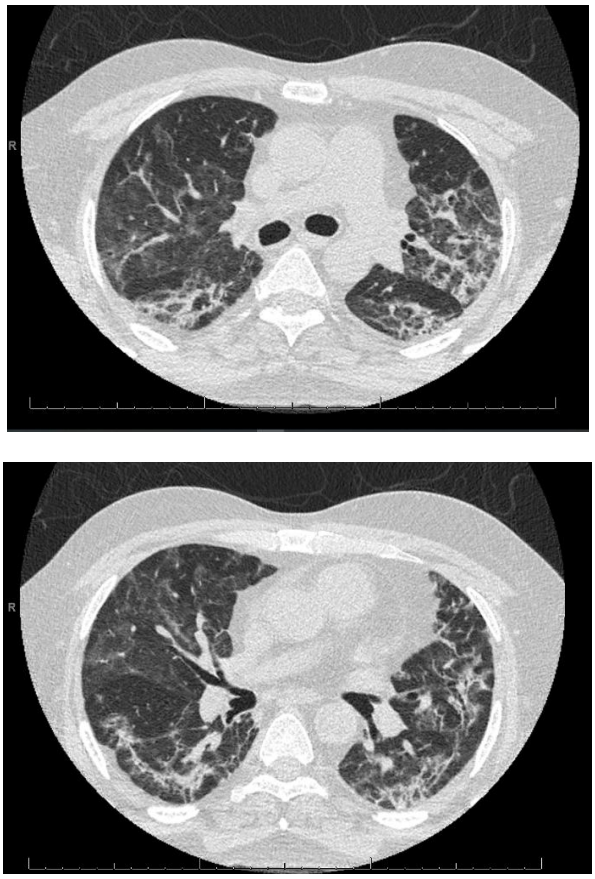


C

Case 15: ICU survivor, a case of glomerulonephritis. A. Chest X Ray on admission, with diffuse bilateral infiltrates. B. Two days later with increased infiltrates. C. One week later with stationary course



Case 15: ICU survivor, a case of glomerulonephritis. Cuts from High resolution C-T shows bilateral ground glass appearance with areas of consolidation

Fig. 1. Chest imaging of five cases admitted to intensive care unit

4. DISCUSSION

Renal patients with immunosuppressive protocols are a brittle population due to their immunosuppressed status. However, there has been a limited number of studies existing that compared this population with the general population concerning clinical presentations and laboratory parameters as well as disease severity and clinical outcomes in COVID-19 infection.

We aimed to observe the effect of modification of the immunosuppressive regimen in response to the severity of COVID-19 infection on the outcome of renal disease patients and to study factors affecting their mortality for nine months from February to October 2021.

In the present study, we observed the clinical course of patients suffering from renal diseases or who had been subjected to renal transplantation that was linked to immunosuppression therapy and suffered from COVID-19 infection during the period of February to October 2021. Locally agreed protocol, regarding immunosuppressive protocol, the antiviral used as well as the used anticoagulant, was planned between the treating team; Nephrology, Chest, and ICU consultants to be followed considering international guidelines for COVID 19 infection in immunosuppressed patients and Saudi MOH guidelines for the management of COVID 19 infection [11,12].

The studied patients were divided into two groups; one group comprised nine patients admitted to ICU and nine patients does not need admission to ICU; there was a further subdivision of the ICU group into deceased and survived groups at discharge.

In the current study, there was a good prognosis for patients who presented early to the hospital and started early cessation of antiproliferative drugs even in patients with severe COVID-19

pneumonia with admission to ICU. This is supported by many researchers who reported that the broad immunosuppressive abilities that make MMF an efficacious drug for transplant and autoimmune diseases might also enhance the risk of infectious complications [13,14,9]. Kantauskaite and his colleagues, 2022 found that the strongest predictor for an impaired response to neutralization capacity after SARS-CoV-2 vaccination was MMF treatment as well as higher trough MMF concentrations correlated with lower antibody titers supporting a dose-dependent unfavorable effect of MMF. On the other side, the other immunosuppressive drugs had no significant influence [7]. In another case study 29 years old male presented with a severe infection of COVID19 pneumonia with admitted to ICU; when He was treated with; modified immunosuppressants; discontinuing MMF, unchanged dose of tacrolimus and oral corticosteroids, antibiotics, antiviral and traditional Chinese medicine, he recovered from COVID-19 pneumonia after 29 days of hospitalization and the renal function returned to normal [15]. Additionally, in the current study, there was a better prognosis with the use of higher doses of systemic steroids mainly dexamethasone and this was supported by Li and his associates, 2017 who stated that the immunosuppressive and anti-inflammatory effects of Dexamethasone were known and used in certain situations as rheumatoid arthritis [10]. In the current study, tacrolimus was stopped on the deterioration of the chest condition and on mechanically ventilated patients spite of this, the three cases died after a few days. Our finding was not matched with Suryantoro and his colleagues, 2021 who decided to stop the immunosuppressive agents and followed administration of lopinavir/ritonavir, hydroxychloroquine, and dexamethasone which gives a good clinical effect on the patient's condition after being worsened and mechanically ventilated [16]. This could be attributed to their use of different antivirals and or their use of hydroxychloroquine in their protocol of management.

In this work, kidney function tests were not affected by the discontinuation of antiproliferative drugs in the whole studied group. This could be attributed to the use of higher systemic steroids with the discontinuation of anti-proliferative drugs. Additionally, kidney function tests were not affected by the use of antiviral medications which were Favipiravir and/or remdisivir. This is partially supported by Wang and his associates, 2020 who found that intravenous remdesivir was adequately tolerated in seriously ill patients with COVID-19 [17]. However, Hassanipour and his colleagues, 2021 found that the mortality rate in the Favipiravir group was approximately 23% lower than in their control group, but this finding is not statistically significant [18].

Gayam and his associates, 2020 reported that COVID-19 primarily manifests as lung infection and had significant extrapulmonary complications affecting most organ systems, including the gastrointestinal tract and myalgia which were the main presentation among African-Americans hospitalized in patients with COVID-19 infection [19]. In the current work, there was a better scenario in COVID-19 patients who presented with isolated gastrointestinal manifestations even though, they did not receive antiviral or change their immunosuppressive protocol. This is reinforced by some authors who found that a small group of patients presented with isolated gastrointestinal symptoms and did not develop fever or respiratory symptoms later Therefore, COVID-19 infection could be considered for patients presenting with primarily gastrointestinal manifestations [20-22]. On the contrary, Hegazy, and colleagues, 2021 conveyed that patients with mild symptoms who present with diarrhea and duration of symptoms longer than 12 days are expected to have a worse prognosis [23]. Moreover, Teimaa and his associates, 2022 found that the presence of associated gastrointestinal symptoms in COVID19 infection patients reflected the severity of the infection [24]. In summary, Sulaiman and his colleagues, 2020 reported that the presence of COVID19-related gastrointestinal symptoms alone carried a better prognosis while their presence with respiratory symptoms was associated with higher morbidity and mortality [25].

In our study, there was no difference in the severity of COVID-19 infection regarding age, male gender, associated comorbidities, or BMI. This could be explained by all the studied groups were CKD and maintained on immunosuppressive medications making all of them a high-risk group. This finding was not coincident with the SYSTEMATIC REVIEW performed by Ali and colleagues, 2020 who assessed the risk factors related to the outcomes of SARS-CoV-2 infections, which were old age, male gender, obesity, and associated co-morbidities in the form of cardiovascular diseases, diabetes mellitus, chronic kidney disease, liver disease, cerebrovascular diseases and COPD [6].

On the other hand, the inflammatory markers in the form of high CRP, and low serum albumin as well as high LDH, high D-dimer, and lower platelet count were more in the severe group that was admitted to ICU particularly, those who passed away in the current study.

Additionally, there was more lymphopenia in the deceased group. This is partially in harmony with Ali and colleagues, 2020 who reported that most of their Laboratory parameters associated with critical COVID-19 disease included lymphopenia, thrombocytopenia, leucocytosis, increased neutrophils, increased C reactive protein and ferritin, increased D dimer, raised ALT and/or AST, decreased albumin, increased cardiac troponin and elevated LDH [6]. Many authors were partially in accordance with our study; Gayam and his associates,2020 concluded that Advanced age, higher BMI, elevated serum ferritin, CRP, and D-dimers at the time of presentation are independent predictors of mortality among hospitalized Africa-American patients with COVID-19 infection [19].In the same context, Ahmeidi and his colleagues, 2020 reported that the inflammatory markers, including interleukin-6, D-dimer, neutrophil-to-lymphocyte ratio, and high-sensitivity C-reactive protein levels were found to be indicative of severe COVID-19 infection and mortality [26]. Furthermore, in a meta-analysis conducted by Tian and his colleagues, 2020, they found that baseline cardiometabolic disease and evidence of increased acute inflammation and end-organ damage (cardiac, renal, liver, and hematologic) on admission were associated with an increased risk of mortality due in COVID-19 infection [27]. In our study, the laboratory parameters could be helpful indicators of COVID-19 infection severity and could be used as early pointers for the management modification before deterioration.

In this work, it is observed that serum albumin was decreased in all cases admitted to ICU but decreased more significantly in the deceased group, however, serum albumin is an acute phase reactant and its impact on survival in COVID-19 patients need to be studied This is strengthened by Violi et al, 2021 who found that serum albumin was independently associated with mortality, irrespective of adjustment for gender, ICU admission, heart failure, COPD, and CRP levels which denote that serum albumin may be used to identify patients at higher risk of mortality in COVID-19 patients [28]. Furthermore, the mortality frequency was higher in the current ICU group, this is could be explained by the presence of severe COVID19 infection and the development of severe sepsis in the deceased group and this is in agreement with Violi and his colleagues, 2021 who found that non-survivors had more prevalence of intensive care unit admission than survivors [28].

In this study, the four vaccinated patients had less severe infections with a better prognosis as they did not admit to the intensive care unit and were discharged directly from the isolation ward. This could be supported by Kantauskaite and his colleagues, 2022, who found that after the vaccination, 24.9% of transplant recipients became seropositive, of whom 68% had neutralizing antibodies. However, they found that this immune response was significantly lower compared to the control group [7].

5. CONCLUSION

Appropriately early discontinuation of antiproliferative drugs in renal immunosuppressed patients and the use higher doses of systemic steroids were associated with better prognosis of COVID 19 infection patients and did not cause deterioration of kidney function. The inflammatory markers including CRP, LDH as well as low serum albumin, and high D-dimer were related to mortality in severe cases of COVID-19 infection.

CONSENT

Informed written consent was obtained from the study participants and/or their relatives.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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