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ORIGINAL ARTICLE

Evaluation of Renal Function in COVID-19 Patients by Using Urinalysis Following the Administration of Vancomycin

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SUMMARY

Background: **The aim of this study was to evaluate renal function by urinalysis in COVID-19 patients following the administration of vancomycin.**
Methods: **A retrospective observational study was performed between October 2020 and January 2021, during which time patients were hospitalized in the Prince Mohammed Bin Abdulaziz Hospital in Riyadh, Saudi Arabia. The patients were free of kidney disease. Urinalysis was performed by an automated laboratory system, and the collected results were based upon age, gender, diabetic status, whether the patients had received vancomycin, the mortality rate, and the urinalysis panel including coinfection by bacteria and yeast.**
Results: **A total of 227 patients were included in this study, 147 (64.75%) of whom were male and 80 (35.25%) of whom were female; 54.63% were diabetic, 11.89% were prediabetic, and 33.48% were non-diabetic patients. Proteinuria, hematuria, glycosuria, coinfection, and ketonuria were detected among all participants within the study group, specifically among diabetic patients. The mortality rate was 16.2% among the study group; 6.6% had received vancomycin, and 9.6% had not received vancomycin. No significant correlation was found between nephrotoxicity and abnormalities in the urine and the mortality rate among members of our study group.**
Conclusions: **Proteinuria, hematuria, glycosuria, ketonuria, and coinfection were common among members of our study group, especially in the diabetic group. Urinalysis abnormalities were less frequent in the vancomycin group than in the others, except the prediabetic group. No correlation between mortality and vancomycin was identified.**
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INTRODUCTION

By June 30, 2021, the World Health Organization's COVID-19 dashboard had reported more than approximately 181 million confirmed cases and approximately 4 million deaths. SARS-CoV-2 respiratory tract infection initiates several systemic effects leading to alveolar damage related to SARS-CoV-2 cytopathy and the immune system response [1]. Pneumonia is the primary clinical outcome of COVID-19; however, several other

outcomes were detected by several reports regarding other organs, such as kidney damage [2-4]. Kidney damage was reported in a high number of cases and is a sign of the severity of the disease [5]. Acute kidney injury (AKI) is common and some of the patients in the intensive care unit may require kidney replacement [5,6]. Kidney injury in COVID-19 patients is due to several factors, such as the application of mechanical ventilators, elevated proteinuria, sepsis, and nephrontoxins acquired during the patient's time spent in clinical care [5,7,8], and those who develop secondary infection are at risk of developing AKI [9]. Due to the high number of hospitalized patients, the risk of nosocomial infection is increasing, especially among COVID-19 patients. A study reported that 15% of hospitalized COVID-19 patients experience secondary infection, which increases the demand for use of antibiotics [5].

In our study, we used urinalysis testing to evaluate the effects of COVID-19 on patients according to their glycemic states. This will help to investigate the value of urinalysis in monitoring the effects of COVID-19.

MATERIALS AND METHODS

Study design and population

This retrospective, observational study was conducted among hospitalized, confirmed COVID-19 patients. Data for this study were obtained from the Prince Mohammed Bin Abdulaziz Hospital in Riyadh, Saudi Arabia for the period between October 2020 and January 2021. The patients were admitted due to confirmed COVID-19. The number of patients included in this study was 227 patients, 147 of whom were male (64.76%) and 80 of whom were female (35.24%). The study group was subdivided into three groups according to glycemic status. Ethical approval for this work was obtained from Taif University and IRB is HAO-02-T-105.

Data collection

Data collected from patients with no history of kidney disease included age, gender, diabetic status, the use of vancomycin, and urinalysis test results including urine pH, RBCs, WBCs, leukocyte esterase, bilirubin, urobilinogen, specific gravity, glucose, calcium oxalate crystals, blood, color, cholesterol crystals, cystine crystals, hyaline casts, granulocytes casts, ketone, leucine crystals, mucous, nitrite, protein, squam epithelial, triple phosphate crystals, tyrosine crystals, uric acid, waxy cast, bacteria, yeast, and sperm.

Statistical analysis

JASP 0.14.1 was applied for statistical analysis. Urine abnormalities, and glycemic status were assessed for normality, which has shown that our data do not follow a normal distribution. The median (interquartile range, IQR) of the age groups according to glycemic status were calculated, and Kruskal-Wallis test was applied for comparison between our study groups. Pearson's chi-squared test was applied to evaluate urine abnormalities, and $p \leq 0.05$ was regarded as a significant difference. Logistic regression and the odds ratio were calculated to correlate between mortality rate and vancomycin.

RESULTS

The following parameters were not detected in the data analysis, and therefore were not reported in the study analysis: cystine crystals, leucine crystals, tyrosine crystals, waxy crystals, triple phosphate crystals, and sperm.

Demographics of the patients

A total of 227 patients were included in this study, of whom 147 (64.75%) were male and 80 (35.25%) were female (Table 1). Patients were grouped according to their glycemic status, into diabetic (54.63%), prediabetic (11.89%), and non-diabetic (33.48%) categories. The median age (interquartile) of normal was 44.25 (44.25 - 68) years, of prediabetic 48.25 (48.5 - 65) years, and of diabetic 59 (46 - 74) years. Regarding age, the patients were divided into four groups, of which the highest age group consisted of those patients age 51 - 75 years.

Physical characteristics of urine

Evaluation of urine color, pH, and specific gravity are shown in Figure 1. Regarding color, the most dominant color for patients in the diabetic group was found to be pale yellow, followed by amber, yellow, and, lastly, brown. Among prediabetic patients, the most dominant color was found to be brown, followed by amber, pale yellow, and, lastly, yellow. Among patients in the non-diabetic group, the most dominant color was found to be brown, followed by yellow, pale yellow, and, lastly, amber. Regarding pH, in the diabetic group the most dominant finding was acidity, followed by alkalinity, and, lastly, neutral levels. In the prediabetic group, the most dominant findings were neutral and alkaline levels, with no acidity detected. For the non-diabetic group, the most dominant findings were neutral levels, followed by alkalinity, and, lastly, acidity. Regarding specific gravity, for the diabetic group, the findings, from the greatest amount to the least amount, were in the following ranges: 1.021 - 1.030, 1.010 - 1.020, and < 1.010. For the prediabetic group, the findings, from the greatest amount to the least amount, were in the following ranges: 1.021 - 1.030, > 1.030, 1.010 - 1.020, and, lastly, < 1.010. For the non-diabetic group, the findings, from the greatest amount to the least amount, were in the following ranges: < 1.010, > 1.030, and 1.010 - 1.020; however, no patients were found to be in the 1.021 - 1.030 range.

Urine abnormalities

The evaluation of urine among members of the study group has shown the following findings (Table 2). RBCs were detected in increasing dominance in prediabetic, then in non-diabetic, and lasty, in diabetic patients

Table 1. Demographic analysis of the study group. Median and interquartile calculated.

	Age	Non-diabetic (%)	Prediabetic (%)	Diabetic (%)	Total (%)
Male	20 - 35	7 (4.76)	1 (0.68)	4 (2.72)	147 (64.75)
	36 - 50	5 (3.4)	4 (2.72)	17 (11.56)	
	51 - 75	31 (21.09)	11 (7.48)	46 (31.29)	
	> 75	4 (2.72)	3 (2.04)	14 (9.52)	
Female	20 - 35	1 (1.23)	1 (1.23)	2 (2.47)	80 (35.25)
	36 - 50	11 (13.58)	2 (2.47)	12 (14.81)	
	51 - 75	13 (6.5)	4 (4.94)	23 (28.4)	
	> 75	5 (6.17)	1 (1.23)	6 (7.41)	
%		33.48	11.89	54.63	227
Median (IQR) (%)		44.25 (44.25 - 68)	48.25 (48.5 - 65)	59 (46 - 73)	

Table 2. Urinalysis comparison between the patient groups.

Abnormalities	Non-diabetic (%)		Pre-diabetic (%)		Diabetic (%)		p-value	95% CI
	Male	Female	Male	Female	Male	Female		
RBC	11 (23.7)	13 (44.83)	6 (31.58)	4 (50)	18 (22.22)	10 (23.26)	0.003	(0.57 - 1.08)
WBC	7 (14.89)	8 (27.59)	6 (31.58)	2 (25)	19 (23.46)	9 (20.93)	< 0.0001	(0.76 - 1.51)
Blood	27 (57.45)	19 (65.52)	10 (52.53)	4 (50)	48 (59.26)	27 (62.79)	0.097	(0.76 - 1.35)
Bacteria	20 (42.55)	14 (48.28)	8 (42.11)	5 (62.5)	41 (50.62)	23 (53.49)	0.344	(0.86 - 1.53)
Yeast	6 (12.67)	4 (13.79)	4 (21.05)	1 (12.5)	15 (18.52)	6 (13.95)	< 0.0001	(0.77 - 1.71)
Leukocyte esterase	11 (23.4)	3 (10.34)	8 (42.11)	2 (25)	11 (13.68)	10 (23.26)	< 0.0001	(0.65 - 1.31)
Squamous epithelial	0	0	0	0	2.26	1 (1.25)	0.998	(0.79 - 1.41)
Calcium oxalate	1 (50)	0	0	0	1 (50)	1 (100)	0.001	(0.32 - 4.25)
Cholesterol casts	0	0	1 (100)	0	0	0	0.087	(0.1 - 6.36)
Hyaline casts	1 (100)	0	0	1 (50)	0	1 (50)	0.07	(0.23 - 2.63)
Granulocytes casts	0	0	0	0	0	1 (100)	0.9	(0.79 - 1.41)
Urobilinogen	12 (25)	11 (41)	10 (21)	4 (14)	12 (45)	26 (54)	0.003	(0.75 - 1.38)
Uric acid	1 (100)	0	0	1 (100)	0	0	0.001	(0.07 - 2.33)
Glucose	9 (19.15)	7 (24.14)	9 (47.33)	1 (12.5)	37 (53.68)	21 (48.84)	0.001	(0.4 - 0.77)
Mucous	15 (31.81)	7 (24.14)	8 (42.11)	4 (50)	20 (24.69)	12 (17.91)	0.001	(0.81 - 1.51)
Ketones	12 (36.53)	7 (24.14)	9 (47.36)	2 (25)	46 (56.79)	27 (63.79)	0.001	(1.51 - 2.83)
Nitrite	2 (4.26)	0	0	0	1 (1.23)	0	0.001	(0.14 - 1.91)
Protein	27 (57.45)	13 (44.83)	9 (47.37)	4 (50)	54 (66.77)	32 (74.42)	0.014	(1.08 - 1.94)

(p-value 0.003). WBCs, yeast infection, and leukocyte esterase were common in prediabetic, diabetic, and non-diabetic patients, respectively (< 0.0001).

Further analysis, as illustrated in Table 3, reveals that urobilinogen was common among diabetic, non-diabetic, and prediabetic patients (0.003). A few cases of casts were detected in the urine: only 3 cases of calcium oxalate casts were detected in a non-diabetic male patient and in 2 diabetic patients, one male and one female. Uric acid was detected in 2 cases, in non-diabetic and prediabetic patients.

Table 3. Urinalysis comparison between the patient groups, according to administration of vancomycin.

	Non-diabetic (%)		Prediabetic (%)		Diabetic (%)		OR	95% CI
	Vancomycin	No.	Vancomycin	No.	Vancomycin	No.		
Cases	19 (25)	57 (75)	9 (33.4)	18 (66.6)	36 (29)	88 (71)	1.095	0.79 - 1.5
RBC	8 (33)	16 (67)	6 (67)	3 (33)	12 (42)	16 (58)	0.069	0.96 - 3.33
WBC	3 (20)	12 (80)	7 (77)	2 (23)	10 (36)	18 (64)	0.826	0.54 - 2.15
Blood	8 (17)	38 (83)	6 (67)	3 (33)	23 (30)	52 (70)	0.223	09 - 1.25
Bacteria	10 (30)	24 (70)	5 (55.5)	4 (44.5)	21 (32)	43 (67)	0.275	0.77 - 2.47
Yeast	2 (20)	49 (80)	8 (88)	1(12)	5 (24)	16 (76)	0.387	0.3 - 1.6
Leukocyte esterase	1 (7)	13 (93)	8 (88)	1(12)	6 (28)	15 (72)	0.087	0.19 - 1.12
Squamous epithelial	0	0	9 (100)	0	1 (33)	2 (67)	0.97	0.1 - 18
Calcium oxalate	0	1 (100)	9 (100)	0	0	2 (100)	0.98	0.1 - 18
Cholesterol	0	0	0	9 (100)	0	0	0.99	0.01 - 1.2
Hyaline	0	1 (100)	9 (100)	0	0	1 (100)	0.99	0.9 - 1.3
Granulocytes casts	0	0	9 (100)	0	0	1 (100)	0.99	0.99 - 1.37
Urobilinogen	3 (13)	37 (20)	5 (55.5)	4 (44.5)	10 (27)	28 (63)	0.191	0.31 - 1.26
Uric acid	0	1 (100)	4 (44.5)	5 (55.5)	0	0	0.99	0.9 - 1.3
Glucose	5 (31)	11 (57)	5 (55.5)	4 (44.5)	9 (15)	49 (85)	0.013	0.21 - 093
Mucous	5 (23)	17 (77)	5 (55.5)	4 (44.5)	8 (25)	24 (75)	0.88	1.06 - 2.14
Ketones	7 (37)	12 (63)	4 (44.4)	5 (55.6)	24 (33)	49 (67)	0.011	1.21 - 4.42
Nitrite	0	2 (100)	9 (100)	0	0	1 (100)	0.99	0.00 - 3.1
Protein	8 (20)	32 (80)	5 (55.5)	4 (44.5)	29 (34)	57 (66)	0.595	0.62 - 2.29
Bilirubin	2 (20)	8 (80)	8 (80)	2 (20)	3 (25)	9 (75)	0.298	0.2 - 1.65
Mortality	4 (27)	11 (73)	4 (80)	1 (20)	7 (41%)	10 (59)	0.499	0.24 - 1.03
Kruskal-Wallis test p-value	0.407		0.224		0.203			

Further analysis, as demonstrated in Table 3, reveals that glycosuria and ketonuria were most common in the diabetic group, followed by in the prediabetic group, and, lastly, in the non-diabetic group (0.001). Mucous was most common in the prediabetic group, followed by in the non-diabetic group, and, lastly, in the diabetic group (0.001). Protein was most common in the diabetic group, followed by in the non-diabetic group, and, lastly, in the prediabetic group (0.014). Nitrite was detected in a small number of male non-diabetic and diabetic patients (0.001).

Urine abnormalities after vancomycin administration

The effect of vancomycin on urine color is shown in Figure 2. Vancomycin was found to lead to an amber color of urine in the diabetic group, and to a yellow color of urine in the prediabetic and non-diabetic groups. The pH of the urine was acidic in all groups (Figure 2). Specific gravity was commonly found to be in the range of 1.010 - 1.020 among all groups (Figure 2). A comparison of urine abnormalities between patients who received vancomycin and those who did not is illustrated in Table 4. By evaluating the odds ratios (OR), urine abnormalities were found to be less frequent in the vancomycin group. The mortality rate was 16.2% among members of the study group, of which 6.6% received vancomycin and 9.6% did not receive vancomycin. The mortality rates are lower with than without vancomycin administration. Only patients in the prediabetic group were found to have a higher mortality rate in the vancomycin group, and all abnormalities were higher among vancomycin-receiving patients than among the others. No significant correlation was found between nephrotoxicity and abnormalities in the urine, and the mortality rate among the members of our study group. By ap-

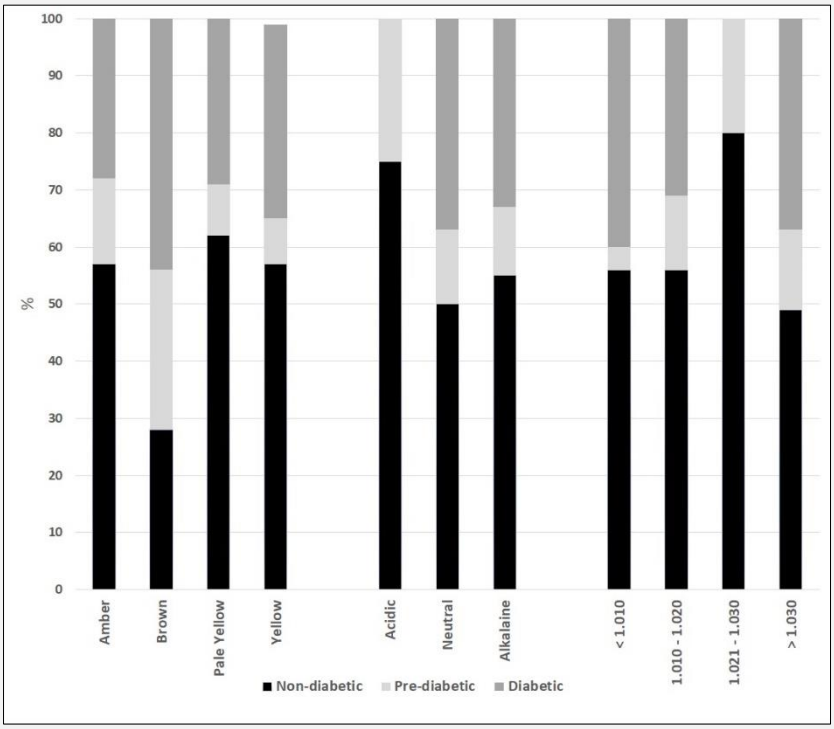

Figure 1. Physical characteristics of urine compared within the study group.

plying logistic regression (Figure 3), a negative correlation was found between the mortality rate and vancomycin, indicating the efficient role of vancomycin in reducing mortality among COVID-19 patients; however, it is statically insignificant.

DISCUSSION

The COVID-19 pandemic has changed the world in the past year. Countries have re-evaluated several policies in order to adapt to the current situation. Healthcare services have suffered a lot and endured many losses. The mortality rate is increasing, and, even with the distribution of vaccines, the virus is still being transmitted, due to mutations and to the public not following the precautions. Developing countries with weak economies have suffered deeply from shortages in vaccines, masks, and even oxygens tanks.

Prescribing antibiotics is a common practice [10]. A study has shown that approximately 58% of COVID-19 patients have received intravenous antibiotics [11]. In Wuhan, the city where the virus first hit, a study has reported that more than two-thirds of patients received antibiotics [12]. Another study of 194 patients reported the empirical use of antibiotics for all patients [13]; furthermore, another study reported the empirical use of antibiotics combined with Chinese medicine and with interferon inhalation [14]. This wide use increases the chance of developing antibiotic-resistant strains that can cause bacterial pandemics in the future. Between 30% to 50% of COVID-19 patients have developed AKI, and viral infection has been detected in kidney cells [15]. Vancomycin is a nephrotoxic antibiotic and can cause AKI [16].

In our study, we have focused on using urinalysis testing as a model for evaluating renal function among COVID-19 hospitalized patients. We have compared urinalysis findings according to the glycemic status of the patients. Then, we compared the effect of intravenous vancomycin on COVID-19 patients. Some parameters were not detected in our study group, including cystine crystals, leucine crystals, tyrosine crystals, waxy crystals, sperm, and triple phosphate crystals. Most of the members of our study group were male, diabetic, and in the age group of 51 - 75 years. The color of the urine was mostly within the normal ranges, except among non-diabetic patients, as 44% had a brown color, indicating infection and kidney problems. The pH was mostly acidic; however, 55% of the urine was alkaline, indicating a current infection [17]. Urine concentration reflects hydration and was evaluated via specific gravi-

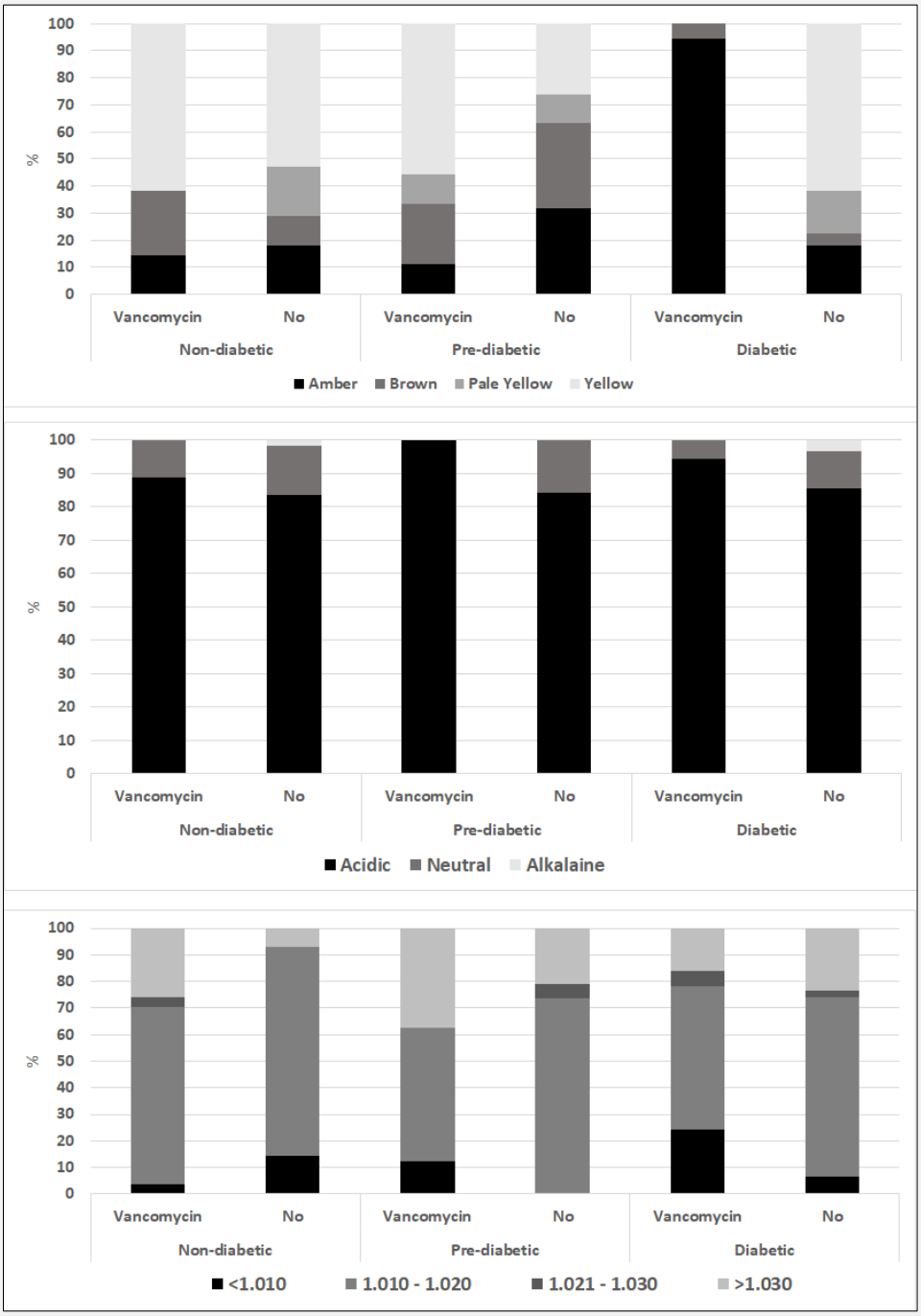

Figure 2. Physical characteristics of urine compared within the study group following administration of vancomycin.

ty, which was > 1.030 in the diabetic group which is common among diabetic patients [17]. Several studies have reported urine abnormalities in COVID-19 patients [2,11,18-20]; in France, a study reported a high prevalence of AKI among severe COVID-19 patients [21], and kidney injuries were reported in living and post-mortem examinations [22–24]. A high percentage of our study group members exhibited high proteinuria, and a majority of these patients were diabetic, indicating kidney injury; this finding is consistent with several other

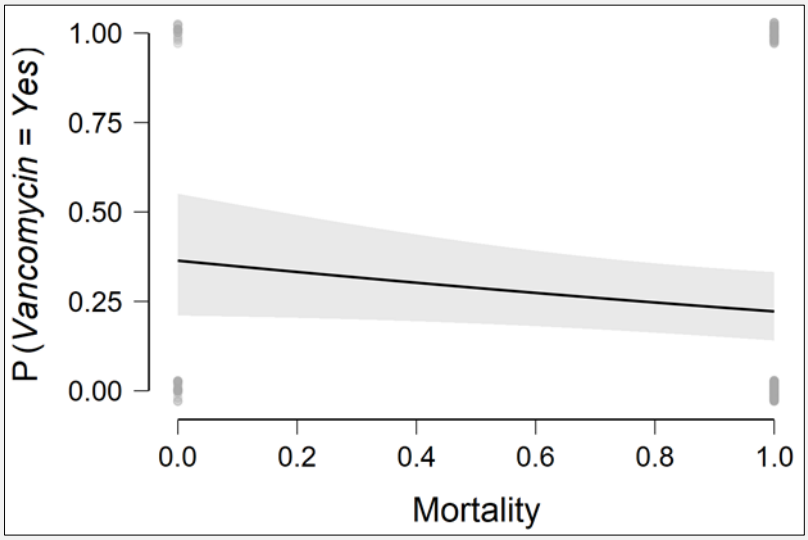

Figure 3. Logistic regression chart showing correlation between vancomycin administration and mortality rate (0 = yes, 1 = no, r = 0.015, p-value = 0.253, OR = 0.572, 95% CI (0.272 - 1.204)).

studies that have reported similar findings [18,20,25-30]. Hematuria was detected in most members of our study group, which is consistent with several other studies [20,25,30,31]. Proteinuria and hematuria are symptoms indicating severe outcomes leading to morbidity and mortality among COVID-19 patients, and especially among hospitalized patients similar to those in our study group [26,30]. WBCs, leukocyte esterase, glycosuria, and urobilinogen were significantly detected, together with coinfections by bacteria and yeast, which are common among viral respiratory tract infections and were detected in our study group, especially at high levels among diabetic patients. Infection among COVID-19 patients is common, and several studies have reported findings similar to ours [26,32]. Several diabetic patients had high levels of ketonuria and pH levels of 7.35 - 7.45, indicating diabetic ketoacidosis, which is similar to the findings of another study [33].

Our study has detected that proteinuria, hematuria, and glycosuria were common among patients who received vancomycin. Bacterial and yeast infection were also common; however, all the previous abnormalities were higher among patients who did not receive vancomycin, except among the prediabetic patients (Table 4). Vancomycin-resistant bacteria among COVID-19 patients was detected in Germany [34]. In our study, vancomycin was administered to 64 patients, of whom 19 were non-diabetic, 9 were prediabetic, and 36 were diabetic patients. Proteinuria, hematuria, and glycosuria were less frequently found in the urine of patients who received vancomycin than in the urine of the others. Among the prediabetic group, proteinuria, hematuria, coinfection, brown urine, squamous epithelia, calcium oxalates, hyaline casts, urobilinogen, nitrite, glycosuria, ketonuria, and bilirubin were all higher in the vancomycin-receiving patients than in the others. These findings were not similar to those of the diabetic and non-diabetic groups. Statistical analysis has shown a non-significant value between the mortality rate and vancomycin. Vancomycin was effective in the treatment of secondary infection in COVID-19 patients [35]. A study by Ramachandran et al. has reported an effective treatment by vancomycin of COVID-19 patients with sickle cell anemia [36]; another study reported consistent findings, as no vancomycin nephrotoxicity and mortality were reported [37]. During SARS-1, a study reported that the use of vancomycin reduced secondary infection in members of their study sample [38].

CONCLUSION

In our study, we have used urinalysis as a model to evaluate the effect of Covid-19 on the urine of the patients with different glycemic statuses. Urinalysis abnormalities were less in vancomycin group than the others except pre-diabetic group. No correlation between mortality and vancomycin was identified.

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Declaration of Interest:
The author declares no conflict of interest.

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