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NEPHROLOGY - ORIGINAL PAPER

Risk factors for infection and mortality among hemodialysis patients during COVID-19 pandemic

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Abstract

Purpose The aim of this study was to evaluate risk factors for COVID-19 infection and mortality and to document if any relation exists between 25 (OH) Vitamin D and COVID-19 infection.

Methods This retrospective study evaluated 151 HD patients. Patients infected with COVID-19 were compared to patients without the infection. Risk factors for intensive care unit (ICU) stay and mortality were analyzed. Deceased infected patients were also compared to patients who died due to other causes.

Results The mean age of all HD patients was 57.15 ± 15.73 years and 51.7% were male. The mean 25 (OH) Vitamin D level of all patients was 16.48 ± 8.45 ng/ml. Thirty-five infected patients were significantly older, had a higher Charlson comorbidity index (CCI) score. They also had a higher number of patients with diabetic nephropathy, cerebrovascular accident (CVA) and coronary heart disease (CHD). Patients who needed to stay in ICU had higher CCI score, a higher number of patients with diabetic nephropathy, pulmonary diseases and had statistically significantly higher CRP levels. Deceased infected patients were significantly older, had higher CCI scores and lower PTH than survived infected patients. Deceased infected patients had lower PTH, but had significantly lower leukocyte, lymphocyte counts and urea levels at admission when compared to patients who died due to other causes. Patients with poor prognosis had lower neutrophil and lymphocyte counts before infection and at admission; respectively. 25 (OH) Vitamin D level was not related to the risk of COVID-19 infection, ICU stay or mortality.

Conclusion Older age, higher CCI scores, diabetic nephropathy, CHD, CVA, pulmonary diseases, and lower neutrophil and lymphocyte counts were found as poor prognostic factors. The comparisons yielded no significant finding for 25 (OH) Vitamin D, acetylsalicylic acid, erythropoietin, intravenous iron, ACEI, ARBs, and dialysis adequacy parameters.

Keywords Vitamin D · COVID-19 · Hemodialysis · Mortality

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was the cause of coronavirus disease 2019 (COVID-19), that infected high number of patients and caused a higher rate of morbidity and mortality [1]. It has been shown that patients who are older and who have chronic diseases like hypertension, diabetes mellitus (DM), and cardiovascular diseases are both more susceptible and are severely affected by this infection [2, 3]. The accompanying co-morbid diseases and immunosuppression caused by uremia also cause hemodialysis (HD) patients to be seriously affected by this infection [4].

Vaccination is expected to decrease morbidity and mortality related to COVID-19 infection. Detection and elimination of risk factors is essential until all HD patients are vaccinated and the positive effect of vaccination is revealed. One risk factor that can be investigated is vitamin D insufficiency. Vitamin D insufficiency is prevalent in HD subjects [5–7] and low serum 25 (OH) D levels are known to be associated with increased risk of infection and mortality [8]. A study by Drechsler et al. [9] found that for every unit decrease in 25 (OH) D levels lower than 20 ng/ml, there was

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an increased risk of mortality from infections. Therefore, we wanted to evaluate the relationship between 25 (OH) D levels and COVID-19 infection.

This study aims to evaluate risk factors for COVID-19 infection and mortality among HD patients and aims to document if a relationship exists between 25 (OH) D level and COVID-19 infection.

Materials and methods

This retrospective study included one hundred seventy-three HD patients recruited from five HD units including Adilcevaz, Ahlat, Bitlis, Güroymak and Tatvan HD units in Bitlis, Turkey. The study period was between 1 January 2020 and 30 December 2020. Patients who were younger than 18 years old ($n = 2$ patients), on HD shorter than 3 months ($n = 5$ patients), treatment incompatible ($n = 6$ patients), and taking HD less than three times per week ($n = 4$) were excluded from the study. Five patients had inadequate follow-up data and were also excluded from the study. After excluding these patients, 151 patients were eligible for the analyses.

Data included age, gender, body mass index (BMI), dialysis vintage, cause of end-stage renal disease (ESRD), co-morbid diseases including hypertension, DM, coronary heart disease (CHD), congestive heart failure (CHF), pulmonary diseases including chronic obstructive pulmonary disease (COPD) and asthma, peripheric artery disease (PAD), cerebrovascular accident (CVA). Types of vascular access including arterio-venous (A-V) fistula or graft and central venous catheter, acetylsalicylic acid (ASA), angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) usage, intravenous (IV) iron and erythropoietin (EPO) doses, treatment with fresh frozen plasma (FFP), symptoms at the time of admission, duration of hospitalization, need of intensive care unit (ICU) and mortality were also included. Charlson's comorbidity index (CCI) calculator was used to calculate CCI score and estimated 10-year survival [10]. For infected and deceased patients, laboratory data until COVID-19 infection and mortality were used; respectively. For others, laboratory data throughout 2020 were used.

Blood was taken from HD patients in each month at mid weak session for laboratory analysis. The data were analyzed by taking a mean of every 3-month test results. Laboratory data included monthly and admission study results and included the following parameters: urea, creatinine, sodium, potassium, corrected calcium, albumin, phosphorus, parathormone (PTH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), serum iron, total iron-binding capacity (TIBC), ferritin, C-reactive protein (CRP), ph, PCO2, lactate, bicarbonate, ferritin, troponin, hemoglobin, leukocyte, lymphocyte, neutrophil and platelet counts, Kt/V, urea reduction rate (URR), thyroid-stimulating hormone (TSH), 25 (OH) vitamin D, Vitamin B12 and anti HbsAg levels. 25 (OH) vitamin D was not studied in Bitlis dialysis unit and hormones were studied two times a year.

Low flux dialyzers were used for all patients and they received low molecular weight heparin (LMWH) during their disease period. The erythrocyte stimulating agents were epoetin alpha or zeta and darbepoetin (DPO) alpha and all were used intravenously. To convert EPO to DPO, a conversion ratio of 200 international units (IU) of EPO to 1 µg of DPO was used [11].

A real-time reverse transcriptase-polymerase chain reaction test (rRT-PCR) for SARS-CoV-2 and lung tomography was performed on patients presented with symptoms thought to be caused by COVID-19. The presence of ground-glass opacities, crazy-paving patterns, and consolidation areas were related to pulmonary involvement of COVID-19 disease. Positive PCR test or typical tomography findings were accepted for the diagnosis of COVID-19 disease.

Favipiravir and Plaquenil were given to patients as suggested by the protocol of the Ministry of Health of Turkey. Favipiravir (2×1600 mg loading and 1×600 mg maintenance dose) was given to all patients for a total of 5 days. Favipiravir therapy was continued for five more days, if no clinical improvement was observed. The Plaquenil loading and maintenance doses were 2×200 mg and 2×100 mg; respectively. Azithromycin was used with Plaquenil before the Favipravir protocol. Fresh frozen plasma was also given to patients when no adequate clinical improvement was observed. Secondary bacterial infections were treated with appropriate antibiotics.

Vitamin D replacement was done considering patients' serum levels of calcium, phosphorus and PTH levels. Cholecalciferol was used for replacement and patients with PTH < 200, Ca > 10.5 mg/dL, $P > 6.5$ mg/dL were not supplemented with cholecalciferol.

The analyses were conducted in statistical software R. Categorical variables were analyzed by using Chi square test of independence and Fisher's exact test of independence. Before conducting any kind of analysis on the continuous variables, normality assumption was checked by the Shapiro–Wilk test of normality. To compare the distributions of two continuous variables, Independent Samples *t* Test was implemented for normal data, whereas Mann–Whitney *U* test was applied for non-normal data. Additionally, to investigate the factors affecting the binary response variable, logistic regression with binomial link function was implemented, and highly correlated independent variables ($r > 0.7$) were not included in the analyses to satisfy the absence of multicollinearity assumption. Finally, the level of significance was 0.05.

Results

Demographic and clinical parameters of all HD patients are shown in Table 1. The mean age of the patients was 57.15 ± 15.73 years and 51.7% of the patients were male. The most common cause of ESRD was diabetic nephropathy (39.6%) and the mean dialysis vintage was 57.81 ± 51.06 months. Mean 25 (OH) Vitamin D level of all patients was 16.48 ± 8.45 ng/ml. The percentage of patients with A-V fistula was 65.56% (n = 99) and only one patient had A–V graft. Among 151 patients; 35 patients were infected with COVID-19. The mean age of the infected and uninfected HD patients was 63.22 ± 12.36 and 55.37 ± 16.21 years, respectively. The number of patients who were PCR positive at least one time was 31 and 4 patients had negative PCR tests during their illness. Thirty-two patients had pulmonary involvement (24 bilateral, 8 unilateral) and the remaining three patients had no pulmonary involvement. Among 35 patients; 1 patient received only Plaquenil, 8 patients received both Favipravir and Plaquenil and the other patients received only Favipravir treatment. Eight patients received FFP and among these patients, 4 died.

Table 1 Demographic and clinical characteristics of hemodialysis patients

Parameters	Results
Age (years, mean ± SD)	57.15 ± 15.73
Male, n (%)	78 (51.70)
Body mass index (kg/m^2, mean ± SD)	24.53 ± 4.73
Patients with A–V fistulas, n (%)	99 (65.56)
Dialysis vintage (months, mean ± SD)	57.81 ± 51.06
Primary kidney disease, n (%)	
Diabetic nephropathy	62 (39.6)
Hypertensive nephropathy	47 (30.51)
Glomerulonephritis	10 (6.5)
CCI score (mean ± SD)	5.40 ± 2.58
Estimated 10-year survival %	33.50 ± 36.60
Urea (mg/dl, mean ± SD)	130.66 ± 26.35
Creatinine (mg/dl, mean ± SD)	7.34 ± 2.32
White blood cell (10^9/l, mean ± SD)	7.03 ± 3.63
Neutrophil (10^9/l, mean ± SD)	4.54 ± 1.87
Lymphocyte (10^9/l, mean ± SD)	1.51 ± 0.50
Hemoglobin (g/dl, mean ± SD)	11.17 ± 1.54
Ferritin (ug/l, mean ± SD)	482.80 ± 208.32
Albumin (g/dl, mean ± SD)	3.84 ± 0.55
Phosphorus (mg/dl, mean ± SD)	4.97 ± 1.07
Parathormone (pg/ml, mean ± SD)	521.64 ± 417.30
TSH (uIU/ml, mean ± SD)	1.80 ± 1.30
Kt/v ≥ 1.2, n (%)	133 (88.01)
Kt/v ≥ 1.4, n (%)	92 (59.74)
C-reactive protein (mg/l, mean ± SD)	17.26 ± 22.56
25 (OH) Vitamin D (ng/mL, mean ± SD)	16.48 ± 8.45
Vitamin B12 (pg/ml, mean ± SD)	413.09 ± 284.93
Treatment	
Acetylsalicylic acid (%)	58.94
ACEI* or ARB* usage (%)	25.16
Intravenous iron dose (mg/month, mean ± SD)	175.79 ± 258.39
Erythropoietin (IU/month, mean ± SD)	6128.02 ± 3134.961
COVID-19 infected patients, n (%)	35 (23.18)
Total mortality, n (%)	22 (14.57)
Mortality related to COVID-19, n (%)	11 (7.28)

A–V Arteriovenous *ACEI* Angiotensin-converting-enzyme inhibitor; *ARB* angiotensin receptor blocker; *TSH* thyroid-stimulating hormone; *CCI* Charlson comorbidity index

As comorbid diseases, 47 patients had hypertension, 62 had DM, 26 had pulmonary diseases, 34 had CHD, 38 had CHF, 15 had PAD and 12 had a history of CVA and 9 had chronic hepatitis B infections. The most common symptoms at hospitalization were fatigue (n = 15), dyspnea (n = 11), fever (n = 11) and cough (n = 9). Other symptoms that the patients complained of at admission include, bloody sputum, joint pain, nausea, diarrhea, chest pain, abdominal pain, and low blood sugar. The mean hospital stay of infected patients was 12.03 ± 10.16 days.

To find risk factors for COVID-19 infections among HD patients; patients infected with COVID-19 were compared to patients who were not infected with COVID-19 (Table 2). Infected patients were statistically significantly older (p = 0.00), had higher CCI score (p = 0.01), lower estimated 10-year survival (p = 0.01) and lower vitamin B12 (p = 0.02) levels. Covid-19 infected patients had statistically significantly higher number of patients with diabetic nephropathy (p = 0.03), and CVA (p = 0.01) and CHD (p = 0.00). They also had significantly higher levels of serum iron (p = 0.03) and total iron-binding capacity (p = 0.04). However, there was no statistically significant difference of 25 (OH) vitamin D level when two groups were compared (p = 0.45). Additionally, multivariate logistic regression analysis was implemented with the significant variables in Table 2, as independent variables (excluding 10-year survival due to multicollinearity) and being COVID-19 infected as the response variable, CVA (p = 0.00) and CHD (p = 0.01) were statistically significant.

COVID-19 patients who needed to stay at ICU were compared to patients who did not (Table 3). Patients who needed ICU stay had higher CCI score (p = 0.03), lower estimated 10-year survival (p = 0.01), higher numbers of pulmonary diseases (p = 0.04) and diabetic nephropathy (p = 0.01), lower neutrophil count (p = 0.01) and neutrophil to lymphocyte ratio (p = 0.02). They also had statistically significantly higher CRP (p = 0.04) level and lower lymphocyte count (p = 0.04) at admission. However, there was no statistically significant result for 25 (OH) vitamin D level when the

Table 2 Comparison of COVID-19 infected and uninfected hemodialysis patients

Parameters	COVID-19 (+) ($n=35$)	COVID-19 (–) ($n=116$)	p
Age (years, mean ± SD)	63.22 ± 12.36	55.37 ± 16.21	0.00*,[1]
Male, n (%)	15 (42.85)	63 (54.30)	0.402
Body mass index (kg/m^2, mean ± SD)	25.01 ± 5.14	24.59 ± 4.62	0.531
Dialysis vintage (months, mean ± SD)	62.55 ± 53.03	56.38 ± 50.60	0.541
Diabetic nephropathy, n (%)	20 (57.14)	43 (37.07)	0.032
CCI score (year, mean ± SD)	6.54 ± 2.69	5.05 ± 2.45	0.01*,[1]
Estimated 10-year survival (%)	20.17 ± 33.4	37.53 ± 36.8	0.01*,[1]
Coronary heart disease, n (%)	19 (54.28)	8 (6.9)	0.00*,[2]
Cerebrovascular accident, n (%)	6 (17.14)	5 (4.30)	0.02*,[3]
Hemoglobin (g/dl, mean ± SD)	10.85 ± 1.49	11.26 ± 1.55	0.161
Serum iron (µmol/l, mean ± SD)	67.73 ± 36.72	51.13 ± 36.72	0.03*,1
TIBC (µg/l, mean ± SD)	131.81 ± 68.08	102.64 ± 69.64	0.04*,[1]
Transferrin saturation (mean ± SD)	0.62 ± 0.61	0.53 ± 0.36	0.47[1]
Ferritin (ug/l, mean ± SD)	525.32 ± 202.32	470.23 ± 209.26	0.17[1]
Parathormone (pg/ml, mean ± SD)	498.06 ± 427.81	528.61 ± 415.79	0.71[1]
Kt/V (mean ± SD)	1.47 ± 0.26	1.55 ± 0.59	0.31[1]
Urea reduction rate (mean ± SD)	71.12 ± 6.13	71.30 ± 5.79	0.88[1]
C-reactive protein (mg/l, mean ± SD)	20.96 ± 27.93	16.16 ± 20.73	0.36[1]
HBsAg titer (IU/l, mean ± SD)	282.60 ± 326.98	282.60 ± 307.22	0.78[1]
25 (OH) Vitamin D (ng/ml, mean ± SD)	18.12 ± 9.91	16.15 ± 8.14	0.45[1]
Vitamin B12 (pg/ml, mean ± SD)	325.59 ± 196.76	441.55 ± 303.81	0.02*,[1]
Acetylsalicylic acid, n (%)	22 (62.85)	67 (57.76)	0.73[2]
ACEI or ARB, n (%)	5 (14.29)	33 (28.44)	0.14[2]
IV iron dose (mg/month, mean ± SD)	213.30 ± 202.60	164.38 ± 272.87	0.25
Erythropoietin (IU/month, mean ± SD)	6164.91 ± 3153.80	6116 ± 3142.61	0.94[1]

CCI Charlson comorbidity index; *ARB* angiotensin receptor blocker; *ACEI* angiotensin-converting-enzyme inhibitor; *TIBC* total iron binding capacity; *IV* intravenous

[1]Independent samples t test

[2]Chi square test of independence

[3]Fisher's exact test of independence

*Statistically significant difference at significance level of 0.05

two groups were compared ($p=0.58$). Multivariate logistic regression analysis was implemented with the significant variables in Table 3 (excluding 10-year survival chance due to multicollinearity) and pulmonary disease ($p=0.01$) and CCI score ($p=0.03$) were found statistically significant.

The number of infected patients who deceased was 11 with a mean hospital stay of 11.72 ± 8.29 days. Among these 11 patients, 7 of them died in ICU and 3 of them in a COVID-19 clinic. One of the patients died in his home four days after hospital discharge. In order to find risk factors for mortality among COVID-19 patients, deceased and survived COVID-19 infected patients were compared (Table 4). Deceased patients were significantly older ($p=0.01$), had higher CCI score ($p=0.01$), and lower estimated 10-year survival ($p=0.01$). Survived patients had significantly higher serum PTH (p:0.03) levels and neutrophil counts ($p=0.04$). Survived patients had also significantly higher lymphocyte counts ($p=0.00$) at admission. However; there was no statistically significant result for 25 (OH) vitamin D level when two groups were compared ($p=0.36$). Multivariate logistic regression analysis was carried out with the significant variables in Table 4 (excluding 10-year survival chance due to multicollinearity) and neutrophil count ($p=0.04$); and CCI score ($p=0.02$) were found to be statistically significant.

Finally, deceased COVID-19 patients were compared to patients whom died due to other causes (Table 5). Deceased COVID-19 patients had significantly lower neutrophil counts ($p=0.04$) and PTH levels ($p=0.03$) before infection, but had also significantly lower leukocyte ($p=0.01$), lymphocyte counts ($p=0.04$) and urea levels ($p=0.02$) at admission. However; there was no statistically significant difference in terms of 25 (OH) vitamin D level between the two groups ($p=0.45$). Multivariate analysis was implemented with the significant variables in Table 5

Table 3 Comparison of infected patients regarding intensive care unit need

Parameters	ICU stay ($n=9$)	No ICU stay ($n=26$)	p
Age (years, median)	70	63	0.18[1]
Male, n (%)	5 (55.56)	10 (38.46)	0.42[2]
Body mass index (kg/m^2, median)	23.02	24.92	0.45[1]
Dialysis vintage (months, median)	18.30	57.71	0.44[1]
Diabetic nephropathy, n (%)	4 (44.44)	16 (61.53)	0.01*[,3]
CCI score (median)	7	6	0.03*[,1]
Estimated 10-year survival % (median)	0	2	0.01*[,1]
Coronary heart disease, n (%)	5 (55.56)	14 (52.85)	0.98[2]
Cerebrovascular accident, n (%)	2 (22.22)	4 (15.38)	0.64[2]
Urea (mg/dl, median)	132.08	134.11	0.59[1]
WBC (10^9/l, median)	5.62	7.03	0.07[1]
Neutrophil (10^9/l, median)	3.41	4.96	0.01*[,1]
Neutrophil/Lymphocyte (median)	2.16	3.23	0.02*[,1]
Hemoglobin (g/dl, median)	10.70	10.92	0.64[1]
Ferritin (ug/l, median)	591.50	595.83	0.49[1]
Parathormone (pg/ml, median)	200.90	431.40	0.08[1]
Kt/V (median)	1.45	1.46	0.92[1]
Urea reduction rate (median)	71.1	72.3	0.74[1]
C-reactive protein (mg/l, median)	10.28	12.15	0.72[1]
25 (OH) Vitamin D (pg/ml, median)	16.07	14.69	0.58[1]
Acetylsalicylic acid, n (%)	7 (77.78)	15 (57.69)	0.43[2]
ACEI or ARB, n (%)	7 (77.78)	23 (88.46)	0.43[2]
IV iron (mg/month, median)	91.67	145.84	0.49[1]
Lymphocyte[†] (10^9/l, median)	1.52	1.36	0.04*[,1]
C-reactive protein[†] (mg/l, median)	137.95	56.87	0.00*[,1]

ICU intensive care unit; *CCI* Charlson comorbidity index; *WBC* white blood cell; *ACEI* angiotensin-converting-enzyme inhibitor; *ARB* Angiotensin II receptor blocker; *IV* intravenous

[1]Mann–Whitney *U* test

[2]Fisher's exact test of independence

[*]Statistically significant difference at a significance level of 0.05

[†]At admission

(excluding 10-year survival due to multicollinearity) and no statistically significant finding was detected.

There were no significant differences for other parameters including gender, BMI, dialysis vintage, hemoglobin, ferritin, Kt/V, URR, ASA, ACEI or ARB, IV iron or EPO when groups were compared in all the analyses.

Discussion

In this study, HD patients were evaluated regarding COVID-19 infection and subjects were from 5 different dialysis centers in Bitlis. The first HD patient was detected with COVID-19 at 3th May 2020. The percentage of COVID-19 infection in this study was 23% in 2020. A study from Spain evaluated 282 HD patients and in one month approximately 36 patients were infected with COVID-19 and the percentage of infected patients was 12% [12]. Another study from Wuhan included patients until 28 February 2020 and the percentage of infection was 11.8% among 627 HD patients [13]. The duration of studies, the crowd of the dialysis units, their logistic ability, and socioeconomic factors all can change the percentage of infected patients.

The most common symptoms at hospitalization were fatigue (42%), dyspnea and fever (both 31%) and coughing (n: 25%). The percentages of symptoms at presentation are lower than other studies reported for the general population and also lower than a study including only HD patients [12, 14–16].

In this study, COVID-19 related mortality rate was 31% in 2020. A study by Tian et al. included 123 patients among 553 HD patients and showed a mortality rate of 4% which was stated as higher and lower from the studies of China and Italy; respectively [17–19]. The study period was short and the number of excluded patients was high and four cases were still hospitalized when the data were

Table 4 Comparison of deceased and survived COVID-19 infected hemodialysis patients

Parameters	Deceased patients ($n=11$)	Survived patients (24)	p
Age (years, median)	70.5	60.19	0.01*,1
Male, n (%)	6 (54.54)	9 (37.50)	0.47[2]
Body mass index (kg/m^2, median)	23.79	24.62	0.51[1]
Dialysis vintage (months, median)	52.56	51.26	0.45[1]
Diabetic nephropathy, n (%)	8 (72.72)	11 (45.83)	0.43[2]
CCI score (median)	7	6	0.04*,1
Estimated 10-year survival % (median)	0	2	0.01*,1
Coronary heart disease, n (%)	5 (%45.45)	11 (45.83)	0.80[3]
Cerebrovascular accident, n (%)	4 (36.36)	2 (8.33)	0.06[2]
White blood cell (10^9/l, median)	5.62	6.92	0.12[1]
Neutrophil (10^9/l, median)	3.64	4.96	0.04*,1
Lymphocyte (10^9/l, median)	1.39	1.42	0.83[1]
Hemoglobin (g/dl, median)	10.75	10.92	0.86[2]
Ferritin (ug/l, median)	591.50	595.83	0.58[2]
Parathormone (pg/ml, median)	285.12	431.4	0.03*,1
Kt/V (median)	1.50	1.43	0.83[1]
Urea reduction rate (median)	72.5	71.0	0.84[1]
C-reactive protein (mg/l, median)	6.35	13.00	0.06[1]
HBsAg titer (IU/l, median)	114.26	178.97	0.97[1]
25 (OH) Vitamin D (pg/ml, median)	16.07	13.04	0.36[2]
Acetylsalicylic acid usage, n (%)	9 (81.81)	13 (54.17)	0.15[2]
ACEI or ARB usage, n (%)	2 (18.18)	3 (54.17)	0.14[2]
IV iron (mg/month, median)	90.91	145.84	0.88[1]
Erythropoietin (IU/month, median)	6000	7250	0.32[1]
Lymphocyte[†] (10^9/l, median)	0.72	1.24	0.00*,1

ACEI Angiotensin-converting-enzyme inhibitor; *ARB* Angiotensin II receptor blocker; *CCI* Charlson comorbidity index; *IV* intravenous

[1]Mann–Whitney *U* test

[2]Fisher's exact test of independence

[3]Chi square test of independence

*Statistically significant difference at a significance level of 0.05

[†]At admission

collected, which should explain why their mortality rate was lower. The previously mentioned study from Spain (duration approximately one month) reported a mortality rate of 30.5%, which is similar to our study. Risk factors including age, DM, obesity, CHD, or COPD were not associated with higher mortality in this study from Spain. They showed that low lymphocyte count and high LDH, and total bilirubin and CRP levels, 7 days after clinical onset, were associated with mortality [12]. Studies evaluating COVID-19 patients reported advanced age and accompanying co-morbidities related to poor prognosis [18, 20–23]. In our study, prognostic factors that were significantly associated with infection risk were older age, higher CCI score, and lower estimated 10-year survival, diabetic nephropathy and CVA and CHD. Also, mortality risk related to COVID-19 was significantly higher in older patients and in patients with higher CCI score and lower estimated 10-year survival. The deceased infected patients also had significantly lower PTH levels. The lower PTH in infected patients was also reported by Min et al. [13]. It was shown again that lower PTH levels can be a significant predictive factor leading to the death of patients [24].

The risk of mortality significantly rises if the patient requires admission to ICU and need of ICU stay was shown to be between 16 and 78% [25]. In diabetic patients, the first line of defense against SARS-CoV-2 is disrupted, which leads to chronic inflammation or increased coagulation activity [26], more severe disease, acute respiratory distress syndrome (ARDS), and increased mortality [27]. In our study, the number of patients who needed ICU had higher number of patients with diabetic nephropathy and pulmonary disease as co-morbid diseases. The insufficient pulmonary reserve

Table 5 Comparison of COVID-19 related and non-related deceased patients

Parameters	COVID-19 related ($n = 11$)	Non-COVID-19 related ($n = 11$)	p
Age (years, median)	71	73	0.77[1]
Male, *n* (%)	6 (54.54)	4 (36.36)	0.20[2]
Body mass index (kg/m^2, median)	23.79	26.29	0.52[1]
Dialysis vintage (months, median)	52.56	22.67	0.09[1]
Diabetic nephropathy, *n* (%)	8 (72.72)	4 (36.36)	0.12[3]
CCI score (median)	7	8	0.73[1]
Estimated 10-year survival % (median)	0	0	1[1]
WBC (10^9/l, median)	5.62	7.07	0.09[1]
Neutrophil (10^9/l, median)	3.64	5.12	0.04[*,1]
Coronary heart disease, *n* (%)	5 (45.45)	5 (45.45)	1[2]
Cerebrovascular accident, *n* (%)	4 (36.36)	2 (18.18)	0.64[3]
Lymphocyte (10^9/l, median)	1.38	1.25	0.68[1]
Hemoglobin (g/dl, median)	10.75	10.63	0.32[1]
Ferritin (ug/l, median)	591.50	583.33	0.62[1]
Parathormone (pg/ml, median)	285.12	349.50	0.03[*,1]
Kt/V (median)	1.50	1.47	0.78[1]
Urea reduction rate % (median)	72.50	71.00	0.90[1]
C-reactive protein (mg/l, median)	6.35	8.85	0.12[1]
Vitamin B12 (pg/ml, median)	246.0	262.5	0.34[1]
25 (OH) Vitamin D (pg/ml, median)	16.07	16.47	0.45[1]
Acetylsalicylic acid, *n* (%)	9 (81.81)	7 ()	0.63[2]
ACEI or ARB, *n* (%)	2 (18.18)	2 (18.18)	1[3]
IV iron (mg/year, median)	90.91	71.88	0.36[1]
Erythropoietin (IU/month, median)	6000	6605	0.30[1]
Urea[†] (mg/dl, median)	165	89.5	0.02[*,1]
WBC[†] (10^9/l, median)	5.01	10.06	0.01[*,1]
Lymphocyte[†] (10^9/l, median)	722	1208	0.04[*,1]

WBC white blood cells; *ACEI* angiotensin-converting-enzyme inhibitor; *ARB* angiotensin receptor blocker; *CCI* Charlson comorbidity index; *IV* intravenous

[1]Mann–Whitney *U* test

[2]Chi square test of independence

[3]Fisher's exact test of independence

*Statistically significant difference at significance level of 0.05

[†]At admission

of patients with pulmonary diseases might have resulted in respiratory insufficiency that resulted in ICU assistance.

A study by Erdinc et al. summarized the hematological manifestations of COVID-19 and reported lymphopenia as the most prominent finding [28]. Zhou et al. reported that COVID-19 patients who persistently had low lymphocyte counts died of the disease, and patients who showed improvements of lymphocyte counts during the hospitalization survived [29]. It was also stated that severe lymphopenia $< 0.6 \times 10^9$/l can be a sign for early admission to the ICU [30]. Lower lymphocyte counts were observed in COVID-19 patients with ARDS and neutrophilia was associated with increased risk of mortality [31]. The increased risk with neutrophilia was thought to be secondary to the disease course becoming complicated by bacterial superinfections [28].

Regarding HD patients, a study by Islam et al. showed that patients who needed ICU and died because of COVID-19 had also significantly lower lymphocyte counts at admission [32]. Another study by Shang et al. showed that patients who deceased because of COVID-19 had significantly higher neutrophil counts at admission [33]. Tian et al. evaluated infected and uninfected HD patients and found no appreciable differences in leukocyte, neutrophil and lymphocyte counts [17]. Regarding our patients with poor prognosis, lower neutrophil and lymphocyte counts were prominent before infection and at admission; respectively.

Increased risk of developing severe and fatal COVID-19 infection is associated with increased ACE2 expression which is caused by the use of ACEI and ARBs [34]. On the other hand, the positive effects of ACEI and ARBs were also shown. They reduce inflammation with decreased cytokines levels and consequently reduce mortality and endotracheal intubation risks in patients with viral pneumonia [26]. In our study, either ACEI or ARBs did not contribute to the risk of infection, mortality, and ICU stay. There was also no significant difference between deceased COVID-19 patients and patients died due to other reasons.

A recent study identified vitamin D among the three top molecules manifesting potential infection mitigation patterns [35]. Regulation of the renin-angiotensin system, cellular innate and adaptive immunity, and physical barriers by vitamin D, decrease the risks of COVID-19 infection and mortality [36]. Radujkovic et al. studied the impact of vitamin D status on the severity of COVID-19 in a total of 185 inpatients and outpatients. Inpatients had significantly lower levels of vitamin D than outpatients and vitamin D deficiency at admissions was related to a greater risk of requiring invasive mechanical ventilation and higher mortality rate [37]. Ilie et al. also showed an association between lower vitamin D levels and COVID-19 mortality in various European countries [38]. A study from Italy also showed an increased risk of SARS-CoV-2 infection, subsequent hospitalization, and in-hospital mortality in patients with lower vitamin D levels [39]. These studies included non-dialysis-dependent patients. For HD patients, vitamin D insufficiency is prevalent [5–7]·and low serum 25 (OH) D levels are known to be associated with increased risk of infection and mortality [8]. However, whether vitamin D is helpful in preventing COVID-19 infection, reducing disease progression, and reducing mortality in HD patients with COVID-19, remains unknown. To our knowledge, no study evaluated the relation between vitamin D and COVID-19 infection in HD patients. In this study, there were no statistically significant results between 25 (OH) vitamin D and infection risk, ICU stay risk or mortality risk, because of COVID-19.

The retrospective design is an important limitation of our study. The second limitation is, that the exact incidence of infection is unknown in our dialysis facility because asymptomatic patients were not tested for COVID-19 infection. However, the laboratory data throughout 2020 before patients being infected strengthened our study. Furthermore, 25 (OH) vitamin D levels of HD patients were also analyzed.

In conclusion; older age, higher CCI score, lower estimated 10-year survival, diabetic nephropathy, CHD, CVA, pulmonary diseases, and lower neutrophil and lymphocyte counts were found as poor prognostic factors. Also, there were no statistically significant results between 25 (OH) vitamin D and infection risk or mortality risk because of COVID-19. The comparisons also yielded non-significant results for ASA, EPO, IV iron, ACEI, ARBs and dialysis adequacy parameters.

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Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained from Van Region Education and Research Hospital's Ethics Committee.

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