COVID-19 and Renal Failure — Adding Insult to Injury? Israel's Experience Based on Nationwide Retrospective Cohort Study

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INTRODUCTION: Renal failure (RF) is a risk factor for mortality among hospitalized patients. However, its role in COVID-19-related morbidity and mortality is inconclusive. The aim of the study was to determine whether RF is a significant predictor of clinical outcomes in COVID-19 hospitalized patients based on a retrospective, nationwide, cohort study.

METHODS: The study sample consisted of patients hospitalized in Israel for COVID-19 in two periods. A random sample of these admissions was selected, and experienced nurses extracted the data from the electronic files. The group with RF on admission was compared to the group of patients without RF. The association of RF with 30-day mortality was investigated using a logistic regression model.

RESULTS: During the two periods, 19,308 and 2994 patients were admitted, from which a random sample of 4688 patients was extracted. The 30-day mortality rate for patients with RF was 30% (95% confidence interval (CI): 27–33%) compared to 8% (95% CI: 7–9%) among patients without RF. The estimated OR for 30-day mortality among RF versus other patients was 4.3 (95% CI: 3.7–5.1) and after adjustment for confounders was 2.2 (95% CI: 1.8–2.6). Furthermore, RF patients received treatment by vasopressors and invasive mechanical ventilation (IMV) more frequently than those without RF (vasopressors: 17% versus 6%, OR = 2.8, $p<0.0001$; IMV: 17% versus 7%, OR = 2.6, $p<0.0001$).

DISCUSSION: RF is an independent risk factor for mortality, IMV, and the need for vasopressors among patients hospitalized for COVID-19 infection. Therefore, this condition requires special attention when considering preventive tools, monitoring, and treatment.

KEY WORDS: COVID-19; renal failure; mortality; invasive mechanical ventilation; vasopressors; risk factor.

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INTRODUCTION

Shortly after the outbreak of coronavirus disease 2019 (COVID-19), data regarding risk factors for adverse outcomes began emerging. Older age, male sex, obesity, hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease were quickly identified as risk factors for COVID-19-related mortality and severe morbidity.[1–3]

Chronic kidney disease (CKD) is a well-known risk factor for adverse outcomes among hospitalized patients with various conditions.[4–6] For example, the pneumonia-related mortality rate in CKD patients is 14–16 times higher than in the general population.[7] Thus, there was a clear need for an evaluation of the impact of renal failure (RF) on COVID-19 prognosis. Data regarding COVID-19-related outcome in end-stage renal disease (ESRD) and renal transplantation were published, marking renal replacement therapy (RRT) as a risk factor for hospitalization, IMV, and mortality.[8–11] However, the effect of RF not requiring RRT on COVID-19 outcome was unclear. For instance, Cai et al. found that CKD was a significant mortality risk factor among patients 70 years of age or younger, but not among patients older than 70 years,[12] while Pilgram[11] described increased mortality in all age groups.

There is a strong correlation between RF and other comorbidities such as hypertension, atherosclerotic cardiovascular diseases, obesity, and insulin resistance, all of which have been identified as risk factors for adverse outcomes of COVID-19 infection. It is possible that these factors mask the causality of RF as a reason for increased risk. Karagiannidis et al. found that in the first wave of the COVID-19 pandemic (Wuhan strain of SARS-CoV-2 virus), each chronic condition increased the risk of IMV and mortality among COVID hospitalized patients in Germany.[13] Pakhchanian et al. studied the issue using propensity

matching of two cohorts of patients, with and without CKD, as well as further stratification of CKD into mild, moderate, and severe.[14] Their results show increased mortality, IMV, and hospitalization in the CKD group, with the worst outcomes in the severe CKD group. However, their conclusions were based on electronic medical records (EMR) without clinical data or EMR data validation. Flythe et al. found a higher mortality among COVID-19 patients with pre-existing kidney disease hospitalized in ICU wards in the USA. However, their conclusions were limited to ICU-admitted patients, thereby omitting the vast majority of COVID-19 hospitalized patients.[15]

The aims of the current study were to determine, based on a retrospective, nationwide, cohort study, whether ARF, CRF, and/or acute on chronic renal failure, all of which are termed in this article renal failure (RF), is a significant predictor for clinical outcomes in COVID-19 hospitalized patients. We also aimed to evaluate clinical and laboratory markers for adverse outcomes among the population with RF.

METHODS

The study sample comprised patients hospitalized in Israel for COVID-19 over two separate periods. The first period, February 21st, 2020, to November 5th, 2020, spanned two waves of the epidemic in Israel, in which the predominant strain was the original SARS-CoV-2 virus (Wuhan strain). The second period, November 6th, 2020, to January 15th, 2021, covered part of the third wave of the epidemic, in which the predominant strain was the Alpha variant which originated in the UK.[16–18] Mass vaccination in Israel with the Pfizer BNT162b2 vaccine was initiated on December 20th, 2020; thus, none of the patients included in this second period was fully vaccinated. (The second dose is given 21 days after the first dose, and full vaccination is achieved approximately 7 days later, which was January 15th at earliest.)

During the first period, we considered 19,308 COVID-19 hospitalizations in 24 of Israel's 26 general medical centers, each with more than 150 such admissions. Two centers were excluded due to administrative difficulties. A stratified random sample of these admissions, comprising approximately 25% of this population, was selected for the study. The strata were defined by (i) hospital and, within hospital, four sub-strata, according to the combinations of (ii) severity of illness (severe versus mild/moderate) and (iii) gender (male versus female). The probabilities of sampling from each sub-stratum varied between 1/6 and 1/2, with a view to obtaining a sample with about twice as many severe disease cases as moderate-to-mild cases. This process yielded a sample of 4697 admissions. From this sample, we excluded patients who had been admitted for a reason other than COVID-19 (but were diagnosed as positive for COVID-19 after admission), those who were not confirmed cases of COVID-19 (defined by a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a specimen collected from a nasopharyngeal swab), and the few patients whose data could not be retrieved. The final sample included 3582 COVID-19 admissions.

During the second period, we restricted our study to six general hospitals, chosen partly for convenience and partly to provide a sample of hospitals with diverse sizes, administrations, and geographical locations. At these hospitals, there were 2994 admissions of COVID-19 patients. We selected a random sample using the same sub-strata and with the same objective as described above, with sampling probabilities varying between 1/5 and 1. This yielded 1632 admissions. The same exclusion criteria described above were then applied, and the final sample size was 1106.

The Israeli Ministry of Health approved the study. Informed consent was waived, and researchers analyzed anonymized data. A team of experienced nurses extracted the data from the patients' electronic files in each hospital. Fifty-eight variables were extracted for each patient, as follows.

Demographic variables (7): date of performing RT-PCR for SARS-CoV-2 virus, date of admission, date of discharge or death, name of medical center, department, age, gender.

Comorbidity (10): diabetes mellitus, arterial hypertension, hyperlipidemia, cardiac disease, lung disease, renal failure, smoking, obesity (BMI>30), active malignancy, immune deficiency.

Clinical symptoms (11): severity of disease at admission (mild, moderate, severe, according to the Israel Ministry of Health definitions[19]), fever of 38° or higher, cough, dyspnea, headache, diarrhea, vomiting, abdominal pain, fatigue, muscle pain, taste or smell changes.

Vital signs and laboratory tests on admission (13): oxygen saturation, blood pressure, hemoglobin, leukocytes, lymphocytes, albumin, calcium, glucose, sodium, potassium, blood urea nitrogen (BUN), creatinine, D-dimer.

Respiratory support and oxygen treatment during hospital stay (8): oxygen mask, high flow oxygen by nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extra corporal membrane oxygenation (ECMO), prone positive ventilation, nitric oxide (NO), hemodialysis.

Drug treatment (5): steroids, remdesivir, convalescent plasma, vasopressors (namely nor-adrenaline or dopamine), vitamin D, enoxaparin.

Clinical outcomes (4): 30-day mortality, in-hospital mortality, discharge with or without oxygen support, length of hospital stay.

The group of patients with RF was defined by two variables: RF comorbidity (yes) and/or high serum creatinine (>1.2 mg/dl).

RF comorbidity was defined as a diagnosis of ARF, CRF, or acute on chronic RF, as coded by the physician(s).

Statistical Analysis

All estimates and distributions were calculated using weights, where the weight of each observation was equal to the inverse of its sampling probability.

Distributions of demographic, comorbidity, clinical symptoms, vital signs and laboratory tests, treatments, and clinical

outcomes were compared between the group with RF comorbidity (with or without high creatinine) and the group with high creatinine but no stated RF. This was done separately for each of the two study periods. Since the distributions of these variables were similar across these two groups (see the "Results" section), they were combined into a single RF group.

The RF group was then compared to the group of patients without RF or high creatinine with respect to all the above-mentioned variables, separately for the two study periods. Regarding prognosis, the focus of our study was 30-day mortality, but we also studied, as prognostic indicators, receipt of treatment by (a) vasopressors and (b) IMV. The proportions receiving these treatments were compared between patients with and without RF, both unadjusted and adjusted for confounders, using logistic regression. Odds ratios (OR) are reported in the "Results" section.

The association of RF with 30-day mortality was investigated using a logistic regression model, initially including only the RF indicator as a covariate, and then adding confounders. Data from both study periods were combined in these models, and an indicator variable, study period, was added as a covariate. The odds ratio for mortality among those with RF, both unadjusted and adjusted for confounders, was estimated from the exponent of its regression coefficients in these logistic regression models. Interactions between confounder variables and the RF indicator were also examined.

Finally, to explore the main prognostic subgroups (with respect to 30-day mortality) within the RF and non-RF groups, a classification tree algorithm was run for each of these groups separately, using data from the study periods.

Analysis was performed with the Statistical Analysis System (SAS) software (Enterprise Guide, version 7.1).

RESULTS

In the first period, of the 3582 admissions, 949 involved patients with RF (24% of the hospitalized population after adjustment for sampling probabilities), of whom 519 had RF reported and the remaining 430 had high serum creatinine without reported RF. In the second period, of the 1106 admissions, 350 involved patients with RF (30% of the hospitalized population), of whom 196 had RF reported and 154 had high serum creatinine without reported RF. The average serum creatinine level in the first period group was 1.18 (median 0.9), and in the second period, 1.31 (median 0.91). The first columns of Table 1 show the distribution of patient characteristics (demographics, comorbidities, laboratory tests, treatments, and 30-day mortality) for admissions in the first period among those with RF reported compared to those with high serum creatinine but no reported RF. For most characteristics, the distributions in these two groups were similar. Notably, 30-day mortality was equally high (30%) in both groups. Because of their similarity, we combined the two groups under the rubric "RF."

The last two columns of Table 1 compare the distribution of characteristics of patients in the RF group with the remainder of the hospitalized patients. It can be seen that the two groups differ substantially with respect to many of the characteristics. RF patients were more likely to be male, older, with more comorbidity and abnormal laboratory test results, to have received more intensive treatment for COVID-19, and to have died. In particular, RF patients received treatment with vasopressors and IMV more frequently than those without RF (vasopressors: 17% versus 6%, OR = 2.8, $p<0.0001$; IMV: 17% versus 7%, OR = 2.6, $p<0.0001$). The 30-day mortality rate for RF patients was 30% (95% CI: 27–33%) compared to 8% (95% CI: 7–9%) among other patients.

Similar results comparing RF with other patients were seen for the second period; although in this second period, an overall larger proportion of admissions involved older patients and those with higher disease severity, and a consequently higher proportion of patients who received more intensive treatment and who died within 30 days. Vasopressors were given to 21% of patients with RF and to only 10% of patients without RF. Similarly, 21% of RF patients received IMV, compared to 11% of patients without RF. Thirty-day mortality in this period was 43% (95% CI: 38–49%) among RF patients compared to 17% (95% CI: 15–20%) among others. Detailed results for the second period are provided in the Supplementary Materials, Table S1.

The differences between the proportions of RF and other patients receiving vasopressors and IMV remained statistically significant ($p<0.0001$) after adjusting for the confounders period, gender, age, diabetes, and smoking.

Using logistic regression, we combined results over the two periods, adjusting for the difference in mortality between the periods. The estimated odds ratio for 30-day mortality among RF patients versus other patients was 4.3 (95% CI: 3.7–5.1). We then estimated how much of this was due to RF patients being more likely to be male, older, and current smokers and having diabetes mellitus. After adjusting for these factors, the odds ratio decreased from 4.3 to 2.3 (95% CI: 1.9–2.8). Adjusting for other factors associated with RF, particularly heart disease, further reduced the estimated odds ratio for mortality to 2.2 (95% CI: 1.8–2.6). This translates to an increase in mortality probability from 10% in someone without RF to 19% with RF, i.e., an approximate doubling of the mortality rate. Detailed results of the logistic regression models are provided in the Supplementary Materials, Tables S2-S4.

To discover whether within the group of patients with RF there were particular factors that predisposed to a higher mortality rate, we conducted a separate logistic regression analysis of mortality within that group. Factors identified were older age, heart disease, severe disease on admission, immunosuppression, low oxygen saturation, low blood pressure, low albumin, low calcium, high leukocyte count, and high blood urea nitrogen. Detailed results are provided in Supplementary Materials, Table S5. Using classification tree

Table 1 Distribution (Percentages) of Patients' Characteristics According to Renal Failure Group in First Period[1]

Characteristic	Renal failure reported (n=519)	High creatinine without kidney disease reported (n=430)	Renal failure[2] (n=949)	No renal failure (n=2633)
Gender:				
Male	64	72	68	51
Female	36	28	32	49
Age:	13	16	14	51
<60y				
60–69	22	24	23	19
70–79	27	27	27	16
80–89	28	23	26	11
90+	11	10	10	4
Disease severity:	55	51	53	66
Mild				
Moderate	20	19	19	17
Severe	25	31	28	17
Current smoker	10	10	10	5
Comorbidities				
Diabetes	60	51	56	26
Hypertension	79	72	76	38
Heart disease	54	46	50	17
Lung disease	19	15	17	11
Obesity	23	22	22	19
Active malignancy	6	6	6	4
Immunosuppressed	6	4	5	3
Laboratory tests				
Low saturation	31	37	34	21
Low blood pressure	3	3	3	1
Low hemoglobin	60	48	54	28
High leukocytes	15	19	17	10
Low albumin	43	37	40	21
Low calcium	47	39	43	25
Low sodium	31	38	34	22
High blood urea nitrogen	45	29	38	1
Treatment in hospital				
Steroids	61	63	62	45
Remdesivir	14	25	19	18
Convalescent plasma	10	12	11	8
Vasopressors	17	18	17	6
Vitamin D	17	17	17	13
Anticoagulants	80	79	80	62
Oxygen ventilation	68	73	70	44
High flow oxygen	28	37	32	15
Invasive mechanical ventilation	15	20	17	7
Mortality in 30 days	30	30	30	8

[1]*February 20th to November 5th, 2020*
[2]*Renal failure reported and/or high creatinine*

methodology, as a guide to identifying the main prognostic subgroups within the group of RF patients (see Supplementary Materials, Figure S1), we found that 66% of patients aged 80 and over with a high leukocyte count died within 30 days. Table 2 shows the main subgroups and their mortality proportions.

We also checked on whether the factors predisposing to higher mortality in the group of RF patients were different from those in the other hospitalized patients. The list of important factors was similar in the two groups, with age, severity of disease on admission, heart disease, low saturation, high leukocytes, low albumin, and high BUN appearing in the list for both groups. Immunosuppression, dyspnea symptoms, and low calcium seemed more important predictors of 30-day mortality among those without RF than those with RF. Prognostic subgroups for patients without RF were best defined by age, low albumin, and low saturation. Details are provided in Supplementary Materials, Table S6 and Figure S2.

DISCUSSION

In this retrospective cohort study, we show significantly increased risk for poor outcome of COVID-19 infection in hospitalized patients with RF compared to patients without RF. The mortality risk odds were 4.3 among patients with

Table 2 Main Prognostic Subgroups within the Group of Renal Failure Patients and their 30-Day Mortality Proportions

Subgroup	Number of patients	Percentage who died within 30 days (95% CI)
Aged 80+, high leukocytes	134	66% (57–75%)
Aged 80+, low or normal leukocytes	395	44% (39–49%)
Aged <80, low albumin	298	36% (30–42%)
Aged <80, normal albumin, high leukocytes	52	43% (29–56%)
Aged <80, normal albumin, low or normal leukocytes	420	14% (11–17%)
Total group	1299	34% (31–36%)

renal failure, while the odds for IMV and for the need for vasopressors were 2.6 and 2.8, respectively.

Excess mortality risk among patients with RF could be attributed to comorbidities such as hypertension, obesity, heart failure, and diabetes, which are all known both as risk factors for COVID-19 adverse outcomes and common conditions among patients with RF. However, we have shown that even after adjustment for sex, age, and comorbidities, RF was associated with doubling the risk of mortality and severe morbidity. Thus, RF was found to be an independent risk factor for mortality, IMV, and the need for vasopressors. Within the RF population, other risk factors, such as age, severity of disease on admission, heart disease, low saturation, high leukocytes, and low albumin, served as independent contributors to mortality risk at a similar level to the general population of patients hospitalized for COVID-19.

Both CKD and acute kidney injury may contribute to the increased risk of adverse outcomes among patients hospitalized with COVID-19. Patients were included in this study if they had either chronic renal failure (based on data from their medical records — our "reported renal failure" group) or creatinine higher than 1.2 mg/dl on admission (our "high serum creatinine without reported renal failure" group), which could reflect a chronic or acute condition. Thus, while the effect of chronic kidney disease (CKD) on COVID-19 prognosis could be investigated in the population with CKD on the medical records, the effect of acute kidney injury on patients' prognosis could not be evaluated separately in the current study. Nevertheless, it is worth noting that the mortality rate among the "high serum creatinine without reported renal failure" group was very similar to that among the "reported renal failure" group, suggesting that acute kidney injury also carries a high risk of mortality.

Increased risks of poor clinical outcomes in RF patients may be explained, at least in part, by uremic-associated reductions in lymphoid cell number and function, as well as increased production of inflammatory cytokines and reactive oxygen species.[20] Furthermore, while social isolation (alongside with vaccination) is currently a major tool for COVID-19 infection prevention, patients with RF may be more exposed to COVID-19 infection than the general population due to a higher need for medical interactions that make it difficult for them to follow isolation requirements. Moreover, as much as a 17-fold increase in the risk of COVID-19 infection among long-term care facilities, dialysis patients, and among those living in a congregate setting has been reported.[8]

Among patients with COVID-19-related AKI, renal involvement of COVID-19 infection may serve as a first sign of severe disease. Previous autopsy-based studies demonstrated acute tubular necrosis as well as increased clotting and disseminated intravascular coagulation with small vessel thrombosis in the glomeruli and peritubular capillaries in patients with COVID-19-related renal involvement.[21–23]

The rate of RF in the study cohort of hospitalized COVID-19 patients was 26.5%, which is significantly higher than the rate in the general population, which has been reported in various screening studies to be 12–15%.[24, 25] However, in a cohort of hospitalized patients, the increased risk for infection and the increased risk for severe disease requiring hospitalization could not be differentiated.

The high rates of RF among patients hospitalized with COVID-19 infection and the risk for adverse outcomes in this population demand careful thinking as well as prioritizing of preventive measures to reduce COVID-19 infection rates. COVID-19 vaccinations have a profound effect on patients' risk of both infection and adverse outcomes. Vaccinations are expected to reduce mortality rates among RF patients as well as in the general population. However, RF is related to impaired immune response, which is associated with a decreased response to various vaccines compared to the response in the general population.[26–28] Data regarding the immune response to the Pfizer BNT162b2 vaccine, given in Israel, shows significantly lower titers of antibody response among patients with chronic renal failure than controls.[29, 30] Thus, with limited immune response to COVID-19 vaccination among the CKD population, the odds ratios for mortality and severe disease may remain high.

The two different periods analyzed in the current study reflect two different viral strains responsible for the different waves. During the first period, the predominant strain was the original SARS-CoV-2 virus (Wuhan strain), and during the second period, the predominant strain was the Alpha variant that originated in the UK. Changes in the criteria for patients' hospitalization and differences in the hospitals that were screened between the two periods make comparison between the strains difficult. However, the same comorbidities have contributed to patients' risk in both periods, thus pointing to patients' characteristics, rather than viral strain characteristics, as the major contributor to patients' risk. It remains to be seen whether the same will be found with the Delta and Omicron strains.

Our study has some limitations: First, pre-infection serum creatinine was not available, making it difficult to determine whether patients admitted with high creatinine had CKD or AKI. Furthermore, an increase in creatinine levels within the normal range could not be identified, which may lead to an underestimation of AKI rates. We believe that our classification of "reported CKD or raised serum creatinine" fits best with real-life conditions, as risk stratification on hospital admission is often performed with limited data regarding patients' past creatinine values. Second, data from the second period analyzed was not available from all the hospitals, and therefore might not reflect patients' outcomes in other centers. However, the consistency of results across the two periods regarding mortality risk associated with RF suggests that this limitation did not introduce substantial bias.

In conclusion, we can state that RF is an independent risk factor for mortality and adverse outcomes from COVID-19 infection among hospitalized patients. Thus, this high-risk population requires special focus when considering preventive tools, monitoring, and treatments.

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Declarations:

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