

# Profiles of Independent-Comorbidity Groups in Senior COVID-19 Patients Reveal Low Fatality Associated with Standard Care and Low-Dose Hydroxychloroquine over Antivirals

Kamaleldin B Said<sup>1,2</sup>, Ahmed Alsolami<sup>3</sup>, Fayez Saud Alreshidi<sup>4</sup>, Anas Fathuddin<sup>5</sup>, Fawwaz Alshammari<sup>6</sup>, Fauwaz Alrashid<sup>7</sup>, Ahmed Aljadani<sup>3</sup>, Rana Aboras<sup>4</sup>, Fatmah Alreshidi<sup>4</sup>, Mohammed H Alghozwi<sup>1</sup>, Suliman F Alshammari<sup>1</sup>, Nawaf F Alharbi<sup>1</sup>

On behalf of the Ha'il COM Research Unit Group

<sup>1</sup>Department of Pathology and Microbiology, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia; <sup>2</sup>Genomics, Bioinformatics and Systems Biology, Carleton University, Ottawa, ON K1S 5B6, Canada; <sup>3</sup>Department of Internal Medicine, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia; <sup>4</sup>Department of Family, Community Medicine, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia; <sup>5</sup>Department of Plastic Surgery, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia; <sup>6</sup>Department of Dermatology, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia; <sup>7</sup>Department of Surgery, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia

Correspondence: Kamaleldin B Said, Department of Pathology and Microbiology, College of Medicine, University of Ha'il, Ha'il, 55476, Saudi Arabia, Tel +966500771459, Email kbs.mohamed@uoh.edu.sa

**Introduction:** The lack of feasible therapies and comorbidities aggravate the COVID-19 case-fatality rate (CFR). However, reports examining CFR associations with diabetes, concomitant cardiovascular diseases, chronic kidney disease, and chronic liver disease (CLD) are limited. More studies assessing hydroxychloroquine (Hcq) and antivirals are needed.

**Purpose:** To examine associations of COVID-19 CFR in comorbid patient groups each with single comorbidities and after treatment with Hcq, favipiravir, and dexamethasone (Dex), either alone or in combination versus standard care.

**Methods:** Using statistical analysis, we descriptively determined these associations among 750 COVID-19 patient groups during the last quarter of 2021.

**Results:** A diabetes comorbidity (40%, n=299) showed twice the fatality (CFR 14%) of the others (CFR 7%;  $P=0.001$ ). Hypertension (Htn) was the second-commonest comorbidity (29.5%, n=221), with similar CFR to diabetes (15% and 7% for Htn and non-Htn, respectively), but with higher significance ( $P=0.0006167$ ). Although only 4% (n=30) heart failure (HF) was reported, the CFR (40%) was much higher than in those without it (8%). A similar rate (4%) for chronic kidney disease was reported, with CFRs of 33% and 9% among those with and without it, respectively ( $P=0.00048$ ). Ischemic heart disease was 11% (n=74), followed by chronic liver disease (0.4%) and history of smoking (1%); however, these were not significant due to the sample sizes. Treatment indicated standard care and Hcq alone or in combination were superior (CFR of 4% and 0.5%, respectively) compared to favipiravir (25%) or Dex (38.5%) independently or in combination (35.4%). Furthermore, Hcq performed well (CFR 9%) when combined with Dex (9%;  $P=4.28 \times 10^{-26}$ ).

**Conclusion:** The dominance of diabetes and other comorbidities with significant association with CFR implied existence of a common virulence mechanism. The superiority of low-dose Hcq and standard care over antivirals warrants further studies.

**Keywords:** COVID-19 medicine treatments, COVID-19 supportive treatment, comorbid COVID-19 elders, COVID-19 survivals and deaths

## Introduction

The emergence of SARS-CoV-2 marked the third devastating transmission of a highly virulent zoonotic coronavirus lineage into the human population that originated in China at the end of 2019.<sup>1</sup> Unlike the other two lineages — SARS-CoV-1 and the Middle East respiratory syndrome — SARS-CoV-2 is believed to have acquired enhanced virulence and epidemicity. The rapid epidemicity with sudden onset and severity of COVID-19 brought about complete chaos, widespread panic, mass confusion, and often justifiable political stumbles in crisis management and biocontainment strategies. Under these circumstances and in the absence of widely available treatment, management depended on standard care and supportive therapy with ventilation while enforcing preventive strategies until protective vaccinations took effect that significantly curtailed global COVID-19 cases.<sup>2</sup> However, there were several challenges affecting preventive measures and vaccinations in different countries and geographic regions. For instance, one of the most impressive COVID-19 response programs was that of the Commonwealth Caribbean regions. Despite devastating previous natural disasters and tropical and chronic diseases with high mortality, the Caribbean region's resilience, performance, and preparedness programs during the COVID-19 pandemic were quite impressive compared to many well-developed countries with quality standard care. Although COVID-19 was relatively slow to affect the islands, the experience was bitter, affecting major sources of income in the tourism industry, education, and labor.<sup>3</sup> Other challenges affecting global COVID-19 measures were population responses. For instance, while women, obese, seniors, and those with chronic disease participants all adhered to preventive measures, women hesitated about vaccination, while participants of older age and higher education showed willingness.<sup>4</sup> At present, several efforts are being made to review protocols and introduce refined clinical, diagnostic, and genomic approaches in the detection and management of the disease and pandemic profiles. For instance, the beneficial effects of statins in reducing mortality in hospitalized COVID-19 patients have been established in a comprehensive, multicenter, retrospective study on 1626 patients in tertiary care hospitals in India.<sup>5</sup> However, patients on drugs that are likely to influence in any way the underlying comorbidities being measured were excluded from this study, particularly steroids, which are known to increase susceptibility to infection.<sup>6</sup>

Although several aspects of COVID-19 have been studied in different demographic and geographic groups, the disease pattern in comorbid patients without any risk of hospitalization has not been understood. For instance, susceptibility of old ferrets to SARS-CoV-2 was attained by an infectious dose of approximately 32 PFU per animal compared to 100 PFU in young ones. This was due to increased transcription of two key viral receptors, ACE2 and TMPRSS2, in respiratory systems of old animals. Several reports have indicated a low risk of COVID-19 in younger age-groups in many countries,<sup>7–10</sup> though similar reports on the older working class and seniors at risk of comorbidities are limited. Therefore, it has become important to mitigate the potential risks for senior populations.

Diabetes is well known globally as a highly potential risk factor for mortality during COVID-19.<sup>11–15</sup> Although many reports have been published, unfortunately most had limitations, such as use of single-center data, small samples, or measuring few or single risk factors. For example, diabetes had twice the COVID-19 patient mortality rates of nondiabetes in one study.<sup>16</sup> Another study reported 9.9% higher mortality in Chinese diabetic COVID-19 patients; however, since a higher prevalence of diabetes mellitus is independently associated with a worse prognosis, the association of diabetes is debatable.<sup>17</sup> The number and death rates of hospitalized COVID-19 patients with underlying diabetes were double that of those without the disease in a retrospective study conducted in Riyadh, Saudi Arabia,<sup>13</sup> with the former group generally experiencing worse clinical symptoms and metabolic profiles in many reports.<sup>18,19</sup> Nevertheless, no correlation of diabetes with mortality was found after consideration of several factors and other preexisting conditions, such as age, sex, BMI, HbA<sub>1c</sub>, fasting, and random blood glucose on admission.<sup>13</sup> These findings indicated the multifactorial nature of diabetes and related disorders leading to mortality in COVID-19.<sup>13</sup> It was also found in large comprehensive cohort investigations in many countries, including China (1561 COVID-19 patients) and the US (463 patients), that diabetes was not merely the underlying cause for poor outcomes. Other disorders and patient conditions, such as hospitalization, ICU admission, and mechanical ventilation, played significant roles.<sup>13,20</sup> In the UK, preliminary data indicate that diabetes is the leading cause of death among patients of COVID-19 who die in hospitals.<sup>21</sup> Despite the lack of an obvious mortality risk in this study, diabetes remains one of the major risk factors for poor prognosis. The authors suggest that the increased risk can also be attributed to chronic diseases clustering together or to cardiometabolic multimorbidity.<sup>13</sup>

In 2010, around 31.1% of adults (1.39 billion) worldwide were hypertensive<sup>22,23</sup> increasing susceptibility to and severity of COVID-19. Though controversial, this indicates the need for more studies in this area of research. In addition, infections with COVID-19 are thought to be more prevalent in hypertensive people<sup>24,42</sup> and have been associated with COVID-19 fatality in those patients. Shi et al looked at 101 nonsurvivors of COVID-19 infection and found that 23% of them had acute kidney injury (AKI) and 11% underlying chronic kidney disease (CKD). In these, patients who died within 3 days had higher blood urea nitrogen and myoglobin levels, where the median period from admission to death was 4 days. However, after correcting for confounding factors, Cheng et al found that elevated levels of creatinine, blood urea nitrogen, proteinuria, hematuria, and AKI stages 2 and 3 were all linked to death.<sup>42,43</sup> Since the known incidence range is very wide (0.7%–47.6%),<sup>44,45</sup> how exactly SARS-CoV-2 aggravates CKD is not yet clearly defined. COVID-19 has been shown to be particularly fatal in cases of kidney disfunctions related to the disease, where the incidence of AKI is higher in patients with established CKD.<sup>45,46</sup> Therefore, it is imperative to objectively study comorbidities as independent variables underlying COVID-19 scenarios.<sup>43,46</sup> Viral hepatitis caused by a novel coronavirus has been reported.<sup>47</sup> It resulted in 60% of patients having impaired liver function. According to another report, 43 cases of COVID-19 had impaired liver function, higher alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, and one in 99 patients had substantial liver injury.<sup>48</sup> Liver-function problems were mostly characterized as abnormal ALT or AST levels, with a minor increase in bilirubin levels. Wang et al<sup>49</sup> found that 23 patients (33%) had increased ALT and 19 (28%) raised AST in a study of 69 individuals. Similarly, Cai et al<sup>50</sup> reported that 44 of 298 patients (14.8%) had liver injury, with 36.2% severe and more likely to have these elevations. According to Zhang et al, the rate of liver injury among 82 nonsurvivors of COVID-19 was as high as 78%.<sup>51</sup> Furthermore, a French national retrospective cohort examined 259,110 patients with acute and postacute COVID-19 cases for chronic liver disease (CLD), including mechanical ventilation and day 30 mortality. COVID-19-related fatality was not associated with mild liver cases, compensated cirrhosis, organ transplantation, including liver transplantation, or **AIDS**. However, COVID-19-related fatality was higher in patients with alcoholism, decompensated cirrhosis, or primary liver cancer, but they were less likely to obtain mechanical ventilation. This study's findings showed that limiting therapeutic effort may have contributed to the increased mortality in French residents with a liver-related problem or an alcohol-use disorder.<sup>52</sup>

One major factor contributing to the uncontrollable transmission of SARS-CoV-2 was the lack of specific and widely available therapeutics. However, enormous global efforts and support to the private sector resulted in the production of novel therapeutics, including Paxlovid (PF-07321332). This product, along with combinations of standard-care bundles, significantly reduced hospitalization time and death rates. Comprehensive studies that summarized the use of hydroxychloroquine against COVID-19 infection have highlighted the major mechanisms, pharmacokinetics, therapeutic applications, and safety profiles of an immunomodulatory and antiviral drug.<sup>53</sup> However, this success was not seen by many, which calls into question the mechanism of action of the drug.<sup>53</sup> Nevertheless, the central issue that undermined the drug's pH-related mode of action in endolysosomal alkalization was essentially the wide variability in its pharmacokinetics among different patients and the associated unacceptable toxicities. Several studies demonstrated factors that influence the effectiveness of hydroxychloroquine and other drugs, including clinical outcome and length of stay,<sup>54</sup> and genetic variants that may alter the pharmacokinetics of hydroxychloroquine/chloroquine (CYP2C8, CYP2D6, SLCO1A2, and SLCO1B1), azithromycin (ABCB1), ribavirin (SLC29A1, SLC28A2, and SLC28A3), and lopinavir/ritonavir (SLCO1B1, ABCC2, CYP3A).<sup>55,56</sup> More studies are required to adequately assess the therapeutic applications of these drugs. Favipiravir (T-705) is a widely known synthetic prodrug, a nucleotide analogue that selectively inactivates the viral RNA-dependent RNA polymerase. However, many studies have pointed to the urgent requirement for more clinical studies to evaluate the efficacy and safety of this antiviral nucleoside for COVID-19 treatment in different population structures.<sup>57</sup> This is particularly important in age-dependent administration, where experimental studies have shown that favipiravir is age- and dose-dependent.<sup>58</sup> Therefore, more studies on local experiences of the drug in humans are necessary to understand cotreatment on other similar viruses since it is well tolerated in humans and has a high barrier to resistance. Moreover, indications and associations of its required high doses with the hyperuricemia have not been examined either.<sup>59</sup> Serious questions were raised during the SARS-CoV-2 pandemic about the management of patients with chronic obstructive pulmonary disease (COPD). These included but were not limited to possible alternative treatment options available, efficient diagnosis of COVID-19 clinical characteristics from existing but not diagnosed

COPD. For these issues, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Science Committee recommended the use of dexamethasone for moderate-to-severe COVID-19, including hospitalization and pneumonia.<sup>60</sup> Dexamethasone has been widely known to reduce death rates in patients with invasive mechanical ventilation. Despite the stigma about corticosteroid use, the treatment of severe COVID-19 pneumonia with high-dose methylprednisolone followed by oral prednisone accelerated recovery time significantly and reduced the need for intensive care, as well as the levels of such markers as CRP, D-dimer, and LDH.<sup>61</sup> In a meta-analysis of 10 trials and 71 observational studies on a total of 45,935 patients, all-cause mortality was significantly lower primarily among old men who were critically ill COVID-19 patients who had been administered low-dose dexamethasone.<sup>62</sup>

## Methods

### Study and Hospital Data

This work was a retrospective (cross-sectional) during the last quarter of 2021. A panel of experts screened the data for eligibility. The inclusion criteria for patients in this study included hospitalized patients with confirmed positive qPCR for SARS-CoV-2 and no other coinfection or underlying disorder other than indicated comorbidities (this is explained below). This criterion described SARS-CoV-2 diagnosis for COVID-19 was as clinically compatible symptoms (and epidemiological criteria for nonsymptomatic carriers) confirmed by approved real-time reverse transcription PCR (RT-PCR) on swabs (nasopharyngeal throat swab or similar recommended specimens at the Ha'il Health Regional Laboratory (HHRL) for COVID-19. The HHRL is a standard laboratory center, certified and accredited by the Saudi Central Board for Accreditation of Healthcare Institutions (CBAHI; code 2739) and associated with KSSH, which is also certified and accredited CBAHI (HAL/MOH/HO5/34213). In addition, the inclusion criteria described all comorbid hospitalized patients' groups as those admitted for 48–72 hours, isolated in KSSH center isolation zones, and with confirmed clinical test data on specific underlying comorbidity diseases. If the test results were not definitive, patients were not included in the study. Furthermore, inclusion criteria on the basic demographics and clinical characteristics included age, where patients  $\geq 50$  years were included. Exclusion criteria primarily included non-COVID-19 patients, those not satisfying age criteria, underlying diseases, comorbidities other than those measured, invasive procedures, outcome status, and survival characteristics of patients coinfecting or who had developed underlying causes as a result. Specifically, patients were excluded if they had existing non-COVID, unspecified comorbidity other than the major underlying ones included in the criteria and for which they were hospitalized, namely, diabetes, hypertension, heart failure, ischemic heart conditions, and CKD. Furthermore, any known community-associated infection(s) (occurring  $< 48$ –72 hours of admission, made them ineligible.

Experts analyzed submitted data from patient admission till outcome. Data were collected for the same time frame for all groups to avoid biases. Hospital data were from records of general clinical signs and major treatment protocols involving the Ministry of Health protocol for COVID-19 in place for the three medications hydroxychloroquine (low dose,  $\leq 400$  mg/day), favipiravir, and dexamethasone. Performances of these were assessed individually and their COVID-19 case–fatality rates estimated in each drug group. For this, all patients were classified into three independent groups based on antiviral drugs they had had administered: hydroxychloroquine group, favipiravir group, and dexamethasone group. Statistical analysis was then performed to understand the significance and case–fatality rates in each case. Any treatment protocol other than these three antivirals that was prone to alter or potentially change the course of the disease and influence prognosis was flagged (especially higher doses of steroids that would increase coinfections). For these data, all e-records on hospitalized COVID-19 patients included in the study retrospectively were reviewed thoroughly. Clinical COVID-19 data referred to for direct involvement and confirmation on comorbidities of survivors or on death records included but were not limited to records of chest X-ray (CXR) used for pulmonary involvement and lung abnormalities related to COVID-19, noninvasive ventilation procedures, intubations and mechanical ventilations, hematology records, and lowest absolute lymphocyte count (LALC). Significance of comorbidity per se on patient outcomes was determined from overall groups of noncoinfecting patients. Since most comorbidities are risks for other related disorders as well as for coinfections, selections were made for comorbid patients with single comorbidity to independently assess the risk. However, recruitment for different comorbidity disorders was studied independently

according to the specific criteria mentioned above. For example, patients with unclear results were removed for analysis of outcomes for the disease. Differences in the following clinical management profiles were monitored for every case to understand any potential change in clinical manifestations.

## X-Ray (CXR)

For monitoring and scoring and disease progressions involving pulmonary in COVID-19, particularly in severe scenarios leading to poor outcomes, we used either portable or departmental devices as per Jacobi et al<sup>63,64</sup> along with PCR tests to designate test results as COVID-19-compatible.

## Oxygen

Supplemental oxygen using noninvasive ventilation procedures were supplied to those with signs of severe respiratory distress or hypoxemia (ie, SpO<sub>2</sub> <90%). Initial oxygen therapy was used at 5 L/min and titrated to SpO<sub>2</sub> ≥90%. If no improvement was seen, high oxygen flows (10–15 or 50–60 L/min) were delivered through a face mask with a reservoir bag to reach a higher concentration of oxygen as per Nava et al<sup>65</sup> and Keenan et al.<sup>66</sup> Oxygenation-intervention strategies usually progress from simple to aggressive: first, a nasal canula (~4 L), then a simple face mask (~10 L), followed by a non-Rebreather mask (~15 L). Noninvasive medical ventilations for high flow included high-flow nasal canula (100 L) or bilevel positive airway pressure (BiPAP). Often, tracheal intubation for high oxygen was required.

## Intubation

Mechanical ventilations were performed on patients with breathing problems or hypoxemia during noninvasive ventilation. An endotracheal tube or tracheostomy was performed by an ICU expert according to the NIH NHLBI ARDS Clinical Network's mechanical ventilation protocol card, available at <http://www.ardsnet.org/system/files/Ventilator%20Protocol%20Card.pdf> (accessed on 5 December 2021).

## Lowest Absolute Lymphocyte Count (LALC)

Since lymphopenia, generally described as a low lymphocyte count, is associated with patients with COVID-19 and disease severity, LALC rates were determined as per Fan et al<sup>67</sup> and Kaushansky et al.<sup>68</sup>

## Statistical Analysis

In this study, independent variables were comorbidities and treatment protocols for three antiviral groups, while the dependent variables were deaths and survival rates. This research was based on a multivariate analysis: two variables were each composed of several subvariables. Statistical analysis was carried out using SPSS 23.0 for Windows. This study was descriptive and stratified: we present absolute numbers and graphical distributions. We conducted  $\chi^2$  statistical tests for proportions, where  $P < 0.05$  was considered statistically significant.

## Results

In this study, we independently examined the influence of different comorbidities on the outcomes of COVID-19 patients (Table 1). We also carried out comparative analysis on the response of these patients to the three medications: hydroxychloroquine (Hcq), favipiravir, and dexamethasone, either alone or in combinations versus standard care (Table 2). To understand the effect(s) of a specific comorbidity, we screened 750 patients and grouped them into comorbidity groups. All nonsurvivors died in the ICU with similar clinical characteristics. These mostly senior patients remained typically positive for COVID-19 on repeated testing with PCR, and showed COVID-19-compatible symptoms, such as CXR and higher oxygen requirements (mostly >4–8 L) through invasive intubation, low hematology counts, including low lymphocytes, and low LALC, (mostly <5). The highest reported comorbidity (40%, n=299) among the 750 COVID-19 patients screened was diabetes. We selected these cases to separately understand its influence on the outcomes. Figure 1A shows the death and recovery rates among diabetic and nondiabetic patients with COVID-19. The COVID-19 case-fatality rate (CFR) among selected diabetic patients was 14% (n=42 of 299) and in nondiabetics was 7%. We found a significant association between the diabetics and CFR among COVID-19 patients ( $P=0.001$ ).



**Table 1** Frequency and case–fatality rates among COVID-19 patients with underlying comorbidities

	Patients studied	CFR among patients with comorbidity	CFR g patients without the comorbidity	P	Association
<b>Diabetes</b>	299 (40%)	14%	6.7%	0.001	Highly significant
<b>Hypertension</b>	221 (29.47%)	15.4%	7.2%	0.0006167	Highly significant
<b>Heart failure</b>	30 (4%)	40%	8.3%	0.00000534	Highly significant
<b>Ischemic heart disease</b>	74 (10.57%)	12.2%	10%	0.27097	Not significant
<b>Chronic kidney disease</b>	27 (3.6%)	33.3%	8.7%	0.00048	Highly significant

**Table 2** Comparative response analysis and associations of COVID-19 case–fatality rates to hydroxychloroquine (Hcq), favipiravir (Favi), and dexamethasone (Dexa) treatments

	n	Patients who took	CFR in those who took	CFR in Those who Did not Take	P-value=	Association			
Hcq	750	345 (46%)	4.10%	14.30%	$1.98^{-7}$	Highly significant			
Favi	750	128 (17.1%)	24.22%	6.59%	$7^{-10}$	Highly significant			
Dexa	750	244 (32.5%)	22.95%	2.69%	$7^{-10}$	Highly significant			
Case–fatality rates among patients who took one or different combinations of Hcq, Favi, and Dexa									
n	Took any of the three								
		Standard care	Hcq alone	Favi alone	Dexa alone	Hcq + Dexa	Favi + Dexa	Took all three	Association (highly significant)
750	480 (64%)	4.07%	0.48%	25.00%	38.46%	8.99%	35.38%	13.16%	$P=4.28^{-26}$

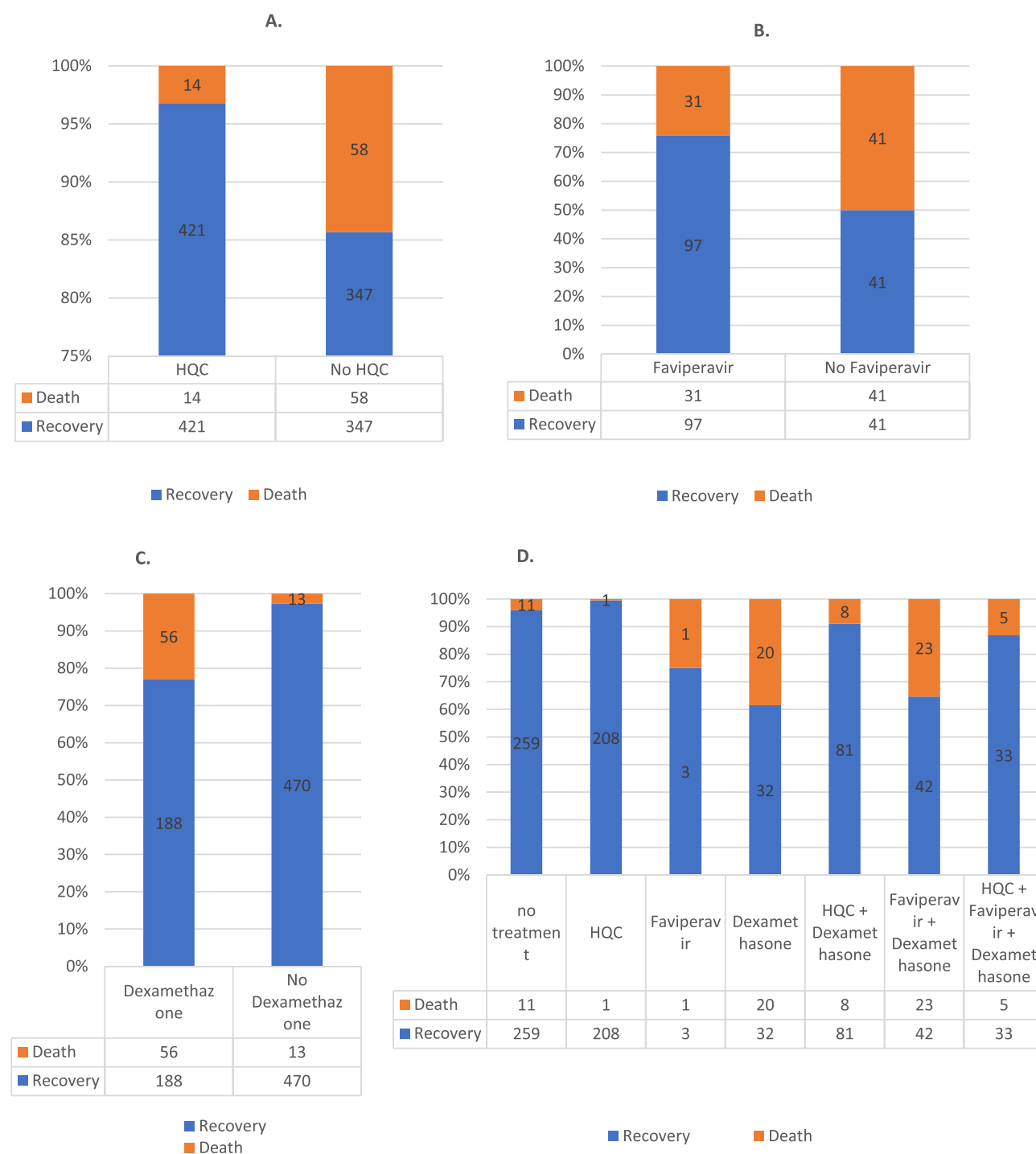
Hypertension (Htn) was the second–most prevalent comorbidity identified. We found that 29.5% (n=221) of 750 patients were hypertensive. The recovery and death rates are shown in [Figure 1B](#). The CFR among patients with hypertension was 15% and in those without the disease it was 7%. Similarly to diabetes outcomes, there was a significant association between Htn and CFR in those patients ( $P=0.0006167$ ).

The third consecutive comorbidity was heart failure (HF). Only 4% (n=30) of the 750 patients with COVID-19 had HF. However, the CFR among COVID-19 patients with HF was 40% compared to only 8% for those without HF. There was a highly significant association between HF and CFR in these patients. [Figure 1C](#) shows the recovery and death rates among patients with and without HF. Ischemic heart disease (IHD) was the fourth–most prevalent comorbidity: 74 (11%) patients. The CFR among patient with IHD was 12%, and in those without IHD it was 9%. [Figure 1D](#) shows the death and recovery rates among COVID-19 patients with and without IHD. However, there was no significant association between the disease and COVID-19 CFR in this study. In addition, 27 (4%) of COVID-19 patients had CKD. The COVID-19 CFR among those with CKD was 33%, while CFR was only 9% among other patients without CKD ([Figure 1E](#)). There was a significant association between the CKD and COVID-19 CFRs in this study ( $P=0.00048$ ).

The sample of patients with CLD was very small (n=3). The CFR was 0.4% in those with CLD and 33% in patients without CLD. However, there was no significant association between the disease and COVID-19 CFR ( $P=0.26155$ ) due to the small sample. Similarly, 10 (1%) patients had a history of smoking; however, the CFR for these patients was 10% and for those without a history of smoking also 10%. There was no significant association between the COVID-19 CFR and smoking, mostly because of the small sample of patients with a history of smoking.



**Figure 1** (A) Recovery and death rates among hospitalized diabetic and nondiabetic COVID-19 patients. (B) Recovery and death rates among hospitalized hypertensive and nonhypertensive COVID-19 patients. (C) Recovery and death rates among hospitalized COVID-19 patients with and without history of heart failure. (D) Recovery and death rates among hospitalized COVID-19 patients with and without ischemic heart disease. (E) Recovery and death rates among hospitalized COVID-19 patients with and without chronic kidney disease.



**Figure 2** (A) Recovery and death rates among hospitalized COVID-19 patients treated and not treated with hydroxychloroquine. (B) Recovery and death rates among hospitalized COVID-19 patients treated and not treated with favipiravir. (C) Recovery and death rates among hospitalized COVID-19 patients treated and not treated with dexamethasone. (D) Recovery and death rates among hospitalized COVID-19 patients who received one drug, two drugs, or different combinations of treatments.

As shown in Table 2, 46% (n=345) were treated with hydroxychloroquine, in whom a CFR of 4% was obtained compared to 14.3% CFR in those who did not receive the medicine, a highly significant association ( $P=1.98^{-6}$ , Figure 2A). However, even though only 17% of patients (n=128) received favipiravir treatment (Figure 2B), the CFR in this group was threefold (24.22%) that of those who did not take the drug (6.59%;  $P=7^{-10}$ ). Similarly, among the 244 (32.5%) patients who were administered dexamethasone (Figure 2C), the CFR of 22.95% was the highest compared to all other drugs used, while a CFR



of only 2.69% was obtained in those who did not receive dexamethasone. For the aforementioned drug, a rate of association was indicated by the same was similar to that of favipiravir ( $P=7^{-10}$ ). However, when the total number of patients who took any of the three drugs (64%,  $n=480$ ) was used for case–fatality rates among the treatment groups (Figure 2D), the following responses were found. The CFR rates were 4%, 0.5%, 25%, 38.5%, 9%, 35.4%, and 13% for those who did not take any drug or who took hydroxychloroquine alone, favipiravir alone, dexamethasone alone, hydroxychloroquine + dexamethasone, favipiravir + dexamethasone, or who took all three drugs, respectively ( $P=4.28^{-26}$ ).

## Discussion

Although an epidemic of comorbidities is uniquely associated with different populations in different places, the significance and underlying mechanisms of their association with infectious diseases is still poorly reported. The globally devastating and one of the fastest-growing comorbidities is diabetes, which is projected to affect nearly 7 million adults by 2045. How the disease is associated with cardiovascular and microvascular complications is still not clearly defined in different populations. Most efforts are focused on monitoring risk factors and glycaemic control that cannot predict the development of vascular complications. This significant gap in research would potentially be closed by subsequent genome-wide studies built on solid foundations, such as the present study. Here, we report new evidence of the high prevalence of diabetes (299/750) in Ha'il and its significant positive association in aggravating COVID-19 CFR. Recent theoretical studies revealed elevated blood glucose as the key facilitator in the progression of COVID-19 by enabling increased immunoevasion, aggressive invasion, and cytokine storm.<sup>69</sup> Since the disease is one of the most epidemic comorbidities in the region, this study would help in the development of intensive monitoring approaches. Reports from different countries identified different outcomes regarding the influence of diabetes. For instance, among 66 Chinese patients classified into severe and nonsevere groups, 22 were diabetic, seven of which had severe COVID-19, significantly higher than that in the nondiabetes group (four of 44, 9.09%;  $P=0.033$ ). Furthermore, a meta-analysis confirmed this positive association (pooled OR 2.58, 95% CI 1.93–3.45).<sup>70</sup> Nevertheless, given the known association between this comorbidity and the genetic population structure, regional studies on large samples specific to local populations are imperative for objective monitoring.<sup>71–73</sup>

Htn (29.5%) was second to diabetes in the group of identified comorbidity with fatal outcomes in COVID-19 patients in this region. The significant association ( $P=0.0006167$ ) between Htn and CFR in those patients makes it another emerging risk for contraction of infectious disease. The increase in COVID-19 fatality by >50% in hypertensive patients is worrisome. The significant association of Htn and related disorders in COVID fatality is consistent with the growing knowledge on the influence of genetic coregulations of key determinants, such as ACE2, MAS receptor, and RAAS pathways.<sup>74–76</sup> However, the interplay between mosaic coregulators in Htn is revealed in a complex multifactorial manifestation of a sequelae of cardiovascular diseases, such as stroke, coronary artery disease, and heart failure, causing 10.4 million deaths annually.<sup>75</sup> Therefore, Htn is a major risk factor in COVID-19; however, the exact mechanisms and how SARS-CoV-2 dysregulates the system is uncertain. This merits study for independently understanding the coexistence of closely related comorbidities under a COVID-19 background. Such information would advance the establishment of a solid foundation for subsequent downstream vertical studies.

Although only 4% of COVID-19 patients suffered HF, the COVID CFR among them was 40% compared to only 8% in those without HF, indicating a highly significant association between HF and CFR. This has been a global trend, with few explanations on the mechanisms underlying the specific associations.<sup>77–81</sup> Viral spread through the blood reaches mucosal linings, giving access to the lymphatic system and the bloodstream, where endothelial cells express levels of ACE2.<sup>82,83</sup> This route sheds the virus to the peripheral tissue and heart systems resulting in complications that cause stroke. However, there is a paucity of quality data on HF and COVID-19 for many geographic regions with discrete genetic population structures. For this, several studies have recommended investigating global profiles of independent prevalence rates of related cardiovascular disorders. In this context, association studies from genetically uniform populations, such as the present study, would give more insight into the mechanisms of HF under a COVID background. HF has among the largest effects on the mortality of elderly inpatients ( $P<0.001$ ) and those with comorbid asthma in major Saudi cities.<sup>84,85</sup> Similar studies from different regions with different epidemiological structures and related socioeconomic strata in the

predominantly uniform and young Saudi population would likely reveal important information. For instance, Africans were the highest in studies on myocardial gene signatures involved in HF, with high coprevalence.<sup>86,87</sup>

Ischemic heart disease (IHD) was the fourth prevalent comorbidity we found: 74 (10%) of the patients. The CFR among patients with IHD was 12%, and in those without IHD it was 9%; therefore, there was no significant association between the disease and COVID-19 CFR in this study. Since the exact mechanisms on the role of COVID-19 in the progression of stable coronary artery disease (CAD) to an acute state is not yet well understood, more attention to COVID-19 patients with stable CAD has been recommended.<sup>88</sup> There was a significant association between CKD and COVID-19 CFR ( $P=0.00048$ ): 33% and 9% in those with and without CKD, respectively. COVID-19 has been found to be frequently associated with AKI; however, this is an independent risk factor for mortality. AKI is potentially related to cytotoxicity as well as cytokine-related systemic reactions increasing the need for continuous renal replacement therapy.<sup>89</sup> A range 5%–15% of AKI cases have occurred during SARS-CoV-2 and MERS-CoV, causing an increased CFR of 60%–90%.<sup>90</sup> The mechanisms involved in kidney injury were not understood initially;<sup>91</sup> however, sepsis as a stimulator of cytokine-storm manifestations or leading to cellular injury due to the virus is known. Nevertheless, while reports on AKI are on the rise, COVID-19 impact on patients with underlying CKD has not yet been fully understood.<sup>89</sup> Therefore, from our findings we assume that the sepsis-induced cytokine-storm syndrome potentially explains AKI being associated with underlying cases of SARS-CoV-2 and microbial coinfections. In this study, the association of CFR with CLD was not significant. Unfortunately, data on CLD are limited globally due to a lack of full understanding of viral tropism in liver cells because of such difficulties as obtaining biopsy samples and the requirement for high-level laboratory-containment facilities. Attempts are being made to determine expression levels of TMPRSS2 and the paired basic amino acid-cleaving enzyme Furin. Despite the fact that TMPRSS2 and Furin have ranges in expression patterns in liver-cell types,<sup>92</sup> single-cell RNA sequencing data sets indicate very few hepatocytes coexpressed with ACE2 and TMPRSS2.<sup>93</sup>

The COVID-19 CFR in those who were prescribed hydroxychloroquine was much lower (4%) than those who took favipiravir (24.22%) and dexamethasone (23%). Conversely, the CFR was higher in those who did not take Hcq (14%), but much lower in those who were not prescribed favipiravir (7%) or dexamethasone (3%). Despite significant controversies on drug toxicity and safety, these findings are consistent with several studies indicating lower mortality-related low-dose Hcq in hospitalized COVID-19 patients diagnosed and treated early or later after symptom onset.<sup>94</sup> This is in agreement with a large-scale meta analysis of 25 cohort studies ( $n=41,339$  patients) and 11 randomized clinical trials ( $n=8709$ ) concluding that Hcq was not associated with mortality in COVID-19 patients.<sup>95</sup> The record of Hcq, in the treatment of malaria and inflammatory disease, including systemic lupus erythematosus and rheumatoid arthritis, shows favorable safety profile.<sup>96</sup> In fact, both CQ and Hcq are permitted by the World Health Organization (WHO) for potential repurposing. Starting with a “low-dose” regimen of Hcq sulfate in monotherapy (400 mg twice on day 1, followed by 200 mg twice a day from days 2 to 5, ie, a total dose of 2400 mg) was recommended for hospitalized COVID-19 patients.<sup>97</sup> Despite the satisfactory performance of Hcq in COVID-19 patients, this could be challenged by expectations of side effect(s) in the long run. Many recommendations call for additional studies from different geographic regions with different population genetic structures, since there is no precise statement on the efficacy or safety of the drug at any time in the course of COVID-19 treatment.<sup>98</sup> Intense debates and constructive criticisms have been raised. For instance, while many satisfactory responses have been summarized, the major mechanisms, pharmacokinetics, therapeutic applications, and safety profiles of the immunomodulatory and antiviral drug,<sup>53</sup> have called into question the safety and mechanism of action of the drug.<sup>53</sup> Nevertheless, the main issue that undermined the primary mode of action of the drug was essentially the wide variability in pharmacokinetics between patients, which made it difficult to achieve adequate target-tissue concentrations without unacceptable toxicities. The major factors influencing patient variability in response to the drug were clinical outcome and length of stay<sup>54</sup> and several drug–gene variant pairs that are prone to altering pharmacokinetics.<sup>55,56</sup> Therefore, more similar studies from different countries are required to adequately assess the therapeutic applications of these drugs in COVID-19.

Similar favipiravir and dexamethasone COVID-19 CFRs were found in this study for favipiravir (24.22%) and dexamethasone (23%), and those who did not take the medicines (favipiravir 7%, dexamethasone 3%), consistent with other regional studies in Saudi Arabia. For instance, although favipiravir treatment has been reported to be safe in

moderate COVID, viral clearance was insignificant and there was no superior therapeutic utility over other medications used.<sup>99–103</sup> This was also the case in major studies from different countries.<sup>104</sup> However, in addition to genetic variations and pharmacokinetics, these findings primarily dictate the dose, stage of the disease, and critical care conditions of the patients. Despite the fact that dexamethasone appears as an attractive anti-inflammatory drug, it did not show a superior performance in this study. However, the drug has revealed promising molecular mechanisms in modulating immature neutrophils and interferon programming in severe COVID-19, obtained by experimental models and single-cell transcriptomics.<sup>105,106</sup> Therefore, we share the common notion that more studies on different disease stages, host conditions, and viral dynamics would potentially reveal more insights into the circumstances where adequate therapeutic applications and drug choice are attained.

## Conclusion

In this comprehensive study, we found independent correlations of major comorbidities with the COVID-19 CFR in this region. The highest prevalence of diabetes as the major comorbidity in the region followed by hypertension and their highly significant independent association with CFR is worrisome. More importantly, the independent association of all comorbidities with COVID-19 fatality strongly implies the existence of a common mechanism of virulence aggravation stimulated by any of these. In addition, the superior performance of low-dose hydroxychloroquine and standard care, either alone or in combination, over other antivirals used in this study warrants further vertical studies on specific host–pathogen pharmacokinetics and population genetic structural variabilities on susceptibility. The limitations of the study include the unavailability of larger or significant data sets on other antiviral treatments that would have given more insights. In addition, large-scale investigations using national and regional hospital experiences may have added more clues regarding the response of comorbid patients to COVID-19.

## Data Sharing

All data are included in the paper.

## Ethics Approval and Institutional Review Board Statement

Standard guidelines were followed during this research according to the IRB protocols. This study complied with the Declaration of Helsinki. This study was reviewed and approved by the Research Ethics Committee at the University of Ha'il, dated October 22, 2020 and endorsed by University President letter 13675/5/42, 08/03/1441 H; for Deanship Project RG20064, H-2020-187. The KACST Institutional Review Board (IRB) registration numbers are H-8-L-074 IRB log 2021-11. The KACST IRB also approved the study.

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

## Acknowledgment

This research was funded by the Scientific Research Deanship at the University of Ha'il, Saudi Arabia through the project number RG20064. Ha'il College of Medicine (COM) Research Unit is a research-intensive hub that co-ordinates and houses advanced research initiatives.

## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest of any type.

## References

1. Umakanthan S, Sahu P, Ranade AV, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). *Postgrad Med J*. 2020;96(1142):753–758. doi:10.1136/POSTGRADMEDJ-2020-138234
2. Umakanthan S, Patil S, Subramaniam N, Sharma R. COVID-19 vaccine hesitancy and resistance in India explored through a population-based longitudinal survey. *Vaccines*. 2021;9(10):1064. doi:10.3390/VACCINES9101064/S1
3. Umakanthan S, Bukelo MM, Gajula SS. The Commonwealth Caribbean COVID-19: regions Resilient Pathway During Pandemic. *Front Public Health*. 2022;10:1288. doi:10.3389/FPUBH.2022.844333/BIBTEX
4. Umakanthan S, Lawrence S. Predictors of COVID-19 vaccine hesitancy in Germany: a cross-sectional, population-based study. *Postgrad Med J*. 2022;98:1164. doi:10.1136/POSTGRADMEDJ-2021-141365
5. Umakanthan S, Senthil S, John S, et al. The Effect of Statins on Clinical Outcome Among Hospitalized Patients With COVID-19: a Multi-Centric Cohort Study. *Front Pharmacol*. 2022;13:2558. doi:10.3389/FPHAR.2022.742273/BIBTEX
6. Thomas Glück M. Infection Risk with Corticosteroid Therapy. *NEJM J Watch*. 2016;2016:43. doi:10.1056/NEJM-JW.NA41557
7. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2021;106(5):429–439. doi:10.1136/ARCHDISCHILD-2020-320338
8. Fischer A. Resistance of children to Covid-19. How? *Mucosal Immunol*. 2020;13(4):563–565. doi:10.1038/s41385-020-0303-9
9. Chan Y, Fong S, Poh C, et al. Asymptomatic COVID-19: disease tolerance with efficient anti-viral immunity against SARS-CoV-2. *EMBO Mol Med*. 2021;13:6. doi:10.15252/EMMM.202114045
10. González-García N, Castilla-Peón MF, Solórzano Santos F, et al. Covid-19 Incidence and Mortality by Age Strata and Comorbidities in Mexico City: a Focus in the Pediatric Population. *Front Public Health*. 2021;9:1298. doi:10.3389/fpubh.2021.738423
11. Acharya D, Lee K, Lee DS, Lee YS, Moon SS. Mortality Rate and Predictors of Mortality in Hospitalized COVID-19 Patients with Diabetes. *Healthcare*. 2020;8(3):435. doi:10.3390/HEALTHCARE8030338
12. Rastad H, Karim H, Ejtahed HS, et al. Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease. *Diabetol Metab Syndr*. 2020;12:1. doi:10.1186/S13098-020-00565-9
13. Alguwaihes AM, Al-Sofiani ME, Megdad M, et al. Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study. *Cardiovasc Diabetol*. 2020;19(1):43. doi:10.1186/s12933-020-01184-4
14. Sheshah E, Sabico S, Albakr RM, et al. Prevalence of diabetes, management and outcomes among Covid-19 adult patients admitted in a specialized tertiary hospital in Riyadh, Saudi Arabia. *Diabetes Res Clin Pract*. 2021;172. doi:10.1016/J.DIABRES.2020.108538
15. Guo L, Shi Z, Zhang Y, et al. Comorbid diabetes and the risk of disease severity or death among 8807 COVID-19 patients in China: a meta-analysis. *Diabetes Res Clin Pract*. 2020;166. doi:10.1016/J.DIABRES.2020.108346
16. Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr*. 2020;14(4):535–545. doi:10.1016/J.DSX.2020.04.044
17. Miller LE, Bhattacharyya R, Miller AL. Diabetes mellitus increases the risk of hospital mortality in patients with Covid-19: systematic review with meta-analysis. *Medicine*. 2020;99(40):e22439. doi:10.1097/MD.00000000000022439
18. Shi Q, Zhang X, Jiang F, et al. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: a Two-Center, Retrospective Study. *Diabetes Care*. 2020;43(7):1382–1391. doi:10.2337/DC20-0598
19. Varikasuvu SR, Dutt N, Thangappazham B, Varshney S. Diabetes and COVID-19: a pooled analysis related to disease severity and mortality. *Prim Care Diabetes*. 2021;15(1):24–27. doi:10.1016/j.pcd.2020.08.015
20. Suleyman G, Fadel RA, Malette KM, et al. Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit. *JAMA Netw Open*. 2020;3(6):e2012270. doi:10.1001/JAMANETWORKOPEN.2020.12270
21. Hillson R. COVID-19: diabetes and death. A call to action. *Practical Diabetes*. 2020;37(3):76–78. doi:10.1002/PDI.2271
22. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol*. 2020;16(4):223–237. doi:10.1038/S41581-019-0244-2
23. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. doi:10.1016/S2213-2600(20)30116-8
24. Ma RCW, Holt RIG. COVID-19 and diabetes. *Diabet Med*. 2020;37(5):723–725. doi:10.1111/DME.14300
25. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst*. 2020;21:2. doi:10.1177/1470320320926899
26. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. *Am J Hypertens*. 2020;33(5):373–374. doi:10.1093/AJH/HPAA057
27. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368. doi:10.1136/BMJ.M1091
28. Libby P, Loscalzo J, Ridker PM, et al. Inflammation, Immunity, and Infection in Atherothrombosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2018;72(17):2071–2081. doi:10.1016/J.JACC.2018.08.1043
29. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in Hospitalized Patients With COVID-19 in a New York City Health System. *JAMA*. 2020;324(8):799–801. doi:10.1001/JAMA.2020.13372
30. Bangalore S, Sharma A, Slotwiner A, et al. ST-Segment Elevation in Patients with Covid-19 - A Case Series. *N Engl J Med*. 2020;382(25):2478–2480. doi:10.1056/NEJMC2009020
31. Modin D, Claggett B, Sindet-Pedersen C, et al. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. *Circulation*. 2020;142(21):2080–2082. doi:10.1161/CIRCULATIONAHA.120.050809
32. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet*. 2021;398(10300):599–607. doi:10.1016/S0140-6736(21)00896-5
33. Team TNCPERE. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Wkly*. 2020;2(8):113.



34. Chow YW, Pietranico R, Mukerji A. Studies of oxygen binding energy to hemoglobin molecule. *Biochem Biophys Res Commun.* 1975;66(4):1424–1431. doi:10.1016/0006-291X(75)90518-5
35. Liang C, Zhang W, Li S, Qin G. Coronary heart disease and COVID-19: a meta-analysis. *Med Clin (Barc).* 2021;156(11):547–554. doi:10.1016/J.MEDCL.2020.12.017
36. Yonas E, Alwi I, Pranata R, et al. Effect of heart failure on the outcome of COVID-19 - A meta analysis and systematic review. *Am J Emerg Med.* 2021;46:204–211. doi:10.1016/J.AJEM.2020.07.009
37. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475–481. doi:10.1016/S2213-2600(20)30079-5
38. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020;97(5):829–838. doi:10.1016/J.KINT.2020.03.005
39. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. *Kidney Int.* 2020;97(5):824–828. doi:10.1016/J.KINT.2020.03.001
40. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, et al. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. *Kidney360.* 2020;1(7):614–622. doi:10.34067/KID.0002652020
41. Li Z, Wu M, Yao J, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. *SSRN Electronic J.* 2020. doi:10.2139/SSRN.3559601
42. Shi Q, Zhao K, Yu J, et al. Clinical characteristics of 101 COVID-19 nonsurvivors in Wuhan, China: a retrospective study. *medRxiv.* 2020. doi:10.1101/2020.03.04.20031039
43. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020;97(5):829. doi:10.1016/J.KINT.2020.03.005
44. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA.* 2020;323(16):1612–1614. doi:10.1001/JAMA.2020.4326
45. Li Z, Wu M, Yao J, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. *SSRN Electronic J.* 2020. doi:10.2139/SSRN.3559601
46. Pan X, Xu D, Zhang H, Zhou W. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. *Intensive Care Med.* 2020;46(6):1114–1116. doi:10.1007/S00134-020-06026-1
47. Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology.* 2004;39(2):302–310. doi:10.1002/HEP.20111
48. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507–513. doi:10.1016/S0140-6736(20)30211-7
49. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis.* 2020;71(15):769–777. doi:10.1093/CID/CIAA272
50. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy.* 2020;75(7):1742–1752. doi:10.1111/ALL.14309
51. Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 cases of death from COVID-19. *PLoS One.* 2020;15:7. doi:10.1371/JOURNAL.PONE.0235458
52. Mallet V, Beeker N, Bouam S, et al. Prognosis of French COVID-19 patients with chronic liver disease: a national retrospective cohort study for 2020. *J Hepatol.* 2021;75(4):848–855. doi:10.1016/J.JHEP.2021.04.052
53. Udupa A, Leverenz D, Balevic SJ, Sadun RE, Tarrant TK, Rogers JL. Hydroxychloroquine and COVID-19: a Rheumatologist's Take on the Lessons Learned. *Curr Allergy Asthma Rep.* 2021;21:1. doi:10.1007/S11882-020-00983-9
54. Alvarez JC, Davido B, Moine P, et al. Population Pharmacokinetics of Hydroxychloroquine and 3 Metabolites in COVID-19 Patients and Pharmacokinetic/Pharmacodynamic Application. *Pharmaceuticals.* 2022;15(2):256. doi:10.3390/PH15020256/S1
55. Giudicessi JR, Roden DM, Wilde AAM, Ackerman MJ. Genetic susceptibility for COVID-19-associated sudden cardiac death in African Americans. *Heart Rhythm.* 2020;17(9):1487–1492. doi:10.1016/J.HRTHM.2020.04.045
56. Takahashi T, Luzum JA, Nicol MR, Jacobson PA. Pharmacogenomics of COVID-19 therapies. *NPJ Genomic Med.* 2020;5(1):35. doi:10.1038/s41525-020-00143-y
57. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: a Simplified Summary. *Drug Res.* 2021;71(3):166–170. doi:10.1055/A-1296-7935/ID/R2020-09-2140-0029
58. Kurt Y, Özmen Ö. Effects of Vitamin C on the Oral-Nasal Mucosal Damage Caused by Favipiravir in Old and Young Rats. *Cureus.* 2022;14:9. doi:10.7759/CUREUS.28796
59. Hashemian SMR, Farhadi T, Velayati AA. A review on favipiravir: the properties, function, and usefulness to treat COVID-19. *Expert Rev Anti Infect Ther.* 2021;19(8):1029–1037. doi:10.1080/14787210.2021.1866545
60. Halpin DMG, Criner GJ, Papi A, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2021;203(1):24–36. doi:10.1164/RCCM.202009-3533SO
61. Pinzón MA, Ortiz S, Holguín H, et al. Dexamethasone vs methylprednisolone high dose for Covid-19 pneumonia. *PLoS One.* 2021;16:5. doi:10.1371/JOURNAL.PONE.0252057
62. Li J, Liao X, Zhou Y, et al. Comparison of Associations Between Glucocorticoids Treatment and Mortality in COVID-19 Patients and SARS Patients: a Systematic Review and Meta-Analysis. *Shock.* 2021;56(2):215–228. doi:10.1097/SHK.0000000000001738
63. Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): a pictorial review. *Clin Imaging.* 2020;64:35–42. doi:10.1016/J.CLINIMAG.2020.04.001
64. Borghesi A, Maroldi R. COVID-19 outbreak in Italy: experimental chest X-ray scoring system for quantifying and monitoring disease progression. *Radiol Med.* 2020;125(5):509–513. doi:10.1007/S11547-020-01200-3
65. Nava S, Schreiber A, Domenighetti G. Noninvasive ventilation for patients with acute lung injury or acute respiratory distress syndrome. *Respir Care.* 2011;56(10):1583–1588. doi:10.4187/RESPCARE.01209
66. Keenan SP, Sinuff T, Burns KEA, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ.* 2011;183:3. doi:10.1503/CMAJ.100071

67. Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol*. 2020;95(6):E131–E134. doi:10.1002/AJH.25774
68. Kaushansky. Williams Hematology, 9e | accessMedicine | mcGraw Hill Medical. Williams Hematology, 9e Eds. Kenneth Kaushansky, et al. McGraw Hill; 2015. Available from: <https://accessmedicine.mhmedical.com/book.aspx?bookid=1581&isMissingChapter=true>. Accessed December 5, 2021.
69. Logette E, Lorin C, Favreau C, et al. A Machine-Generated View of the Role of Blood Glucose Levels in the Severity of COVID-19. *Front Public Health*. 2021;9:695139. doi:10.3389/FPUH.2021.695139/FULL
70. Wu J, Zhang J, Sun X, et al. Influence of diabetes mellitus on the severity and fatality of SARS-CoV-2 (COVID-19) infection. *Diabetes Obes Metab*. 2020;22(10):1907–1914. doi:10.1111/DOM.14105
71. Abu-Farha M, Al-Mulla F, Thanaraj TA, et al. Impact of Diabetes in Patients Diagnosed With COVID-19. *Front Immunol*. 2020;11. doi:10.3389/FIMMU.2020.576818
72. Roganović J. Downregulation of microRNA-146a in diabetes, obesity and hypertension may contribute to severe COVID-19. *Med Hypotheses*. 2021;146. doi:10.1016/J.MEHY.2020.110448
73. van Niekerk G, van der Merwe M, Engelbrecht AM. Diabetes and susceptibility to infections: implication for COVID-19. *Immunology*. 2021;164(3):467–475. doi:10.1111/IMM.13383
74. Perez A, Naljayam M, Shuja I, Florea A, Reisin E. Hypertension, Obesity, and COVID-19: a Collision of Pandemics. *Curr Hypertens Rep*. 2021;23(6). doi:10.1007/S11906-021-01153-6
75. Ravichandran B, Grimm D, Krüger M, Kopp S, Infanger M, Wehland M. SARS-CoV-2 and hypertension. *Physiol Rep*. 2021;9(11). doi:10.14814/PHY2.14800
76. Augustine R, Nayeem SA, et al. Increased complications of COVID-19 in people with cardiovascular disease: role of the renin-angiotensin-aldosterone system (RAAS) dysregulation. *Chem Biol Interact*. 2022;351. doi:10.1016/J.CBI.2021.109738
77. Cowie MR, Mourilhe-Rocha R, Chang HY, et al. The impact of the COVID-19 pandemic on heart failure management: global experience of the OPTIMIZE Heart Failure Care network. *Int J Cardiol*. 2022;363:240–246. doi:10.1016/J.IJCARD.2022.06.022
78. Prabhakaran D, Singh K, Kondal D, et al. Cardiovascular Risk Factors and Clinical Outcomes among Patients Hospitalized with COVID-19: findings from the World Heart Federation COVID-19 Study. *Glob Heart*. 2022;17:1. doi:10.5334/GH.1128
79. Dan S, Pant M, Upadhyay SK. The Case Fatality Rate in COVID-19 Patients With Cardiovascular Disease: global Health Challenge and Paradigm in the Current Pandemic. *Curr Pharmacol Rep*. 2020;6(6):315–324. doi:10.1007/S40495-020-00239-0
80. Ruge M, Gomez JMD. Impact of pre-existing heart failure on 60-day outcomes in patients hospitalized with COVID-19. *Am Heart j Plus*. 2021;4:100022. doi:10.1016/J.AHJO.2021.100022
81. Babapoor-Farrokhran S, Alzubi J, Port Z, et al. Impact of COVID-19 on Heart Failure Hospitalizations. *SN Compr Clin Med*. 2021;3(10):2088–2092. doi:10.1007/S42399-021-01005-Z
82. Desforges M, Le Coupandec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. *Virus Res*. 2014;194:145–158. doi:10.1016/J.VIRUSRES.2014.09.011
83. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. *Lancet*. 2020;395(10234):1417–1418. doi:10.1016/S0140-6736(20)30937-5
84. Al-Ghamdi MA, Al-Raddadi RM, Ramadan IK, et al. Survival, mortality, and related comorbidities among COVID-19 patients in Saudi Arabia: a hospital-based retrospective cohort study. *Saudi Med J*. 2022;43(8):915–926. doi:10.15537/SMJ.2022.43.8.20220182
85. Aljuaid M, Alotair H, Alnajjar F, et al. Risk factors associated with in-hospital mortality patients with COVID-19 in Saudi Arabia. *PLoS One*. 2022;17(6):e0270062. doi:10.1371/JOURNAL.PONE.0270062
86. Hahn VS, Knutsdottir H, Luo X, et al. Myocardial Gene Expression Signatures in Human Heart Failure With Preserved Ejection Fraction. *Circulation*. 2021;143(2):120–134. doi:10.1161/CIRCULATIONAHA.120.050498
87. Manolis AS, Manolis AA, Manolis TA, Melita H. Sudden death in heart failure with preserved ejection fraction and beyond: an elusive target. *Heart Fail Rev*. 2019;24(6):847–866. doi:10.1007/S10741-019-09804-2
88. Shafeghat M, Aminorroaya A, Rezaei N. How Stable Ischemic Heart Disease Leads to Acute Coronary Syndrome in COVID-19? *Acta Biomed*. 2021;92(5):65. doi:10.23750/ABM.V92I5.12013
89. Adapa S, Chenna A, Balla M, et al. COVID-19 Pandemic Causing Acute Kidney Injury and Impact on Patients With Chronic Kidney Disease and Renal Transplantation. *J Clin Med Res*. 2020;12(6):352–361. doi:10.14740/JOCMR4200
90. Naicker S, Yang CW, Hwang SJ, Liu BC, Chen JH, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. *Kidney Int*. 2020;97(5):824. doi:10.1016/J.KINT.2020.03.001
91. Ma Y, Diao B, Lv X, et al. 2019 novel coronavirus disease in hemodialysis (HD) patients: report from one HD center in Wuhan, China. *medRxiv*. 2020. doi:10.1101/2020.02.24.20027201
92. Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: putative mechanisms of liver involvement in COVID-19. *Liver Int*. 2020;40(8):2038–2040. doi:10.1111/LIV.14500
93. De Smet V, Verhulst S, van Grunsven LA. Single cell RNA sequencing analysis did not predict hepatocyte infection by SARS-CoV-2. *J Hepatol*. 2020;73(4):993–995. doi:10.1016/J.JHEP.2020.05.030
94. Catteau L, Dauby N, Montourcy M, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. *Int J Antimicrob Agents*. 2020;56(4):106144. doi:10.1016/J.IJANTIMICAG.2020.106144
95. Di Castelnuovo A, Costanzo S, Cassone A, Cauda R, De Gaetano G, Iacoviello L. Hydroxychloroquine and mortality in COVID-19 patients: a systematic review and a meta-analysis of observational studies and randomized controlled trials. *Pathog Glob Health*. 2021;115(7–8):456–466. doi:10.1080/20477724.2021.1936818
96. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol*. 2020;16(3):155–166. doi:10.1038/S41584-020-0372-X
97. Task Force Therapeutics Viral Disease. Interim Clinical Guidance for Adults with Confirmed COVID-19, Belgium 2022. Available from: [https://kce.fgov.be/sites/default/files/2023-03/COVID-19\\_InterimGuidelines\\_Treatment\\_ENG.pdf](https://kce.fgov.be/sites/default/files/2023-03/COVID-19_InterimGuidelines_Treatment_ENG.pdf). Accessed April 29, 2023.
98. Boralli VB. COVID-19 Pandemic-A Narrative Review of the Potential Roles of Chloroquine and Hydroxychloroquine. Available from: <http://www.prisma-statement.org>. Accessed November 30, 2022.



99. Almoosa Z, Saad M, Qara S, et al. Favipiravir versus standard of care in patients with severe COVID-19 infections: a retrospective comparative study. *J Infect Public Health*. 2021;14(9):1247. doi:10.1016/J.JIPH.2021.08.022
100. Bosaeed M, Alharbi A, Mahmoud E, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. *Clin Microbiol Infection*. 2022;28(4):602. doi:10.1016/J.CMI.2021.12.026
101. Mutair A, Shamou J, Alhumaid S, et al. Overview of clinical outcome and therapeutic effectiveness of Favipiravir in patients with COVID-19 admitted to intensive care unit, Riyadh, Saudi Arabia. *J Infect Public Health*. 2022;15(4):389. doi:10.1016/J.JIPH.2022.01.013
102. Al-Muhsen S, Al-Numair NS, Saheb Sharif-Askari N, et al. Favipiravir Effectiveness and Safety in Hospitalized Moderate-Severe COVID-19 Patients: observational Prospective Multicenter Investigation in Saudi Arabia. *Front Med*. 2022;9:826247. doi:10.3389/FMED.2022.826247
103. AlQahtani M, Kumar N, Aljawder D, et al. Randomized controlled trial of favipiravir, hydroxychloroquine, and standard care in patients with mild/moderate COVID-19 disease. *Sci Rep*. 2022;12(1):4925. doi:10.1038/S41598-022-08794-W
104. Özlüsen B, Kozan Ş, Akcan RE, et al. Effectiveness of favipiravir in COVID-19: a live systematic review. *Eur J Clin Microbiol Infectious Dis*. 2021;40(12):2575. doi:10.1007/S10096-021-04307-1
105. Sinha S, Rosin NL, Arora R, et al. Dexamethasone modulates immature neutrophils and interferon programming in severe COVID-19. *Nat Med*. 2022;28(1):201. doi:10.1038/S41591-021-01576-3
106. Wyler E, Adler JM, Eschke K, et al. Key benefits of dexamethasone and antibody treatment in COVID-19 hamster models revealed by single-cell transcriptomics. *Molecular Therapy*. 2022;30(5):1952. doi:10.1016/J.YMTHE.2022.03.014

## Journal of Multidisciplinary Healthcare

Dovepress

### Publish your work in this journal

The Journal of Multidisciplinary Healthcare is an international, peer-reviewed open-access journal that aims to represent and publish research in healthcare areas delivered by practitioners of different disciplines. This includes studies and reviews conducted by multidisciplinary teams as well as research which evaluates the results or conduct of such teams or healthcare processes in general. The journal covers a very wide range of areas and welcomes submissions from practitioners at all levels, from all over the world. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-inflammation-research-journal>