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ORIGINAL RESEARCH

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

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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–^{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

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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.[1] 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.[2] 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.[3] 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.[4] 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.[5] 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.[6]

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,[7–10] 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.[11–15] 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.[16] 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.[17] 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,[13] with the former group generally experiencing worse clinical symptoms and metabolic profiles in many reports.[18,19] Nevertheless, no correlation of diabetes with mortality was found after consideration of several factors and other preexisting conditions, such as age, sex, BMI, HbA_{1c}, fasting, and random blood glucose on admission.[13] These findings indicated the multifactorial nature of diabetes and related disorders leading to mortality in COVID-19.[13] 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.[13,20] In the UK, preliminary data indicate that diabetes is the leading cause of death among patients of COVID-19 who die in hospitals.[21] 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.[13]

In 2010, around 31.1% of adults (1.39 billion) worldwide were hypertensive[22,23] 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[24,42] 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 myoglogin 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.[42,43] Since the known incidence range is very wide (0.7%–47.6%),[44,45] 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.[45,46] Therefore, it is imperative to objectively study comorbidities as independent variables underlying COVID-19 scenarios.[43,46] Viral hepatitis caused by a novel coronavirus has been reported.[47] 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.[48] Liver-function problems were mostly characterized as abnormal ALT or AST levels, with a minor increase in bilirubin levels. Wang et al[49] found that 23 patients (33%) had increased ALT and 19 (28%) raised AST in a study of 69 individuals. Similarly, Cai et al[50] 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%.[51] 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.[52]

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.[53] However, this success was not seen by many, which calls into question the mechanism of action of the drug.[53] Nevertheless, the central issue that undermined the drug's pH-related mode of action in endolysosomal alkalinization 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,[54] 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).[55,56] 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.[57] This is particularly important in age-dependent administration, where experimental studies have shown that favipiravir is age- and dose-dependent.[58] 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.[59] 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.[60] 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.[61] 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.[62]

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 ≥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 coinfected 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, ≤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 noncoinfected 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[63,64] 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_2 <90%). Initial oxygen therapy was used at 5 L/min and titrated to SpO_2 ≥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[65] and Keenan et al.[66] 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.pd (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[67] and Kaushansky et al.[68]

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 subvariates. 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 χ^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
Diabetes	299 (40%)	14%	6.7%	0.001	Highly significant
Hypertension	221 (29.47%)	15.4%	7.2%	0.0006167	Highly significant
Heart failure	30 (4%)	40%	8.3%	0.00000534	Highly significant
Ischemic heart disease	74 (10.57%)	12.2%	10%	0.27097	Not significant
Chronic kidney disease	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.

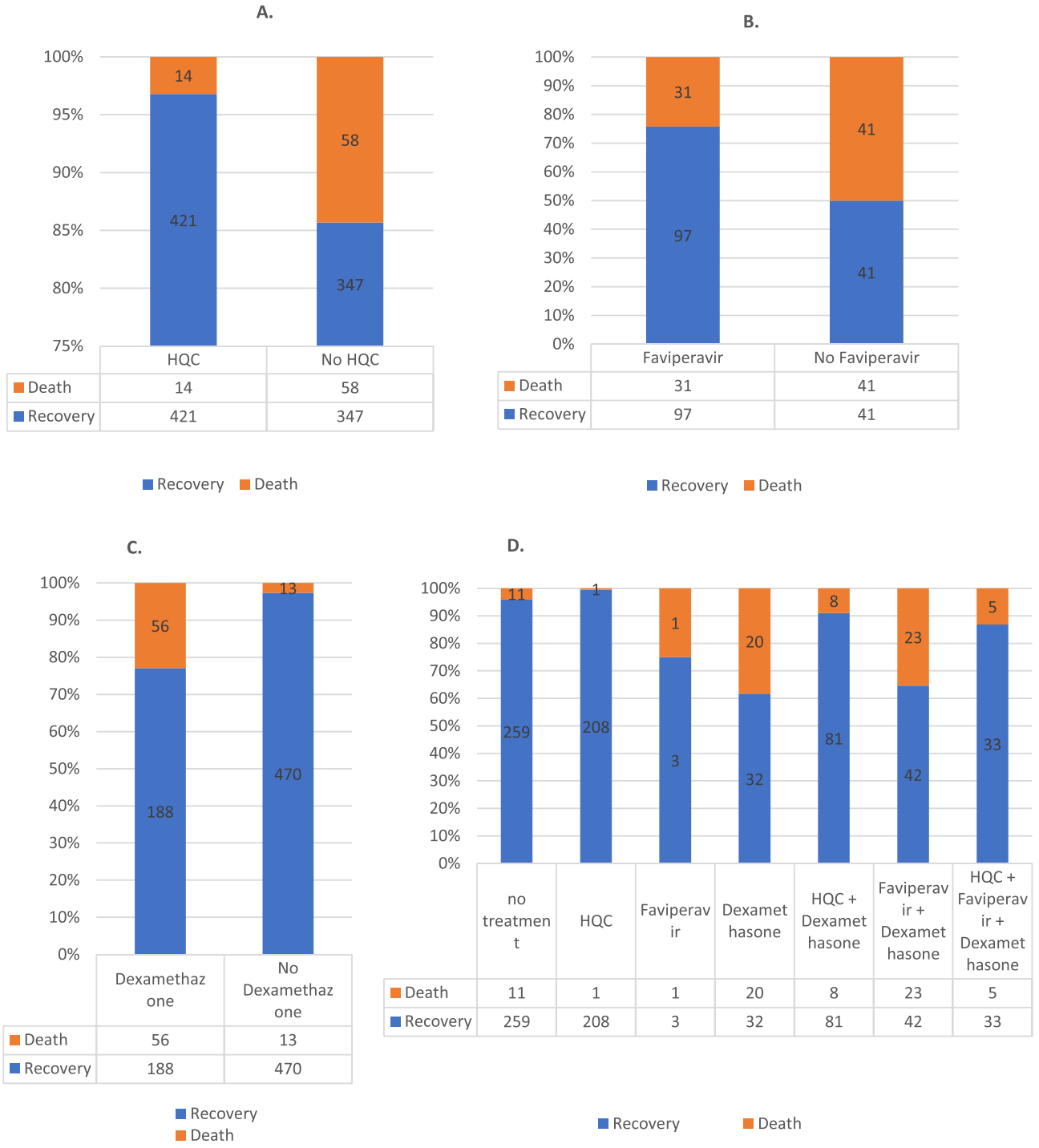

Figure 2 (**A**) Recovery and death rates among hospitalized COVID-19 patients treated and not treated with hydroxychloroquine. (**B**) Recovery and death rates among hospitalized COVID-19 patients treated and not treated with favipiravir. (**C**) Recovery and death rates among hospitalized COVID-19 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.[69] 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).[70] 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.[71–73]

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.[74–76] However, the interplay between mosaic coregulators in Htn is revealed in a complex multifactorial manifestation of a sequalae of cardiovascular diseases, such as stroke, coronary artery disease, and heart failure, causing 10.4 million deaths annually.[75] 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.[77–81] Viral spread through the blood reaches mucosal linings, giving access to the lymphatic system and the bloodstream, where endothelial cells express levels of ACE2.[82,83] 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.[84,85] 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.[86,87]

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.[88] 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 cytotropism as well as cytokine-related systemic reactions increasing the need for continuous renal replacement therapy.[89] A range 5%–15% of AKI cases have occurred during SARS-CoV-2 and MERS-CoV, causing an increased CFR of 60%–90%.[90] The mechanisms involved in kidney injury were not understood initially;[91] 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.[89] 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,[92] single-cell RNA sequencing data sets indicate very few hepatocytes coexpressed with ACE2 and TMPRSS2.[93]

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.[94] 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.[95] The record of Hcq, in the treatment of malaria and inflammatory disease, including systemic lupus erythematous and rheumatoid arthritis, shows favorable safety profile.[96] 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.[97] 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.[98] 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,[53] have called into question the safety and mechanism of action of the drug.[53] 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[54] and several drug–gene variant pairs that are prone to altering pharmacokinetics.[55,56] 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.[99–103] This was also the case in major studies from different countries.[104] 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 attrative 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.[105,106] 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.

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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.

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