Original article

Journal of INDEPENDENT MEDICINE

Low Rates of Hospitalization and Death in 4376 COVID-19 Patients Treated With Early Ambulatory Medical and Supportive Care: A Case Series and Observational Study

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Abstract

This study evaluates early ambulatory protocols for treating 4376 COVID-19 patients at All Valley Urgent Care (AVUC) facilities in Imperial County, California, and compares outcomes with other patients in the same region during a nearly identical period. The goal was to contribute to evidence on whether early outpatient treatment reduces hospitalization and mortality rates. The protocols, based on data from neighboring countries, included Protocol 1 (a multivitamin pack, selective use of hydroxychloroquine, two antibiotics, and inhaled steroids) and Protocol 2 (which added ivermectin). Results were stratified by disease severity at presentation. The average patient age was 40.5 years; 12.8% of patients were under 20 years old. For the 3962 mild COVID-19 patients treated early, no deaths occurred, compared to a 3.03% mortality rate (2.25% risk-adjusted) in the same county during the same period. Hospitalization rates for this group were 0.05%, compared to 22.68% (20.76% risk-adjusted) in the general population. When treated within 7 days, patients had a 100% success rate, while those treated later had a 99.9% success rate. Mild symptom patients had lower hospitalization (OR = 0.0293; P < .0001) and mortality (OR = 0.0000; P = .0008) rates. These results suggest the multidrug protocols significantly reduced adverse outcomes, with no serious side effects observed during follow-up (3–14 days).

Keywords: COVID-19, hospitalization, hydroxychloroquine, ivermectin, mortality, multidrug, SARS-CoV-2

Introduction

The SARS-CoV-2 infection (COVID-19) continues to spread across the United States, despite mass vaccination efforts using both new and established technologies. These efforts have proceeded without a publicly demonstrated cost-benefit analysis, while questions about short- and long-term safety remain. It may now be too late in the global response to achieve optimal results. (1) There are still no drugs or drug combinations specifically indicated in the United States for the ambulatory treatment of COVID-19 or its complications. Furthermore, no potentially conclusive randomized trials of early ambulatory multidrug therapy are currently in progress.

Although promising treatments were announced early in the pandemic (2, 3), often as multidrug therapeutic protocols administered as early as possible after symptom onset (4), these protocols have not been validated by the U.S. Food and Drug Administration or other major Western medical bodies, despite multiple randomized controlled trials suggest-

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ing effectiveness. (5) Numerous studies cited on the webpage *c19early.org* have reported the efficacy of hydroxychloroquine (HCQ) and ivermectin (IVM) in the outpatient treatment of mild COVID-19 patients, particularly those who could benefit from early ambulatory care. (6, 7) The use of HCQ in outpatient treatment protocols by doctors at AVUC, along with others in the United States and worldwide, provided the rationale for the treatments examined in this paper. Later, IVM was added as further evidence of its apparent efficacy emerged. (8) However, a substantial pool of often uncollected or unpublished data regarding these treatments remains (personal correspondence).

As with all serious medical conditions, there is a role for empiric treatment to reduce fatalities. (9) This study updates the totality of real-world data regarding multidrug protocols for the ambulatory care of a substantial number of patients with mild COVID-19 before progression to moderate or severe conditions. Hospitalization and death data were collected during follow-up telemedicine visits or calls with family members. For this paper, patients treated through October 21, 2020, were managed using Protocol 1, which included all options described above except IVM. Patients treated between October 22, 2020, and March 31, 2021, were managed using Protocol 2, which added IVM as an option.

Methods

Study Setting and Design

This study reports clinical outcomes associated with empiric multidrug regimens for confirmed COVID-19 patients who presented to AVUC, a large, dedicated SARS-CoV-2 treatment center in El Centro, California. Patients were treated during two protocol periods: Protocol 1 (January 12, 2020, to October 21, 2020) and Protocol 2 (October 22, 2020, to March 13, 2021), inclusive of endpoints. Outcomes for patients treated under these protocols were compared with those of 20,921, other known COVID-19 cases in Imperial County, California, during a similar time period (through May 3, 2021). Comparisons between groups and subgroups were calculated using Excel or GraphPad Prism. Patient data for both AVUC and Imperial County were verified through the Imperial County Public Health Department.

The study emphasizes treatment optimization rather than reliance on a rigid hierarchy of methodological preference. When delays could result in the loss of lives, rapid experimentation with safe, low-cost treatments represents practical, economic science that every physician can employ. Such efforts align with ethical medical practice.

Risk stratification and recommended nutraceuticals followed previously published guidance, as shown in Figure 1 (10), although physicians retained discretion. For example, HCQ or IVM was prescribed to high-risk, polymerase chain reaction (PCR)-positive patients before symptom onset. All patients received empiric treatment on the first day of presentation, prior to COVID-19 test results, with treatment continuing for those with confirmed COVID-19.

The protocols included agents with antiviral activity against SARS-CoV-2 (zinc, HCQ, IVM) and one antibiotic (azithromycin, doxycycline, or ceftriaxone), along with inhaled budesonide intramuscular dexamethasone, or both. Even though Favipiravir was part of the protocol, it was not given to patients because it was deemed unnecessary. Severely ill patients, either at presentation or upon return to the clinic, received additional interventions, including albuterol nebulization, inhaled budesonide, intravenous volume expansion with supplemental parenteral thiamine (500 mg), magnesium sulfate (4 g), folic acid (1 g), and vitamin B12 (1 mg). (11) Severely ill patients also received intramuscular dexamethasone (8 mg) and ceftriaxone (1 g). Eight patients received monoclonal antibody treatment. All patients were followed up in person or via telemedicine within 48 hours and as needed, depending on the duration and intensity of symptoms. (12)

Patient Inclusion, Exclusion, and Categorization

Of the 4385 COVID-19 patients recorded by AVUC, 3962 patients treated were categorized as having mild COVID-19 upon presentation, defined by symptoms of upper respiratory infection without chest pain, shortness of breath, or changes in Continuity of Care Records. A total of 414 treated patients who were not immediately hospitalized had already progressed to moderate or severe stages of COVID-19. One patient treated for severe COVID-19 refused immediate hospitalization. Nine patients were excluded from this study due to nontreatment, either because they were immediately sent to a hospital or declined treatment.

Before computing P values using Fisher's exact test, we adjusted for age by applying mortality factors implicit in the county-wide data, excluding patients in the Protocol 1 and 2 groups.

Confirmation of COVID-19 Diagnosis

Prior to May 15, 2020, patients were diagnosed with COVID-19 based on antibody-positive tests and symptom presentation, following standard case definition guidance. Beginning May 15, 2020, patients underwent real-time PCR testing using anterior nasal swab samples to confirm their COVID-19 diagnosis.

Protocol Rationale

Before the COVID-19 pandemic, researchers identified several general and specific properties of HCQ that suggested its potential for treating future coronavirus outbreaks. (13-16) Shortly after the emergence of SARS-CoV-2, South Korea (17) and China (18) quickly recommended HCQ and the closely related chloroquine as part of their treatment protocols. Multiple early rationale papers urged the research and medical communities to investigate the effects of HCQ as a potential treatment option. (19-21)

As HCQ use expanded globally for prophylaxis and early ambulatory treatment, particularly in countries such as India (22, 23) and Italy (24), no reports indicated that physicians abandoned the use of HCQ in outpatient settings of empiric medicine, except where it was prohibited. This observation should not be dismissed as merely anecdotal; rather, it provides compelling evidence that warrants prioritization by public health authorities and a concerted effort to convert these accounts into actionable data.

Additionally, numerous studies have evaluated the use of HCQ, either as monotherapy or as part of multidrug regimens, for treating COVID-19 patients (available at *c19hcq.org*). Notably, more of these studies reported favorable outcomes among patients receiving HCQ. These findings, observed in both monotherapy and multidrug regimens, included results that either achieved or did not achieve statistical significance when evaluated in isolation. (25) While one study can conceivably demonstrate a high likelihood of a causal reduction in disease progression or mortality through traditional tools of inferential statistics, some have claimed to demonstrate a lack of efficacy or even harm associated with HCQ use. The latter form of conclusion results *prima facie* from the fallacy of assuming that no other protocols exist that could enhance the performance of the applied treatment. In fact, in 14 out of 14 published studies examining the mortality outcomes of early treatment—primarily at the mild stage prior to moderate disease progression—COVID-19 patients receiving moderate doses of HCQ (typically between 1.6 g and 4.0 g, not exceeding 6.0 g in total over several days) demonstrated lower mortality rates compared to the control arm. (25) Logically, the success of any treatment protocol reflects the effectiveness of the medications involved. For instance, the results presented in Figure 2 suggest a successful outcome, given a sufficiently powered sample size.

Furthermore, there appears to be minimal effort to systematically review the existing literature on the use of HCQ, IVM, and other potentially effective therapeutics to optimize patient outcomes. Such optimization could foster a virtuous cycle, further enhancing the efficacy of multidrug regimens. By dismissing the value of empirical evidence and physicians' experiences with early ambulatory protocols, health authorities forgo critical opportunities to collect valuable data and foster collaboration among clinicians to share lifesaving insights.

Analysis of Patient Outcomes by Protocol, Time Dependence, and Aggregation

Evaluating the efficacy of potential antiviral agents requires progression-dependent stratification of results, as antiviral effects are most pronounced before the viral replication process matures. For an antiviral drug to be effective in treating COVID-19, the outcomes of patients treated early, during the mild disease stage, should differ categorically from those treated at the moderate stage, and even more so from patients treated after the onset of severe disease. Aggregating the results of treatments of a potential antiviral agent can significantly alter effect sizes and even produce Simpson's paradox (or more broadly, "Simpson's effects," where data trends may not reverse but appear diminished in magnitude), making effective treatments seem less beneficial or even harmful. When patients at differing stages of viral progression are aggregated, the skew in treatment effects for an effective antiviral is clearly monotonic and negative. This aggregation obscures or even reverses the measured effects.

Figure 3 illustrates the importance of stratifying results by disease severity and treatment timing to avoid misleading conclusions. In this hypothetical example, drug XYZ reduces mortality by 60% when administered to patients at Severity Score 4 of the World Health Organization's ordinal scale. This benefit is evident when comparing outcomes at the protocol level between hospitals 1 and 3. However, when results are aggregated without stratification, a

naïve analysis misleadingly suggests a 37% relative increase in mortality for patients treated with drug XYZ compared to untreated patients.

Often, studies attempt to address such analyses with insufficient corrections. For example, grouping hospitals 1 and 2 (which administer drug XYZ) against hospital 3 would indicate a 40% reduction in mortality, falling short of the full 60% reduction observed in direct protocol-level comparisons.

Furthermore, this hypothetical analysis provides no insight into the efficacy of drug XYZ when administered earlier than hospitalization, where its antiviral effects are likely to be optimal. There is no evidence to contradict the possibility that drug XYZ, which appeared to do more harm than good in the initial hypothetical analysis, could cure 100% of patients if administered very early in the disease course. Such outcomes would remain consistent with the expected behavior of an effective antiviral agent. Although statisticians use Bayesian rubrics to correct for such flaws, these adjustments may not achieve perfect accuracy, as the true optimal efficacy of drug XYZ could plausibly range from 60% to 100%. Stratifying results based on disease severity at the time of treatment helps avoid these preventable analytical errors.

Furthermore, we suggest that much of the COVID-19 literature—particularly studies examining the effects of HCQ as a treatment—undergo re-analysis within a framework that stratifies results by protocol, specifically accounting for disease severity at the time of treatment. This approach would avoid the oversimplification of categorizing patients into binary groups based solely on whether they received a particular drug, without sufficient regard for the overall treatment protocol.

We also recommend that meta-analyses of HCQ treatment results exclude studies that fail to distinguish results at the protocol level, including stratification by timing of treatment. Studies included in such analyses should be grouped according to the stage of COVID-19 at which treatment is administered. As the saying goes, "garbage in, garbage out," and this principle should apply to meta-analyses and individual studies, such as the SOLIDARITY trials (26) and other randomized controlled trials (RCTs) that administered HCQ as monotherapy at exceptionally high and potentially dangerous doses to late-stage patients. (27) Any conclusion that such an RCT demonstrates the lack of efficacy of HCQ in other protocols is a non sequitur and underscores that basic logic and critical thinking have always been the true gold standards of science.

Finally, we note that the retrospective observational analyses presented in this paper generate results nearly identical in nature and magnitude to those of RCTs using similar protocols. (28, 29) While it is technically conceivable that an unknown confounding variable both differentiates patients visiting AVUC clinics from those in the general population and influences disease progression, such bias is likely mitigated by the demographic risk analysis applied in the following results—particularly given the recognized importance of age as a predictor of outcomes and its substantial, albeit imperfect, correlation with primary comorbidities. By this stage of the pandemic, most unknown confounding variables would likely have been observed and documented. The number of patients in this study is sufficient to reduce the variance inherent in the random sorting of unexamined risk factors relative to the sample size, and the effect sizes observed in this analysis are notably large. As sample sizes increase, the results of observational studies and RCTs tend to converge. (28, 29)

Sensitivity Analysis

First and foremost, this study presents a large case series. We strive to maximize the value of the results by comparing them to both the local county case summary data and synthetic versions of the county data. The primary limitation of our analysis lies in the synthetic comparator. In particular, nursing home patients, who account for a substantial proportion of COVID-19 fatalities, rarely overlap with those seen at facilities such as ACUV. While our age mapping improves compatibility, it remains imperfect. To address these limitations, we compared the treatment group outcomes to ideal cohorts under varying assumptions of hospitalization and mortality rates. The resulting confidence intervals suggest that even if imperfections in the comparison warrant wider bounds, the observed odds ratios remain compelling.

Results

Among the 4376 patients treated by AVUC staff, 2137 (48.8%) were male, 2239 (51.2%) were female, and 1391 (31.8%) were aged 50 years or older. Among these patients, 1370 (31.3%) were asymptomatic at presentation. A total of 1980 (45.2%) patients received HCQ, 365 (8.3%) received IVM, and 347 (7.9%) received both HCQ and IVM.

Given the low progression rates to moderate or se-

vere COVID-19 among patients in Protocols 1 and 2, the results lacked sufficient variation to confidently distinguish between the protocols statistically without extraordinarily large patient cohorts. While both HCQ and IVM are hypothesized antiviral agents, the positive outcomes of the multidrug regimen may be more readily attributed to HCQ, although patients receiving IVM also fared exceptionally well. Overall, the observed effects can only be attributed to the protocols, suggesting potential synergistic interactions among some agents or specific benefits from others, such as steroids. Patient data for Protocols 1 and 2, along with the combined patient aggregates, demonstrated dramatically lower hospitalization and mortality rates compared with the general population in Imperial County, California.

This analysis acknowledges the limitations of retrospective observational studies using synthetic controls, as randomization or matching by propensity score was not feasible. Nevertheless, the extremely low odds ratios, combined with the large patient sample and robust sensitivity analysis, provide strong support for the significance of these positive outcomes. Notably, the safety of various medications, including HCQ, IVM, azithromycin, doxycycline, albuterol, and budesonide, is evidenced by the lack of serious adverse events among the patients, with only minor symptoms such as nausea, upset stomach, and diarrhea reported in a small proportion.

The patient population at AVUC differed slightly from the broader county population. COVID-19 patients aged 70 years or older represented 6.3% of the AVUC cohort compared with 9.3% in Imperial County overall, and patients were more often male (48.8% versus 47.4%). Mortality rates for COVID-19 in Imperial County skewed heavily toward male patients. It remains unclear how many patients outside of AVUC also received early ambulatory treatment, including the medications used in Protocols 1 and 2, potentially dampening relative risk measures for such outpatient care.

Among 20,921 COVID-19 patients in Imperial County who were not treated by AVUC, 4770 (22.8%) were hospitalized, and 636 (3.0%) died.

For mild COVID-19, of the 1585 patients treated with Protocol 1, there was 1 hospitalization (0.06%) and no deaths (0%). Of 2356 patients treated with Protocol 2, there was 1 hospitalization (0.04%) and no deaths (0%). Detailed age-specific data for these patients are shown in Table 1. Among 21 patients whose date of treatment was obscured after data blinding but were treated for mild COVID-19, none were hospitalized or died. In total, of 3962 patients (Table 1) treated for mild COVID-19 by AVUC before progression to moderate or severe disease, there were 2 hospitalizations (0.05%, RR = 0.0019; $P < .0001$) and no deaths (0%, RR = 0.00; $P < .0001$).

For moderate COVID-19, of 222 patients treated with Protocol 1, there were 2 hospitalizations (0.5%) and no deaths (0%). Among 190 patients treated with Protocol 2, there were 5 hospitalizations (2.6%) and 3 deaths (1.6%). One additional patient with blinded treatment dates was treated for moderate COVID-19 without hospitalization or death. In total, of 412 patients (Table 2) treated for moderate COVID-19 by AVUC, there were 7 hospitalizations (1.7%) and 3 deaths (OR = 0.0659, $P < .0001$). Table 2 provides a detailed breakdown of hospitalization, mortality, and treatment distribution by age group for moderate COVID-19 patients treated under Protocols 1 and 2. One patient with severe COVID-19 who refused hospitalization and instead chose outpatient treatment with AVUC recovered fully.

Patients treated for mild COVID-19 had significantly lower hospitalization rates (OR = 0.0293; $P < .0001$) and no mortality (OR = 0.0000; $P = .0008$).

To understand the limitations of the comparison, we conducted sensitivity analyses. Comparison groups included Imperial County data through May 15, 2021, age-adjusted cohorts aligned with the AVUC patient profiles, and cohorts with progressively lower hospitalization and mortality rates. The lower bounds of hospitalization and mortality for which AVUC showed statistically significant improvements were a 0.20% hospitalization rate and a 0.10% case fatality rate (Table 3).

Corrections for comorbidities or symptoms were deemed unnecessary and unfeasible. Such information is rarely collected before hospitalization, the typical demarcation between mild and moderate COVID-19. These variables are also closely correlated with age distribution.

Given the large sample size, it is unlikely that the relationships among variables would change substantially.

Discussion

A limited number of analyses have been published on the early ambulatory care of COVID-19 patients. These studies have been almost uniformly positive regarding HCQ and IVM, as well as smaller num-

bers of studies on fluvoxamine, proxalutamide, bromhexine, and other drugs. However, there remains a substantial amount of uncollected data on these and numerous other treatments. Collecting such data should be a high priority for health officials and the larger medical community. Moving forward, no organization should discourage the collection, organization, examination, or analysis of empiric treatment regimens developed by diligent and collaborative health professionals. Public health authorities have an inherent responsibility to encourage and, when possible, actively participate in this process as a primary obligation.

We contend that the case for early ambulatory care for COVID-19 patients using multidrug regimens has been amply demonstrated. These regimens include those described in this paper, employing HCQ, IVM, or potential improvements upon these options. Further collection and analysis of unexamined data pools, stratified by protocol level, will strengthen the case for early ambulatory treatment, particularly using multidrug regimens under similar or other protocols. The optimization of medical treatment cannot be fully achieved until these results are acknowledged, by health officials or the broader community of physicians capable of delivering these treatments to their patients.

It is difficult to envision that optimal care would align with the current standard of withholding treatment until patients develop moderate or severe COVID-19 symptoms. All pertinent data suggests otherwise.

Conclusion

Our study demonstrates that early ambulatory treatment for SARS-CoV-2 infection and the resulting COVID-19 disease is safe, feasible, practical, and scalable to large patient populations. Encouraging early ambulatory treatment among both patients and physicians is critically important. The results show that hospitalization and death were nearly nonexistent when patients received multidrug regimens, including HCQ and IVM, prior to progression beyond the mild disease stage. Similar therapies also resulted in statistically significant reductions in hospitalization and mortality among patients treated during the moderate disease stage.

Given the severity of the COVID-19 crisis and the high mortality rate associated with hospital-initiated treatment, we conclude that early ambulatory multidrug therapy should be established as the standard of care for high-risk patients. Delaying early treatment until hospitalization is no longer tenable for patients who can be effectively managed as outpatients with well-structured protocols.

Acknowledgments

The authors thank the doctors and medical staff at AVUC clinics, the Public Health Department of Imperial County, California, and the maintainers of the Imperial County COVID-19 data and tracking systems for their assistance with this quality improvement study. We also thank David Wiseman, PhD, for his review of the data and guidance on various aspects of the study. Additionally, we express our gratitude to the many doctors and researchers who have contributed valuable research throughout the pandemic, particularly those whose insights into early ambulatory treatment protocols encouraged the implementation of effective care at AVUC and informed this analysis.

Funding

This study was entirely self-funded, with no external financial support.

Competing Interests

None of the authors report any conflicts of interest.

Authors' Contribution: All authors had access to the data and wrote the manuscript.

Table 1. AVUC Patients Presenting as Mild COVID-19

Protocol 1						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	
0-9	42	0	0	42	2	
10-19	136	0	0	136	13	
20-29	322	0	0	322	64	
30-39	329	0	0	329	81	
40-49	290	0	0	290	60	
50-59	266	0	0	266	83	
60-69	129	1	0	129	41	
70-79	60	0	0	60	21	
80-89	10	0	0	10	2	
90+	1	0	0	1	0	
Total	1585	1	0	1585	367	
Protocol 2						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	Ivermectin
0-9	90	0	0	90	0	0
10-19	280	0	0	280	39	12
20-29	393	0	0	393	202	46
30-39	495	0	0	495	288	49
40-49	389	0	0	389	245	52
50-59	320	0	0	320	196	51
60-69	237	0	0	237	162	61
70-79	110	1	0	110	85	24
80-89	39	0	0	39	25	5
90+	3	0	0	3	2	2
Total	2356	1	0	1356	1244	302
All Patients Treated for Mild COVID-19						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	Ivermectin
0-9	132	0	0	132	2	0
10-19	418	0	0	418	52	12
20-29	722	0	0	722	266	46
30-39	828	0	0	828	369	49
40-49	682	0	0	682	305	52
50-59	587	0	0	587	279	51
60-69	368	1	0	368	203	61
70-79	172	1	0	172	106	24
80-89	49	0	0	49	27	5
90+	4	0	0	4	2	2
Total	3962	2	0	3962	1611	302

Table 2: AVUC Patients Presenting as Moderate COVID-19

Protocol 1						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	
0-9	1	0	0	1	0	
10-19	2	0	0	2	2	
20-29	28	0	0	28	22	
30-39	35	0	0	35	31	
40-49	58	1	0	58	53	
50-59	46	1	0	46	42	
60-69	32	0	0	32	29	
70-79	13	0	0	13	12	
80-89	7	0	0	7	6	
90+	0	0	0	0	0	
Total	222	2	0	222	197	
Protocol 2						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	Ivermectin
0-9	1	0	0	1	0	0
10-19	5	0	0	5	2	1
20-29	16	0	0	16	13	8
30-39	23	0	0	23	21	7
40-49	33	1	0	33	29	12
50-59	41	1	1	40	38	15
60-69	42	2	2	40	40	12
70-79	22	0	0	22	22	6
80-89	6	1	0	6	6	2
90+	1	0	0	1	1	0
Total	190	5	3	187	172	63
All Patients Treated for Moderate COVID-19						
Age Range	Total N	Hospitalizations	Non-Survivors	Survivors	Hydroxychloroquine	Ivermectin
0-9	2	0	0	2	2	0
10-19	7	0	0	7	4	12
20-29	44	0	0	44	35	46
30-39	58	0	0	58	52	49
40-49	91	2	0	92	82	52
50-59	87	2	1	86	80	51
60-69	74	2	2	72	69	61
70-79	35	0	0	35	34	24
80-89	13	1	0	13	12	5
90+	1	0	0	1	1	2
Total	412	7	3	410	369	302

Table 3. Comparison of hospitalization, mortality, and odds ratios for mild COVID-19 patients treated under Protocols 1 and 2 at AVUC, including comparisons with Imperial County and synthetic cohorts. This table supports the statistical significance of outcomes discussed in the Sensitivity Analysis section

	Protocol 1 N= 1585	**Protocol 2** N= 2356	**All Patients** N= 3962
Hospitalized	1(0.06%)	1(0.04%)	2(0.05%)
Died	0(0.00%)	0(0.00%)	0(0.00%)
Imperial County, CA N= 20921			
Hospitalized 4,770 (22.80%)	OR= 0.0021 p <0.0001	OR= 0.0014 p <0.0001	OR= 0.0017 p <0.0001
Died 636 (3.04%)	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001
Imperial (Corrected) N= 20921			
Hospitalized 4,770 (22.80%)	OR= 0.0024 p <0.0001	OR= 0.0016 p <0.0001	OR= 0.0019 p <0.0001
Died 636 (3.04%)	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001
Synethic 1 N= 20921			
Hospitalized 4,343 (20.76%)	OR= 0.0036 p <0.0001	OR= 0.0024 p <0.0001	OR= 0.0029 p <0.0001
Died 471 (2.25%)	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001
Synethic 2 N= 20921			
Hospitalized 3,138 (15.00%)	OR= 0.0057 p <0.0001	OR= 0.0038 p <0.0001	OR= 0.0045 p <0.0001
Died 314 (1.50%)	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001
Synethic 3 N= 20921			
Hospitalized 2,092 (10.00%)	OR= 0.0120 p <0.0001	OR= 0.0080 p <0.0001	OR= 0.0096 p <0.0001
Died 209 (1.00%)	OR= 0.0000 p <0.0008	OR= 0.0000 p <0.0001	OR= 0.0000 p <0.0001
Limit for Significance N= 20921			
Hospitalized 41 (0.20%)			OR= 0.2572 p <0.0376
Died 21 (0.10%)			OR= 0.0000 p <0.0380

Figure 1. Early sequential multidrug therapy for COVID-19 incorporates risk stratification, nutraceuticals, approved medications, and U.S. Food and Drug Administration Emergency Use Authorization agents. This protocol outlines treatment options based on disease severity and patient risk factors. (9)

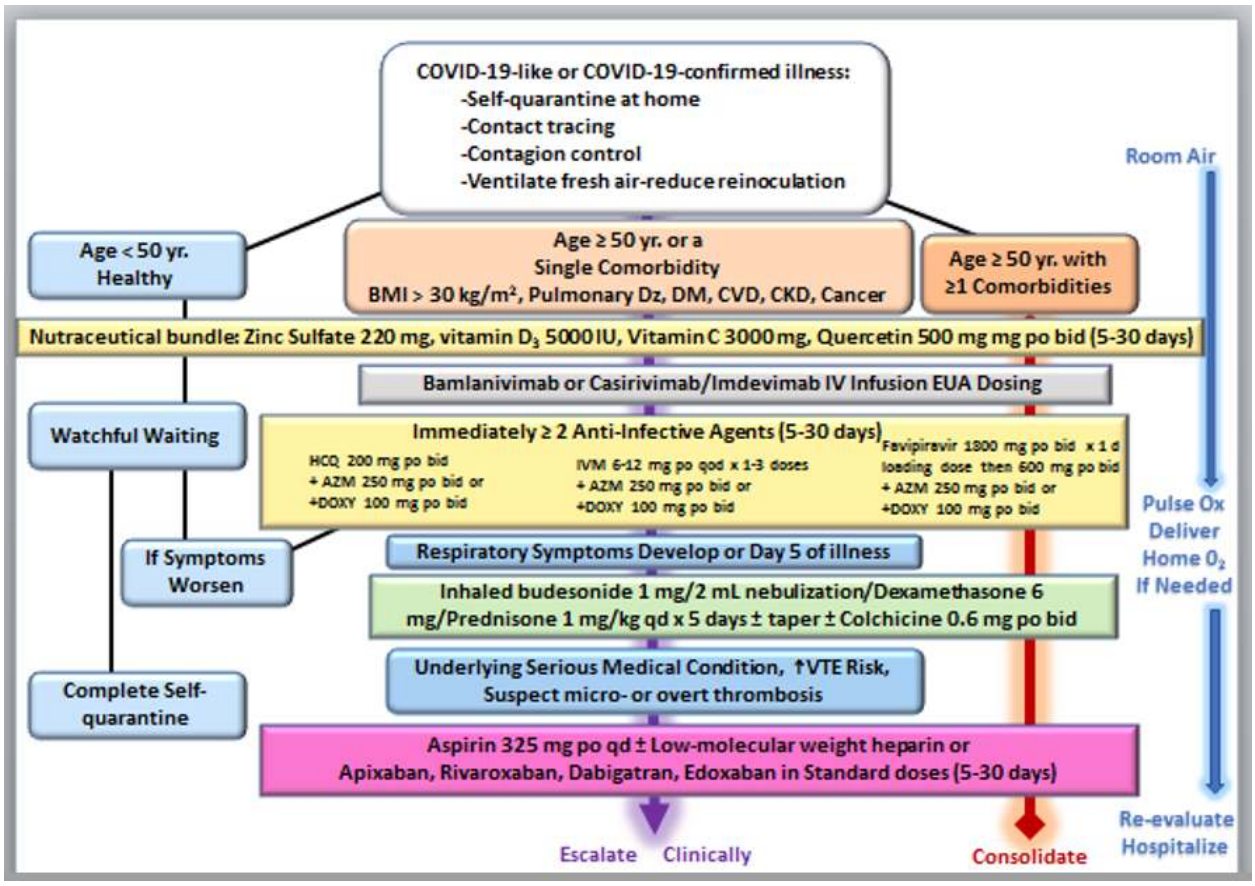

Figure 2. Effectiveness of hydroxychloroquine (HCQ) at different phases of COVID-19 treatment. HCQ demonstrates success during early stages (first 4 days of symptoms) and fails in pre-exposure prophylaxis (PrEP), late treatment phases, and critical illness. (22, 23, 26, 27)

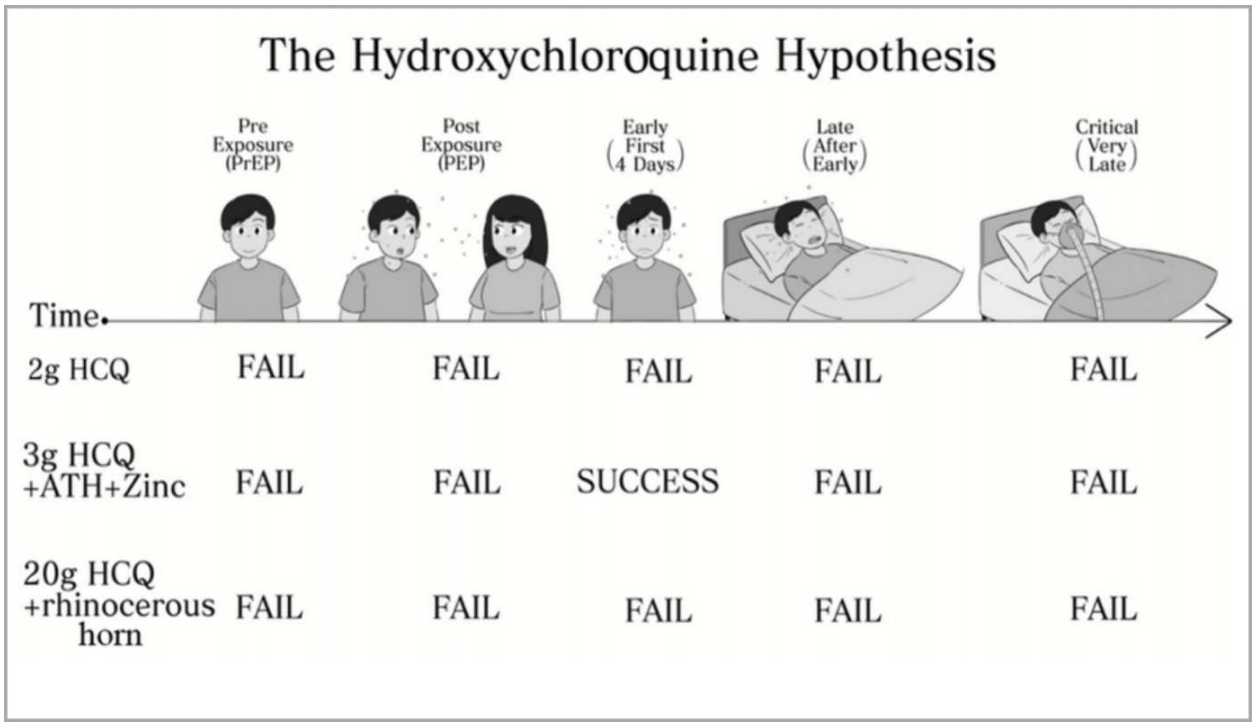

Figure 3. Protocol aggregation without stratification by disease severity or treatment timing can cause inverted results. The data demonstrate how aggregated mortality rates can misrepresent treatment effectiveness

COVID-19 Severity	Hospital 1 Drug XYZ Treatment for all cases			Hospital 2 Drug XYZ Treatment for severe cases only			Hospital 3 No Treatment	
	Patients Progressing to Each Stage			Patients Progressing to Each Stage			Patients Progressing to Each Stage	
	Number	Percent (%)		Number	Percent (%)		Number	Percent (%)
4	1000	100%		1000	100%		1000	100%
5	500	50%		850	85%		850	85%
6	240	24%		400	40%		400	40%
7	120	12%		200	20%		250	25%
8	60	6%		120	12%		150	15%
9	30	3%		80	8%		90	9%
10 (death)	**20**	**2%**		**40**	**4%**		**50**	**5%**

Analysis of Drug XYZ Mortality From All Three Hospitals		
	XYZ Treatment	**No XYZ Treatment**
# of Patients	1400	1600
# Deceased	60	50
Mortality Rate	**4.3%**	**3.1%**

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