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# Commentary on "Statistical Analysis Methods Applied to Early Outpatient COVID-19 Treatment Case Series Data" by Gkioulekas, McCullough and Zelenko": A Return Back to the Future

**Marc Rendell***

*Medical Director, The Rose Salter Medical Research Foundation, USA*

## ABSTRACT

**Context:** This commentary deals with the article "Statistical analysis methods applied to early outpatient COVID-19 treatment case series data" by Gkioulekas, McCullough and the late Dr. Vladimir Zelenko, published in COVID in August, 2022. Although highly mathematical, the work is readily understandable as a framework to extract valid information from case series data, outside the randomized, placebo, controlled clinical trial ordained approach.

**Objective:** The gist of the approach is to recognize probable benefit when results of treatment show a large magnitude of difference with those obtained in the wider population derived lower bounds for mortality. The particular application of the mathematical construct was to the use of empirical treatments, notably the Zelenko and McCullough protocols, in patients with early phase SARS-Cov-2 infections. Yet, the formalism is quite generally applicable to data obtained from case series in conditions where the safety of interventions is well known historically.

**Conclusion:** The mathematical formulation proposed is very well suited to the large population studies which have essentially superseded randomized control trials in evaluation of current COVID-19 prevention and treatment modalities.

**Keywords:** Randomized control trials; COVID-19; Nirmatrelvir-ritonavir; Molnupiravir

## INTRODUCTION

The article "Statistical analysis methods applied to early outpatient COVID-19 treatment case series data" by Gkioulekas, McCullough and the late Dr. Vladimir Zelenko, published in COVID is fascinating on many levels: mathematics, statistics, clinical research, clinical care, and historical [1]. Many readers will no doubt be deterred by the complex mathematical constructs presented. Yet, the concepts introduced are readily understandable in simple terms. In the history of medicine, the presentation of case series data by treating physicians has been a cornerstone of clinical progress. The mathematical formalism introduced by Gkioulekas et al enables the use of case series results without randomized controls as a basis for concluding value of certain treatments, provided the apparent magnitude of benefit is very large relative to the untreated overall population.

## DESCRIPTION

### The Tension between Clinical Research and Clinical Care

Offering a view of the Dark Age of human history of COVID-19, the Gkioulekas et al narrative deals with initial attempts to treat patients during the tragic pandemic and forthrightly points to the conflict between treating physicians, desperately trying to alleviate the progression of COVID-19 to severe illness and death, and the clinical researchers who insisted that response to proposed treatments be objectively measured in

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**Corresponding author** Marc Rendell, Medical Director, The Rose Salter Medical Research Foundation, USA, Email id: rendell@asndi.com

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randomized placebo controlled clinical trials. The gold standard to establish that a given treatment for a condition is safe and effective is to compare to alternative accepted treatment in a trial randomly selecting from an affected pool of similar individuals [2]. The COVID pandemic has raised questions about that traditional approach. COVID-19 is a disease with multiple phases resulting from infection by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [3].

The disease proceeds as a primary viral attack, manifesting initially as influenza like illness with cough, fever, myalgia and fatigue, which may then subsequently incite an overlapping excessive immune reaction to the viral spike protein, resulting in protean clinical manifestations. It is that later phase, often affecting the lungs with dyspnea and hypoxia, which can then progress to acute respiratory distress syndrome and a hypercoagulable syndrome that has been responsible for high mortality. Less well documented are serious neurologic effects of the infection, which can be a part of the long term recovery phase of the disease, with cognitive impairments sometimes referred to as "brain fog". Yet, the clinical severity of COVID-19 is highly variable, ranging from asymptomatic or mild upper respiratory symptoms in the majority of patients to severe illness requiring hospitalization in a minority of those infected. The severity of COVID-19 increases exponentially with age and in patients with significant chronic diseases [4].

The approach of public health authorities from the outset of the pandemic was to focus exclusively on patients sick enough to require hospitalization, rather than attempting to prevent and treat the initial phase of viral replication. There were no recognized treatments. In fact, the officially recommended approach to diagnosed COVID-19 patients was to monitor symptoms and oxygenation levels at home until some patients were at a stage requiring hospitalization, by which point there was a high likelihood of need for intubation. Mortality in some series approached 25% or more of those hospitalized [5,6].

A number of treating physicians elected to offer patients early in the course the use of agents which had some theoretical potential benefit, albeit with no randomized placebo controlled trial to prove those agents had an effect. So, a number of nutritional supplements, vitamins, and pharmaceutical agents with speculative beneficial immunological effects were offered to patients. Among those used were zinc, vitamin C, vitamin D, quercetin, ivermectin and hydroxychloroquine (HCQ). HCQ has antiviral properties and is also used chronically to suppress autoimmune harm in diseases such as lupus and rheumatoid arthritis.

Dr. Didier Raoult, head of the Institut Hospitalo-Universitaire Méditerranée, a large and highly successful academic program for infectious disease research in Marseille, France, began treatment of large numbers of COVID-19 afflicted citizens. He combined HCQ with azithromycin in an empirical attempt to treat outpatients with PCR diagnosed COVID-19. His group was so impressed by the results that they stated that a placebo controlled trial, denying HCQ to patients was unethical [7].

Dr. Vladimir Zelenko was a physician practicing in an Orthodox Jewish community outside New York City. Orthodox Jews often participate in large social gatherings and, hence, are particularly susceptible to rapid viral transmission. Zelenko enhanced Raoult's treatment protocol with the addition of zinc sulfate; motivated by the hypothesis that hydroxychloroquine increases intracellular zinc concentration, further enhancing its antiviral mechanisms of action [8]. Zelenko also introduced risk stratification criteria to classify patients into a low risk vs high risk category, and noticed empirically that, for the purpose of reducing hospitalizations and deaths, it is sufficient to offer the triple drug therapy only to the high risk patients [9]. Over time, he introduced a quercetin based protocol requiring no prescription for low risk patients, with additional prescription only medications (dexamethasone, budesonide, and the anticoagulant apixiban) for the treatment of high risk patients, for whom the triple drug therapy did not result in a typical turnaround. His results in terms of preventing hospitalization and mortality in COVID-19 infected patients were far superior to those of other physicians practicing in his area.

However, in the United States and in countries tributary to American medicine, there was insistence on randomized control clinical trials. Yet, the trials sponsored by the public health authorities and pharmaceutical companies were directed solely at inpatients with COVID-19. Dr. Peter McCullough, an impressively credentialed, heavily published academic cardiologist, became concerned about the devastating suffering and death inflicted by COVID-19. Dr. McCullough was well known for his research output. He had over 600 peer reviewed publications, including the interface between heart and kidney disease, and had held high administrative positions in several academic institutions. He also had a degree in public health. He began treating patients using HCQ and other supportive agents in a protocol convergent with that of Dr. Zelenko, also adding immune modulation with glucocorticoids, colchicine and anticoagulants. He argued for the need to offer such treatment to COVID-19 diagnosed patients very early in the course of the disease [10].

His advocacy of early treatment was directly contrary to official public health policy and ignited surprisingly fierce opposition from the established academic and governmental public health community. The National Institutes of Health focused all resources on treatment of severely ill hospitalized patients. When HCQ did not demonstrate benefit in this group of patients, the NIH proceeded to shut down a projected outpatient trial [11]. In the United Kingdom, clinical trials of HCQ were banned [12]. Dr. McCullough had been the personification of academic medicine, highly respected in that select community and faithfully obedient by the book to all the tenets of that culture. Yet, he did not agree to abandon support for early pharmaceutical treatment of COVID-19. His insistence rapidly led to a separation from his academic positions. It is not clear what then led McCullough to become a particularly outspoken public figure arguing persuasively in every possible venue for early treatment of those diagnosed with COVID-19. What was unusual about Peter McCullough was an uncanny ability to personally communicate with people of all manner of experience personally in their own terms. So he was able to interact with ordinary non-academic people, listening attentively to what they had to say and achieve mutual understanding. Dr. McCullough has since become a respected commentator on all types of popular social media.

## Mathematical Formulation of Magnitude of Benefit

Among those in his circle was Eleftherios Gkioulekas, Professor of Mathematics at the University of Texas, Rio Grande. Gkioulekas is an applied and theoretical mathematician, of unquestioned academic persuasion, who shared with McCullough the ability to communicate outside the limits of his own profession. Gkioulekas had formed his own perceptions of the need for prophylaxis and treatment in the face of the SARS-Cov-2 pandemic. The subject of this commentary is the treatise authored by Gkioulekas, McCullough and Zelenko on "Statistical analysis methods applied to early outpatient COVID-19 treatment case series data" [1]. Actually the title is somewhat misleading in that statistical analysis is a highly developed form of applied mathematics with formulations evolved over the years into a package of doctrine established approaches. Gkioulekas did not go in that direction; rather, he went back to the basic concept of probability of an event p and the probability of that event not occurring (1-p). If the outcome of a form of COVID treatment was favorable, that was assigned the probability p, unfavorable (1-p). He then conceptualized the case series of outcomes in COVID treated patients as a binomial trial. Gkioulekas was intrigued by the high contrast in the empirical outcomes between treated and untreated patients in the initial Zelenko results and by the mathematical question of quantifying how much contrast with results in the wider population is sufficient to establish the existence of a treatment effect. Gkioulekas recognized that because Zelenko used a precise risk stratification definition for the high risk patient categories and reported the total number of high risk patients treated and the corresponding number of hospitalizations and deaths, these reported outcomes could be directly compared with a strict lower bound of the hospitalization and mortality rate for untreated high risk patients using both historical controls and population level data. He then invoked the binomial theorem to assess overall probabilities. He recognized that although randomized controlled protocols required an active intervention in a population coupled with an inactive control in a different similar population, denying treatment to patients was not acceptable to clinicians like Zelenko, Raoult, or McCullough in the face of the dire outcomes of COVID-19. They had case series of treated patients, but no randomized control group to whom they denied treatment.

So, Gkioulekas, McCullough and Zelenko proposed that the untreated control group would be composed of those patients in the population who did not receive care from the investigators, very often effectively the whole population [1]. They deduced population derived lower bounds for mortality and hospitalization risks of high risk patients without treatment. Then they compared the lower bounds with what was observed in the case series of high risk patients treated by clinicians like Zelenko. When the lower bounds exceed an efficacy threshold, then the existence of treatment efficacy is strongly suggested by the preponderance of evidence. They also noted that Zelenko's mortality statistics were far more favorable than those of the local Orthodox Jewish population treated by others. Similarly, they found that mortality among the Raoult patients was far lower than that in the Marseille area and, in fact, the case fatality ratio in all of France. Now, clearly the argument could be made that patients who were treated by these investigators were selected with bias towards more favorable outcomes. Gkioulekas et al. allowed for bias by calculating higher thresholds beyond which there was a high likelihood that treatment was beneficial in spite of possible selection issues [1].

So, in addition to the examples cited by Gkioulekas et al [1], the data on the use of HCQ plus azithromycin for patients at the IHU showed no deaths whatsoever in any of the 8414 COVID outpatients under the age of 60 [13]. In contrast, the cumulative COVID 19 mortality for all men under age 60 in France, with or without any documented COVID infection, was 3.45/100,000 and 1.69/100,000 for women [14]. In 10,429 patients treated at the IHU, the case fatality ratio was 0.15% [13]. For 8315 patients treated with the combination of azithromycin and HCQ, the case fatality ratio was only 0.06%. These numbers contrast with a case fatality ratio ranging from 6% initially down to 2% at the lowest point in all of France for the period during which the IHU obtained their data [1]. This huge difference cannot be easily explained by bias in patient selection. Selection bias clearly decreases as the number of patients in a case series increases. The 10,000 patients presented by Raoult and coworkers is a non-insignificant fraction of the Marseille infected population.

## The Future of Clinical Investigations

Gkioulekas, et al., take us back to an era of case series reports wherein investigators reported their findings using selected treatments in their patient groups as justification for wider adoption of their approach [1]. The "control" population then invoked was the entire population in which the case series was embedded. In a sense, we are now being taken back to the future; the COVID era has accelerated a movement away from randomized placebo controlled studies. Given the highly variable outcomes of the phases of COVID-19 ranging from asymptomatic infection to death, it has proven challenging to create randomized placebo controlled studies with sufficient statistical power to prove benefit of treatments. Death is a hard endpoint; fortunately, death from COVID-19 death is actually relatively infrequent given the massive case burden. The World Health Organization dashboard, as of 7:26 pm CEST, 10 October 2022 shows globally that there have been 618,521,620 confirmed cases of COVID-19, including 6,534,725 deaths, reported to WHO for a case fatality ratio of 1.1% [15]. Furthermore, mortality has clearly decreased substantially from the original Wuhan and subsequent viral strains in the Omicron period, despite the huge number of cases, because the severity of Omicron illness is significantly reduced compared to prior SARS-Cov-2 variants [16].

Consequently, from a clinical trials standpoint, a very large number of subjects are required to assess a meaningful change in COVID mortality due to an intervention. So realizing that the number of patients required to compare mortality of treated with untreated subjects would be impractical, the FDA adopted the combination of hospitalizations and deaths as a primary efficacy criterion, which, in practice, translates to hospitalizations. Yet, the decision to hospitalize is highly subjective. The FDA review acknowledged that there may be significant differences in the criteria for hospitalization in different geographic areas. Current NIH COVID guidelines state "There are no fixed criteria for admitting patients with COVID-19 to the hospital;

criteria may vary by region and hospital facilities" [17]. In a multicriteria decision analysis, Di Nardo et al. concluded that the most important factors assessed for possible hospital admission included PaO2 [16.3%], followed by peripheral O2 saturation [15.9%], chest X-ray [14.1%], MEWS [11.4%] Modified Early Warning Score-MEWS, respiratory rate [9.5%], comorbidities [6.5%], living with vulnerable people [6.4%], BMI [5.6%], duration of symptoms before hospital evaluation [5.4%], CRP [5.1%], and age [3.8%] [18]. Certainly, this constellation of criteria is variable.

There are only a few agents which have ever met the FDA standard for protection against hospitalization and death. The monoclonal antibodies, notably, have been successful in randomized trials of about 1000 patients, but that was at a time of relatively high hospitalization. The most transmissible SARS-Cov2 variants of the Omicron family have generated many more COVID-19 cases than the original Wuhan species and the subsequent Beta, Gamma, and Delta variants. Rapidly, most of the monoclonal antibodies have lost effectiveness as the variants mutate away from effective neutralization [19]. In addition, the severity of the Omicron offshoots has been lower, requiring less frequent hospitalization [20].

Nirmatrelvir-ritonavir and molnupiravir were endorsed by the NIH and CDC each on the basis of a single randomized placebo controlled study in enriched high risk populations infected with COVID-19 [21,22]. Yet Pfizer subsequently shut down studies of COVID-19 patients with standard as opposed to high risk as well as a prevention study in contacts of COVID-19 patients claiming that benefit did not reach statistical significance [23-25]. Pfizer has not published the results of either study to this day.

Fortunately, the current standard of evidence for benefit of preventive measures or treatment of COVID-19 has shifted away from randomized control studies with insufficient subject numbers toward large scale population studies based on mining of massive clinical databases. So, the current recommendations for mRNA SARS-Cov-2 vaccination are based on observation of results primarily in the Israeli and British populations where their National Health system affords comprehensive homogeneous data [26-28]. The most successful studies of COVID vaccination actually emanate from Cuba where they have developed protein subunit vaccines which appear to have protected their population of ten million even during the highly infectious Omicron surge [29,30].

Similarly for Nirmatrelvir-ritonavir, analysis of large databases has been much more informative as to true benefit than the randomized controlled Pfizer studies. The most recent publication of the Hong Kong experience with Nirmatrelvir-ritonavir and the SARS-Cov-2 RNA polymerase inhibitor molnupiravir illustrates the strength of real world evaluation of treatment effects [31].

They studied 1856 COVID patients who received molnupiravir and 890 Nirmatrelvir-ritonavir recipients. They selected similar numbers of "controls" from 40,776 total patients who did not receive the antivirals. They showed a lower risk of all-cause mortality in molnupiravir recipients (crude incidence rate per 10 000 person-days 19.98 events [95% CI 16.91-23.45]) versus matched controls (38.07 events [33.85-42.67]; HR 0.48 [95% CI 0.40-0.59], p<0.0001) and in Nirmatrelvir-ritonavir recipients (10.28 events [7.03-14.51]) versus matched controls (26.47 events [21.34-32.46]; HR 0.34 [0.23-0.50], p<0.0001). It should be noted that the molnupiravir patients were slightly older (80.8 ± 13.0) versus 77.2 ± 14.1 for the Nirmatrelvir-ritonavir patients and had a higher level of comorbidities (Charlson index 5.8 ± 1.9 versus 5.1 ± 1.7) for Nirmatrelvir-ritonavir. Only 6.2% of the molnupiravir patients were considered fully vaccinated compared to 10.5% for Nirmatrelvir-ritonavir.

In an electronic health records (EHRs) search of 92 million patients using TriNetX Advanced Analytics Platform, a multicenter and nationwide database in the US, 11,270 outpatients treated with Nirmatrelvir were compared to 2,374 molnupiravir treated individuals [32]. Once again, molnupiravir patients were older with more comorbidities. After propensity score matching, the 30 day rate of hospitalization of the molnupiravir patients (1.39%) did not differ significantly from that for molnupiravir (1.21%).

The Gkioulekas et al. formalism can easily be applied when the case series have high numbers of subjects [1]. There is a limitation when attempting to assess benefit when the safety profile of the treatment intervention is not established. For agents like zinc, HCQ, and ivermectin with established safety data obtained over many decades, benefit can be evaluated solely based on efficacy. That is clearly the case in the ivermectin prophylaxis study in Itajai observing a large fraction of the population of a small Brazilian city [33,34] and the Mexico Social Security program of ivermectin treatment of COVID with almost 8000 patients [35]. The mathematics becomes more complicated when there are potential safety issues such as myocarditis post SARS-Cov-2 vaccination, such data once again only discoverable in analysis of large national databases, not in small randomized clinical trials [36,37].

The need for large sample size becomes clear when the safety issues, while rare, are very serious, such as death due to vaccine related myocarditis [38]. That is not to say that bias cannot occur in massive population studies. On the contrary, physician selection of patients for treatment is a clinical decision, so that one must always be suspicious of conclusions based on small fractions of very large populations. For example, the claim that treatment with Nirmatrelvir-ritonavir is not beneficial in patients less than 65 years old originated from an Israeli study evaluating only 3902 patients out of a total of 109,254 [39].

## CONCLUSION

It is apparent that COVID-19 has accelerated an evolution in assessing real benefits of treatment moving away from randomized controlled studies with small numbers of subjects to large scale studies of real world populations. That evolution will continue to gain force as digital collection of data becomes progressively more accurate and comprehensive. The formalism introduced by Gkioulekas, McCullough and Zelenko will assume increasing importance in analyzing results in large scale population studies. Sadly, Dr. Vladimir Zelenko died of cancer at the young age of 48. His legacy as a primary care physician using all means to prevent suffering and death of his patients should be well commemorated by this important paper published in COVID.

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None

## CONFLICT OF INTEREST

The author declares there is no conflict of interest in publishing This article has been read and approved by all named authors.

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