

# Frequentist and Bayesian analysis methods for case series data and application to early outpatient COVID-19 treatment case series of high risk patients

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## Abstract

When confronted with a public health emergency where the pre-existing standard of care is inadequate, significant innovative treatment protocols can sometimes be discovered by medical doctors at the front lines based on repurposed medications. We propose a statistical framework for analyzing the case series of patients treated with such new protocols, that enables a comparison with our prior knowledge of expected outcomes, in the absence of treatment. The goal of the proposed methodology is not to provide a precise measurement of treatment efficacy, but to establish the existence of treatment efficacy, in order to facilitate the binary decision of whether the treatment protocol should be adopted on an emergency basis. The methodology consists of a frequentist component that compares a treatment group against the probability of an adverse outcome in the absence of treatment, and calculates an efficacy threshold that has to be exceeded by this probability, in order to control the corresponding  $p$ -value, and reject the null hypothesis. The efficacy threshold is further adjusted with a Bayesian technique, in order to also control the false positive rate. A random selection bias threshold is then calculated from the efficacy threshold to control for random selection bias. Exceeding the efficacy threshold establishes the existence of efficacy by the preponderance of evidence, and exceeding the more demanding random selection bias threshold establishes the existence of efficacy by the clear and convincing evidentiary standard. The combined techniques are applied to case series of high-risk COVID-19 outpatients, that were treated using the early Zelenko protocol and the more enhanced McCullough protocol.

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