Case series: an essential study design to build knowledge and pose hypotheses for rare and new diseases

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PRACTICAL SCENARIO

At the end of December of 2019, a pneumonia outbreak of unknown origin appeared in China. Soon afterwards, the causative virus was identified—SARS coronavirus 2 (SARS-CoV-2), and the disease was named coronavirus disease 2019 (COVID-19). In January of 2020, Chinese investigators published a detailed case series describing the characteristics and outcomes of 41 adults with confirmed COVID-19.[1] The study showed that 15% of those patients died during the study period. That case series[1] was extremely important because it was the first published description of the impact of the new disease, helping clinicians around the world to face a new pandemic.

CONCEPTS AND APPLICATION

A case series includes a description of the characteristics and outcomes among a group of individuals with either a disease or an exposure (which can be an intervention) over a period of time and without a control group. Data are collected retrospectively or prospectively, and there is no randomization. The objective is to describe the population and outcomes, rather than compare risks across groups. Therefore, a case series differs from cohort studies because the latter compares the risk between two groups (exposed and unexposed) and allows for the estimation of an absolute risk for the occurrence of a given outcome in the exposed group and of a relative risk in comparison with the unexposed group.

The case series design is not considered the strongest source of evidence due to the absence of a control group and the risk of bias, in particular selection bias, since typical or severe cases of the disease are more easily identified, and rare presentations or mild cases may not be included. In the Chinese report,[1] for example, patients with less severe COVID-19 were not hospitalized and therefore were not included in the case series. However, case series are particularly important when a new disease or treatment emerges, because it provides descriptive information and contributes to building knowledge and generating hypotheses. Case series is also an appropriate study design to describe new treatments, previously unknown medication adverse events, and rare diseases.[2]

METHODOLOGY AND QUALITY OF CASE SERIES STUDIES

- Inclusion criteria - A precise operational definition of a "case" is crucial for the reliability of the study.
- Sampling - Two strategies are possible: 1) based on disease or exposure; 2) based on a specific outcome.
- Selection of variables of interest - A detailed selection and a clear definition of predictive variables of interest are necessary, as well as test results, interventions, complications, adverse events, and outcomes.
- Systematic collection of data and robust analysis - They assure the quality of a case series study.

Table 1 presents a tool for evaluating the methodological quality of case series.[2]

Table 1. A tool for evaluating the methodological quality of case series.

Domains	Leading explanatory questions
Selection	1. Were all the potentially eligible patients included or is the selection method unclear to the extent that other patients with similar presentations may not have been reported?
Definition of exposure and outcomes	2. Was the exposure adequately and clearly defined? 3. Was the outcome adequately and clearly defined?
Causality	4. Were other alternative causes that may explain the observation ruled out? 5. Was there a challenge/rechallenge phenomenon? 6. Was there a dose-response effect? 7. Was follow-up long enough for outcomes to occur?
Reporting	8. Are the cases described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

Adapted from Murad et al.[2] Questions 4, 5 and 6 are more relevant for adverse drug events.

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