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Editorial

What is case series?

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Abstract

This is the second part of a series on case reports and case series studies. It will help junior researchers to comprehend what is the case series/exposure series as a type of research. It highlights the definition, types, importance, limitations, and differences between case series and exposure series. Examples of important historical case series that were instrumental in the early identification of health problems will be mentioned. A special editorial will be devoted to consecutive controlled case series (CCCS)/ self-controlled case series (SCCS) as an important research method.

Keywords:

Case series, exposure series, definition, types, importance, limitations.

Introduction

Case series (also known as clinical series) represents one of the most basic types of study designs, in which researchers describe the experience of a small group of people. It presents a detailed account of the clinical experience of individual study subjects and can evaluate large numbers of individuals and summarize the data using descriptive statistical measures [1]. A case series is a variation of a single case report in which the author describes several cases and their relation to one another and to the existing body of literature.

Definition

The Dictionary of Epidemiology defined a case series as "a collection of patients with common characteristics used to describe some clinical, pathophysiological or operational aspects of a disease, treatment or diagnostic procedures"[2]. Case series is an observational, descriptive research design. It is most useful for describing the potential effectiveness of new interventions, for describing the effectiveness of interventions on unusual diagnoses, and for describing unusual responses (either good or bad) to interventions. Case series can be conducted retrospectively or prospectively. The primary distinction between case reports/series and the single-subject experiment is that the researcher does not manipulate the intervention in a case report/series but merely describes/documents what happened during the normal course of the intervention. Despite limitations, case series can often have a significant impact on the current practice of medicine and they are often used to put together case definitions of new diseases and to define future areas of clinical study [3]. However, no causal inferences should be made from case series regarding the efficacy of the investigated treatment [4]. A case series samples patients with both a specific outcome and a specific exposure, or samples patients with a specific outcome and

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includes patients regardless of whether they have specific exposures [5].

Types of case series

There are many classifications for case series.

***Informal vs. formal case series**: [6, 7]

-*Informal case series*: cases are selected for specific reasons: best case, worse case, significant variations. The format of this kind of case series is: introduction; case 1, case 2, case 3, etc. (each case is presented like a short case description); discussion (cases will be compared to one another, related cases to the current literature, implications of the findings, teaching points and what changes in clinical practice this might engender).

-*Formal case series*: include all cases of a specific type, or with specific selection criteria, presented more like a cohort study than a single case report and its format is introduction methods, results, and discussion/conclusions.

***Consecutive vs. non-consecutive case series**: [5, 8]

-*Consecutive case series*: includes all eligible patients identified by the researchers during the study period. The patients are treated in the order in which they are identified. Consecutiveness increases the quality of the case series.

-*Non-consecutive case series*: includes some, but not all, of the eligible patients identified by the researchers during the study period.

***Exposure or outcome-based sampling:** [5, 9]

-*Exposure-based sampling*: include all patients treated and have specific outcomes or adverse events. Sampling is based on both a specific outcome and presence of a specific exposure.

-*Outcome-based sampling*: includes patients with the specific outcome regardless of exposure. Thus neither absolute risk nor relative risk can be calculated. Selection is based only on a specific outcome, and data are collected on previous exposures.

***Clinical vs. population-based series:** [10, 11, 12]

-*Clinical case series:* usually a coherent and consecutive set of cases of a disease recruited from one or more center by one or more researcher. It is a clinic-based register of cases that are analyzed together to learn about the disease. They are of value in epidemiology for studying symptoms and signs, creating case definitions as well as clinical education, audit, and research.

-*Population-based case series*: when a clinical case-series is limited and complete for a defined geographical area for which the population is known, it is a population-based case-series consisting of a population register of cases. It is usually compiled for administrative and legal reasons.

By knowing the past history of these patients, including examination of past medical records, and by continuing to observe them to death, health professionals can build up a picture of the natural history of a disease in clinical case series. Population case-series is a systematic extension of this series but which includes additional cases, e.g. those dying without being seen by the clinicians. It adds breadth to the understanding of the spectrum and natural history of the disease. Information on the population permits calculation of rates, understanding the distribution of disease in populations and to the study of variations over time, between places and by population characteristics. Epidemiologically the most important case-series are registers of serious diseases or deaths, and of health service utilization, e.g. hospital admissions.

Design of case series

Case series research is a descriptive study to present patients in their natural clinical setting. The case series can be retrospective or prospective and may be consecutive or non-consecutive depending on whether all cases presenting to the reporting authors over a period were included, or only a selection [13].

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The study question should be focused and appropriate. The question should not be whether the investigated treatment is more effective or safer than another treatment. It should list the study population, the intervention and the primary outcome [4].

The setting: Select a suitable observation period and identify cases with events in this period. It may be tempting to include patients seen over a large period of time to increase sample size. However, the use of a short inclusion period minimizes known and unknown changes over time in co-interventions, prognosis, and even in the intervention under study [4, 14].

Number of cases: there is no thumb rule or a magic number. The general number of cases reported in a case series range from 20 to 50, but may vary from as few as 2 or 3 to as many as more than 100 [10] or even thousands [6].

N.B. Case-only analyses are sometimes performed in genetic epidemiology to investigate the association between an exposure and a genotype [15].

What to look for: Look at when the events arose in relation to the exposures. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment [4, 16, 17].

• *What:* The diagnosis or case definition should be clear and applied equally to all individuals in the series. The case definition should mention the inclusion and exclusion criteria, which should be based on widely used validated definitions. If authors use their own criteria, definition and justification are necessary to enable readers to compare the studied population with their own patients.
• *When:* The date when the disease or death occurred (time).
• *Where:* The place where the person lived, worked etc (place).
• *Who:* The characteristics of the population (person).

Noting the socio-demographic characteristics of a series of cases, as well as the temporal and spatial distributions can sometimes provide a clue to risk factors and hence help generate a hypothesis. This can be tested subsequently with more elaborate analytic studies.
• The opportunity to collect additional data from medical records (possibly by electronic Data linkage) or the person directly.

A detailed description of the intervention and the co-intervention should be stated. This will ensure repeatability of the study by other investigators. It is very important to thoroughly describe co-interventions. Additionally, indications for the studied treatment should be explained. This will primarily determine the consistency of the patient group [4].

The blinding of outcome assessors is ideal in every kind of research design and can be implemented quite usefully in case-series studies (e.g., by having some investigators collect data only on an outcome and others collect data only on patient characteristics). This prevents the investigators' measurements from being influenced (intentionally or unintentionally) by their personal treatment preference [4].

The method of data acquisition (telephone interview, clinical measurement, or chart review) should be addressed in the study report for the sake of repeatability and the appraisal of measurement bias [4].

Analysis: As the design of a case series is descriptive, only descriptive statistics should be used. Case-series data are analyzed using rates. In three circumstances (spatial clustering, stable population and when there is no suitable denominator) use proportional ratios, not rates.

Findings can be presented as proportions (%) of the study populations with the outcome, confidence intervals; means, standard deviations for continuous variables and consider subgroups that need data presented separately [18]. No comparative tests yielding p values

should be done. By describing summary statistics, the author errs on the conservative side of speculation and avoids misleading with fancy probability statistics [19].

Reporting: A statement of the external validity of the obtained data should be given. This includes (1) patient characteristics and (2) completeness of follow-up. The presence of chance and the presence, direction, and magnitude of bias should be acknowledged [4].

Patients may differ according to prognostic variables, such as age, etiology, and disease severity among geographical regions. This may complicate comparisons with other reports or explain discrepancies.

The follow-up rates and reasons for loss to follow-up should be stated. Completeness of follow-up varies considerably among similar case series, making it difficult for readers to compare them. Therefore, authors should be cautious when interpreting their own results in relation to results of apparently similar case series [20].

No absolute conclusions on the studied treatment should be stated, the lack of a comparison group prohibits any hypothesis from being tested. Valid conclusions basically repeat the descriptive study findings e.g. our patients treated by treatment X showed good outcome Y after Z months of follow-up [21].

Advantages [4, 14, 22, 23, 24, 25, 26]

1) High external validity: the study results are closer to those obtained in routine clinical practice and may, therefore, be considered more relevant.
2) It could be useful when a randomized controlled trial is not appropriate or possible.
3) No interference in the treatment decision process
4) A wide range of patients
5) Study conduct takes little time
6) Easy to write and can be useful in new observations or disease.
7) Useful for hypothesis generation, but conclusions about etiology cannot be made.
8) Informative for very rare disease with few established risk factors
9) Informs patients and physicians about natural history and prognostic factors
10) Easy and inexpensive to do in hospital settings
11) Can help identify potential health problems such as the acute outbreaks of the severe acute respiratory syndrome (SARS).
12) Stimulate interest in an area, leading to more detailed studies, and advancing knowledge
13) An important link between clinical medicine and epidemiology
14) One of the first steps in the outbreak investigation
15) Can provide the key to sound case-control and cohort studies and trials. Many case series are followed by clinical trials.
16) Provides "anecdotal" evidence about a treatment or adverse reaction
17) The case series method is self-matched: estimation is within-individuals.
18) As a result, all fixed confounders are automatically controlled: for example, socio-economic level, genetic factors, location, diet, state of health.
19) Only uses information on cases: no controls are required.
20) Clinical case-- series are of value in epidemiology for:

- Studying predictive symptoms, signs, and tests
- Creating case definitions
- Clinical education, audit, and research
- Health services research
- Establishing safety profiles

Disadvantages [1, 4, 10, 16, 20, 22, 26, 27, 28]

1) Lack of a control (or comparison) group this raises the question "compared to what?"
2) Data collection often incomplete
3) Generally short-term
4) Lack of a denominator to calculate rates of disease
5) Strong publication bias favoring positive results
6) Cannot study cause and effect relationships
7) Cannot assess disease frequency
8) Lacks external validity because cases may not

be representative
9) An outcome may be a chance finding, not characteristic of the disease
10) Cannot easily examine disease etiology
11) Not planned before and lacks hypothesis and are often not considered by many authorities to be research studies.
12) Selection bias (investigators self-select): The selective nature and the limited amount of information provide little evidence of causality and cannot say much about patterns of disease occurs due to seasonal nature of some diseases. A series of patients with a certain illness and/or a suspected linked exposure draw their patients from a particular population (such as a hospital or clinic) which may not appropriately represent the wider population.
13) Very low internal validity due to the lack of a comparator group exposed to the same array of intervening variables. The effects seen may be wholly or partly due to intervening effects such as the placebo effect, Hawthorne effect, time effects, practice effects or the natural history effect.
14*) Information bias*: Cases can be retrieved retrospectively or collected prospectively. Information on cases retrieved retrospectively is generally more objective, as it is collected routinely in relevant medical records. Missing or incomplete information could be an issue. For prospectively collected information, it is desirable to have standard protocols and forms to collect the necessary information, to avoid missing data for some patients. In a purely descriptive case series, confounding is not a concern, as the association between a certain factor and an outcome is not being studied.
15*) Sampling variation*: A precise estimate of the rate of a disease, independent from chance, can be obtained only by increasing the number of diseased subjects.

Case series that was instrumental in the early identification of health problems: [26]

-*Congenital rubella syndrome*: The classic description of a series of infants born with congenital cataracts, some with additional cardiac abnormalities, in Australia in 1941. This led Gregg in Sydney to postulate a causal link between a severe epidemic of rubella that had occurred six to nine months before the children were born and the subsequent abnormalities. It is now well known that if a woman develops rubella during pregnancy it may affect her unborn baby.

-A case report published in the UK in 1961 described the development of a pulmonary embolism in a 40-year-old pre-menopausal woman, five weeks after she had started using an oral contraceptive (OC) to treat endometriosis. Because pulmonary embolism is rare in women of that age, the author suggested that it might have been caused by the OC, particularly since it was a novel exposure at that time. More detailed studies have consistently shown that there is an association between the use of OCs and the risk of pulmonary embolism.

-A report of a series of five cases of Pneumocystis carinii pneumonia that occurred in young, previously healthy, homosexual men in three Los Angeles hospitals in a six-month period during 1980–81. Until then, this disease had been seen almost exclusively in immunosuppressed e.g. the elderly, the severely malnourished and those on anti-cancer chemotherapy. This cluster of cases in young men suggested that the men were suffering from a previously unknown disease, possibly related to sexual behavior which was proved to be HIV/AIDS.

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