Scoping Review

Definitions and Methods for Analysis of Multiple Cause of Death: A Scoping Review

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Abstract

Objective: This review aims to identify and categorize demographic methods used in modelling multiple causes of death. The assumption that each death is caused by exactly one disease is debatable, as other possible diseases or causes may be associated with the main cause. Hence, the multiple causes of death approach is essential for understanding mortality. Therefore, through this study, we will carry out a Scoping Review of the existing literature on the topic of MCOD.

Inclusion criteria: This review considers literature pertaining to methods for the analysis and utilization of multiple cause of death data. Papers that discuss the methods used as well as the strengths and limitations of multiple cause of death approach will be considered for this study.

Methods: Preliminary searches were conducted in July 2022 and focused on concepts of multiple cause of death mortality and multiple causes of death. Searches were conducted in PubMed, Web of Science, and Scopus and was conducted in English, French, Spanish and Portuguese. There were no time constraints on the studies to be included in this review. Articles were initially screened by title and abstract and then reviewed by full text by three independent reviewers. Two reviewers extracted the data from the eligible articles.

Results: A total of 769 papers were reviewed at the abstract and title level. Of these, 124 were screened for full-text eligibility. A total of 53 articles were included in the final analysis. Among the articles included, 31 were articles from the United States, 14 were from Europe and 8 were from other countries. The papers were categorized as methodological (33) papers, data assessment papers (19), papers discussing socioeconomic differences in mortality (13) and mixed method papers (11).

Conclusions: There are many different types of methodologies and procedures used to analyse multiple cause of death statistics. All papers included in this study used descriptive methods (mostly frequency tables and cross-tabulations) to analyze multiple cause of death data, and almost half of them use visualizations to model the results. One of the most common limitations cited among the articles is the comparability of the statistics. Accurate data and analysis of vital statistics require resources, and many countries do not have the to report high-quality statistics. This could explain why most of the papers selected for this study focused on data from developed countries.

Keywords: mortality; cause of death; contributing cause of death; multiple cause of death; underlying cause of death

1. Introduction

The analysis of the causes of death from a single cause represents a significant limitation to understanding the burden and impact of various conditions on mortality in a population. It has long been recognised that multiple causes of death (MCOD) may be defining factors in mortality outcomes. As such, is not always a single underlying disease or condition on the
death certificate that shows the most accurate picture of what triggered a person’s death. The World Health Organization (WHO) defines the Underlying Cause of death as the disease or injury that initiates the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury. While a contributing cause of death is defined as “any other significant condition that contributes to the fatal outcome but are not related to the disease or condition that directly causes the death.” (WHO, 1948)

In the 1930's, associated or contributing causes of death started to be recorded on death certificates along with the previously recorded underlying causes of death (29). Demographers, epidemiologists, physicians, and professionals from various health fields saw the value in multiple causes of death as the opportunity to have an in-depth mosaic to the health conditions presented at the time of death. Despite the early recognition, MCOD are not routinely reported in national statistics or included in mortality analyses. This gap is partially due to the complexity in determining how various diseases and conditions may contribute to an individual’s death; but it is equally due to the confusion and lack of clarity surrounding methods for reporting MCOD. Demographic methods for analysing and reporting MCOD have grown slowly and are often not easily interpretable or comparable and the limitations of different methods are not widely understood.

This scoping review seeks to fill this gap by examining the literature regarding the analysis of MCOD and to categorise the available methods. A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted. Although in some papers a review of the literature and the main methods used were carried out, (1,15,16) no current or in-progress scoping reviews or systematic reviews on the topic were identified.

From the review of the included literature, we have found three fundamental axes in which the studies on MCOD are divided: data assessment, socioeconomic studies, and methodological analyses. Studies that focus on data evaluation aim to measure the accuracy of the data observed on the death certificate. In many cases, alternative measurement proposals are made (8,15), and new recording and processing methodologies are analyzed (7, 18, 22, 29). More than a few of these studies have a purely descriptive approach (8, 10, 18,29), while others use more complex models (11,19,27,44). Second, socioeconomic studies seek to identify correlations between MCOD, the socioeconomic profile of the deceased, and their environment in general. Third, studies that are methodological in approach try to identify new methods for analysing MCOD data, explore how to use multiple cause mortality, and how to interpret the resultant information.

2. Methods

Review Question

Three specific questions will guide our study: how is the concept of multiple causes of death defined in literature; what are the methods and procedures used to analyse and enumerate MCOD; and what are the strengths and limitations of the identified methodologies?

Inclusion Criteria

This review considered studies that explored methods used for modeling contributing causes of death in relation to underlying causes of death. Papers discussing statistical methods that are used to measure the differences and rates for MCOD analysis were considered for this study. Also included in this review was the literature that evaluates the strengths and weaknesses of methods to analyze MCOD. Papers discussing analysis and usage of methods of analysis of MCOD data were also taken for this review. Finally, we considered studies examining methods for analyzing sociodemographic inequalities following the MCOD approach.

Participants

This review was not narrowed by population or participant group and considered all studies that analysed multiple causes of death.

Context

This review considered studies that were written in English, Spanish, Portuguese, or French in any country or locale.

Types of sources
This scoping review considered peer-reviewed publications using mixed methods, data assessment, or methodological study designs for inclusion in the review. In addition, systematic reviews, text, and opinion papers were considered for inclusion in this scoping review.

**Search Strategy**

The search strategy aimed to locate both published and unpublished primary studies, reviews, methodological studies, data assessment papers, and text and opinion papers. An initial limited search of Scopus, PubMed and Web of science was undertaken to identify key articles on the topic. The text words contained in the titles, abstracts, and the index terms of relevant articles were used to develop a full search strategy. The search strategy, including all identified keywords and index terms, was adapted for each information source and a second search was undertaken in July 2022. The full search strings are provided in Appendix I. The reference lists of articles included in the paper were also screened for additional papers that may not have been included in search results.

Studies published in English, French, Spanish and Portuguese were included as all reviewers fluently speak English and some of the reviewers are fluent in French, Spanish and Portuguese. There is no date range on the studies, published or unpublished, that were included as this scoping review aims to highlight the various definitions and methods that have been developed and used in practice for the analysis of MCOD.

Articles were excluded if they were not explicitly methodological in nature or did not discuss methods for MCOD analysis. This excluded a significant number of articles that used MCOD approaches but did not discuss or compare the methods used.

**Source of Evidence Selection**

Following the search, all identified records were collated and uploaded into a custom database and duplicates removed. Following a pilot test, titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria. Potentially relevant papers were retrieved in full, and their citation details imported into a reference management software. Full-text studies that did not meet the inclusion criteria were excluded, and reasons for their exclusion are provided in Appendix III. Any disagreements that arose between the reviewers were resolved through discussion, second review by both reviewers or/and with a third reviewer.

Table 1. Search strategy. Retrieval results from PubMed (via NLM) on Dec. 12, 2022.

<table>
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</tr>
<tr>
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<td>#4 OR #5</td>
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</tr>
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<td>#7</td>
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<td>12,284,057</td>
</tr>
</tbody>
</table>
Data Extraction

Data were extracted from included papers by two independent reviewers using a custom data extraction tool. The data extracted included specific details about the author, country, sub-geography, data source used, period, pathology, level of analysis, cause coding (ex: International coding of diseases), cohort or period study, age group and sex of participants, social disparities, methods (descriptive, analytic, visual), type of study (data assessment, methodological, mixed method, socioeconomic study) and conclusions relevant to the review question. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer. Authors of papers were contacted to request missing or additional sources where required.

Data analysis and Presentation

The types of methodology (descriptive, analytic, visualization) and the specific procedure (cross-tabulation, total mention, CDAI, Poisson regression, and others) is presented in tabular form. Some of the more specific methods will be explained in depth in an accompanying narrative text. A narrative summary accompanies the presentation of information, describes, and evaluates the methods used in the selected literature. We also discuss strengths and weaknesses of the methods for MCOD analysis in relation to the methods used to analyze underlying cause of death data.

3. Results

Study Inclusion

The searches done in three independent databases identified a total of 769 unique sources after the removal of duplicates. After title and abstract screening, there were 696 articles excluded and 73 of the papers were selected to be reviewed in full. In the full-text search, 54 papers were identified as relevant to the research. An additional article was excluded upon further investigation for reasons mentioned in the flowchart (Figure 1), the article did not pertain specifically to multiple-cause-of death data. A total of 53 articles were included in the final data extraction and analysis.

Characteristics of Included Studies

Since the mid 1980’s there has been a steady increase of research into MCOD and the methods to analyse and present MCOD statistics compared to the traditional approach of analyzing only underlying cause of death data. Of the articles selected, 24% (24.528% [13/53]) of the articles were published in the last 5 years (2021-2016), 53% (52.8301% [28/53]) were published in the last 20 years (2021-2001) and 92% were published in the last 40 years (1981-2021) with just five articles published before 1981. Over half of the articles included in the study were methodological papers (56.60% [30/53]), followed by papers focusing on data assessment (37.74% [20/53]), twenty percent were articles addressing socioeconomic
inequities (22.64% [13/53]) and mixed studies representing a fifth of the papers included in the study (20.75% [11/53]).

Due to the limited accessibility of reliable mortality statistics and the process involved in the analysis of vital statistics, most articles included in the study are from authors or case studies in developed countries. An overwhelming majority of the papers used data from North America (58.49% [31/53]), 14 of the papers used data from Europe (26.42% [14/53]), and the remaining 8 papers were from other countries. Of the datasets in the papers, 48 (90.57% [48/53]) used vital statistics, 3 (5.66% [3/53]) of the papers used linked administrative data, 4 (7.55% [4/53]) of the articles used survey or census data, 2 of the other papers used other types of data (3.77% [2/53]).

**Types of Methods and Designs**

The studies used four main types of procedures: descriptive, analytic, mixed, and primarily visualization, although all studies included some element of descriptive methods. Analytic methods were used in 20 (37.74% [20/53]) of papers, 10 (20.75% [11/53]) studies used mixed methods of analysis, and 24 (45% [24/53]) used visualizations to present and provide interpretation of results. There were many different types of descriptive methods used to analyze data, such as standardized mortality rates, ratios of total mention per underlying cause of death, counts of contributing causes in compared to counts of underlying causes, and the number of expected deaths versus observed deaths for underlying and contributing causes.

Most papers used some form of cross-tabulation (53.85% [28/52]) and frequency tables (79.25% [42/52]). Around 8% (7.54% [4/53]) of the papers used matrices to support their findings. Mortality rates (28.85% [15/52]) and rate ratios (25.00% [13/52]) were frequently used along with cross tabulations and frequency tables. In addition to descriptive methods, 25 (47.16% [25/53]) also included visualizations via as line, bar, or pie charts to represent their findings, but only 2 papers used more advanced visualization techniques.

**Key Findings**

Most of the papers reviewed suggest the inclusion of other practices to analyze human mortality as alternatives to the traditional approach of using only the underlying cause of death. More than 73% (73.58% [39/52]) of the papers suggested that using MCOD enhances mortality analysis and should be presented alongside underlying cause statistics. The overarching findings from the papers included in this study were that using only underlying cause of death method of analysis chronically underestimates the role of certain diseases and conditions play in a population. There was a widespread consensus that there needs to be more accurate methods of mortality analysis employed globally to obtain an accurate idea of the MCOD and to compare results from different regions and countries.

Papers focused on data assessment found that in some cases the classification of diseases can differ between countries as doctors may perform different procedures. One example was between France and Italy, where differing practices can result in both overestimation and underreporting of specific causes of death in one or another country and influence comparability between countries (13, 14). Hence, the preparation of the certifying physician and practitioner is essential, with the advice and training from international organizations important for a better homogenization in the completion of the cause of death and subsequent coding of the MCOD (14).

The use of MCOD can reveal valuable information for the elaboration of public policies. In this sense, if some diseases such as diabetes are observed only as underlying cause, the actual impact on the population would be unknown due to its high incidence as a contributing cause (43). Socioeconomic studies, such as Manton (1980), highlight the importance of MCOD analysis for public policies that mitigate racial inequality. After a correct validation of the coding, the analysis of the MCOD makes it possible to measure inequity in access to health among certain populations, as was the case between whites and blacks in the United States in 1969. A better knowledge of the health condition and therefore, the presence of a greater number of comorbidities among whites in relation to blacks seems to be the result of precarious access to health services and lower life expectancy among the US black population at that time (33).

Even though the fact that United Nations have structured the International Classification of Diseases (ICD) globally since 1948, not all countries can carry out its execution in the same fashion. This highlights the imbalance in terms of health information, as MCOD can disproportionally influence public policies and further increase health asymmetries between
low-income and high-income countries. Necessarily, developing countries need more training and financial resources in order to improve the collection and dissemination of vital statistics and thus enhance international comparability levels.

**Descriptive Models**

There were numerous types of descriptive methods used in the articles reviewed. Outlined in this section are the most used descriptive models. Frequency tables and cross tabulations are commonly used in the analysis of mortality statistics as they are relatively simple models and are easily interpretable by non-specialists. Cross tabulations are used to highlight relationships that otherwise might seem unrelated, with the most common combinations being number of mentions for specific causes, counts by cause, mortality rates, standardized rates (age, sex and race standardized) by the specific cause of death, type of mention (underlying, contributing, total mentions), sex, socioeconomic identifiers (race, education, income, region). Some papers analysed death certificates by the number of causes mentioned by the country of the death certificate (26). Other papers (32) examine the age-adjusted prevalence ratio by the underlying and secondary cause of death.

Most (73.58% [42/53]) of the papers included in this study used frequency tables in their analysis. Frequency tables most often included standardised rates per 100,000 by cause of death, race, and year of death (11).

Two types of basic ratios were often employed. The first is the ratio of contributing to underlying causes of death for various underlying causes (8, 28, 37, 51) and the second calculates the ratio of total mentions to underlying cause of death (10, 11, 33, 36).

The average number of causes included on the death certificate is another indicator used, where the average number of contributing diseases reflects the pattern of the health of the deceased. It is expected that those with a lower number of contributing causes indicate better health conditions, while a higher number of contributing causes reflect worse health at the time of death. This is clearly related to age at death, where the longer a person lives, the more comorbidities they are likely to accumulate.

There are other variables present in death certificates that are relevant to mortality analysis. One example is marital status, if the deceased partner survives them then they can provide more in-depth information on the person’s health status at death and give information about the state of health the decedent was in at the time of death (16). The basic limitation to these indicators is the difficulty in terms of homogeneity, therefore reinforcing the need to establish a standardized method of mortality statistics reporting, such as standardized rates by sex and age of the decedent.

Many studies performed calculations of mortality rates by age and sex. This is done to find patterns and make comparisons. In several of them, the specific rates were standardized by age and sex allowing comparisons between populations. An example is sex-specific mortality rates calculated using Total Mentions (TM) or UCD assignments as the numerator and population at risk of dying as the denominator (10). While age-specific mortality rates were calculated by sex and race for specific causes of death. In the latter, the age-specific mortality rates were calculated by the age-specific number of deaths by the given cause of death which are specified as either UCD or MCOD divided by the number of the population alive at a specific age.

Another common method was the standardized ratio of multiple to underlying causes (SRMU), which is used to determine the extent to which certain causes of death are underestimated in the mortality process and investigate other diseases that are noted on death certificates (4, 13, 14, 15, 16). The SRMU is primarily used to investigate the roles that selected infections and diseases play in mortality processes. Often, SRMU is used as an indicator, where for a specific cause of death, the SRMU is calculated as the ratio between the MCOD mortality rates and the UCD mortality rates, both standardized by sex and age. The SRMU is also used for the calculation of CDAI, another indicator that could be very useful in the analysis of mortality statistics.

Several studies have proposed a cause of death association indicator (CDAI) which eliminates the possible effects of age structure (14, 15, 16, 48). This method was initially performed to calculate the contributing disease of senility, Parkinson’s, dementia, and Alzheimer’s for deaths occurring at the age of 65 or older in the year 2008 for France and Italy respectively.

**Analytic Models**
In the literature dealing with MCOD, a variety of models have been used, ranging from the calculation of odds ratios to the use of Logit regression or complex multilevel analysis models. In most cases, these methods used to analyze a given period, but are also sometimes used for selected cohorts over several years. Among the studies that analyze a specific disease or group of diseases for a period, those that examine from the point of view of life tables can be highlighted for trying to estimate or eliminate the independence between the causes of death (34, 35, 37, 39).

Among the analytical models, in the literature on MCOD, logistic regressions are used to estimate odds ratios of dying from a certain disease (45) or to know if there were multiple causes or not in the death certificate (50). Poisson regressions have been used to determine the impact of some socioeconomic variables on the average number of multiple causes (16). In addition, ordinary least squares regressions have been tested both to estimate measurement errors in the number of deaths (19), and to measure the impact of sociodemographic variables such as race, sex, or education on people who died as a result of a single cause in relation to deaths due to multiple causes (23). In most cases, cross-sectional analyzes have predominated, making it difficult to determine the relations of causality.

In this sense, some longitudinal studies have been carried out through the use of Cox proportional hazard models. For example, in (11) the authors examined the associations of each of six factors with either underlying cause or any mention mortality for cardiovascular diseases; cancer; diabetes; Influenza-pneumonia-bronchitis; renal diseases and other conditions. While in (27) Cox proportional hazard models were used to estimate the gross and net associations of ethnicity with the overall sex-specific, age-specific, and cause-specific mortality.

Visualization

Most articles analyzed were accompanied by basic graphs, maps, or diagrams to visualize analytic outcomes or descriptive statistics. Half of the papers (47.17% [25/53]) used visualizations to model the relationship between contributing causes of death and underlying causes of death. Most commonly, papers used simple line or bar graphs comparing elements such as mortality rates (and age-standardised mortality rates), average number of reported causes and number of deaths by sex, race, year of death, age/age groups, and/or type of attribution (10,14). Some papers also have used scatter plots to illustrate the standardized mortality ratio for MCOD on the y axis and the SMR for underlying causes (51).

Of the 25 papers using visualisations in their analysis, 6 of them used a visualization matrix in their analysis. Three of the 6 used matrices to model the relationships between underlying causes and contributing causes using CDAI values (14, 15, 16). Two of the matrices presented values using the area of circles at the intersection points, which gives a rough estimation of the difference in CDAI values (14,16). Other methods include using squares with different shading to indicate different levels of association between the causes of death (15).

Maps were only used in one paper (53), to show the life expectancy for males and females within an urban area. This was done to highlight the life expectancy differences in different areas of Vancouver, and to show how those in lower income/low socioeconomic classes have a lower life expectancy.

Lastly, one of the papers included in the study uses network analysis to analyse the associations between causes of death for males and females. This model shows the connections between underlying and contributing causes by connecting them with different coloured lines creating a network web to signify the type of relationship they have to each other.

4. Discussion

The results from this comprehensive scoping review indicate that there are numerous methods and models used in the analysis of and presentation of results from multiple cause of death data. While most studies use common demographic calculations such as crude mortality rates, age-standardised mortality rates, and rate ratios, there are few consistent indicators that take advantage of the power of MCOD data. The inclusion of MCOD in regular reporting of mortality will at the most basic level, be consistent with the conclusion that no single cause can adequately describe the morbid conditions responsible for a death (Janssen 1940, Dorn & Moriyama 1964, Guralnick 1966). Standard methods of reporting mortality have certain limitations when considering MCOD, particularly in assumptions about independence/dependence among causes (Desequelles 2012). However, there are basic guidelines and
powerful indicators that can be used for MCOD data. In addition, new methods of visualization show the potential for using graphics to extend the interpretation of basic statistics and indicators.

**Purpose:** The selection of methods for MCOD analysis is highly dependent on the purpose for which they are conducted. Most contemporary studies focus on calculating mortality rates that are reflective of all conditions indicated on a death certificate, or on exploration of cause of death combinations.

**Ease of interpretation:** An aspect of demographic or epidemiologic indicators that is often overlooked is the ease by which they are interpretable by non-specialists.

**Availability of data:** While multiple causes of death are recorded on most death certificates globally, the extent to which these data are of high quality. Furthermore, data are often not comparable between countries or over time given differences in coding practices or even differences in health interventions at the end of life.

Many of the methods used by the reviewed depend highly on the availability of high quality data. For example, in (51) they managed to find interesting results based on the large number of sociodemographic variables that are present on US death certificates. According to the authors, the place where death occurs, whether a long-term care institution, a hospital or a household, may imply that there is a better knowledge of the health history of the patients and, therefore, a greater number of comorbidities appear in the certificate. This important result could indicate that any information regarding the MCOD must consider the place where the death occurred in order to avoid bias in certain comparisons such as the number of comorbidities that an individual presented at the time of death. On the other hand, longitudinal studies as the Cox proportional hazard model (11, 27), allow the evaluation of changes in the age and disease composition of a society and support the MCOD approach with the theory of demographic and epidemiological transition. In addition, they offer a more approximate overview about the causal relationship that may be operating. They have the disadvantage that they require more information and data processing may take longer.

It should be highlighted that the use of analytical models does not imply obtaining better results in the domain of MCOD. Some articles based on descriptive analysis (e.g: 14, 18, 29, 34, 43) manage to explore causal relationships and serve as input for the development of health policies. In this sense, the use of a single source of data, such as vital statistics, calls into question the results of analytical models that try to find socioeconomic explanations using data with a limited scope. Indeed, the analysis of data linked to the Census would be an alternative to achieve a better accuracy using analytical models. Hence, the question of inequality between countries and regions arises again. In contexts of greater poverty and inequality, the need to explore the triggers of death is frustrated by the absence of vital statistics with adequate accuracy. Furthermore, the high cost of collecting other sociodemographic variables on a regular basis has a negative impact on the preparation of public health diagnoses for poorer countries. This shows the inequality in terms of the concerns on which researchers from one or another context are focused. If, on the one hand, academics from developed countries can now concentrate on seeking socioeconomic explanations (5, 10, 11, 16) about the cause of death of an individual due to the quality and scope of the statistical information they have. Researchers from developing countries concentrate on methodological and data assessment studies (45, 46, 48).

5. Conclusions

This review has found a wide variety of methods and models used to analyze and present statistics related to the MCOD. While other papers have reviewed demographic methods used for MCOD analysis, there have been no other comprehensive scoping reviews on this topic.

The literature on human mortality is wide and varied, since historically researchers have tried to explain the reasons that lead to the fatal outcome of a human being. It is widely recognized by demographers, epidemiologists and especially by professionals in the health domain that studying mortality through a single cause implies a considerable loss of information since other potential factors that may be associated with the death of a person are not considered. From these considerations, the study on MCOD begins to be understood as essential in the mortality analysis. As vital records have evolved, different authors have proposed numerous methodologies that allow the information contained in death certificates to be investigated in greater depth. The interaction between academia and medical praxis has also led to an expansion of the information collected on death certificates beyond demographic variables. In this sense, other considerations such as education or income level,
marital status and race are also included in the vital statistics or can be obtained through the link with the census data. From this, several studies analyze not only the technical part but also go further by observing the sociodemographic relationship of the MCOD and the individual’s environment.

In this scoping review we have found three main research axes about the analysis of MCOD: Data assessment, methodological and socioeconomical papers. A large part of the articles studied comes from developed countries, which are the ones that ultimately have the best vital registration systems. In this sense, to the extent that a country has an adequate quality of registration and manages to collect a greater number of socioeconomic variables, it is possible that the analysis of deaths goes beyond the validation of the vital records themselves. For this reason, methodological and socioeconomic analyzes of MCOD have expanded in recent years. However, a fundamental aspect for better cohesion and homogenization that allows the comparability of the MCOD is an adequate registration and coding of the diseases listed either as CCD’s or the UCD. To achieve this, training programs that guarantee a better specialization of practitioners as well as the massification of automated coding systems would be essential. Hence, the support of developed countries is becoming more evident at a time when contagious diseases with a global impact, such as COVID-19, emerged. The approach of the MCOD becomes extremely necessary in this context for which the investment in the improvement of vital statistics appears as urgent.

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