Global, regional, and national time trends in myocarditis-related mortality, 1990-2019: An age-period-cohort analysis

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Abstract. – OBJECTIVE: The aim of this study was to analyze the tendency of myocarditis mortality in 204 countries and areas during the last three decades and its connection with age, epoch, and birth cohort.

MATERIALS AND METHODS: The Global Burden of Disease 2019 Study acquired a cause-specific myocarditis mortality estimate. The net drift, as well as the influence caused by age, period, and birth cohort, were evaluated by the age-period-cohort model. Additionally, we analyzed the tendency in research intensity and international collaboration across countries using 3,983 myocarditis-related publications from four periods during 1990-2019.

RESULTS: During the last three decades, 101 of 204 countries and areas experienced an increase (net drifts ≥0.0%) or stagnant declines (≥-0.5%) in the death rate. In particular, increasing death rate was generally discovered in most countries whose Socio-demographic indexes (SDIs) are high and middle-high, such as the United States [net drift=2.11% (95% CI 1.71-2.51)] and Italy [2.65% (1.24-4.08)]. Countries with a higher number of deaths were more active in this field of study, such as the United States (237 publications), China (120), and Italy (73). The United States and Italy, whose total link strengths were 209 and 135, respectively, were more active in international collaborative studies.

CONCLUSIONS: Despite the global decrease in myocarditis death rate during the last three decades, negative period and cohort effects and elevated mortality were discovered in numerous countries, especially in those whose SDIs were high, and the age distribution of deaths shifted from adolescent to middle-aged and older populations. We also observed a decline in myocarditis research in some countries with increased mortality.

Key Words:
Myocarditis, Bibliometrics, Death rate.

Abbreviations

APC: Age-period-cohort; GBD: Global burden of disease; LMICs: low- and middle-income countries; SDI: Socio-demographic index.

Introduction

Myocarditis is a common disease that may result in sudden death or chronic dilated cardiomyopathy, which has a wide range of syndromes from mild dyspnea or thorcalgia (which can be resolved without no special treatment) to cardiogenic shock or death[1,2]. The risk factors for morbidity and mortali-

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ty tend to differ between regions. As for developed areas, myocarditis usually results from immune diseases and viral infections; however, for developing areas, bacterial and parasitic infections such as rheumatic heart disease, Chagas disease, and diphtheria remain important etiologies[1,2]. Although the prognosis of acute myocarditis in the short term is generally good, patients may suffer from recurrent dilated cardiomyopathy and cardiac failure after several years. Studies[3-5] have discovered that biopsy-proven myocarditis can grow into dilated cardiomyopathy in up to 30% of cases and is in relation to adverse outcomes. Myocarditis is generally considered to be a disease with a high prevalence in pediatric and adolescent populations, but it has the potential to cause permanent myocardial damage across the entire life span[6,7]. Therefore, chronic condition tracking and cardiac care are of great significance for patients with myocarditis throughout their lifespan.

It is essential to conduct a deep analysis of the time tendency in myocarditis death rate in all countries for the purpose of tracking the changing trends in mortality and identifying policy priorities for prevention and control. As for patients who suffer from myocarditis, death rate risks can be deconstructed into age, period and birth cohort effects. The risk of death resulting from myocarditis not only depends on the age but there may also be differences between birth cohorts as new diagnostic and therapeutic approaches are introduced. The diagnosis of cardiac defects in adolescence has a long-term influence on life outcomes[8]. Technical progress, as well as health policy changes associated with the diagnosis and management of myocarditis, may also have an influence on all individuals over a specified period, irrespective of age and birth cohort. In that respect, the analysis of death rate tendency, with special attention to its relation to age, period and cohort effects, may determine the positive and negative effects of different healthcare and lifestyle habits and the treatment gap. For instance, a preceding study[8] carried out by the United Kingdom analyzed age, period and birth cohort tendency in coronary heart disease death rate among children with the purpose of determining the progress in pre-production test and pediatric cardiac surgery during 1959-2009.

To our knowledge, no studies have delineated global trends in myocarditis mortality and distinguished the relative influence age, period, and cohort effects have on the death rate. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is a cooperation among nations that adopts a consistent approach and all obtainable population-level data to calculate population health metrics, offering a special chance to analyze disease tendencies across the globe[9]. Particularly, its 2013 GBD project[10] refines the epidemiological statistics on myocarditis by incorporating a more comprehensive database and more precise case definitions, providing analyses based on this data. We introduced GBD 2019 data and age-period-cohort (APC) models with the purpose of analyzing changes in myocarditis death rate in 204 countries and areas during the period 1990-2019.

Materials and Methods

Data Sources

GBD 2019 offers recent estimates of the descriptive epidemiology data about 369 kinds of diseases across 204 countries and areas from 1990-2019[11,12]. Each death in the GBD dataset was allocated to a singular potential cause in a disease list that is mutually exclusive and collectively exhaustive[12]. Details of data entry, handling, synthesis, and eventual models are obtainable in the attached GBD 2019 publications[11]. The GBD network adopts standardized tools within a Bayesian framework with the purpose of making use of all obtainable data on time, age, geography and health area in order to acquire disease estimation; which can benefit the estimation of the global burden of myocarditis in all countries. All disease estimates offered by GBD include 95% uncertainty intervals (UI) for each metric based on the 25th and 975th orderly values of 1,000 simulated draws of the posterior distribution. Generally speaking, countries that have little or even no data sources have a 95% UI relatively larger, indicating that disease estimates have higher incorrectness. In particular, many countries, especially those in Africa, are short of primary data for myocarditis mortality[13]; as a result, death rate estimates for such areas include modeling results using data for myocarditis from other regions. This investigation adopts the Socio-demographic Index (SDI) obtained from every country, a comprehensive Index of average per capita income, average Year of education, and fertility rate in females younger than 25 years old. The SDI ranges from 0 to 1. The higher the numerical value, the higher the socio-economic level is. All areas were categorized into one of five SDI quintiles according to the 2019 SDI from highest to lowest[11].

Analysis of Overall Time Tendency in Death Rate

Time tendency in death rate was evaluated according to death rate of all age and age-standardized death rate, and the relative percentage variation in death rate from 1990 to 2019. The global age-standard population data was adopted to calculate the age-standardized death rate[12]. By dividing death counts into five age strata (0-9, 10-19, 20-29, 30-49, and 50+ years), we also analyzed the age structure of deaths and calculated the death ratio of every age group.

Age-Period-Cohort Modeling Analysis of Death Rate Data

This essay utilized an APC model to examine the potential correlation between age, period, and birth cohort[14] and the mortality rate, with the objective of uncovering the impact of biological factors in relation to age, technological advancements, and social factors on disease susceptibility[15]. The APC model is applied by introducing R tools which are free[16]. The model introduces the GBD 2019 death rate estimates on myocarditis and the population information of every country, in which the age and period intervals are equal, both at 5 years. As the GBD estimates are generated with the data format with unequal intervals, we arranged the data by choosing them according to death and population from the middle of the year in 18 five-year periods (i.e., 1992 for 1990-1994, 1997 for 1995-1999 and so forth) to represent the specific period. For age and cohort data, the input data consisted of 18 age groups (from 0-4 years to 85+ years in five-year group intervals) and 23 partially overlapping five-year birth cohorts, from 1903-1907 (the 1905 cohort) to 2013-2017 (the 2015 cohort). The fitted APC model estimated the overall time tendency in death rate, represented as the percentage variation per year of death rate. The APC model also makes an assessment of the time tendency of death rate in every age group, represented as the percentage variation per year of age-specific death rate, from which the tendency in birth cohort effects can be observed[15]. Even a drift of ±1% per year is considered a significant change in death rate[15].

Bibliometric Analysis

We checked the Web of Science core collection (account owned by Peking Union Medical College) for all literature for four time periods: 1990-1991, 2000-2001, 2010-2011, and 2018-2019, using the keyword "myocarditis", and obtained 444, 692, 1,143, and 1,704 papers, respectively, for inclusion in the study. The analysis and visualization of inter-country collaboration were performed using VOSviewer (version 1.6.16)[17]. Documents and total link strength were used to evaluate the intensity of research and the level of activity in international collaborations in each country during each period. Countries with more research papers had a greater frequency of occurrence (documents), corresponding to a larger relative area of points. For countries with more co-authors from different countries, the corresponding inter-dot connection line (indicating total link strength) is thicker. The data from four temporal periods were also used to show the academic trends in 13 countries.

Patient and Public Involvement

The data used in this essay is offered by the GBD database and involves the contents of patients and public participation statements.

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Statistical Analysis

The distinctiveness of tendency in percentage variation per year was analyzed by introducing a Wald Chi-squared test[15]. The comparative risk was calculated as the ratio of age-specific rates in each phrase relative to the reference phrase. Statistical tests were bilateral, and $p<0.05$ was considered significant. All studies were carried out in R (The R Foundation for Statistical Computing, Vienna, Austria), whose version is 3.6.3[16].

Results

Global and Regional Tendency in Myocarditis Mortality, 1990-2019

Supplementary Table I and **Supplementary Figure 1** show the population, death roll, death rate in all ages and age-standardized death rate, and net drift of death rate (on the basis of the APC model, which is similar to the percentage variation in death rate per year but covers both constituent parts of the tendency ascribing to calendar time and consecutive birth cohorts)[15]. The population across the globe increased from 5.3 billion (95% UI 5.2-5.5) to 7.7 billion (7.5-8.0); the amount of myocarditis deaths increased from 20,000 (16,000-27,000) to 32,000 (23,000-37,000), a 60% increase. Globally, the all-age-related mortality rates for myocarditis were 0.37 (0.29-0.5) per 100,000 in 1990, rising to 0.42 (0.3-0.48) in 2019. Nevertheless, the age-standardization death rate for myocarditis declined from 0.46 (0.38-0.6) per 100,000 in 1990 to 0.43 (0.31-0.5) per 100,000 in 2019. All-age mortality rates increased by 50% and 43.8% in regions whose SDIs are high and middle-high, respectively, but declined by 31.9% in regions whose SDIs are low. On a global scale, the APC model estimated a net drift of myocarditis death rate at -0.62% (95% CI -0.76 to -0.48) per year, with a decreasing tendency in all areas except those whose SDI was as high as 0.54% (0.33-0.75). The most significant decline was -1.24% (-1.38 to -1.1), in those regions whose SDI was in the middle level. Over the period 1990-2019, the regions whose SDI were high and middle-high accounted for a growing proportion of the deaths resulting from myocarditis globally.

National Tendency in Myocarditis Mortality, 1990-2019

Of the 204 countries and regions which are analyzed, 61 had at least 50 deaths in 2019, with China [N=13,141, (95% UI 7,672-16,378)], India [2,118 (1,565-2,808)], Italy [1,187, (190-2,005)], and Russia [1,186 (634-1,572)] accounting for 54.3% of deaths resulting from myocarditis across the globe. Meanwhile, 101 countries displayed an upward trend or a stagnant decline (≥-0.5%) in death rate, and the most pronounced rise was in Kazakhstan [net drift=8.87% (95% CI 7.31-10.46)]. In 2019, 51 countries had death rate rates in all ages for myocarditis that were higher than global levels, and 19 countries had rates that were more than two-fold higher than global levels. Age-standardized mortality rates also exceeded the global average by more than two-fold in 19 countries, the seven highest being Romania, Guyana, Mongolia, Bulgaria, Turkmenistan, and Croatia, most of which are countries with low SDI. Although lower mortality was discovered in countries whose SDI are higher such as North America, Europe, and the Asia-Pacific region, there was an increasing trend, such in the United States [net drift=2.11% (95% CI 1.71-2.51)], Italy [net drift=2.65% (95% CI 1.24-4.08)], and France [net drift=2.00% (95% CI 0.49-3.53)]. China and India, with the largest amount of deaths due to the enormous population, showed a declining tendency in mortality with a net drift of -1.19 (-1.39 to -1) and -0.36 (-0.63 to -0.09), respectively. Together, such outcomes show that the tendencies in myocarditis mortality were unbalanced for different countries and that the decline in the death rate was not necessarily matched with the SDI of the country.

Time Tendency in Myocarditis Mortality Among Various Age Groups

Supplementary Figure 2A displays the annual percentage variation in the myocarditis death rate among all age groups, from 0-4 years to 85+ years. The net drift reflects the overall percentage variation per year, with values <0 indicating a reduction in myocarditis mortality. Globally, decreasing trends in mortality were seen in those younger than 50 years, most notably in those aged 0-5 years (-3.02% per year, 95% CI 3.32 to -2,73), whereas increases in mortality were seen in the older age groups (>75 years). For high-SDI areas, there was an increase in mortality for those aged 20-80 years and a decrease in mortality for those younger than 20 years old or older than 80 years old. The steepest mortality increase occurred in women aged 50-55 years (1.31% per year, 95% CI 0.62-2.00). In the high-middle-SDI regions, mortality rates showed a decreasing trend for all those who are younger than 20 years old, particularly for those who are between 0 years old and 5 years old (-2.94% per year, 95% CI -3.57 to -2.30). The regions whose SDI is in the middle level showed a decreasing trend in mortality in the under-70 age group, most notably in the 0-5-year age group (-3.13% per year, 95% CI -3.40 to -2.86).

Supplementary Figure 2B presents the time variation in the age structure for death, which can be regarded as an indirect indicator of survival for those who suffer from myocarditis. The number of dead people across the globe transferred from the pediatric population (under 20 years old) to the adult (older than 20 years old), which was more evident in countries whose SDIs were in middle, low-middle and low levels.

Age, Period, and Cohort Effects on Myocarditis Mortality

We calculated the estimated value derived from the APC model in different SDI levels (i.e., age effects, represented as longitudinal curves to reflect the natural history of myocarditis death rate associated with age; period effects, represented as the relative risk of death rate by period and utilized to analyze advancement in various periods; cohort effects, represented as the relative risk of death rate by cohort and utilized to investigate variation in death rate in various birth cohorts). Overall, similar patterns of age effects, in which the risk of death increases with age, were found across SDI levels and were particularly evident in regions with SDI in the middle, high-middle, and low-middle levels. Compared with other regions, countries whose SDIs were high had lower death rates for all age groups. However, the mortality risk was 63.2% higher for women than men in the higher age groups (>85 years).

It could be seen that the risk of death rate across all countries is decreasing except those with high-SDI levels during the study period. However, only the countries whose SDIs were in middle and low level showed consistent decreases. Countries whose SDIs were in high, high-middle and low-middle level all showed an upward and then downward trend and started to decline after reaching a maximum in 2002, 2007, and 2007, respectively. In addition, in almost all countries, the risk decrease was greater in women than that in men.

A consistent decreasing risk in consecutively younger birth cohorts only occurred in low-SDI countries. The rest of the countries showed an increasing and then decreasing trend similar to that of period effects. Such relative cohort risk, in countries whose SDIs were at high, high-middle and low levels, reached their highest points in 1985, 1920, 1935, and 1965, respectively.

Age-Period-Cohort Effects in Selected Countries

We present examples of several countries of SDI quintiles for the purpose of better characterizing the principal tendency in myocarditis death rate by APC effects across the globe. The United States is a typical example of countries with high SDIs, but its risk of myocarditis mortality shows an accelerating trend, especially in those older than 50 years, and a progressive increase in cohort risk over time. Italy stood out for its unique population distribution of deaths and showed a new twist in the age structure of deaths, with the risk of death rate particularly evident in the older age groups. Brazil and Mexico showed similar trends in age and cohort risk, but Brazil's period risk began to decline after reaching a maximum during 2000-2005, whereas Mexico showed a continuous increase. Pakistan presented comparatively moderate local drifts in death rates in age groups but increased mortality rates in the adolescent and middle-aged (10 to 50 years) population.

China currently has the highest number of myocarditis deaths, but its period risk has been decreasing, while cohort risk declined rapidly after reaching a peak in 1930-1940. South Africa and South Korea are middle- and high-SDI countries, respectively, but they had similar tendencies in APC effects, with higher death rates in the youngest (0-5 years) and oldest (80+ years) age groups. India also presented comparatively moderate local drifts in death rate for age groups, and its period and cohort risks continued to decline. In Ecuador and Ethiopia, there has been only a small advancement in period or cohort tendency during the last three decades. In contrast, Saudi Arabia and Nigeria, which are high- and low-middle-SDI countries, respectively, both showed increasing numbers of deaths in younger age groups (10-50 years) while period and cohort risks continued to improve. The APC analysis results of all 204 countries and regions are shown in **Supplementary Table II**.

Number of Myocarditis Studies and Trends in International Cooperation

Supplementary Figure 3A-D shows the trends of myocarditis research and international collaboration in four time periods: 1990-1991, 2000-2001, 2010-2011, and 2018-2019. Over this timespan, the United States has consistently been the country reporting the most relevant research. After 2000, countries whose SDI was at a high level, such as Italy, Germany, France, and Japan, also have made outstanding contributions in this field. After 2010, China significantly increased its research in this field and initiated international collaborations with many countries. **Supplementary Figure 3E** shows that research in this field decreased after 2001 in the US and South Korea, while China, Italy, and India maintained research growth. Meanwhile, international collaborative research continued to grow, with the United States and Italy performing particularly well. In addition, there were notably very few research results on myocarditis in low-SDI regions, and no results were retrieved from Ethiopia, Nigeria, or Ecuador.

Discussion

This essay proves that despite the overall decline in myocarditis mortality worldwide during the last 30 years, healthy diversity in myocarditis death rate seems to be expanding across countries. Analyses[10] of GBD mortality estimates suggest that myocarditis mortality has increased in many high-SDI countries and that the increase in death rate is not commensurate with the anticipated socioeconomic status at the country level (e.g., United States, Italy, and the United Kingdom), supposing changes in the efficiency of health care are closely related to SDI. In contrast, there is a decreasing trend in some newly emerging nations (such as China and India). As from some low-SDI countries (e.g., Yemen, Ecuador, Ethiopia), there seems to be no significant change in mortality risk for myocarditis during the last three decades. Overall, the age distribution of deaths has shifted from pediatric and adolescent populations to middle-aged and older populations, indicating the significance of healthcare systems for myocarditis throughout the whole lifetime. Research and international collaboration on myocarditis will require long-term attention and support, especially for patient populations in countries whose SDIs are at low levels.

Our essay utilizes APC models with the purpose of analyzing the tendency in global myocarditis death rate and allowing comparative analysis across 13 countries. Different from related studies[18-21] already reported, the significant contribution of this essay is that it offers a more comprehensive and detailed analysis of the disease tendency, and utilizes estimates obtained from APC model to carry out a deep analysis in myocarditis death rates. Furthermore, because of the ability of this approach to assess the trends in disease occurrence by utilizing the overall rate, we avoided omitting significant information. Our essay provides an example of deep research of disease tendencies by utilizing GBD data. Applying the APC model to investigate disease tendency also provides clearer information on the efficiency of the healthcare system, thus aiding in tracking progress toward the Sustainable Development Goals (SDGs) in specific countries.

Regarding the mismatch between national SDI levels and expected myocarditis mortality trends, we believe that this should be interpreted in the context of each country's situation and that it may be related to various factors such as local medical level, dietary habits, and epidemiological disease spectrum. For example, Wuhan is among the more economically developed cities in China, but some dietary habits lead to the increased local prevalence of enterovirus, which becomes an important causative factor for fulminant myocarditis, an important component of myocarditis deaths[19,20]. Many of the areas of increased myocarditis mortality found in the study are concentrated in coastal and high-latitude areas, which may be related to local enteric and respiratory virus epidemics triggering fulminant myocarditis[10]. Additionally, populations in high-SDI regions have greater access to medical resources, meaning that adolescent myocarditis patients are more likely to survive into middle and old age, but the eventual death caused by persistent myocardial injury may also drive alteration in the age structure of dead individuals. Of course, these ideas will require confirmation by further studies. However, as aging progresses in many countries, cardiovascular diseases must receive more attention[22].

In contrast, the decrease in myocarditis mortality in newly emerging nations such as India may reflect the improvement in healthcare in these countries[23-26]. For example, the construction of primary healthcare systems in China[23] and the construction of cardiovascular specialty facilities in India[25] could benefit their large patient groups. This change has also been reflected in the rapid growth in research results in this field in both countries in recent years (**Supplementary Figure 3E**).

We found that countries with a strong research focus on myocarditis tend to have a high prevalence of the disease and some economic capacity. The United States, currently the largest contributor to research in this area, has seen a possible decline in research concentration. This may be related to its low mortality for myocarditis (108th in age-standardized mortality), but its incidence is increasing rapidly, and the net drift is 2.11% (95% CI 1.71-2.51), ranking 11th worldwide. Therefore, research on myocarditis should receive more attention.

There are two points to note when converting the research conclusion into the public health perspective. At first, the estimated value from low- and middle-income countries that lack initial data should be handled with care because they are derived from model estimates and require the validation of another independent original research. Second, we utilized death rate estimates at a country level to enter into the APC model; therefore, the conclusions we drew cannot be directly introduced by subnational areas because geographic health differences exist in almost all areas, and advancement may be made in some areas but not in others.

Limitations

Our research also has some limitations. First, our investigation shows limitations that come from GBD models due to the limited availability of initial data in low- and middle-income countries (LMICs) and estimated values based mainly on data from regions with more abundant data[10]. Some countries did not have initial data on LMICs, and their estimated value was necessarily largely driven by covariates[10]. Such countries may face uncertainty bounds in GBD mortality estimates; this is mainly distributed in countries whose SDIs were at a low level[10]. There is an urgent need for initial data on cardiovascular disease death rates with higher quality in many LMICs, such as cohort research in the long term and registries of patients with myocarditis. Secondly, the GBD studies use accounts of mutual repulsion and a single account of death for myocarditis. For the elderly, it is not likely that myocarditis will be determined as the potential account for death, and deaths resulting from complicating diseases such as heart failure and dilated cardiomyopathy resulting from myocarditis may not have been included. As a result, the mortality from myocarditis in the GBD research may be undervalued actually. To handle the changeable age structure of myocarditis, it is necessary to set up a synthetic disease monitoring system to obtain morbidity associated with myocarditis and death rate in age groups. Third, due to insufficient data availability, this research did not analyze the death rate tendency for different myocarditis subtypes. Thanks to the combination of sub-classification data, the types of myocarditis that need specific attention for every country can be determined. Fourth, this essay analyzed death rate data at the level of the country, while the subnational differences were not taken into account. A more refined analysis that utilized subnational data was able to determine areas with various tendencies. At last, a lack of relevant data prevented us from carrying out a separate attribution analysis of myocarditis deaths, making it difficult to explain further the mismatch between national SDI levels and expected trends in myocarditis mortality. In future iterations of GBD, separate data on risk factors for myocarditis would allow for better interpretation of the findings.

Conclusions

Our APC research of myocarditis death rate across the globe discovered that increases in death rate over the last three decades have not always corresponded to the country's socio-economic level. Negative period and cohort effects present that the existing resources are not enough to serve myocarditis populations in a large number of countries. Therefore, the myocarditis death rate can be regarded as a useful indicator in the supply of cardiac care for patients of all ages. Increasingly, these changes will require countries to extend the scope of health care for patients with myocarditis from adolescent populations to middle-aged and older populations. Meanwhile, research on myocarditis should be further emphasized and disseminated.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Materials

All the initial data included in this research are from published articles and websites, which can be obtained online. Please refer to this website: https://ghdx.healthdata.org/.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Authors' Contributions

XP made a contribution to the research design, manuscript conceptualizing and supervision. ZL carried out the formal research and composed the paper. ZS, WL, FZ, WO, SW, RX and YL examined and put forward suggestions for the manuscript. All authors have confirmed the eventual manuscript.

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