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RESEARCH ARTICLE

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The global case fatality rate of coronavirus disease 2019 by continents and national income: A meta-analysis

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Abstract
The aim of this study is to provide a more accurate representation of COVID-19's case fatality rate (CFR) by performing meta-analyses by continents and income, and by comparing the result with pooled estimates. We used multiple

worldwide data sources on COVID-19 for every country reporting COVID-19 cases. On the basis of data, we performed random and fixed meta-analyses for CFR of COVID-19 by continents and income according to each individual calendar date. CFR was estimated based on the different geographical regions and levels of income using three models: pooled estimates, fixed- and random-model. In Asia, all three types of CFR initially remained approximately between 2.0% and 3.0%. In the case of pooled estimates and the fixed model results, CFR increased to 4.0%, by then gradually decreasing, while in the case of random-model, CFR remained under 2.0%. Similarly, in Europe, initially, the two types of CFR peaked at 9.0% and 10.0%, respectively. The random-model results showed an increase near 5.0%. In high-income countries, pooled estimates and fixed-model showed gradually increasing trends with a final pooled estimates and random-model reached about 8.0% and 4.0%, respectively. In middle-income, the pooled estimates and fixed-model have gradually increased reaching up to 4.5%. in low-income countries, CFRs remained similar between 1.5% and 3.0%. Our study emphasizes that COVID-19 CFR is not a fixed or static value. Rather, it is a dynamic estimate that changes with time, population, socioeconomic factors, and the mitigatory efforts of individual countries.

KEYWORDS

case fatality rate, continents, COVID-19, proportion meta-analysis

1 | INTRODUCTION

Pandemics are defined as the global spread of epidemics, causing excess mortality and morbidity worldwide and leading to the disruption of the social and economic status of the many affected countries. Among other factors, globalization has enabled and advanced sharing of information and experiences yet simultaneously facilitated the spread of diseases during pandemics through global trade and travel.[1] Coronavirus disease 2019 (COVID-19) is one among many pandemics that have occurred throughout the history of humanity.[1,2] COVID-19, caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[3] represents the third coronavirus outbreak of the 21st century after the 2002 SARS-CoV and the 2012 Middle East respiratory syndrome (MERS)-CoV.[4] The World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020.[5] As of July 18, 2021, 190 169 833 confirmed cases, with 4 086 000 deaths, were identified across all WHO regions, territories, and areas.[6]

The case fatality rate (CFR) of COVID-19 is one essential epidemiologic metric that aids all stakeholders to better understand the outbreak, its characteristics, and dynamics. It remains one of the great tools available to express the fatality of the disease. CFR has been developed and reported in emerging infectious diseases[7,8] such as SARS (CFR 9.6% on a global scale)[9] and MERS (CFR 34.5%).[10] Therefore, many researchers and scientists have attempted to estimate the COVID-19 CFR by simply dividing the number of confirmed deaths by the number of reported cases or by using a simple linear regression method.[11–19]

Estimation of the CFR has many flaws and is subject to many biases. Examples of these biases include the time lag that exists between diagnosing a case and reporting it, in addition to the variable degree of underreporting of cases.[7,11] This is especially true at the beginning of an epidemic, where several deaths caused by the pathogen may not be reported as a consequence of the infection. Another challenge in CFR calculation is the actual definition of cases. COVID-19 cases can be either defined as laboratory-confirmed (total cases) or recovered/died (closed cases).[20] Furthermore, CFRs are dependent on the phases of the pandemics, which are different in each country. Likewise, COVID-19 associated deaths are counted differently in different countries. Additionally, even though this might not be considered a bias by itself, CFR is contingent on the policies, response, and efficiency of local health care systems.[7] To overcome some of the limitations and biases of the "traditional" way of calculating CFR, we performed proportion meta-analyses to estimate the average CFR for each calendar date. Proportion meta-analyses calculate the overall proportion of CFR from a set of CFR proportions already reported and calculated in the literature, for each country and region. Our team previously applied this method to calculate the global CFR of COVID-19 comparing since the outbreak of the first confirmed case,[21] and we aim to expand this subject by continents and territories with similar economic status for a broader perspective.

This approach is relatively novel in providing a new insight that lays the foundation for a proper analysis of CFR. A proportion meta-analysis was thus carried out for CFR using the data of every country/territory reporting COVID-19 cases. On the basis of results, we first performed a meta-analysis for global COVID-19 CFR by continents and national income level, which may be more accurate and less subject to distortion and biases. Besides this, this study has a unique aspect which is confirmed by the International COVID-19 Research Network including 172 people in 160 countries.

2 | METHODS

There were several data sources collecting worldwide data reports of COVID-19 (https://www.worldometers.info/coronavirus/, https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases, https://coronavirus.jhu.edu/data/mortality, https://covid19.who.int/). We chose sources updating data of the cumulative cases and mortality data on a daily basis, allowing us to view past data in a downloadable file. We extracted the country, calendar date, the country's cumulative confirmed cases of COVID-19 of that date, and the country's cumulative deaths with COVID-19 of that date. Subsequently, proportion meta-analyses were performed to obtain the average CFR for each calendar day. We collected global data of COVID-19 confirmed cases and deaths from the European Centre for Disease Prevention and Control website (https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases). These data revealed each country's information from December 31, 2019 to October 30, 2020. To offset the effect of the vaccine on the disease, the endpoint was determined before the date on which the vaccination began. The CFR was defined using the following mathematical equation:

$$\frac{\text{number of deaths due to COVID 19}}{\text{number of confirmed cases of COVID 19}} \times 100(\%).$$

Since the number of confirmed cases and deaths are not reported on a daily basis, we encountered missing data. These referred to the reported numbers from countries that contained "blanks", and existed from almost every country, mostly during the early phases of the pandemic. We decided to fill missing data by processing the data as the number of cases in the most recent report before the blank rather than dividing the number of cases equally among the missing days. We adjusted the COVID-19 data for each country according to the calendar date of reported cases.

Using the extracted data, we performed a proportion meta-analysis on CFR in every country. On the basis of results, we performed a meta-analysis for global COVID-19 CFR. Each analysis referred to the calendar date of the reported cases.

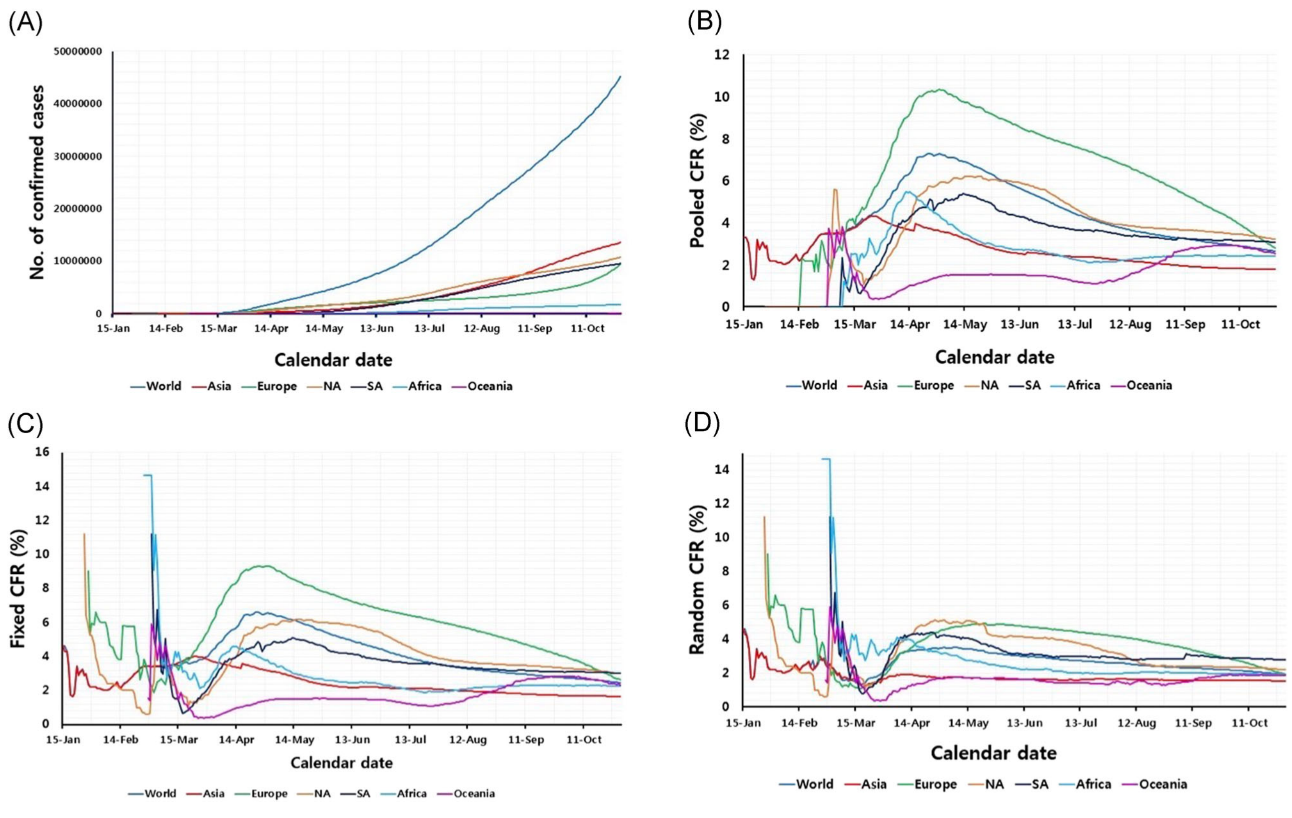

FIGURE 1 Timeline of variables among countries with COVID-19 reported as of October 30, 2020: (A) No. of patients, (B) pooled-estimated CFR, (C) fixed-estimated CFR, and (D) random-estimated CFR. fixed: fixed-effect model, random: random-effect model, and pooled: calculated CFR based on incidence and mortality data. CFR, case fatality rate; COVID-19, coronavirus 2019; NA, North America; No., number; SA, South America

Analyses were carried out using MedCalc version 19.2.1 software (MedCalc Software). Summary effects were calculated with a 95% confidence interval (CI) and between-study heterogeneity. A proportion meta-analysis was carried out to estimate the summary effects. We used figures to visually represent the summary effects obtained by the proportion meta-analysis of the CFR under the fixed- and random-effect model. We provided a summary of the 95% CI in Tables S1 and S2. The heterogeneity tests with Higgins' I^2 statistic were used as an estimator of heterogeneity between studies.[22] An I^2 value less than 50% represented low or moderate heterogeneity, while I^2 above 50% represented high heterogeneity.[22] Microsoft Excel version 2013 was used to graph the patterns of CFR in all countries.

3 | RESULTS

Figure 1 shows the number of confirmed COVID-19 cases, the pooled estimate of CFR, the fixed-model meta-analysis results, and the random-model meta-analysis results over time. Figure 2 shows the same models and estimates over time according to national income. Figures 3 and 4 show the fixed- and random-model meta-analysis results, pooled CFR estimates, and the number of confirmed cases according to the calendar date, stratified by continent and national income, respectively. There are organized classifications of the analysis we performed and the numbers of the corresponding figures (Figures 1A–D and 2A–D [variables stratified by date], Figures 3A–G and 4A–C [CFR stratified by calendar date], and Figures S1A–S3A, S2A–C, S3A–C, S4A–C, and S5 [CFRs of countries in every continent stratified by calendar dates]). Regardless of whether the CFR was a pooled estimate, fixed-model, or random-model, it was visually observed that the CFR stratified by calendar date continuously changed over time. Due to a large amount of data, we present the results according to each main classification.

3.1 | Outbreak characteristics of individual continents

We compared the worldwide number of confirmed cases and the number of confirmed cases of each continent over time (Figure 1A) and did likewise for the pooled estimate, fixed-model meta-analysis estimates, and the random-model estimates (Figure 1B–D). Until March 10, 2020, the graph of the worldwide cumulative number of confirmed cases follows that of Asia, since there were few confirmed cases from continents other than Asia. As confirmed cases increased

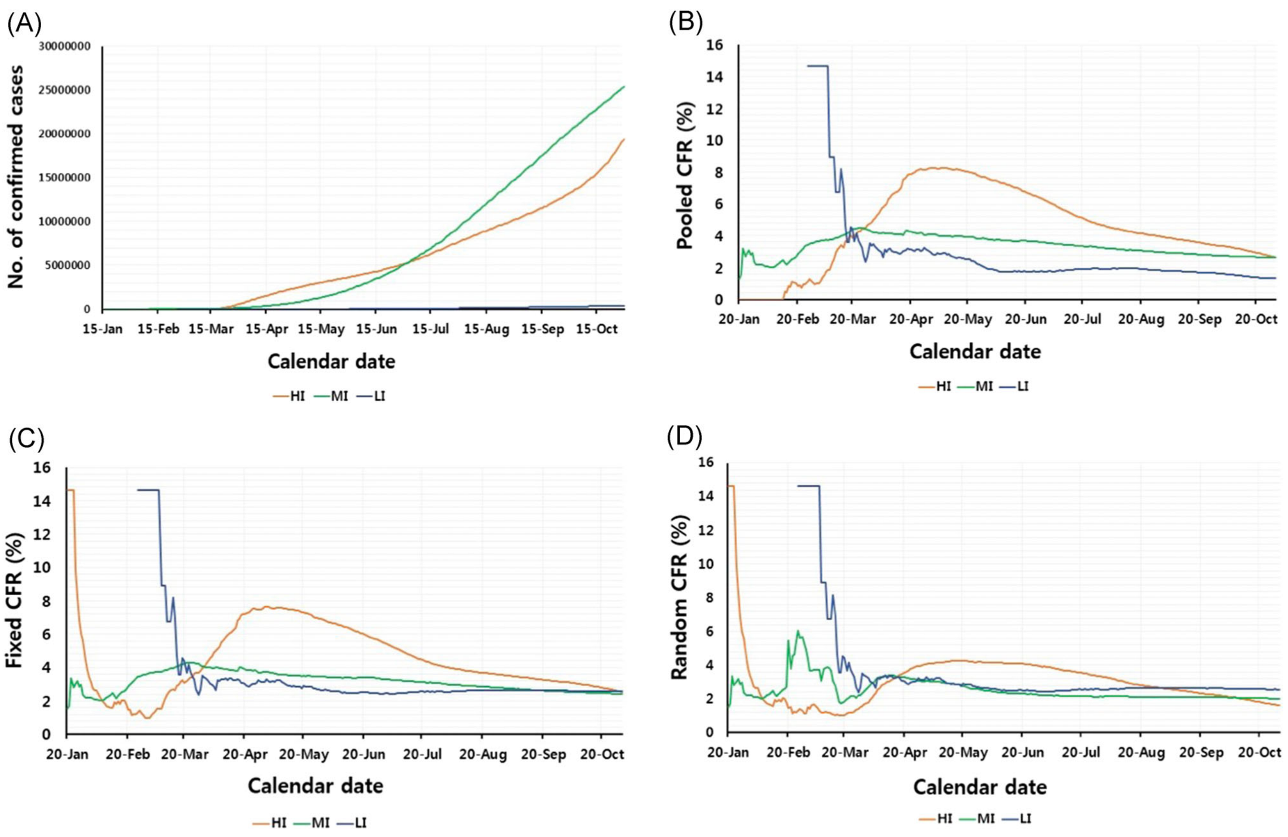

FIGURE 2 Timeline of variables classified grade of income among countries with COVID-19 reported as of October 30, 2020: (A) No. of patients, (B) pooled-estimated CFR, (C) fixed-estimated CFR, and (D) random-estimated CFR. Fixed: fixed-effect model, random: random-effect model, and pooled: calculated CFR based on incidence and mortality data. CFR, case fatality rate; COVID-19, coronavirus 2019; HI, high income; LI, low income; MI, middle income; No., number

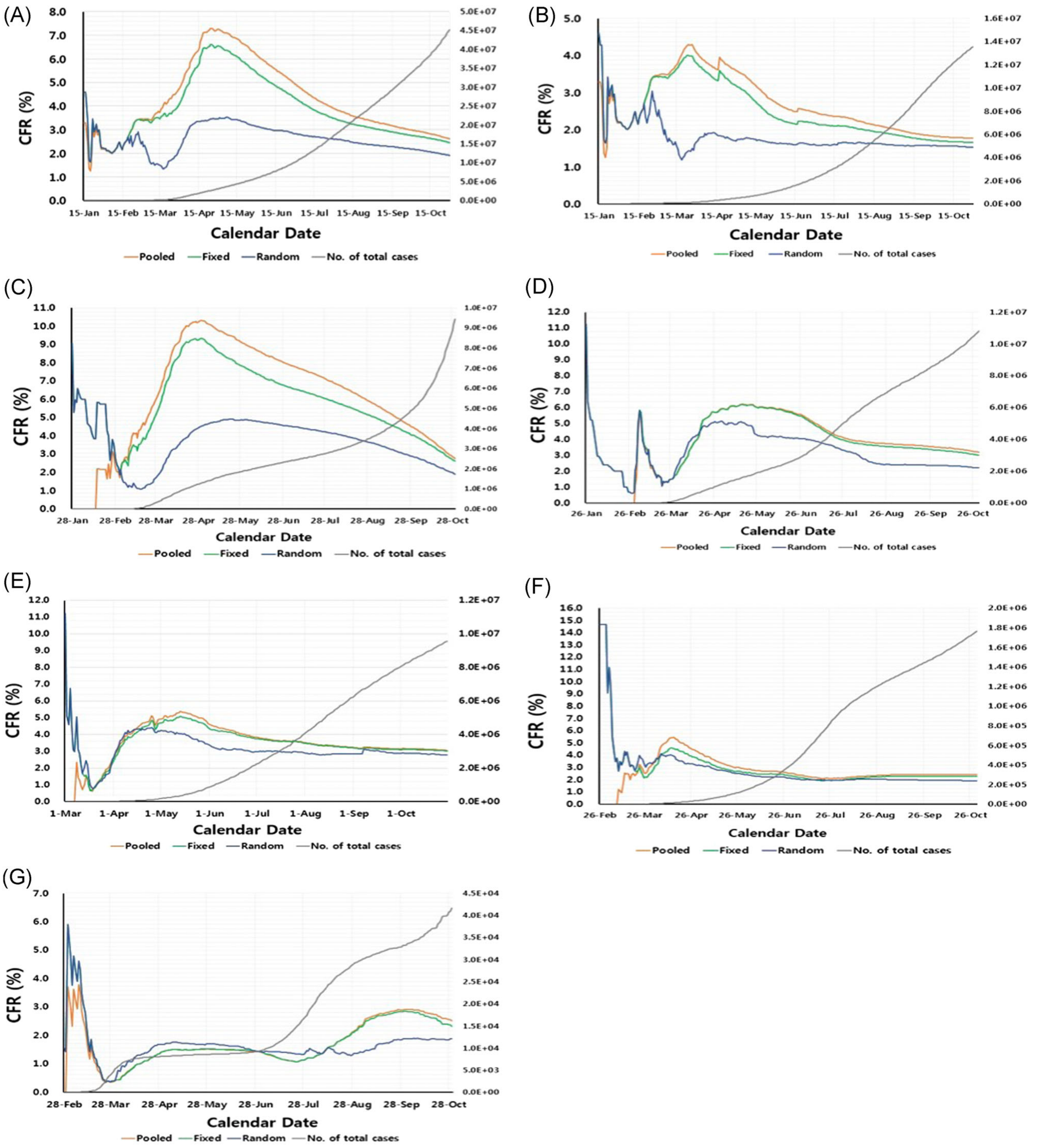

FIGURE 3 Timeline of CFR according to calendar date (reported as of October 30, 2020) in: (A) the whole world, (B) Asia, (C) Europe, (D) North America, (E) South America, (F) Africa, and (G) Oceania. Fixed: fixed-effect model, random: random-effect model, and pooled: calculated CFR based on incidence and mortality data. CFR, case fatality rate; No., number

in all continents, especially in Europe and North America, the worldwide number of confirmed cases rapidly increased (Figure 1A). The random-model and the fixed-model estimates coincided until a certain period (March 10). After this period, the fixed-model followed the pooled estimates while the random-model estimates were smaller in comparison (Figure 1B–D).

3.2 | Comparison of COVID-19 incidence based on income

All enrolled countries are classified into three categories according to income based on The World Bank stratification: high (HI), middle (MI), and low income (LI).[23] Cases of confirmed patients increased rapidly

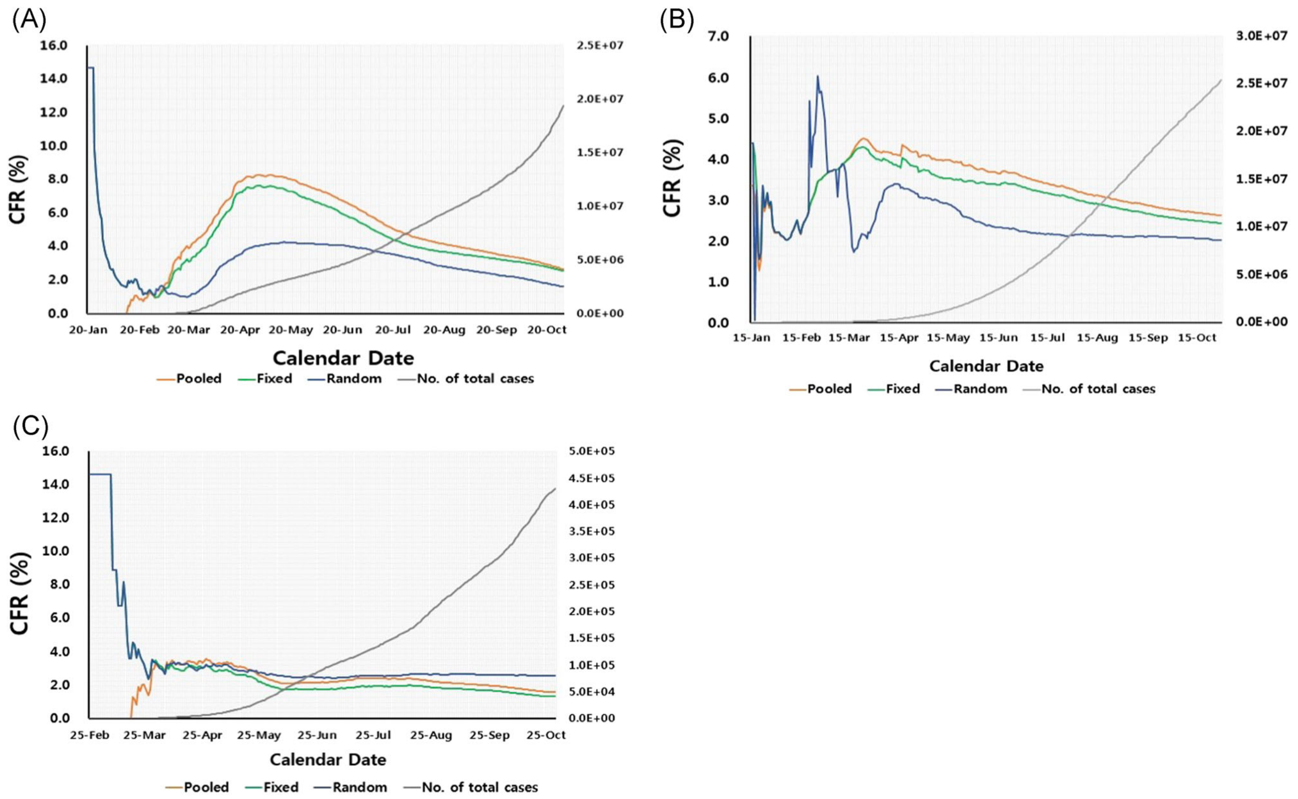

FIGURE 4 Timeline of CFR according to calendar date (reported as of October 30, 2020) in: (A) high-income countries, (B) middle-income countries, and (C) low-income countries. Fixed: fixed-effect model, random: random-effect model, and pooled: calculated CFR based on incidence and mortality data. CFR, case fatality rate; No., number

after March 20 in HI countries, and the increase started from April 1 in MI countries. There were no differences between all three income categories until May, however, confirmed cases rapidly increased in MI after then. Cases in LI countries were notably different than MI and HI countries (Figure 2A). In the case of pooled estimates, cases increased gradually since COVID-19 emerged in MI countries but confirmed cases in HI countries began to be identified from February 12 and increased sharply to 8.1% until April 26. In contrast, this was first confirmed on March 18 and rose to 3.4% in LI countries (Figure 2B). The rest of the fixed- and random-model in the three categories showed similar patterns to each other since early March (Figure 2C,D).

3.3 | CFR according to the calendar date

We also conducted a meta-analysis of the CFR of each continent and presented the fixed- and random-model meta-analysis estimates, pooled CFR estimates, and the number of confirmed cases according to date (Figures 3A–G and 4A–C).

3.3.1 | Globally

Globally, until February 19th, all three types of CFR remained approximately at 2.7% following a similar pattern. However, after February 19, the fixed-model results and the pooled estimate of CFRs showed a rapid increase up to 6.6% and 7.3%, respectively. This was continued until May, which was followed by a decreasing trend since. In contrast, the random-model results of CFR did not show significant changes, moving between 3% and 4%, until May and slowly decreased since then (Figure 3A).

In other perspectives, till March 10th, the graph for global CFR follows the graph for the CFR for Asia as initially most of the cases were reported from the Asian continent. However, after March 10th, the global number of cases increased sharply.

3.3.2 | Per continent

In Asia, until February 19th, the CFR pattern was very similar to the global CFR pattern: All three methods of CFR calculation reported values of approximately 2.0% and 3.0% in a similar pattern. Since then, in the case of pooled estimates and the fixed-model results, the values increased to cross the 4.0% mark before gradually decreasing again. Till October 30th, the fixed model showed a CFR of 1.6% while the random model showed 1.5%. In the case of the random-estimated model, it remained under 2.0% since March 6th (Figure 3B).

In Europe, the fixed- and random-model results of CFR before February 15th represent a statistical bias as there were zero confirmed cases at the time. The fixed-model results of the CFR showed a similar trend with the pooled estimates since March 2nd. The results from the two methods of CFR calculation increased until reaching between 9% and 10%, followed by a gradual decrease since the beginning of May. After February 15th, the calculated CFR from the random-model approach showed a slower increase until late May, reaching close to 5%, and then gradually decreasing to 1.9% in October 30th (Figure 3C).

CFR patterns from North America were very similar to those from Europe. The first confirmed case of COVID-19 began on March 1, and all three calculated CFRs showed a sharp rise to 5.8% within the first 3 days only, and then decreased to 1.0% again until March 20. After March 20, all three estimates of CFRs gradually rose again, showcasing a plateau pattern: pooled estimates (about 6.0%), fixed-model estimates (approximately 6.0%), and the random-model estimates (about 5.0%). This result from North America is similar to other continents, as the three CFR estimates show a noticeably decreasing trend (Figure 3D).

The first confirmed case in South America was reported on February 21, relatively late compared to other continents. Until March 18, the three CFR estimates showed varying patterns, but thereafter, gradually increased to about 5.0% (in pooled estimates and the fixed-model estimate) and 4.0% (in the random-model estimate). After May 14, all three CFR estimates gradually decreased and a plateau pattern since September (about 3.0%) (Figure 3E).

Africa also showed a similar pattern of CFRs with South America, with only a 1- or 2-day delay compared to South America. The first confirmed case in Africa was reported on February 15, which is likewise relatively late compared to the other continents. The three CFRs increased in a similar pattern from March 20 to mid-April, the maximum ranging between about 4.0% and 6.0%. Afterward, the three CFR estimates gradually decreased, and recently, the gap between them has narrowed, converging to similar values of about 2.2% (Figure 3F).

The COVID-19 pandemic was confirmed to have reached Oceania on January 25, 2020 with the first confirmed case reported in Australia. All three CFR estimates showed a similar pattern since the end of March. Although there is a slightly decreasing pattern in May, all three CFRs were below 2.0%. Both pooled and fixed calculated CFRs showed a rapid rise to 2.8% in early October, and then decreased to about 2.5% again. (Figure 3G).

3.3.3 | Per income

In the HI countries, pooled estimates and the fixed-model showed gradually increasing trends after the three CFRs matched to 1.3% on February 27th, and pooled estimates and the random-model reached about 8.0% and 4.0% in May, respectively. All three CFR estimates had decreased since mid-May, although the number of confirmed cases increased rapidly since mid-March (Figure 4A).

In MI countries, the three CFR estimates showed a similar pattern since the first COVID-19 case appeared. Starting from February 19th, the random-model severely fluctuated. Since then, the pooled estimates and estimates based on the fixed-model gradually increased to 1.3%, reaching up to 4.5% by March 25. From February 20, the pooled estimates and estimates based on the fixed model rapidly increased from 2.8% to 3.4% until February 25 and then gradually increased to 4.5% on March 25th. Similar to HI countries, although the number of confirmed cases increased rapidly from the end of March, all three CFR estimates decreased (Figure 4B).

Pooled estimates in the LI category were first identified relatively late on March 18th. As of March 31st, the three CFR estimates remained similar, between 1.5% and 3.0% of each other (Figure 4C).

4 | DISCUSSION

In this study, we applied methods using meta-analyses to calculate CFR. Given that the CFR constantly fluctuates with time, location, and population, for the first time, we, thus, calculated the fixed- and the random-model results of the meta-analysis, the pooled estimate, and the number of total cases included in each analysis. We obtained the time trend of CFR by calculating pooled estimates, fixed- and random-effect estimates from meta-analyses by calendar date. In this context, it is important to view CFR as a function of time, rather than presenting CFR as a single, absolute, and static value.

As for the patterns of CFR, there were differences among continents. In terms of the pooled estimated and fixed-effect model, Europe showed the highest CFR until mid-October, followed by North America and South America. Asia, where CFR was high when COVID-19 was emerging, has experienced a continuous decrease since March 2020. Europe's high CFR also affected global CFR, which showed a CFR value between that of Europe and North America. Different continents have different periods of CFR increase, and when one continent increases, the other continents show a pattern of decrease or plateau. But overall, the difference between continents in CFR is also related to the number of confirmed cases: Europe and North America showed the fastest increase of confirmed cases, and the CFR increased rapidly accordingly (Figures 1A and Figure 3). This may be because the greater availability of testing of critically ill patients allowed for more deaths to be attributed to COVID 19. Another reason why CFR may increase with the rapidly increasing number of confirmed cases may be due to strain on healthcare systems to deliver high-quality care when capacity is exceeded. In terms of country income level, CFRs in HI countries, such as Europe and North America, tended to increase explosively, compared to LI countries. Of note, LI countries may have lower reporting and testing capacities due to financial hardships, which may have led to the underreporting of mortality cases from COVID19. Another aspect to be considered is the fact that LI countries may have lower global travelers compared to HI countries, and, therefore, lower global transmission rates.

On the basis of pooled estimate, HI countries had CFRs twice as high in comparison to MI countries (about 8.0% vs. 4.0%, respectively) (Figure 4). This may relate to the fact that in HI countries there is a higher percentage of older people above 70 years of age, who have higher mortality and/or a higher percentage of people affected by obesity, which also increases mortality.[24] Additionally, a rapid increase in case confirmation could lead to higher mortality in some of these countries. As we have observed from our results, we have proven that significant differences exist between continents. One of the factors contributing to these variations includes the population size of countries. Countries with a relatively large population such as the U.S. affect the overall pooled estimated and fixed-model CFR as they have more weight. Therefore, these CFR have a more accurate relative representation because of this weight-adjustment factor.

Our results show different outcomes from the CFR patterns mentioned in other previously published papers.[11–19] First, when the number of confirmed cases increases, CFR is not fixed and rather increases, resulting in a sharp increase of confirmed cases. In addition, CFR seems to be relatively high in countries with HI, such as Europe and North America. Although CFR is currently falling in these continents, it is still relatively high compared to other territories as the global CFR has not fallen significantly. From these results, the CFR of COVID-19, or any highly infectious disease, may have the potential to be presented differently due to the epidemiologic phase of the spread, or the characteristic of the continent we aim to present.

It has been well-established that CFR estimations are affected by a multitude of biases and confounders. Consequently, the methods used to assess CFR should be used conservatively and utilized with caution. CFR estimates may be skewed in either direction: they have the potential to be over- or under-estimated. Over-estimation of CFR can be a result of multiple factors. These include the inaccuracy of the total confirmed cases, representing that denominator of the CFR mathematical equation. This imprecision in accounting for all laboratory-confirmed COVID-19 cases stems from the fact that these figures depend on the testing abilities and strategies of the affected countries.

During the early phases of the pandemic, testing for COVID-19 was impacted by financial and technical challenges. Therefore, severe cases of the disease were given priority for testing over mild and asymptomatic cases.[25,26] This led to an overall over-representation of more acute cases of the disease rather than the total burden of the pandemic. Another salient point is that at this stage of the pandemic, precisely reporting the mortality of cases that are directly related and secondary to COVID-19 infection is not achievable. Actually, many deaths that are associated with COVID-19 might actually be secondary to fatal comorbid conditions. Therefore, over-emphasizing the triggering condition will potentially lead to elevated CFR estimates. The variability and inconsistency of the medical systems' capabilities and response to the pandemic across different geographical locations further distort the reporting of COVID-19 cases and deaths.

Accurate CFR calculation is contingent on a truthful estimation of the incidence of COVID-19 cases. Incidence of COVID-19 cases are inconstant and are subject to the different diagnostic criteria and testing abilities of countries. As the disease progressed and expanded geographically, estimating confirmed cases has seen a great variation. This is secondary, in part, to a better understanding of the pandemic spread and its clinical outcomes. The country-specific screening strategies and criteria changed in real-time to adapt to the national governmental and WHO recommendations and directives.

Extensive testing is one of the many factors that helped explain the discrepancy in fatality ratio between two neighboring countries, Germany and Italy. It has been hypothesized that extensive testing protocol strategies adopted by Germany were able to detect asymptomatic cases that would have been undiagnosed otherwise. Subsequently, this had greatly impacted Germany's CFR.[27,28] On the other hand, countries such as India and Egypt which did not adopt large-scale testing had an initial misleading CFR.[27] Therefore, the response and preparedness of healthcare systems and their testing strategies of COVID-19 are of utmost importance. Mild or asymptomatic cases might be underrepresented at the expense of an overall presentation of hospitalized, severe, and acute hospitalized COVID-19 cases. This will result in artificially inflated CFR estimations. Therefore, the readiness and vigilance of healthcare systems are key in understanding and responding to the pandemic.

The direct temporal relationship between infected patients and those who died because of the disease represents another barrier for precise CFR estimations. A proposed modification offered a time delay-adjusted CFR to correct the delay between confirmation of cases and death of patients.[11,18] This mathematical amendment provided an average of two weeks adjustment to calculate the confirmed infected cases concurrently with those who passed away from the disease. This fine-tuned temporal adjustment methodology has been used by researchers at Oxford University to estimate the global COVID-19 CFR according to the date since the start of the pandemic.[29] However, this approach is not without flaws. It has been reported that even adjusting the calculations temporally does not guarantee the preciseness of the dates of the actual infected patients.[17] Other challenges to accurate CFRs estimation include laboratory positivity despite clinical recovery and time delays between testing and reporting of the results.[13,17] In this manuscript, we resorted to using the conventional methods of calculating CFR estimates.

In the current study, we observed diverse CFRs estimations resulting from our meta-analysis of the COVID-19 pandemic when analyzed based on continents and levels of income. One possible explanation is that a statistical bias has occurred because our model included countries and groups without normalizing their numbers. Therefore, a more standardized and homogeneous analysis of the data is warranted in future studies. One mitigation action would be to include results of confirmed cases only after a certain understanding of the threshold level of these cases is achieved within the country. Hence, we propose that the fixed-effect model may be more accurate and reliable than the random effect model.

Remarkably, we identified that following a concurrence in the initial estimation of the random and fixed model, these two estimates diverge at a certain point in time, which is approximately Day 15 from the first identified case of every country. On Day 15 and thereafter, we observed that the fixed and random model estimates split. On the other hand, the fixed model continues in an analogous and close direction of the pooled model estimation. Even though these findings are exciting, we caution against the extrapolation of this model to predict future CFR estimates because the pandemic is still active and unfolding. Continents that included countries, such as China, Italy, or Spain, have resulted in more weight at the end of the CFR trend compared to other countries where the pandemic was still at earlier stages.

This study is of primordial importance as it once again highlights the healthcare discrepancies and inequalities among counties driven by different levels of income. One essential element determining the speed of responsiveness and preparedness competencies is public health infrastructures directly related to the level of income and level of country development. Government interventions to mitigate the COVID-19 CFR are proportional to the income level of a country. Therefore, our study has once more shown that continents with a high concentration of LI countries were hit the hardest, as shown by a higher CFR estimation. Additionally, this study has not only exposed differences between HI and LI countries with regard to CFR estimation, geographical differences were apparent among nations of similar income and development, uncovering gaps and needs in their respective healthcare system. For instance, differences in CFR estimation in Asia compared to North America could be partially explained by the number of beds per 1000 inhabitants. South Korea possesses on average 12.3 beds/1000 inhabitants, compared to 2.8 beds/1000 in the US.[30]

Socioeconomic disparities in health are well known and established. Pandemics such as COVID-19 has only exacerbated its manifestations. Variation in CFRs when estimated according to continents and income levels is one of the indicators of these inequalities. The variation shown in this manuscript has provided further evidence supporting efforts to mitigate health inequities. We have demonstrated that when looking at the patterns of CFR, there are differences among continents. Overall, the difference between continents in CFR is also related to the number of confirmed cases. Additionally, we showed that notable CFR differences exist between continents. This stems from the fact that large population size affects the overall pooled estimated CFR and fixed-model CFR. Therefore, these CFRs have a more accurate relative representation because of this weight-adjustment factor. As such, we caution that this indicator alone should not be used in isolation for COVID-19 decision making. There is a need to examine CFR in parallel with other indicators such as synthetic CFRs and age-standardized mortality rates. As the pandemic is still in progress, it is uncertain whether the CFR time-trend could be explained by the proposed epidemic stages of COVID-19. Future studies and discussions, especially toward the end of the pandemic, are needed to satisfy the unmet need for a consensus on the definition of each phase.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to all of the following: conception and design of the study, data acquisition, or analysis and interpretation of data; drafting or critical revision of the article for intellectual content; and final approval of the version to be submitted.

DATA AVAILABILITY STATEMENT

The supporting data are available within the article and Supplementary Files.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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