Fatality assessment and variant risk monitoring for COVID-19 using three new hospital occupancy related metrics

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Summary

Background Though case fatality rate (CFR) is widely used to reflect COVID-19 fatality risk, its use is limited by large temporal and spatial variation. Hospital mortality rate (HMR) is also used to assess the severity of COVID-19, but HMR data is not directly available globally. Alternative metrics are needed for COVID-19 severity and fatality assessment.

Methods We introduce new metrics for COVID-19 fatality risk measurements/monitoring and a new mathematical model to estimate average hospital length of stay for deaths (L_{dead}) and discharges (L_{dis}). Multiple data sources were used for our analyses.

Findings We propose three, new metrics: hospital occupancy mortality rate (HOMR), ratio of total deaths to hospital occupancy (TDHOR), and ratio of hospital occupancy to cases (HOCR), for dynamic assessment of COVID-19 fatality risk. Estimated L_{dead} and L_{dis} for 501,079 COVID-19 hospitalizations in 34 US states between 7 August 2020 and 1 March 2021 were 18·2(95%CI:17·9-18·5) and 14·0(95%CI:13·9-14·0) days, respectively. We found the dramatic changes in COVID-19 CFR observed in 27 countries during early stages of the pandemic were mostly caused by undiagnosed cases. Compared to the first week of November 2021, the week mean HOCRs (mimics hospitalization-to-case ratio) for Omicron variant (58·6% of US new cases as of 25 December 2021) decreased 65·16% in the US as of 16 January 2022.

Interpretation The new and reliable measurements described here could be useful for COVID-19 fatality risk and variant-associated risk monitoring.

Funding No specific funding was associated with the present study.

Keywords: COVID-19; Hospital occupancy mortality rate (HOMR); Ratio of total deaths to hospital occupancy (TDHOR); Ratio of hospital occupancy to cases (HOCR); Case fatality rate (CFR); Range-to-mean ratio (R/M)

Introduction

The case fatality rate (CFR), which represents the fraction of individuals with a particular disease who die from that disease, is one of the most commonly used metrics for assessing the severity of infectious disease outbreaks. CFR has been important in aiding county, state, and national leaders in making informed public health decisions related to the ongoing COVID-19 pandemic, as well as management of many other outbreaks such as those involving influenza, SARS-CoV-1, and MERS-CoV, diseases in which the CFR has ranged from as little as 0·12% to as high as 32·7%.[1–3] CFR can have large temporal and spatial variation. For example, reported COVID-19 CFR values have varied from 0·048% (Singapore) to 10·16% (Mexico) as of 20

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Research in context

Evidence before this study

We searched PubMed, medRxiv, and bioRxiv for peer-reviewed articles, preprints, and research reports on risk and health care evaluation for COVID-19 using the search terms "hospital occupancy mortality rate", "ratio of total deaths to hospital occupancy", and "ratio of hospital occupancy to case" up to 20 January 2022. No similar concepts or studies were found. No similar mathematical models based on "hospital occupancy mortality rate" for the estimation of hospital length of stay for deaths and discharges have been identified to date.

Added value of this study

Our new metric, HOMR, is a proxy measurement for HMR for COVID-19 fatality risk assessment and utilize readily available data for many US states and countries around the world. HOCR is a proxy for hospitalization-to-case ratio (HCR). We also provide evidence that explains why COVID-19 CFR has such dramatic changes at the beginning of a COVID-19 outbreak. We have additionally provided new metrics for COVID-19 fatality risk dynamic monitoring, including Omicron variant, and showed that these metrics provided additional information.

Implications of all the available evidence

The results of this study, including average hospital length of stay for deaths and discharges for over 500,000 COVID-19 hospitalizations in the US, can aid county, state, and national leaders in making informed public health decisions related to the ongoing COVID-19 pandemic. This is a new study to provides quantitative evidence to address why CFR has a such a large variation at the beginning of the COVID-19 pandemic in most countries and will hopefully encourage more countries to release hospital occupancy data, which we show is both useful and easy information to collect. The new metrics introduced by our study are effective indicators for monitoring COVID-19 fatality risk, as well as potentially fatal COVID-19 variants, and could also be expanded to other fatal infectious diseases.

October 2020.[4] CFR can also vary highly even within an individual country or region at different stages of a disease outbreak. For example, the CFR in France was 1.4% (with 285 cases) on 5 March 2020, rose to 19.6% (with 28596 cases) on 27 May 2020, and then dropped to 2.3% (with 2,170,863 cases) on 26 Nov 2020.[5] A multitude of factors could potentially contribute to regional CFR incongruities, including patient access to health care, testing capacity, age, race, sampling, vaccination status, personal compliance to government guidance, and evolving SARS-CoV-2 variants.[6–9]

RNA viruses, which include SARS-CoV-2, are more rapidly mutating than DNA viruses. New viral variants raise widespread concern, especially when the mutations cause substantial changes in antigenicity, transmissibility, and virulence. SARS-CoV-2 variants of concern, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and the recently emerged, highly infectious Omicron (B.1.1.529) variant, which have already spread around the world.[10–15]

The world's COVID-19 experience has clearly demonstrated the reliance of informed public health decision making on having available easy, accurate, and reliable methods to rapidly monitor fatality and hospitalization risk of newly emerging variants and diseases. To address this need, and improve existing methods, we here propose hospital occupancy mortality rate (HOMR), ratio of total deaths to hospital occupancy (TDHOR), and ratio of hospital occupancy to cases (HOCR) as three, new, alternative, and complementary measurements for COVID-19 fatality risk evaluation, early CFR variation analysis, and dynamic monitoring.

Methods

Data sources

All data are updated as of 20 January 2022, unless specifically mentioned in the text. These data included cases, deaths, current hospital bed occupancy, and cumulative hospitalizations, as well as symptomatic and asymptomatic cases in mainland China. Cases, deaths, and hospitalizations were confirmed for COVID-19.

Global data, which includes the US but excludes mainland China, was collected from "Our World in Data",[16] which was derived from Johns Hopkins Coronavirus Resource Center and European Centre for Disease Prevention and Control based on its descriptions.

Chinese data was manually collected from the Chinese government by looking at authorized daily announcements for COVID-19 in Chinese areas (National Health Commission of China, http://en.nhc.gov.cn/news.html).

US COVID-19 information was gathered from the "COVID-19 tracking project" before 2 March 2021 (directly from the websites of US state/territory public health authorities, https://covidtracking.com). After 2 March 2021, cases and death data were collected from the US Centers for Disease Control and Prevention, and hospital data were taken from the US Department of Health and Human Services (HHS) (https://healthdata.gov/Hospital/COVID-19-Reported-Patient-Impact-and-Hospital-Capa/g62h-syeh).

Daily cases, deaths, hospital occupancy, and cases and deaths from long term care (LTC) facilities for 34 US states from 26 June 2020 to 1 March 2021 were used for estimation of average hospital length of stay for death and discharges numbers. Global daily cases, deaths, and hospital occupancy data from 24 February 2020 to 14 November 2021 were used for early volatility

of global CFR analysis and fatality monitoring. UK and US Data from 16 October 2021 to 20 January 2022 was used for Omicron variant monitoring.

Ethics

All data used for this study were from publicly available datasets and ethical approval was reported for the original studies.

Statistical analysis

Regression analysis was used for estimating of average hospital length of stay for discharges and deaths. Correspondence analysis was used for the study of associations between metrics, such as TDHOR and HOMR.

Additional formulas and mathematical derivation for analysis

Formula 3:

Hospital mortality rate (HMR) = hospital deaths (N_{dead}) / hospitalizations (N_h)

Where:

Hospitalizations (N_h) = discharges (N_{dis}) + hospital deaths (N_{dead}) + current hospitalizations (N_{hc})

$\mathrm{HMR} = N_{dead}/(N_{dis} + N_{dead} + N_{hc})$

Formula 4:

$1/\mathrm{HMR} = (N_{dead} + N_{dis} + N_{hc})/N_{dead} = 1 + N_{dis}/N_{dead} + N_{hc}/N_{dead}$ and

$N_{dis}/N_{dead} \approx 1/\mathrm{HMR} - 1$, If N_{hc}/N_{dead} is negligible

Formula 5:

Period hospital occupancy (HO) = hospitalizations $(N_h) * L_{mean}$

$$\mathrm{HO} = (N_{dis} + N_{dead}) * L_{mean} + f(N_{hc}) = \sum_{i=1}^{date\ j} HC_{date\ i}$$

Formula 6:

Total deaths (T_{dead}) = hospital deaths (N_{dead})+ deaths in LTC facilities (N_{LTCd}) + deaths at home (N_{hd}) $= N_{dead} + N_{LTCd} + N_{hd}$

Formula 7:

Hospital occupancy mortality rate (HOMR) = hospital deaths/hospitalization occupancy

$$\mathrm{HOMR} = N_{dead}/(L_{mean} * (N_{dis} + N_{dead}) + f(N_{hc}))$$

$$= N_{dead}/\Big((N_{dis} * L_{dis} + N_{dead} * L_{dead}) + f(N_{hc})\Big)$$

Formula 8:

Ratio of total deaths to hospital occupancy (TDHOR) = total deaths/hospital occupancy

Where:

Total deaths (T_{dead}) = hospital deaths (N_{dead}) + long-term care facility deaths (N_{LTCd})

+ home deaths (N_{hd})

$\mathrm{TDHOR} = (N_{dead} + N_{LTCd} + N_{hd})/\mathrm{HO} \approx (N_{dead} + N_{LTCd})/\mathrm{HO}$, assuming N_{hd} is very small

Formula 9:

Ratio of hospital occupancy to cases (HOCR) = hospital occupancy /cases

$\mathrm{HOCR} = \mathrm{HO}/N_c = N_h * L_{\mathrm{mean}}/N_c = \mathrm{HCR} * L_{mean}$ (derived from formula 5)

Formula 10:

Ratio of total deaths to hospitalizations (TDHR) = total deaths / hospitalizations=T_{dead}/N_h

Formula 11:

Case fatality rate (CFR) = total deaths /cases= T_{dead}/N_h

= (total deaths / hospitalizations) * (hospitalizations /cases) = TDHR * HCR

= total deaths / diagnosed symptomatic cases

= total deaths / (total symptomatic cases − undiagnosed symptomatic cases)

Formula 12:

Hospitalization − to − case ratio (HCR) = hospitalizations/symptomatic cases $= (N_{dead} + N_{dis} + N_{hc})/N_c$

Note: 1) deaths, cases, and hospitalizations are all cumulative, and cases are symptomatic cases if not specified. 2) LTC facilities include nursing homes, assisted living, and other long-term care facilities. N_{LTCd} is the deaths in LTC facilities and N_{hd} is the deaths at home with COVID-19. 3) L_{mean}, L_{dis}, and L_{dead} are length of stay for hospitalizations (in-patients), discharges, and deaths, respectively.

These formulas demonstrate that: 1) HMR is determined majorly by the N_{dis}/N_{dead} ratio (formula 4) and HOMR depends on L_{dead}, L_{dis}, and the N_{dis}/N_{dead} ratio and 2) The difference between HOMR (hospital deaths / hospital occupancy) and TDHOR (hospital deaths + LTC deaths)/hospital occupancy) is the LTC deaths. HOMR = TDHOR if LTC deaths equals zero. CFR can be segregated by TDHOR * HOCR and TDHR * HCR based on mathematical derivation (formula 10). Under the condition of N_{hc} is negligible or $N_{dead} >> N_{hc,}$ $1/\mathrm{HOMR} = L_{\mathrm{dis}} * (N_{dis}/N_{dead}) + L_{dead} = L_{dis} * (1/\mathrm{HMR} - 1) + L_{dead}$.

Estimation of average length of stay and comparison with reported data (see Supplementary Material)

Range1-to-mean2 ratio calculation

A new metric, "range1-to-mean2 ratio" (R1/M2), was used to measure the dispersion of CFR and TDHOR for two stages (phases). The range was calculated from the first stage, and the mean was derived from the second stage. For this calculation, the range1 is derived from the first, dramatic change stage (9 March 2020 to 31 October 2020), while the mean2 is calculated from the month immediately following the dramatic change (November 2020), the second, flat stage (Supplementary Figure. 2).

Here, we use R1/M2, rather than MR1/M2 (mid-range1 to mean 2 ratio), or Q3R/M2 (Q3 range1 to mean2 ratio) because these calculations are largely similar in this situation.

CFR, TDHOR, and HOCR variation analysis for 27 countries

The first 14 days of each dataset were omitted if the data was not zero for all analyses due to variations in disease onset, unless indicated in the text. The onset effects of TDHOR were caused by the time gap of when the first daily hospital occupancy data was released and the first death. All CFR, HOCR, HCR, HOMR, TDHOR, and HMR calculations were cumulative unless specified. HOMR is not available for this analysis due to the lack of LTC data in other countries, except in the US.

Globally, a total of 35 countries have released daily hospital occupancy and deaths data. Eight countries, including Australia, China, and six European countries were excluded for analysis due to some reasons. Of these, six European countries, including Finland, Iceland, Lithuania, Norway, Spain, and Malta, had some data missing for either weekends or certain days. Australia does not have a flat stage followed by dramatic change stage in CFR and only had one death in November. In the case of China, a country that had a unique trend in incidence and transmission pattern of COVID-19, it only had four COVID-19 deaths from 18 April 2020 to 20 January 2022. In total, the remaining 27 countries were used for TDHOR, CFR, and HOCR comparison as a single group.

Cause of CFR volatility analysis using TDHR and HCR for 31 US states

These metrics for all US states and one district showed a similar pattern as the 27 countries previously analysed, except with some TDHOR onset effects in some states. Based on CFR= HCR*TDHR (formula 10), we first quantitatively analysed COVID-19 HCR and TDHR contributions in the US. We examined CFR changes between two months (May 2020 and December 2020) in 35 US states for two reasons: 1) only 35 states had cumulative hospitalization data for HCR and TDHR calculations and 2) May 2020 was the peak month for CFR and December 2020 was the month after the dramatic change stage for most of the US states.

Four states (Indiana, Nebraska, New Jersey, and Washington) did not have complete cumulative hospitalization data in May 2020. CFR, TDHR, and HCR were calculated for the remaining 31 states for two months (May 2020 and December 2020). Fold decrease for TDHR and HCR between May 2020 and December 2020 were used to calculate the contributions to the CFR changes.

Cause of CFR volatility analysis using TDHOR and HOCR for 27 countries

From 9 March 2020 to 1 November 2020, dramatic changes for CFR in 27 countries occurred within an eight-month period, followed by a stagnant stage after 1 November 2020. Australia was excluded from analysis because of the same reason mentioned in an earlier Methods subsection.

Based on CFR= TDHOR*HOCR (formula 2), we quantitatively analysed COVID-19 TDHOR and HOCR contributions in these 27 countries and examined CFR changes between two months (May 2020 and November 2020). CFR, TDHR, and HCR were calculated for 31 states between May 2020 and November 2020. Fold decrease for TDHR and HCR between May 2020 and November 2020 were used to calculate the contribution to the CFR changes.

Fatality risk monitoring using TDHOR for 28 countries

To explore the possibility of using TDHOR and HOCR for COVID-19 fatality risk monitoring, we set the criterion for elevation as values of three continuous days above 30% of the previous three consecutive days among 28 countries between 24 March 2020 and 15 November 2021. Australia was included in fatality risk monitoring and a total of 28 countries were analysed.

Omicron monitoring using HOCR for USA and UK

A criterion was set for elevation or decrease in HOCR as the values of three continuous days after 15 November 2021 above or below 30% of the three consecutive days before 31 December 2021 for 28 countries or before 11 January 2022 for the UK and US.

Role of funders

There was no specific funder for this study.

Results

Concepts of three, new hospital occupancy related metrics and their relationships to CFR and HMR

Hospital mortality rate (HMR) is commonly used as an indicator of patient safety and quality of care in healthcare facilities, and it is also being used to assess the severity of the COVID-19 pandemic.[17–18] COVID-19

hospital deaths and cumulative hospitalization data are needed to calculate HMR; however, this information is not available for most countries, and is only available for 35 states in the US.[19] The US, China, Canada, Israel, Malaysia, Australia, and approximately half of the European countries (29 countries total) have, on the other hand, released continuous daily hospital occupancy data.[20] Is there any way to link daily hospital occupancy to cumulative hospitalization? We found that the sum of daily hospital occupancy (HO) for a period and cumulative hospitalization can be bridged together by average length of stay for hospitalizations ($L_{mean,}$ for both deaths and discharges). That means "sum of daily hospital occupancy" equals L_{mean} times cumulative hospitalizations for a specific period.

If HMR for COVID-19 is a ratio of hospital deaths to cumulative hospitalizations, what is a ratio of hospital deaths to the sum of daily hospital occupancy for a period? We propose this to be hospital occupancy mortality rate (HOMR), which is the daily HMR of the hospital stay period since HMR equals HOMR times L_{mean}. HOMR is a new hospital occupancy related metric and may mimic HMR to a certain degree since it is directly related to HMR through L_{mean}.

As noted above, CFR variation for COVID-19 can arise from variation in deaths, cases, or both. Some countries and US states provide COVID-19 death data broken down into hospital deaths, LTC deaths, and deaths at home. China and another 27 countries only release total deaths. To address this limitation in available data, we introduce a concept of ratio of total deaths to the sum of daily hospital occupancy (TDHOR) for a specific period. In contrast to hospitalization-to-case ratio (HCR, a ratio of cumulative hospitalizations to cases), the ratio of hospital occupancy to cases (HOCR) is an additional hospital occupancy metric derived in this study, and HOCR is a proxy measurement for HCR since HOCR equals HCR times L_{mean}. Together, HOMR, TDHOR, and HOCR provide three, new hospital occupancy related metrics.

In regional population screening in mainland China, asymptomatic cases have been reported to represent 38·23% of total cases from 18 April 2020 to 23 January 2022 (Supplementary Table 1). Such information is generally not available since in most parts of the world COVID-19 cases were found not from population screening, but rather from diagnosed cases with symptoms, which equals total symptomatic cases minus undiagnosed cases. The CFR mentioned in the present study refers to symptomatic CFR if not otherwise specified[21]. The intrinsic relationships among CFR, HMR, and these three, new metrics, are shown in formulas 1-2 below and Methods, formulas 3-12:

Formula 1: 1/HOMR

$$= (L_{dis} * N_{dis} + L_{dead} * N_{dead} + f(N_{hc}))/N_{dead}$$

$$\approx L_{dis} * (N_{dis}/N_{dead}) + L_{dead}, \text{ If } f(N_{hc}) / N_{dead} \text{ is negligible}$$

Formula 2: Case fatality rate (CFR) = total deaths/cases

= (total deaths/HO) * (HO/cases) = TDHOR * HOCR

Notes for the formulas: 1) L_{mean}, L_{dis}, and L_{dead} are length of stay for hospitalizations (in-patients), discharges, and deaths, respectively; 2) N_{dead}, N_{dis}, and N_{hc} are in-patient numbers for deaths, discharges, and patients currently in the hospital; 3) HO is hospital occupancy for a period (Methods, formula 5); 4) The $f(N_{hc})$ is the sum of a period hospital stay for N_{hc}. Usually N_{hc} < sum of recently new admitted patients for n days, n is close to L_{mean} and $f(N_{hc}) < N_{hc}* L_{mean}$.

Average hospital length of stay for COVID-19 deaths (L_{dead}) and discharges (L_{dis}) were estimated using HOMR in the US

Average length of stay refers to the average number of days patients spend in the hospital. Length of stay in the hospital for deaths and discharges are useful fatality risk measurements for the COVID-19 pandemic because they reveal risk information for severe cases, which is missing in the CFR calculation. Several studies have addressed this at the beginning of the COVID-19 outbreak.[22–23] L_{dead} and L_{dis} can be estimated if we know HOMR and HMR for multiple days, since 1/HOMR$\approx L_{dis} * (N_{dis}/N_{dead}) + L_{dead} = L_{dis} * (1/\text{HMR} - 1) + L_{dead}$ (combination of formulas 1 and 4 is similar to a linear equation y = ax + b).

There were 34 states within the US that we could use publicly available hospital deaths and cumulative hospitalization data for analysis, with 174,167 deaths and 501,079 hospitalizations within this period (Table 1). Interestingly, the regression plot for these states revealed different correlations at three different time periods: 26 June 2020 to 6 August 2020 (42 days), 7 August 2020 to 15 November 2020 (101 days), and 16 November 2020 to 1 March 2021 (106 days) (Figure 1a). While the latter two time periods had nearly perfect linear correlation (r^2 values of 0·97 and 0·99), for the first period the correlations were limited (r^2 value of 0·57). Estimated L_{dead} and L_{dis} for the latter two time periods are shown in Table 1 based on their intercepts of the Y axis and slope (Figure 1b-d). These data indicated that L_{dead} and L_{dis} were constant within these two periods, and the changes between them were subtle. At the time of 15 February 2021, only 4·24% of the US population was fully vaccinated against COVID-19, so our estimations should not likely be affected by vaccination rates.[4]

Can these estimations can be supported by other data? L_{mean} is equal to hospital occupancy divided by cumulative hospitalizations, and these are independent

	7 August 2020 – 15 November 2020	16 November 2020 – 1 March 2021	Combined
Hospital occupancy	2,400,088	4,891,845	7,291,935
Total deaths	46,774	127,393	174,167
Hospital deaths	28,621	90,953	119,574
Hospitalizations	164,391	336,688	501,079
HOMR (%)	1·19	1·86	1·64
TDHOR (%)	1·95	2·6	2·39
HMR (%)	17·41	28·72	23·78
Length of stay in hospital for discharges (day)	14·3 (95%CI:13·8-14·9)	13·8 (95%CI:13·6-14·0)	14·0 (95%CI:13·9-14·0)
Length of stay in hospital for deaths (day)	20·3 (95%CI:17·4-23·3)	17·5 (95%CI:16·6-18·5)	18·2 (95%CI:17·9-18·5)
Correlation (r^2)	0.97	0.99	NA[a]
L_{mean} (period hospital occupancy/cumulative hospitalizations)	15·3 (95%CI:15·2-15·3)	14·5 (95%CI: 14·4-14·5)	14·9 (95%CI:14·8-14·9)

***Table 1*: Hospital occupancy data and estimation of average length of hospital stay in the US.**
[a] NA, Not Applicable.

results. Our estimations for lengths of stay in the hospital for deaths (L_{dead}) and discharges (L_{dis}) matched the L_{mean} (14.9± 0·4 days, Table 1). Our estimated LOS for deaths (L_{dead}) and discharges (L_{dis}) were 18·2(95%CI:17·9-18·5) and 14·0(95%CI:13·9-14·0) days, different from previously reported by Verity et al., who found the mean duration from onset of symptoms to death (T_{od}) and recovery (T_{or}) for severe cases of COVID-19 in mainland China were 18·8 and 24·7 days, respectively.[22] Similar studies estimated the mean time from onset to death T_{od} was 20·0 days,[23] and the average mean time from onset to hospitalization (T_{oh}) was 7·0 days.[24,25] Based on these estimations and formula $L_{dead} = T_{od}$-T_{oh} and L_{dis}= T_{or}-T_{oh}, we calculated L_{dead} and L_{dis} and found that the Verity's estimation was L_{dead}= 18·8−7·0=11·8 days and L_{dis}= 24·7−7·0=17·7 days, while the Wu's estimation was L_{dead} =20·0−7·0=13·0 days. This may reflect differences between countries and pandemic stages.

We next wanted to know whether HOMR correlated with HMR in the US. To confirm this, we calculated L_{mean} for the combined 34 states and found that the L_{mean} is very steady (14·9 days, 95%CI:14·8-14·9) for a period of months spanning from 7 August 2020 to 1 March 2021 (Figure 1e). Thus, HMR, which is a fatality risk index for hospitalizations, can be mimicked by HOMR in these states within a seven-month period (HMR = HOMR*L_{mean}). The coefficient of determination was 0·943 (Figure 1f). The COVID-19 mean HMR in this period (23·78%) was 2·98-fold that of the US CDC-estimated HMR for seasonal flu for the 2019−2020 period.[1]

We were interested in whether TDHOR could reflect the trend of HOMR. HOMRs in 34 US states highly correlated with TDHOR, with a 0.99 coefficient of determination (Figure 1g). The LTC facility CFR and LTC-to-total death ratio declined from 26 June 2020 to 1 March 2021 (Figure 1h). This indicated that the prevention in LTC improved in this period. TDHOR and CFR correlated well between 34 states and all US states with coefficients of determination of 0·96 and 1·00, respectively (Supplementary Figure 1).

Early volatility of global CFRs can be attributed to undiagnosed, symptomatic cases

Considering CFR has large temporal and spatial variations, we were interested in how much variation exists for TDHOR and HOCR. Since CFR = TDHOR* HOCR =TDHR*HCR (Methods, formula 10), there are two contributing factor pairs causing major fluctuations in CFR (TDHOR* HOCR or TDHR*HCR). CFRs for most of these 27 countries can be divided into two stages, a more volatile, or dramatic change stage, followed by a stagnant, or relative flat stage. COVID-19 CFRs in these countries fluctuated considerably over time as the pandemic progressed (Figure 2a). TDHORs did not exhibit dramatic changes with outbreak stage (Figure 2b).

Here, we first introduced another new metric, named the "range1-to-mean2 ratio", to measure the variation of CFR and TDHOR for two stages (dramatic change stage and flat stage, Supplementary Figure 2). The average range1-to-mean2 for CFRs of 27 countries was 3·57±1·78 (Methods). The average range1-to-mean2 ratio for 27 countries TDHORs was 0·80±0·22, which was smaller than the average range1-to-mean2 of CFR, indicating TDHOR are spatially comparable between countries (Table 2). HOCR showed a similar pattern to CFR (Figure 2c).

The more consistent TDHOR index, compared to the highly volatile CFR and HOCR metrics, suggest that CFR variations are majorly derived from HOCR. Therefore, we sought to quantitatively analyse the contribution to the dramatic change of CFRs. We examined CFR, HOCR, and TDHOR in 27 countries and US states (Figure 2d-f). The approximate 78·66% decrease in CFR was from HCR (hospitalization-to-case ratio)

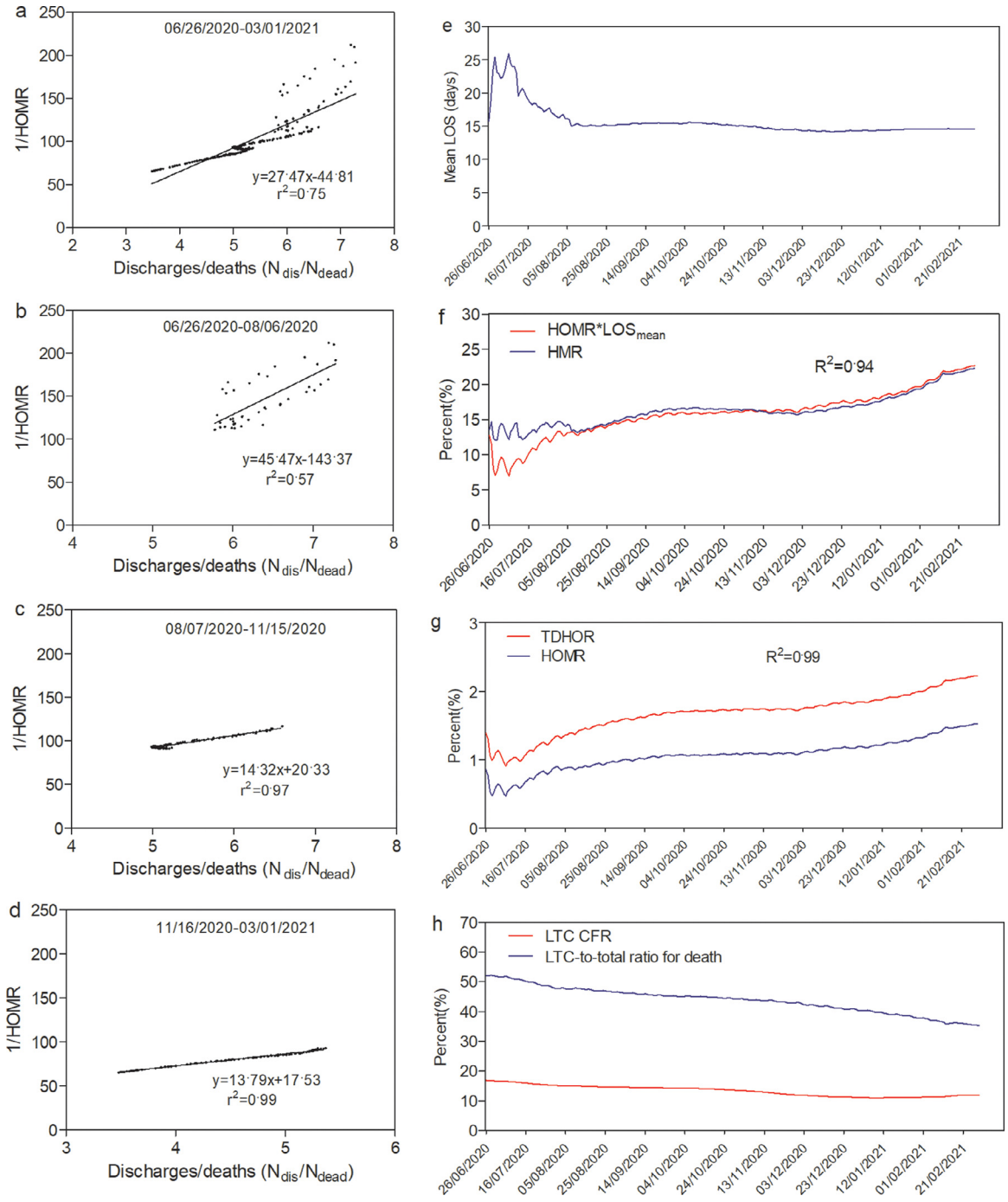

Figure 1. Estimations of average hospital length of stay for COVID-19 deaths and discharges and its correlation with HMR and TDHOR within the US. a-d, Scatterplots of COVID-19 data from 34 US states combined showing the relationship between 1/HOMR and N_{dis}/N_{dead}. Linear regression was used to estimate average length of hospital stay for COVID-19 deaths and discharges. Estimations were made for the COVID-19 infection time course of **a,** 26 June 2020 to 1 March 2021, as well as shorter time periods **b,** 26 June 2020 to 6 August 2020, **c,** 7 August 2020 to 15 November 2020, and **d,** 15 November 2020 to 1 March 2021. The linear regression equations and r^2 values are included when applicable. **e,** L_{mean} calculations for the combined 34 states from 26 June 2020 to 1 March 2021. **f,** COVID-19 HMR and HOMR*L_{mean} for US states between 26 June 2020 and 1 March 2021. **g,** COVID-19 TDHOR and HOMR for US states within the seven-month period. **h,** LTC CFR and LTC-to-total ratio for COVID-19 deaths in the US between 26 June 2020 and 1 March 2021. The LTC-total death ratio declined during this outbreak period.

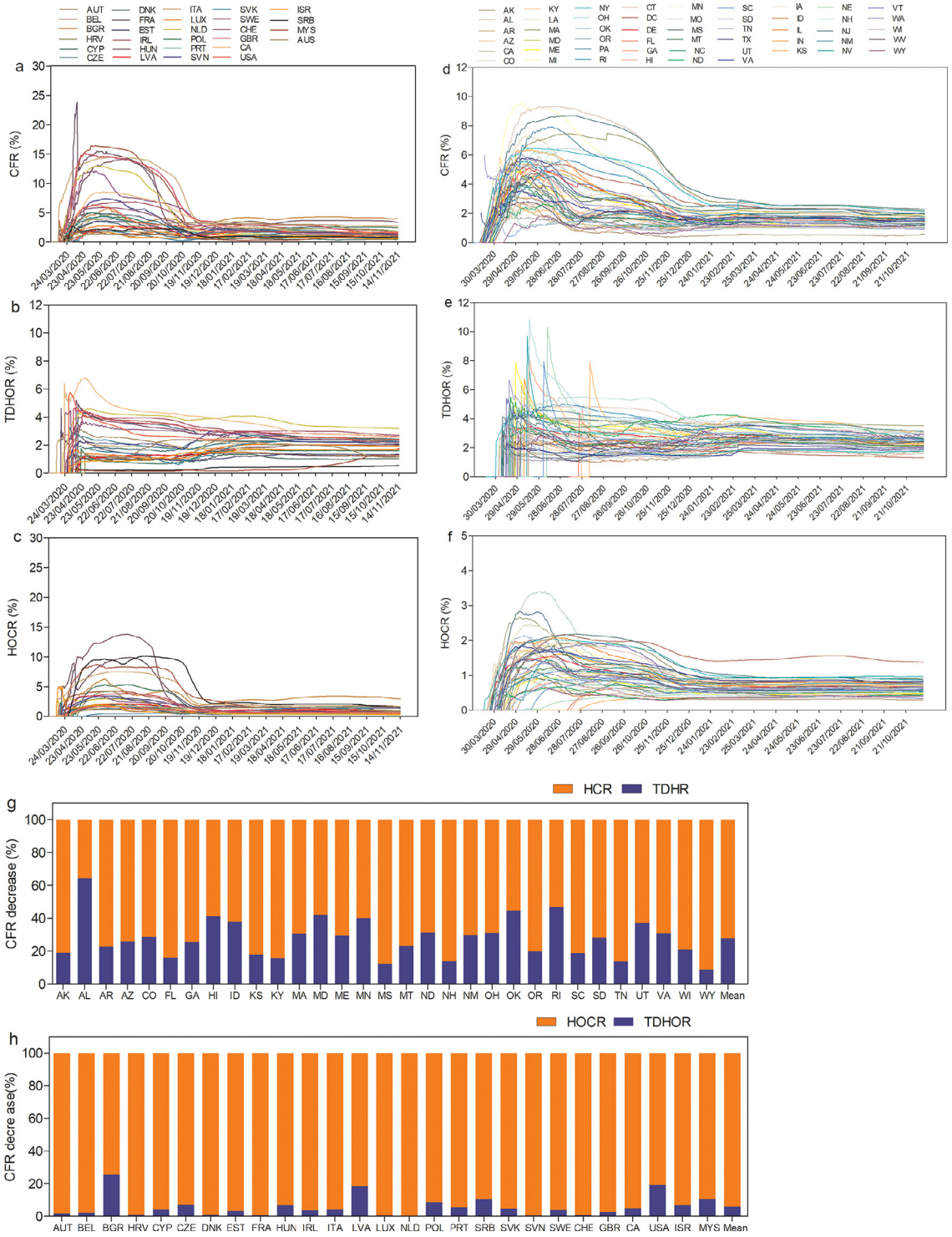

Figure 2. Global and statewide comparisons of COVID-19 CFR, TDHOR, and HOCR. a, CFR, **b,** TDHOR, and **c,** HOCR data for COVID-19 among the US, Canada, Israel, Malaysia, and 23 European countries between 24 February 2020 and 14 November 2021. **d-f,** COVID-19 **d**, CFR **e,** TDHOR and **f,** HOCR in all US states/district. **g,** Quantification of the CFR decrease due to HCR and TDHR variables for 31 states (including a combined average) between May 2020 and December 2020 and 27 countries (between May 2020 and Nov 2020).

	CFR				TDHOR			
	Peak	Range (R1)	November mean (M2)	R1/M2	Peak	Range (R1)	November Mean (M2)	R1/M2
Austria	4·02	3·9	0·97	4·03	3·22	1·49	1·81	0·82
Belgium	16·42	15·97	2·73	5·85	4·1	2·61	3·05	0·86
Bulgaria	6·05	5·03	2·35	2·14	1·59	0·72	1·18	0·61
Croatia	4·76	4·53	1·25	3·62	2·17	1·18	1·59	0·74
Cyprus	3·09	2·64	0·51	5·14	1·48	0·67	0·95	0·71
Czechia	3·54	3·46	1·33	2·6	2·35	0·79	2·27	0·35
Denmark	5·02	4·9	1·22	4·0	4·94	2·23	2·9	0·77
Estonia	3·67	3·52	1·10	3·19	1·39	0·52	0·91	0·58
France	23·84	22·20	2·27	9·76	2·91	1·66	1·35	1·23
Hungary	14·11	12·74	2·21	5·78	1·74	1·23	1·43	0·86
Ireland	6·83	6·44	2·93	2·2	4·36	3·86	3·34	1·15
Italy	14·53	11·06	4·06	2·73	2·76	1·04	1·73	0·60
Latvia	2·72	2·53	1·21	2·09	1·63	1·03	1·33	0·78
Luxembourg	2·76	2·16	0·86	2·50	1·88	0·83	1·33	0·63
Netherlands	12·92	11·92	1·89	6·31	4·61	3·22	3·82	0·84
Poland	5·05	4·12	1·52	2·71	1·77	1·09	1·17	0·93
Portugal	4·37	4·14	1·58	2·62	3·30	1·61	1·83	0·88
Serbia	2·71	2·49	1·22	2·04	0·42	0·22	0·27	0·79
Slovakia	1·88	1·67	0·53	3·12	1·74	1·11	1·08	1·03
Slovenia	7·4	7·14	1·46	4·90	3·01	2·07	2·38	0·87
Sweden	12·18	12·02	3·51	3·43	4·46	2·09	2·84	0·74
Switzerland	5·9	4·95	1·46	3·40	5·20	2·43	2·8	0·87
United Kingdom	15·24	14·8	3·89	3·80	4·69	1·77	3·16	0·56
Canada	8·56	8·23	3·7	2·22	6·81	3·00	4·06	0·74
United States of America	6·25	4·54	2·23	2·04	5·77	3·39	2·50	1·36
Israel	1·71	1·63	0·84	1·93	1·51	1·08	1·50	0·72
Malaysia	1·74	1·52	0·66	2·31	0·28			
Mean ±SD	7·31±5·50	6·68±5·15	1·83±1·03	3·57±1·78	2·97±1·68	1·60±0·98	1·95±1·02	0·81±0·22

***Table 2*: COVID-19 CFR and TDHOR variations in 27 countries.**

and 21·34% from TDHR (ratio of total death to hospitalization, Figure 2g) in 31 US states.

There are two possibilities for HCR to contribute majorly to the CFR dramatic decrease, since HCR equals hospitalization/ (total symptomatic cases-undiagnosed symptomatic case): real hospitalization rate reduction or artificial hospitalization rate reduction (caused, for example, by a decrease of undiagnosed symptomatic cases). If the HCR decrease was majorly caused by a real decrease in the ratio of hospitalizations within the total symptomatic cases (real hospitalization rate reduction, also means the severe cases rate dramatic decrease), then the LTC CFR would dramatically decrease accordingly, which was not consistent with the LTC CFR (Figure 1h). Second, real hospitalization rate change also could be caused by virus mutation or a shift in the infected age groups. There was no new COVID-19 variant nor a dramatic shift in cases to a different age group reported in this period that could cause the severe cases rate to change dramatically (hospitalization rate reduction). Thus, the change in undiagnosed most likely accounts for the CFR change.

Similarly, HOCR contributed 89·37% and TDHOR contributed 10·63% to the CFR changes in 27 countries (Figure 2h, Supplementary Table 3). It is reasonable to assume that the major contributing factor for the 27 countries with highest peak CFRs came from undiagnosed, symptomatic case numbers because the TDHORs did not have the same dramatic change during this time.

COVID-19 fatality monitoring using TDHOR for more than 20 months detected obvious elevations in 17 countries when Alpha variant was first reported

The COVID-19 pandemic has progressed as a series of waves, making healthcare facilities overwhelmed and staffing shortages inevitable in certain regions and time periods over the last 20 months. Therefore, fatality risk monitoring and surveillance for short-term and longer-term COVID-19 trends is critical.

To explore the possibility of using TDHOR for COVID-19 fatality risk monitoring, we set a criterion for elevation as values of three continuous days above 30% of the previous three consecutive days from 1 April

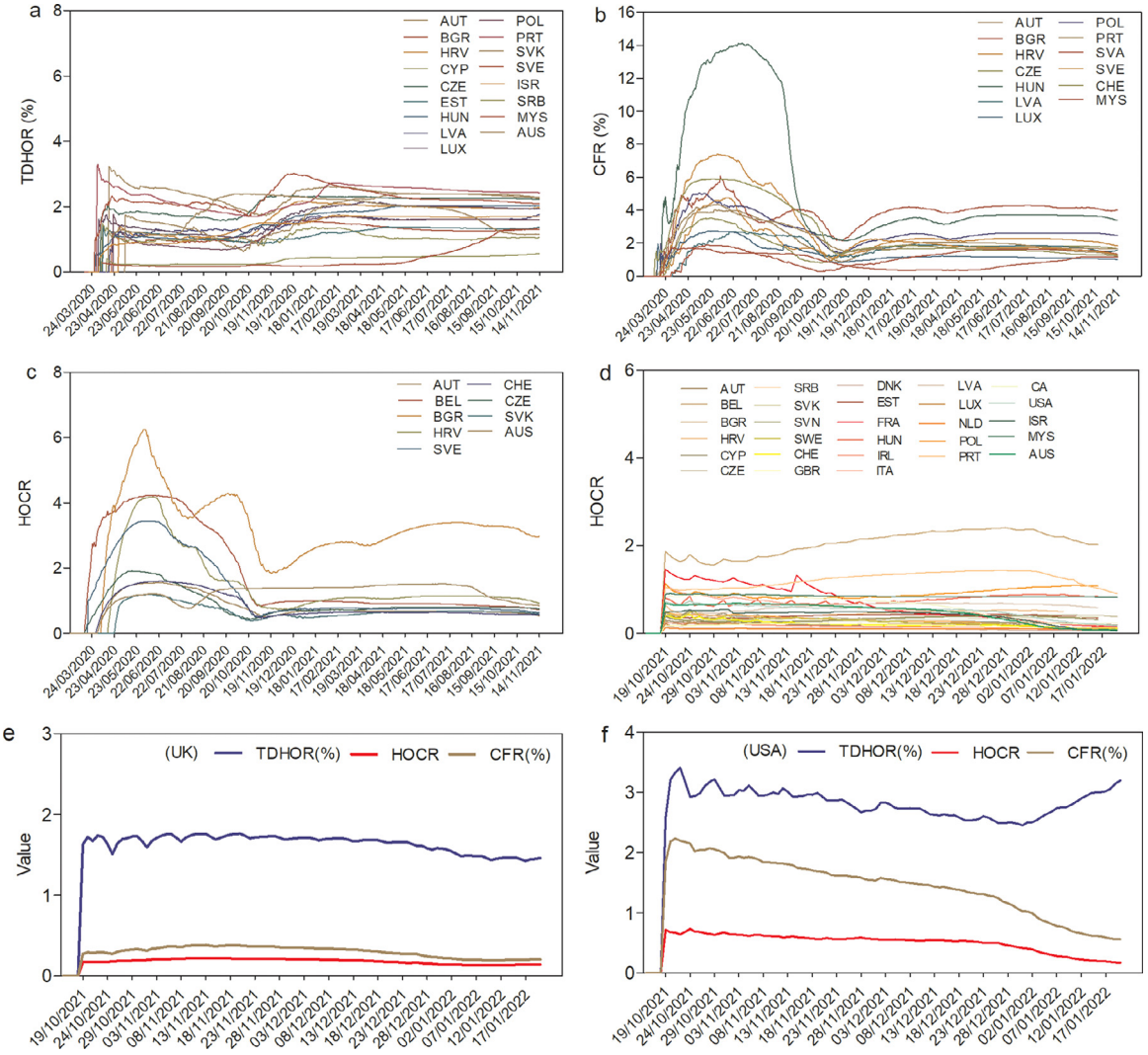

Figure 3. Using TDHOR and HOCR to monitor COVID-19 risk and Omicron variant- associated hospital rate. a-c, risk monitoring for 28 countries from 24 March 2020 to 15 November 2021 with **a,** TDHOR. **b,** CFR, and **c,** HOCR elevations. **d-f,** Comparison of TDHOR, HOCR, and CFR from 16 October 2021 to 20 January 2022. **d**, HOCR for 28 countries. **e,** TDHOR, HOCR, and CFR for the UK. **f,** TDHOR, HOCR, and CFR for the US.

2020 to 15 November 2021. For the TDHOR in the 17 countries that met this elevation criterion, which match the time when Alpha variant was first reported (samples taken in September 2020 in the UK),[26] 11 countries showed no elevations (Figure 3a). Thirteen countries had CFR elevations, and 15 showed no CFR elevations (Figure 3b). Nine countries had HOCR elevations, while 19 countries showed no HOCR elevations (Figure 3c, Supplementary Figure 3). HOCR and TDHOR provided additional information because they mimic HCR and HMR (Supplementary Table 3).

The TDHOR was able to detect elevations for 16 states in the US between 1 September 2020 and 1 March 2021, while CFR only detected elevations in five states. Fourteen states, among 16 states with detected TDHOR elevations, were confirmed to have both HMR and TDHR elevations. The remaining two states (Missouri and Vermont) were not able to be confirmed since these states did not have cumulative hospitalization data to include in our analysis (Supplementary Figure 4). Interestingly, TDHOR and CFR decreases were shown in some US states between 1 August 2021 and 15 November 2021 (all less than 20%) while there was no obvious decrease in HOCR within this period (Figure 2d-f).

Monitoring of Omicron variant-associated risk using HOCR showed hospitalization-to-case ratio decreased from 15 November 2021 to 16 January 2022 in the UK and US

Genomic surveillance has shown that Omicron variant has spread to the many countries after Omicron was first discovered on 24 November 2021 based on samples

collected on 11 November 2021 in South Africa.[15,27] It raises serious concerns due to a much higher transmission rate and potential immune escape compared to the Delta variant.[28]

The Omicron variant accounted for 58·6% of US new cases as of 25 December 2021, as estimated by the US CDC.[29] One of the most important questions is whether the variant increases severe rate or hospitalization-to-case ratio (HCR). The average length of stay in hospital of US (L_{mean}) was constant within seven months (Figure 1e). The L_{mean} of the UK was also relatively steady within 18 months (Supplementary Figure 5). These indicate HCR can be monitored using HOCR for the UK, US, and other countries since HOCR equals HCR times L_{mean}.

We measured the TDHORs and HOCRs of the most recent three months for 28 countries from 16 October 2021 to 16 January 2022 and compared them to CFRs (Figure 3d, Supplementary Figure 6). As of 16 January 2022, 12 among 28 countries were found to have more than 50% decrease of HOCR compared with the week mean HOCRs of the first week of November 2021 (as of 7 November 2021). In particular, the UK and the US had decreases in mean week HOCR by 34·08% and 65·16% respectively (Figure 3e-f, Table 3), which mimics the hospitalization-to-cases ratio in these countries.

Countries	Mean week HOCR as of 7 November 2021	Mean week HOCR as of 16 January 2022	HOCR week Change (%, 16 January 2022 vs 7 November 2021)
Austria	0·23	0·22	−5·51
Belgium	0·24	0·20	−16·45
Bulgaria	1·67	2·07	24·31
Croatia	0·41	ND[a]	ND[a]
Cyprus	0·39	0·12	−69·96
Czechia	0·31	0·42	31·12
Denmark	0·12	0·06	−54·15
Estonia	0·35	0·37	4·91
France	1·16	0·18	−84·72
Hungary	0·68	0·85	25·15
Ireland	0·20	0·08	−60·04
Italy	0·78	0·19	−75·48
Latvia	0·52	0·61	19·04
Luxembourg	0·21	0·12	−44·35
Netherlands	0·11	0·09	−15·27
Poland	0·85	1·08	27·79
Portugal	0·41	0·10	−76·13
Serbia	1·04	1·13	8·51
Slovakia	0·29	0·37	29·78
Slovenia	0·26	0·33	27·01
Sweden	0·34	0·12	−66·19
Switzerland	0·29	0·13	−53·51
United Kingdom	0·20	0·13	−34·08
Canada	0·88	0·21	−75·58
United States	0·64	0·22	−65·16
Israel	0·47	0·09	−80·14
Malaysia	0·88	0·83	−5·56
Australia	0·68	0·08	−88·00

***Table 3*: Omicron risk monitoring using HOCR.**
[a] ND, No data.

Discussion

It is of the utmost importance to accurately assess and understand the risk for unknown diseases like COVID-19, which continues to be a prominent threat to global health. As an alternative for COVID-19 risk assessment, we have introduced HOMR, TDHOR, and HOCR, three novel indexes for COVID-19 fatality risk assessment. TDHOR is valuable as a risk measurement in early stages of COVID-19 outbreaks and has the potential to monitor SARS-CoV-2 mutations that affect the death rate.

Here, in addition to describing the concept and the relationships of HOMR, TDHOR, HOCR, CFR, and HMR, we have applied them to estimate the length of hospital stay in 34 states. The period between 26 June 2020 and 6 August 2020 did not show a linear correlation between 1/HOMR and N_{dis}/N_{dead}. This could reflect either that $f\ (N_{hc})/N_{dead}$ and N_{hc}/N_{dead} need to be included in the calculation of HOMR or that missing hospitalization information in this data set have a big effect on estimation of L_{dis} and L_{dead} during this time period. Together, this is important information for decision makers to properly allocate healthcare resources for COVID-19, as well as for other future infectious diseases.

HOMR showed a high correlation with TDHOR, and imitated HMR well in 34 US states within the first seven months of the COVID-19 outbreak. This allows us to use TDHOR as another assessment of COVID-19 fatality risk. Based on our analysis, more than two-thirds of the dramatic changes in CFR were caused by undiagnosed symptomatic cases in the US, while less than one-third were attributed to case-independent data. Notably, TDHORs are less spatially and temporally variable than CFRs on a global level (among 27 countries analysed), supporting our hypothesis and providing additional value in fatality risk dynamic monitoring. This is additionally supported by CFR data from US long term care facilities, where COVID-19 cases are far less likely to be undetected, and therefore had no dramatic change stage.

Numerous variants have been identified for the SARS-CoV-2 virus, including the highly transmissible Delta variant[14] and the newly detected Omicron variant.[15] We observed TDHOR elevations in 17 of 28 countries analysed, along with 16 of the 50 US states in 20 months monitoring. Although there is no direct evidence to link the increase in TDHOR values to the

origin of new Alpha variants, this is a possibility that warrants further investigation. The HOCRs of the US and other 11 countries decreased more than 50%, suggesting that Omicron does decrease the hospitalization-to-case ratio as of 16 January 2022. This is consistent with other reports about Omicron risk.[30]

New variants, like Omicron, cause less severe cases than the initial strain of SARS-CoV-2, as well as more asymptomatic patients as a result.[31] They are sometimes more virulent and transmissible because of an increase of R0 and asymptomatic cases ratio. Thus, infection fatality rate (IFR) and CFR will be smaller than the initial strain. As these variants arise, efforts may need to be made to modify various metrics.

Range1-to-mean2 ratio is a new metric that directly reflects the range change in the stage one and mean change of stage 2. The limitation is that it cannot reflect temporary spread changes in stage 1. An alternative is interquartile range (IQR) ratio for the two stages. Here we used Range1-to-mean2 ratio to reflect the changes.

Different countries/regions may have varied criteria of cases and hospitalizations for COVID-19 patients. For example, mainland China used 40 cycles for quantitative PCR detection, while most other countries use only 35 cycles.[32,33] This can cause differences in assay sensitivity and thus variation in "positive" cases between countries. Similarly, the criteria of hospitalization for countries could vary between countries, especially for those that have different medical and insurance systems. This could be a limitation for our proposed metrics, as well as other metrics like CFR and HMR.

The criteria for COVID-19 hospitalization in different countries may affect HOMR and TDHOR. The overwhelming healthcare conditions brought about by COVID-19 also restricted available hospitalization capacity at surge times for COVID-19. HOMR, TDHOR, and HOCR provide additional information for disease fatality risk assessment and monitoring that are complementary to CFR. It would be interesting to compare HOMR, TDHOR, and HOCR for other viruses like seasonal influenza, SARS-CoV-1, MERS-CoV, or Ebola, as well as future, unknown, and potentially fatal diseases.

Overall, these indexes of hospital occupancy related metrics provide the public health sector with additional, effective indicators for monitoring COVID-19 fatality risk, possibly encouraging more countries to release hospital occupancy data in the future since these calculations require data that is relatively easy to collect.

Contributors

P.W.Z. initiated ideas and concepts. P.W.Z., S.H.Z., W.F.L., C.J.K., F.T., S.L. and C.A.B. collected data and did analysis, J.S. and J.W. contributed to statistic and epidemiological modelling choices. D.J.Z. and P.W.Z. supervised the whole process of data collection, analysis, results interpretation and manuscript writing and they verified the underlying data. All authors read and approved the final version of the manuscript.

Data sharing statement

The authors declare that all data generated or analysed during this study are included in this published article (three excel files in Mendeley Data Datasets: DOI: 10.17632/vrw26gj3wx.1; DOI: 10.17632/4b45k75nmg.1; DOI: 10.17632/ngnyrbgymw.1).

Declaration of interests

The authors declare no conflicts of interests.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104225.

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