Methods and Applications

Collective and Individual Assessment of the Risk of Death from COVID-19 for the Elderly, 2020–2022

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has had profound disruptions worldwide. For a population or individual, it is critical to assess the risk of death for making preventative decisions.

Methods: In this study, clinical data from approximately 100 million cases were statistically analyzed. A software and an online assessment tool were developed in Python to evaluate the risk of mortality.

Results: Our analysis revealed that 76.51% of COVID-19-related fatalities occurred among individuals aged over 65 years, with frailty-associated deaths accounting for more than 80% of these cases. Furthermore, over 80% of the reported deaths involved unvaccinated individuals. A notable overlap was observed between aging and frailty-associated deaths, both of which were connected to underlying health conditions. For those with at least two comorbidities, the proportion of frailty and the proportion of COVID-19-related death were both close to 75 percent. Subsequently, we established a formula to calculate the number of deaths, which was validated using data from twenty countries and regions. Using this formula, we developed and verified an intelligent software designed to predict the death risk for a given population. To facilitate rapid risk screening on an individual level, we also introduced a six-question online assessment tool.

Conclusions: This study examined the impact of underlying diseases, frailty, age, and vaccination history on COVID-19-related mortality, resulting in a sophisticated software and a user-friendly online scale to assess mortality risk. These tools offer valuable assistance in informed decision-making.

INTRODUCTION

It is essential to recognize that coronavirus disease 2019 (COVID-19) presents unique characteristics, including asymptomatic predominance (*1*), asymptomatic transmissibility (*2*), and reinfection/recurrent infection (*3*), which contribute to undetectable transmission and unforeseen risks. Consequently, it is crucial to effectively and accurately assess the risk of death for both populations and individuals in order to appropriately allocate health resources and take optimal preventive measures. However, an ideal assessment tool for this purpose remains unavailable at this time.

Several key factors including age (*4*), underlying diseases (*4*), vaccination history (*5*), and frailty (*6*) were identified as the primary factors that contribute to COVID-19-related fatalities. Notedly, underlying diseases, aging, and frailty often overlap in certain populations. Hence, understanding their interrelationship with COVID-19 mortality is crucial for predicting and assessing the risk of death.

This study analyzed clinical data and examined the associations among age, comorbidities, frailty, and vaccination history with COVID-19 mortality to create a straightforward mathematical model. Subsequently, we developed a forecasting software for population-level assessment and a web-based tool for individual risk evaluation. Our innovative tools provide reliable support for decision-making.

METHODS

Collected and Analyzed Clinical Data: Clinical data from approximately 100 million cases were collected through a comprehensive literature search using international databases and statistically analyzed. See Supplementary Material for details of collection and analysis.

Development of the Locally Run Software SEIP-RA: Initially, we developed the K-SEIR-Sim software (*7*), followed by its enhancement through the creation of the SEIR-AS software (*2*). Here, we designed an improved software, SEIP-RA, which focuses on pinpointing high-risk populations. Our risk prediction

formula is incorporated into the software, allowing for corresponding recalculation of necessary results. The software is programmed in Python, with detailed formulas and parameters designed as described in Supplementary Table S1 (available in https://weekly.chinacdc.cn). The software can be freely downloaded for noncommercial use (http://peiyun.cn/download/seir_sim.files/SEIR-RA%202.64.exe).

Developed the Remotely Run Simple Tool COVID-RA: We developed a scale to assess individual risk of death by considering all critical factors contributing to mortality. This scale employs 6 questions and 14 answer choices to evaluate risk through a question-answer-score system (Supplementary Table S2, available in https://weekly.chinacdc.cn). The evaluation outcomes were categorized into low, moderate, and high risk groups. Subsequently, we converted it into an easily accessible rapid assessment tool to encourage its implementation. We incorporated this tool into a web-based platform, utilizing Python for its development, and stored the data in MySQL. The online tool in both English and Chinese languages can be accessed free of charge and without any setup requirements (http://peiyun.cn/SEIR-AS-query/).

RESULTS

Relationships between Risk Factors and the Death from COVID-19: We examined 106,103,566 COVID-19 cases from 20 countries, revealing that individuals aged over 65 years represented 76.51% of the deaths, frailty and pre-frailty (an intermediate stage between normal and frail) accounted for 83.20%, hypertension for 63.44%, cardiovascular diseases for 42.64%, dyslipidemia for 37.33%, diabetes for 35.44%, heart diseases for 28.63%, arrhythmias for 27.11%, depression for 26.84%, coronary artery disease for 25.48%, dementia for 23.18%, and renal disease for 18.86% of the fatalities (Figure 1A).

Among the elderly patients (a total of 38,645,762 cases), hyperlipidemia was present in 49.21% of the cases, hypertension in 48.22%, gastroesophageal disease in 46.98%, heart disease in 27.47%, cerebrovascular disease in 22.97%, diabetes in 20.27%, heart failure in 15.94%, depression in 14.85%, renal disease in 14.68%, and cancer in 12.91% (Figure 1B). In contrast, among patients with frailty (a total of 890,586 cases), hypertension was a factor in 63.89% of the cases, rheumatoid arthritis in 36.31%, high blood cholesterol in 36.11%, osteoporosis in 28.18%, heart disease in 26.87%, diabetes in 25.47%, depression in 23.57%, dementia in 20.13%, renal disease in 19.29%, and coronary artery disease in 18.57% (Figure 1C).

To further investigate the relationship between aging, frailty, and mortality in COVID-19 patients, we analyzed the number of underlying diseases these patients had. A nearly 75% similarity was observed in the proportion of patients with frailty who had more than two underlying diseases to that of COVID-19 related deaths with two underlying diseases (Figure 1D). In comparison, the older adult group had an approximate proportion of 62.59%. This finding suggests that the presence of two or more underlying diseases in patients with frailty can serve as a useful indicator for determining the risk of death in COVID-19 patients.

By examining clinical data and assessing the proportion of vaccination history among COVID-19-related deaths (7,348,213 total cases), we found that less than 20% of the deceased individuals were vaccinated (Figure 1E). This outcome indicates that vaccination history also serves as a valuable predictor for evaluating the risk of death in COVID-19 patients.

The Formula Proposed for Predicting the Deaths in COVID-19: Based on the analysis results and the logical relationships among population factors, we derived a mathematical formula to estimate the potential number of deaths as follows: $A = A_1 \times A_2 \times (1 - A_3) \times A_4$. This equation implies that the high-risk population (i.e., the deaths) can be calculated by multiplying the total infections by the proportion of individuals over 60 years, then by (1 – vaccination rate), and finally by the proportion of frail elderly individuals (Figure 2A). The estimated number of high-risk populations closely aligns with the actual number of COVID-19 deaths in areas with strict control measures in place, such as New Zealand, and Singapore (Figure 2B), as well as in areas with less stringent control measures, including the USA, Brazil, India, Italy, England, Germany, and Spain, Republic of Korea, Russia, Australia, Iran, Mexico, Türkiye, Viet Nam, and the Netherlands (Figure 2C). To evaluate the accuracy of our prediction, we assessed the difference between our predicted values and the reported numbers of deaths. We found that the highest discrepancy was 42.06% and the lowest was 2.60%, resulting in a mean variation of 16.24% (Figure 2D).

Software Developed for Assessing the Risk of Death for a Population Suffering from COVID-19: We developed a software tool designed to assess the risk of mortality within a population, providing a reference framework for decision-making at country or regional levels. This software incorporates our risk assessment

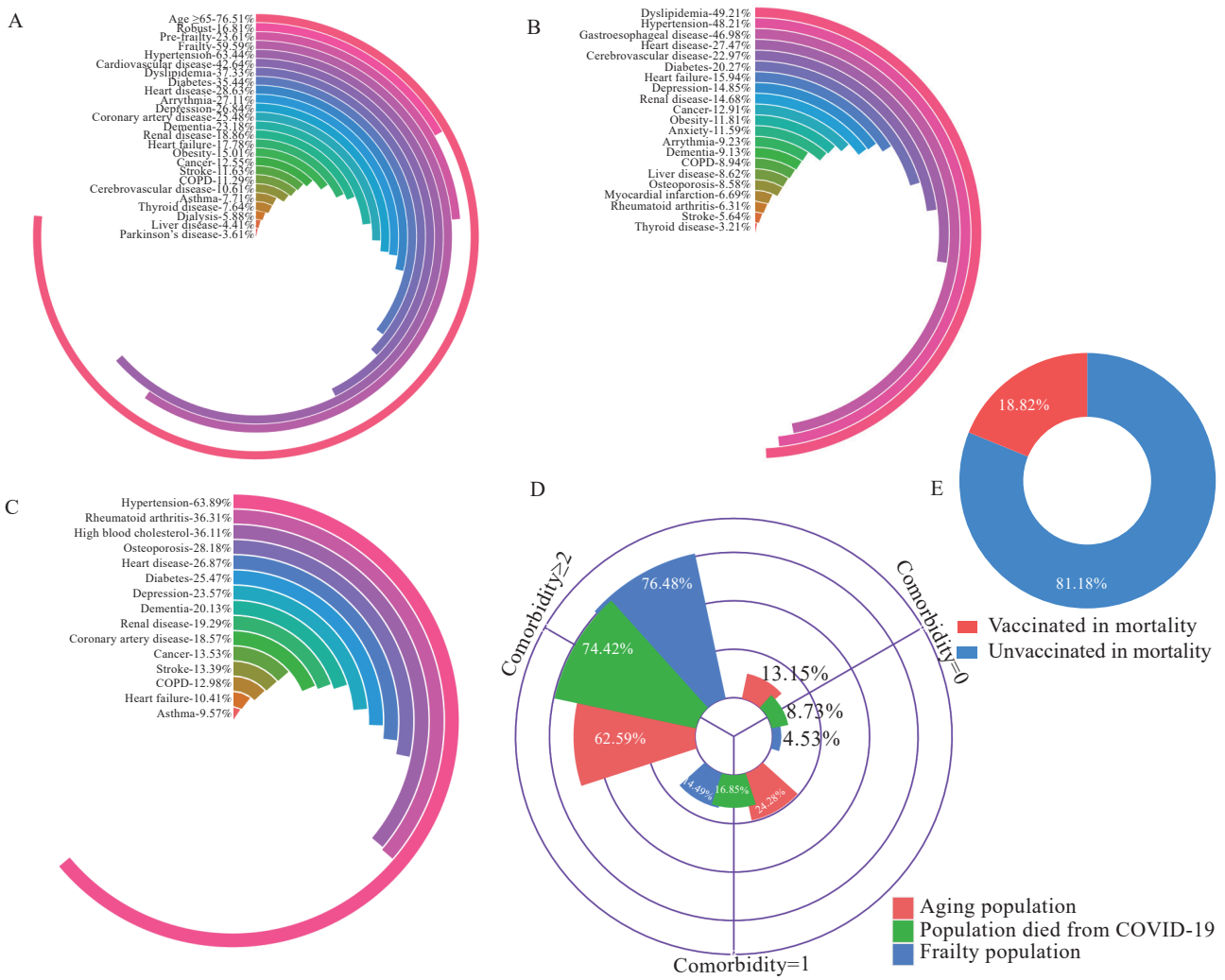

FIGURE 1. Examining the complex relationships between aging, frailty, underlying disease, and medical history and COVID-19 mortality. (A) Proportion of individuals with aging, frailty, and underlying conditions among the total cases who died of COVID-19. (B) Proportion of underlying conditions in elderly patients. (C) Proportion of various underlying conditions among patients with frailty. (D) Number of coexisting diseases and frailty syndrome correlated with COVID-19 deaths. (E) Vaccination history affecting deaths of COVID-19.
Abbreviation: COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019.

formula into the traditional SEIR model, which is frequently employed for simulating the progression of an epidemic (Figure 3A). Our software offers both out-of-the-box and customizable functionality (Figure 3B). Users can input relevant epidemic parameters and click the "simulate" button to obtain the predicted total infection and death counts.

Using data from the United States between December 1, 2021 and March 1, 2022, we entered these values and executed the software. The 90-day simulation results are presented within the software interface and can be exported for further analysis (Figure 3C). We compared the predicted and reported numbers of total infections and deaths. The reported figures were 30,140,720 and 168,655, whereas the simulated figures were 30,263,302 and 186,820, respectively (Figure 3D). These findings demonstrate the practical utility of our software tool.

Scale Designed for Assessing the Risk of Death for an Individual Suffering from COVID-19: We designed a scale that considers the above main key factors that lead to COVID-19 deaths to rapidly assess the risk of death for an individual. This scale consists of four domains: frailty phenotype, comorbidity number, vaccine dose, and COVID-19 symptom (Figure 4A). We can assess the risk by way of the question and answer scoring (Figure 4B). It has 6 questions and 14 answers, and the score is rated from 0 to 6 (Supplementary Table S2). The evaluation results are as follows: low risk at <3.5; moderate risk at 3.5–5;

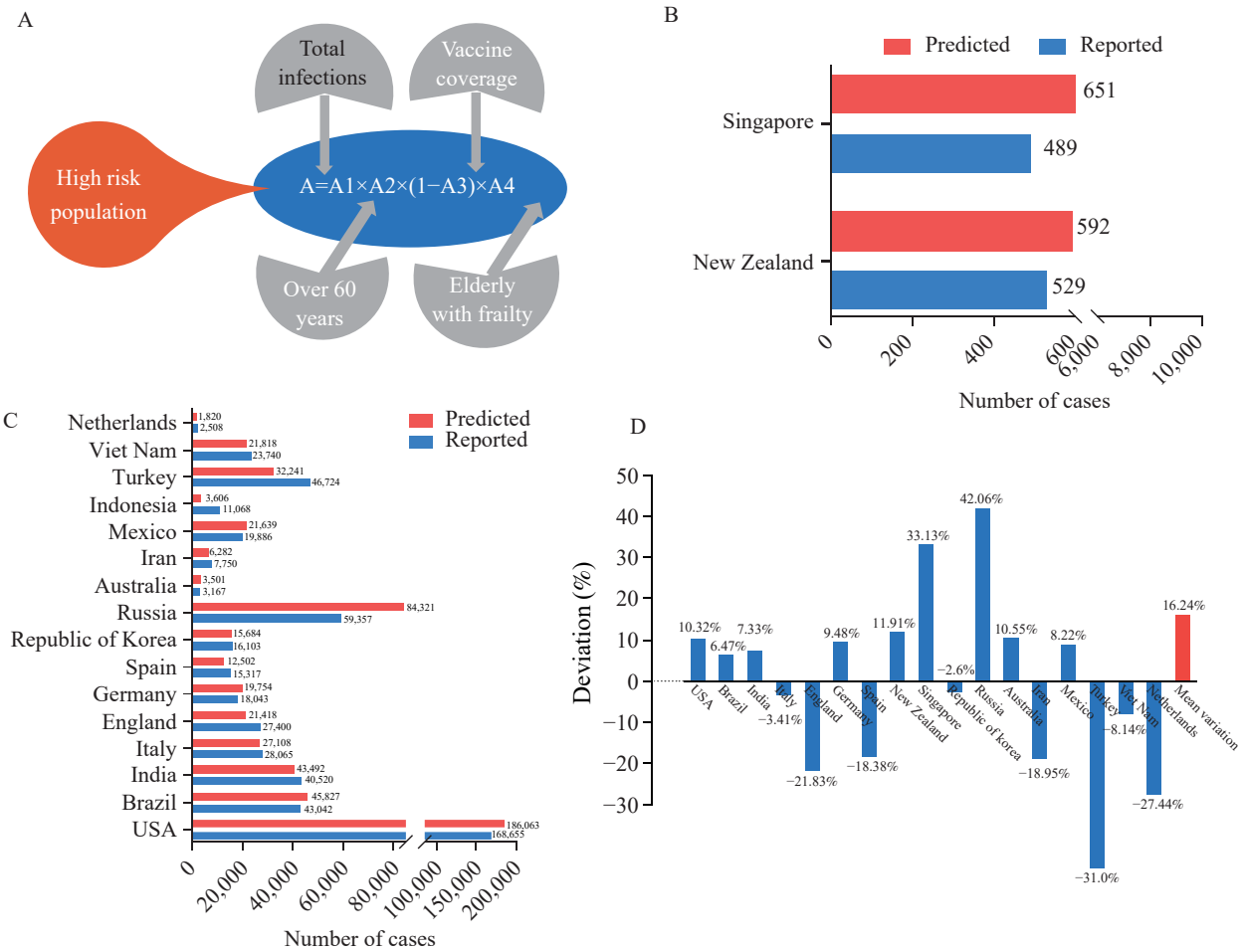

FIGURE 2. Comparison of predicted high-risk populations and actual COVID-19-related deaths. (A) Proposed formula for predicting the deaths. (B) Comparison of predicted and reported case numbers in New Zealand, and Singapore. (C) Comparison of predicted and reported COVID-19 cases in the United States, Brazil, India, Italy, United Kingdom, Germany, Spain, Republic of Korea, Russia, Australia, Iran, Mexico, Türkiye, Viet Nam, and the Netherlands. (D) Bias generated by prediction for all analyzed regions.
Abbreviations: USA=the United States of America; COVID-19=coronavirus disease 2019.

and high risk at >5. Presently, we are in the information age. We have designed an online web page for risk assessment anytime and anywhere to facilitate individual prediction (Figure 4C). Completing this scale may only take 1–3 minutes due to its free and out-of-the-box availability, which will allow a simple and quick individual assessment.

DISCUSSION

Frailty characterized by a decline in physiological reserves across multiple organ systems can result in increased susceptibility to external stressors (*8*). Risk assessment based on frailty has been employed in clinical resource allocation in various fields since its introduction 20 years ago (*9*–*10*). Frailty has also been suggested as a criterion for priority access to medical care for COVID-19 patients (*10*). However, relying solely on frailty as an indicator may not be sufficient in addressing the novel epidemic strain, which is predominantly characterized by asymptomatic cases. We incorporated age, frailty, and vaccination history into our risk assessment tool to enhance its accuracy and applicability using a mathematical formula based on the product effect to estimate the number of fatalities (Figure 2A). Subsequently, we refined this formula and developed a population risk assessment software, SEIP-RA (Figure 3), by adapting our previous SEIR model (*7*) to make it more practical. The reliability of this formula was demonstrated to be accurate to 83.76% using epidemic data from 20 countries and regions (Figure 2D). Although discrepancies exist between our predictions and the available reports (Figure 2B–D), these variations can be

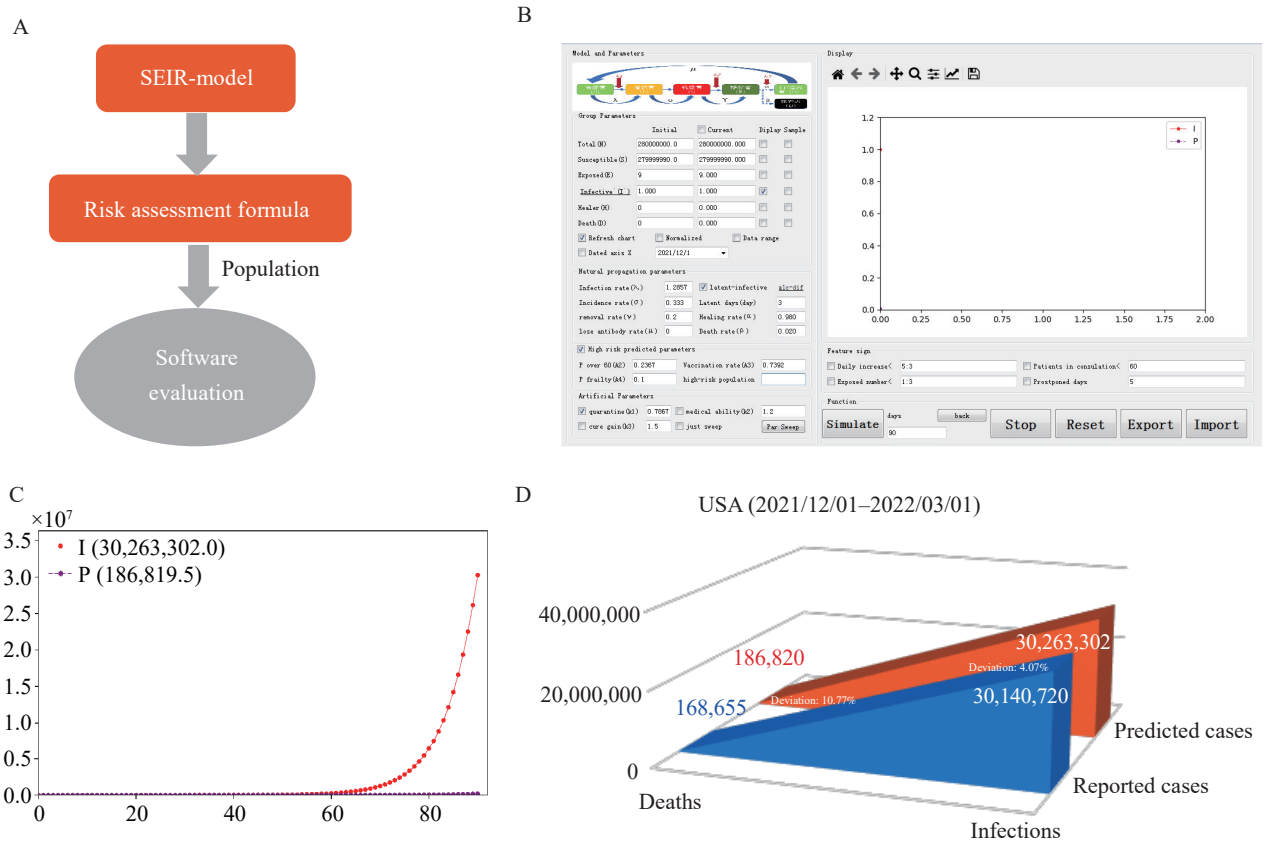

FIGURE 3. Software for population risk assessment for coronavirus disease 2019. (A) Design principle of the software. (B) Software interface and operating parameters. (C) Projected total number of infections and deaths in the United States from December 1, 2021 to March 1, 2022, utilizing predictive modeling software. (D) Comparison of predicted and reported total infections and deaths in the United States from December 1, 2021 to March 1, 2022.
Abbreviations: USA=the United States of America.

mainly attributed to the regional heterogeneity of the frailty index and the ongoing changes in vaccination rates.

For individual risk assessment, relying solely on age, frailty, and vaccination history may be inadequate. Factors such as the number of comorbidities and the presence of COVID-19 symptoms also significantly influence the severity of the disease. To improve accuracy, we integrated these two factors into our assessment tool. The tool is based on the Fried phenotype, a frailty assessment method, with the removal of complex indicators. Key risk factors, such as vaccination status and number of comorbidities, were extracted from the population level and combined with clinical symptoms of COVID-19 to create a straightforward and rapid personal risk assessment tool. The weight of each item is assigned according to the scoring system of the frailty scale (Fried phenotype) (*11*). Clearly, retrospective research methods are insufficient to rigorously verify and fine-tune the weight of each item. Further refinement will necessitate years of clinical experience in multiple countries or regions with ongoing COVID-19 outbreaks. Unfortunately, we could not provide individualized clinical data for risk assessment due to current conditions. It is our hope that widespread use of this scale will generate valuable data in the future, assisting in the tool's improvement.

In accordance with prevailing logic, factors such as aging, comorbidities, frailty, and vaccinations significantly contribute to the mortality associated with infectious diseases, irrespective of viral mutations. Consequently, our risk assessment tools remain broadly applicable. In summary, these tools may offer valuable insights for enhancing life preservation, resource allocation, cost-effectiveness, and the advancement of social and economic development.

Funding: This study was financially supported by the National Natural Science Foundation of China (82101631) and the Key Specialty Construction

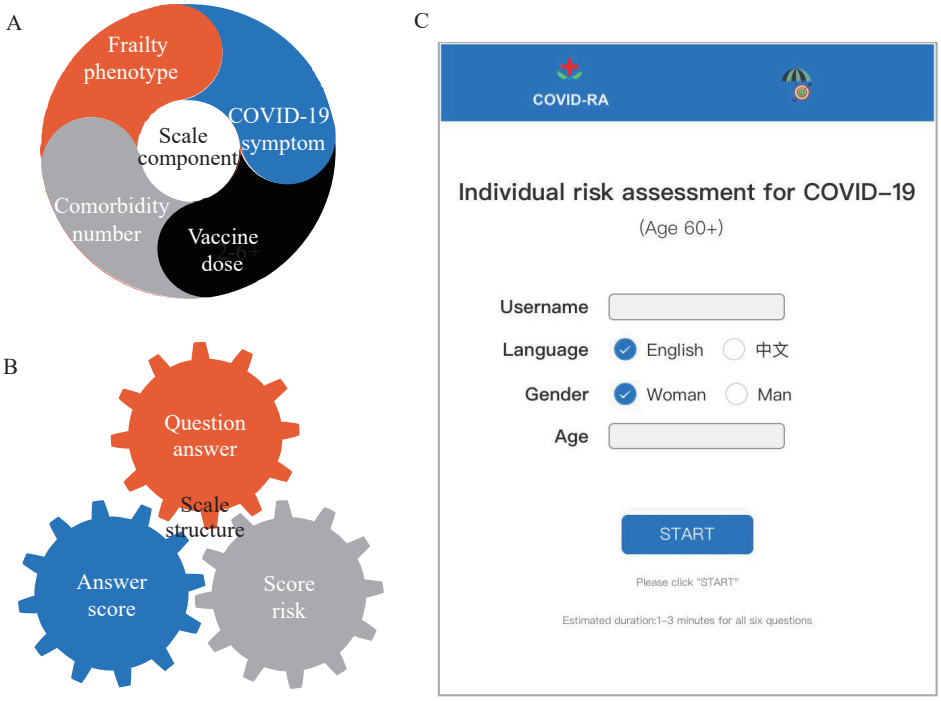

FIGURE 4. Web-based version of scale for individual risk assessment for coronavirus disease 2019 (COVID-19). (A) Scale component. (B) Scale structure. (C) Online risk assessment tool.

Project of Pudong Health and Family Planning Commission of Shanghai (PWZzK2022-05).

doi: 10.46234/ccdcw2023.077

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Submitted: January 09, 2023; Accepted: April 28, 2023

REFERENCES

1. Yan HH, Ding YD, Guo WB. Epidemiological, radiographical, and laboratorial characteristics of Chinese asymptomatic cases with COVID-19: a systematic review and meta-analysis. Front Public Health 2022;10:808471. http://dx.doi.org/10.3389/fpubh.2022.808471.
2. Zhang CB, Wang HZ, Wen ZL, Gu MJ, Liu LY, Li XQ. Asymptomatic transmissibility calls for implementing a Zero-COVID strategy to end the current global crisis. Front Cell Infect Microbiol 2022;12:836409. http://dx.doi.org/10.3389/fcimb.2022.836409.
3. Elzein F, Ibrahim A, Alshahrani F, Mahrous M, Murshid E, Aldhehyan T, et al. Reinfection, recurrence, or delayed presentation of COVID-19? Case series and review of the literature. J Infect Public Health 2021;14(4):474 – 7. http://dx.doi.org/10.1016/j.jiph.2021.01.002.
4. Zhang YP, Luo W, Li Q, Wang XJ, Chen J, Song QF, et al. Risk factors for death among the first 80 543 coronavirus disease 2019 (COVID-19) cases in China: relationships between age, underlying disease, case severity, and region. Clin Infect Dis 2022;74(4):630 – 8. http://dx.doi.org/10.1093/cid/ciab493.
5. Barda N, Dagan N, Cohen C, Hernán MA, Lipsitch M, Kohane IS, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet 2021;398(10316):2093 – 100. http://dx.doi.org/10.1016/S0140-6736(21)02249-2.
6. Aw D, Woodrow L, Ogliari G, Harwood R. Association of frailty with mortality in older inpatients with COVID-19: a cohort study. Age Ageing 2020;49(6):915 – 22. http://dx.doi.org/10.1093/ageing/afaa184.
7. Wang HZ, Miao ZY, Zhang CB, Wei XN, Li XQ. K-SEIR-Sim: a simple customized software for simulating the spread of infectious diseases. Comput Struct Biotechnol J 2021;19:1966 – 75. http://dx.doi.org/10.1016/j.csbj.2021.04.004.
8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752 – 62. http://dx.doi.org/10.1016/S0140-6736(12)62167-9.
9. O'Caoimh R, Sezgin D, O'Donovan MR, Molloy DW, Clegg A, Rockwood K, et al. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. Age Ageing 2021;50(1):96 – 104. http://dx.doi.org/10.1093/ageing/afaa219.
10. Sablerolles RSG, Lafeber M, van Kempen JAL, van de Loo BPA, Boersma E, Rietdijk WJR, et al. Association between Clinical Frailty Scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study. Lancet Healthy Longev 2021;2(3):e163 – 70. http://dx.doi.org/10.1016/S2666-7568(21)00006-4.
11. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet 2019;394(10206):1376 – 86. http://dx.doi.org/10.1016/S0140-6736(19)31785-4.

SUPPLEMENTARY MATERIAL

Detailed Collection and Analysis of Clinical Data

Data on comorbidity in the aging and frailty population were collected through a comprehensive literature search. International databases, including PubMed, ScienceDirect, and EMBASE, were queried utilizing the terms: "aging" or "older," "comorbidity" or "coexisting diseases" or "multiple diseases" or "complex disease" or "underlying disease," and "frailty." The search encompassed articles published between 2010 and 2022. All retrieved articles were subjected to further exclusion criteria by removing those containing the terms "COVID-19" and "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)."

Case reports including fewer than 1,000 patients in total, or 100 frailty patients, were excluded due to insufficient sample size and a lack of representative information. Data visualization was conducted using RStudio.

Data on comorbidities in COVID-19-related fatalities were collected through a systematic literature review. The search was conducted using PubMed and EMBASE databases to gather relevant risk factor data associated with deaths in individuals infected with COVID-19. The search terms utilized were "COVID-19," "death" or "mortality," and "clinical." The inclusion criteria were articles written in English and published prior to April 1, 2022. Studies with a sample size of fewer than 100 deaths were excluded due to inadequate patient representation and insufficient data.

This study sought to gather data on the influence of frailty and vaccination status in COVID-19-related fatalities. A comprehensive literature search was conducted using both PubMed and EMBASE databases to collect information on frailty and vaccination history in COVID-19 fatalities, employing keywords such as "COVID-19," "frailty," and "vaccine." Inclusion criteria consisted of English-language articles published prior to April 1, 2022. Studies with fewer than 100 cases regarding frailty or vaccination history in COVID-19 fatalities were excluded due to an inadequate sample size and lack of representative data.

In this study, critical data — including "Total infected cases," "Population proportion over 60 years," "Vaccination rate," and "Frailty population proportion" — were collected from the top twenty countries and regions most affected by the COVID-19 pandemic to predict the high-risk population among confirmed cases. Additionally, data from Singapore, New Zealand, and other countries and regions were gathered for comparative analysis in predicting high-risk populations. Moreover, a prediction formula was developed for identifying high-risk groups, as detailed below:

$$A = A_1 \times A_2 \times (1 - A_3) \times A_4$$

where A is the predicted total number of high-risk populations; A_1 is total infections; A_2 is population proportion over 60 years; A_3 is vaccination rate among the population; and A_4 is proportion of elderly individuals with frailty. Frailty parameters were obtained from literature reports.

In the proposed prediction formula, A_1 represents the total number of infections, either known or predicted. The estimation of total infections was achieved using parameters associated with the relevant infectious disease. Values for A_2, A_3, and A_4 were obtained from publicly accessible data sources specific to each location and entered into the software for analysis. For aging populations and regions, an increase in A_2 may be observed. Additionally, A_3 may gradually rise and eventually plateau as vaccination efforts continue. Notably, the derived formula highlights the significant contribution of frailty and vaccination history to the predictive outcome, with vaccination history being particularly impactful.

Due to space limitations, all original data and references can be obtained from the first author.

SUPPLEMENTARY TABLE S1. Formulas and parameters of SEIP-RA software.

Population	Formula	Parameter
Susceptible (S)	$\frac{dS(t)}{dt} = -\lambda S(t)S(t)/N$	λ: Average daily infection rate *S(t)*: Number of the population (S) at time t *I(t)*: Number of the population (I) at time t *N*: Number of total populations in a certain region
Exposed (E)	$\frac{dE(t)}{dt} = \lambda S(t)I(t) - \sigma E(t)$	σ: Infected cases per day *E(t)*: Number of the population (E) at time t
Infectious (I)	$\frac{dI(t)}{dt} = \sigma E(t) - \gamma I(t)$	γ: Average daily treatment probability for the infections
High-risk Population (P)	$P(t) = a_2(1-a_3)a_4\mathrm{I}(\mathrm{t})$	$P(t)$: High-risk populations at time t a_2: Rate of over 60 year a_3: Rate of vaccination a_4: Rate of frailty
	$S(0)+E(0)+I(0)+R(0)=N$	0: time $t = 0$
	$\lambda = R_0/T$	R_0: Reproducing coefficient *T*: Average infectious days
	$\sigma = 1/L$	*L:* Average latent day
	$\gamma = 1/C$	*C:* Average self-healing days
	$\lambda_k = \lambda k_1$	k_1: Interpersonal contact rate

SUPPLEMENTARY TABLE S2. Scale for individual risk assessment for COVID-19.

Domain	Question	Answer	Score
Frailty Phenotype	1. You have lost 4.5 kg or over 5.0% of your body weight in the past year.	A. Yes	1
		B. No	0
	2. You have walked less than 2 hours per week (except for quarantine or under restrictions) in the past 6 months.	A. Yes	1
		B. No	0
	3. One of the following has happened to you in the past week (*1*). I feel that I have to work hard to do everything (*2*). I cannot walk forward	A. Yes	1
		B. No	0
Comorbidity Number	4. The number of underlying diseases you suffered from the following: hypertension, obesity, hyperlipidemia, vascular disease, diabetes, depression, heart disease, Alzheimer's disease, chronic kidney disease, cancer, stroke, chronic pulmonary embolism, hemodialysis, thyroid disease, allergy, liver disease, and Parkinson's disease.	A. 0 or 1	0
		B. 2 or 3	0.5
		C. ≥4	1.5
Vaccine Dose	5. The number of COVID-19 vaccinations you have received:	A. Unvaccinated	1.5
		B. 1–2 injections	0.5
		C. ≥3 injections	0
COVID Symptom	6. Your symptoms of COVID-19 are as follows: common cold symptoms, such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, a new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea.	A. No	0
		B. Yes	0.5
Score Evaluation	Low-risk: <3.5, Moderate risk: 3.5–5, High-risk: >5		