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REVIEW ARTICLE

Risk factors and spatial distribution associated with deaths due to COVID-19: an integrative review

Fatores de risco e distribuição espacial associados aos óbitos por COVID-19: uma revisão integrative

Factores de riesgo y distribución espacial asociados a las muertes por COVID-19: una revisión integradora

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ABSTRACT

Background and objectives: understanding the clinical-epidemiological and environmental factors related to deaths due to COVID-19 and their distribution in space can serve as subsidies to direct and implement more effective health actions for vulnerable populations. Thus, the objective was to synthesize the scientific evidence related to risk factors and spatial distribution of deaths due to COVID-19 in the world. **Content:** this is an integrative literature review, and the following guiding question emerged: what is the scientific evidence related to risk factors and spatial distribution of deaths due to COVID-19 in the world? Searches were carried out in the Scientific Electronic Library Online (SciELO) and the Scopus, Web of Science and National Library of Medicine (PubMed) databases in June 2021. Original studies in Portuguese, English or Spanish, without time frame, excluding studies with a specific age group or with an audience with specific comorbidity, were used. A total of 25 studies were included, with findings in different scenarios around the world. Factors such as age, sex, pre-existing diseases were associated with deaths due to COVID-19, which had a heterogeneous spatial distribution and occurred in environmental, socioeconomic and geographic conditions peculiar to these territories. **Conclusion:** age equal to or greater than 60 years, males, cardiovascular diseases, diabetes mellitus and geographic areas with greater environmental pollution, greater population density and precarious sanitary conditions influenced the mortality of COVID-19.

Keywords: COVID-19; Mortality; Risk Factors; Spatial Analysis; Global Health.

RESUMO

Justificativa e objetivos: compreender os fatores clínico-epidemiológicos e ambientais relacionados aos óbitos por COVID-19 e sua distribuição no espaço pode servir de subsídio para direcionar e implementar ações de

saúde mais efetivas para populações vulneráveis. Assim, o objetivo foi sintetizar as evidências científicas relacionadas aos fatores de risco e distribuição espacial dos óbitos por COVID-19 no mundo. **Conteúdo:** trata-se de uma revisão integrativa da literatura, e emergiu a seguinte questão norteadora: quais são as evidências científicas relacionadas aos fatores de risco e distribuição espacial dos óbitos por COVID-19 no mundo? As buscas foram realizadas nas bases de dados Scientific Electronic Library Online (SciELO) e Scopus, Web of Science e National Library of Medicine (PubMed) em junho de 2021. Estudos originais em português, inglês ou espanhol, sem recorte temporal, excluindo estudos com faixa etária específica ou com um público com comorbidade específica. Um total de 25 estudos foram incluídos, com achados em diferentes cenários ao redor do mundo. Fatores como idade, sexo, doenças pré-existentes foram associados aos óbitos por COVID-19, que tiveram distribuição espacial heterogênea e ocorreram em condições ambientais, socioeconômicas e geográficas peculiares a esses territórios. **Conclusão:** idade igual ou superior a 60 anos, sexo masculino, doenças cardiovasculares, diabetes mellitus e áreas geográficas com maior poluição ambiental, maior densidade populacional e condições sanitárias precárias influenciaram na mortalidade por COVID-19.

Palavras-chave: COVID-19; Mortalidade; Fatores de risco; Análise espacial; Saúde global.

RESUMEN

Justificación y objetivos: comprender los factores clínico-epidemiológicos y ambientales relacionados con las muertes por COVID-19 y su distribución en el espacio puede servir como subsidio para orientar e implementar acciones de salud más efectivas para poblaciones vulnerables. Así, el objetivo fue sintetizar la evidencia científica relacionada con los factores de riesgo y la distribución espacial de las muertes por COVID-19 en el mundo. **Contenido:** se trata de una revisión integrativa de la literatura, y surgió la siguiente pregunta orientadora: ¿cuál es la evidencia científica relacionada con los factores de riesgo y la distribución espacial de las muertes por COVID-19 en el mundo? Las búsquedas se realizaron en las bases de datos Scientific Electronic Library Online (SciELO) y Scopus, Web of Science y National Library of Medicine (PubMed) en junio de 2021. Estudios originales en portugués, inglés o español, sin marco de tiempo, excluyendo estudios con se utilizó un grupo de edad específico o con un público con comorbilidad específica. Se incluyeron un total de 25 estudios, con hallazgos en diferentes escenarios alrededor del mundo. Factores como la edad, el sexo, las enfermedades preexistentes se asociaron a las muertes por COVID-19, que tuvo una distribución espacial heterogénea y se produjo en condiciones ambientales, socioeconómicas y geográficas propias de estos territorios. **Conclusión:** la edad igual o mayor a 60 años, la maldad, las enfermedades cardiovasculares, la diabetes mellitus y las áreas geográficas con mayor contaminación ambiental, mayor densidad poblacional y precarias condiciones sanitarias influyeron en la mortalidad por COVID-19.

Palabras clave: COVID-19; Mortalidad; Factores de riesgo; Análisis espacial; Salud global.

INTRODUCTION

COVID-19 is a disease that presents rapid spread, mainly affects the respiratory system[1], but can affect other organs and systems of the human body.[2] Since it demonstrates high contagion, accelerated transmission between humans[3] and dissemination in many countries on several continents, the World Health Organization (WHO) declared, on March 11, 2020, a pandemic state.[4]

It is a viral, infectious disease with respiratory symptoms, whose etiological agent is SARS-CoV-2, a type of beta coronavirus. The predominant symptoms are fever, malaise and cough, with mild course in most infected[5]. However, some patients develop the most severe form, and when the organism cannot recover, they evolve to death.[6]

It is in this context and pandemic scenario that many cases and deaths related to the disease worldwide have been and continue to be recorded. Assessing the overview of COVID-19 deaths worldwide, until October 24, 2021, there were a total of 4,927,723 deaths. To date, the United States had the highest cumulative number of deaths, with 726,846, followed by Brazil, with 604,228, India, with 453,042, Mexico, with 285,347, and Russia, with 228,453.[4]

As for the global mortality rate, until October 23, 2021, a rate of 627.8 deaths/1 million inhabitants was recorded. Among countries with a population of more than 1 million, Peru had the highest rate, with 5,995.9 deaths/1 million inhabitants, followed by Bosnia, with 3,469.3/1 million inhabitants.[7] It is believed that individual and collective factors can interfere with these rates and influence the outcome of discharge or death, such as socioeconomic factors and vulnerabilities related to housing, population income conditions, aging and level of social exclusion.[8] Moreover, the approach, clinical guidance and previous identification of comorbidities are equally important, as these are significant points in the course of a disease.

The clinical management of SARS-CoV-2 infection still requires further clarification to obtain better control over the disease, and, as in other pathologies, it is inferred that early diagnosis and follow-up act positively and can prevent the most serious manifestations of COVID-19. The virus causes an acute respiratory syndrome that ranges from mild to very severe cases, with evolution to severe respiratory failure, and its lethality differs ac-

cording to associated comorbidities and age.[9]

With regard to comorbidities, the most severe cases have been recorded in older adults who have some associated disease, especially hypertension and diabetes mellitus, but this association was also verified in cardiac and respiratory diseases.[10] Regarding age, it is verified that over 50 years old is positively associated with cases of deaths.[11,12]

It is also noteworthy that knowledge of how diseases are distributed and disseminated in time and space is a central point of spatial epidemiology and health geography. Spatial analysis is essential to understand the spatial spread of an infection and its association with the community and the environment,[13] and can thus be used in the field of health research, as it brings a significant contribution to the observation of diseases and injuries in an area or region, making it possible to verify how each territory's particularities influence the dissemination of a given disease.

Understanding the clinical-epidemiological and environmental factors and their distribution in space can serve as an instrument for directing more effective health actions to vulnerable populations. Considering that conducting literature review studies related to risk factors and their associations with COVID-19 mortality can collaborate with professionals, managers and health services in promoting a more efficient clinical and epidemiological management, the objective was to synthesize the scientific evidence related to risk factors and spatial distribution of COVID-19 deaths worldwide.

METHODS

This is an integrative literature review, which aims to synthesize the knowledge about a given subject, making use of a systematic process and with scientific rigor.[14] The construction of this review consisted of the following phases: research question formulation; database search and primary study selection; study screening; analysis and synthesis of selected studies; and presentation of results.

For data collection, the PICo strategy (Population or problem, Phenomenon of Interest and Context) was used.[15] Problem (P) covered the deaths due to COVID-19, Interest (I), risk factors and spatial analysis, and Context (Co), studies published worldwide. Thus, the following guiding question was formulated: what is the scientific evidence related to risk factors and spatial distribution of COVID-19 deaths in the world?

The searches for the studies took place in June 2021, in the Web of Science, Scopus, National Library of Medicine (PubMed) and in the Scientific Electronic Library Online (SciELO) databases, using the Descriptors in Health Sciences (DesC) in Portuguese: "COVID-19", "*Mortalidade*", "*Fatores de Risco*", "*Análise Espacial*" e "*Saúde Global*". The corresponding terms in English of the Medical Subject Headings (MeSH) of the National Library were used in the databases: "COVID-19", "Mortality", "Risk Factors", "Spatial Analysis" e "Global Health". The descriptors were combined with Boolean operators AND and OR. The crosses were performed as follows: (COVID-19) AND (mortality) AND ((Risk Factors) OR (Spatial

Analysis)) AND (Global Health).

In study selection, we included original studies, made available free of charge, in Portuguese, English or Spanish, and without time frame. Editorials, letters to the editor, expert opinions, reviews (literary, integrative and systematic), theses, dissertations, studies that did not answer the guiding research question and studies in which research was conducted with groups of patients with specific age and/or comorbidity were excluded.

For the initial analysis of pre-selected articles, the Rayyan Systems Inc instrument was used, a free technological application web version, which presents in its interface the studies' main information, collaborating with the initial screening of the articles through a semi-automated process.[16] At this stage, a thorough reading of titles and abstracts was carried out in order to verify which were related to the research question and the inclusion and exclusion criteria adopted.

The strategy adopted in article search and selection was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyzes (PRISMA) model.[17] The studies selected for the application of eligibility criteria were read and analyzed in full, in order to identify which met the objective of this review and thus select those that composed the final sample.

Thus, study characterization was carried out through an instrument designed to present the data related to the objective of this review. The data for descriptive analysis of this instrument are authorship, year of publication, country where the study was conducted, population, data source, objective(s), main findings and study limitations.

RESULTS AND DISCUSSION

Based on the criteria established for review, 25 articles were selected, published between 2020 and 2021. Figure 1, adapted from PRISMA[17], synthetizes the steps for sample selection.

As for the setting of the studies, five were carried out in the United States of America (USA), three in Brazil, two in Mexico, one in Africa, China, Spain, France, India, Indonesia, England, Italy and Iran. Continent-wise, one assessed the European continent and five studies made the analysis at the world level. Most studies were published in English (96.00%), and only 4.00% of them were available in Portuguese.

Among the included studies, more than half investigated the association of COVID-19 mortality with sociodemographic characteristics such as age and sex,[10,12,18-28] pointing out that age from 65 years and being male are risk factors for deaths.[10,18,20,22,26] It was also noted that comorbidities were associated with the outcome of death and constituted important risk factors,[1,11,18,20,23,27-32] especially those resulting from cardiovascular complications, especially hypertension and diabetes mellitus (DM).[18,20,23,29-31]

As for the spatial analysis, ten studies were selected, which investigated which risk factors were associated with deaths in the studied areas and in certain populations. [1,19,24,29,30,33-37] In these investigations, different
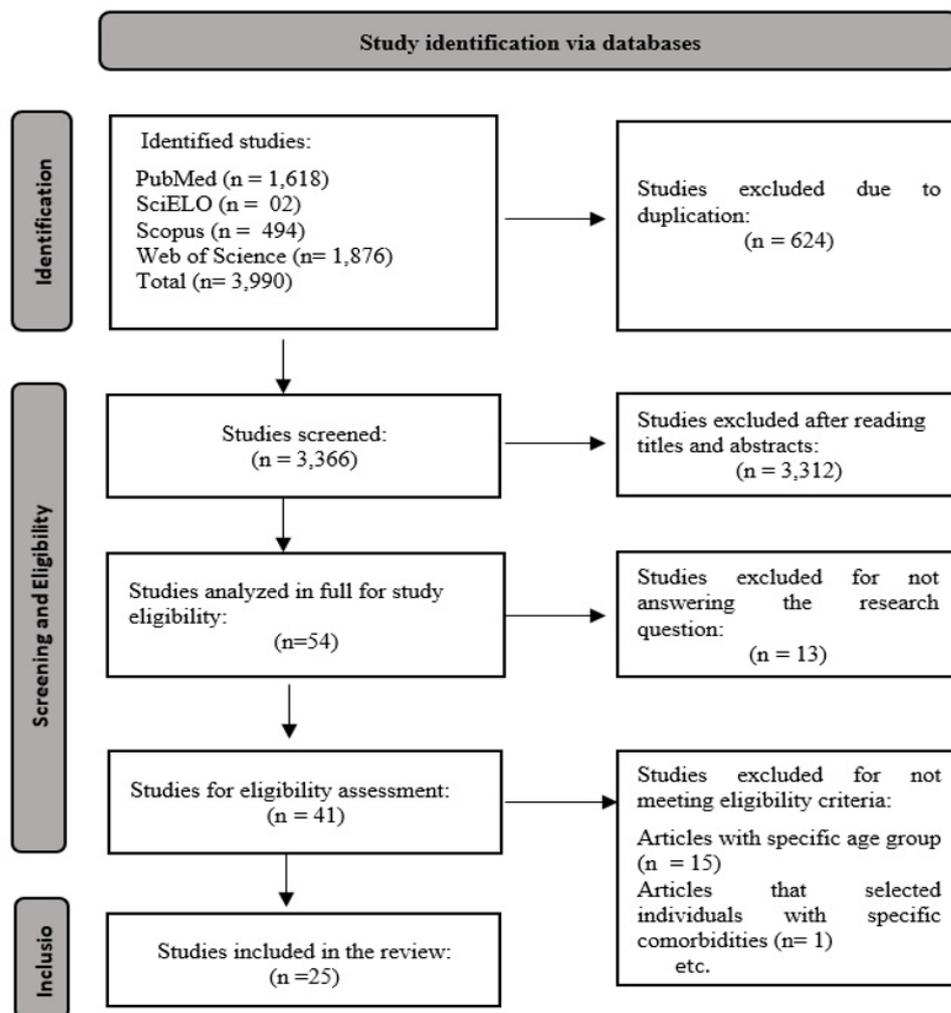
Source: own elaboration, 2021.

Figure 1. Adapted PRISMA flowchart.[17]

techniques were used, among them: empirical Bayesian estimate (EBE);[37] geographically-weighted random forest (GW-RF);[1] geographically-weighted regression (GWR);[33] spatial Durbin model;[30] Least Absolute Shrinkage and Selection Operator (LASSO);[24] space-time scanning techniques (discrete Poisson model);[34-36] spatial correlation (Moran's Index);[29,30,33,37] and Pearson's correlation.[29,34,37] With the use of such tools, a heterogeneous distribution of deaths and/or mortality rates was evidenced, with socioeconomic and environmental conditions[1,19,29,30,33] and population density[24,29,30,35,37] being explanatory factors for the occurrence of events in these territories in space and space-time.

Regarding selected studies' limitations, incomplete feeding of some variables in consulted databases, possibility of underreporting and ecological fallacy stood out.

Chart 1 shows the synthesis of studies included in this review.

It was identified in the global context that several factors appeared as potentiators or associated with deaths due to COVID-19. Some of these factors were distinct or had significant differences depending on the region,

country, or continent. Variables such as advanced age and male gender were associated with the risk of death due to the disease in almost all studies.

COVID-19 mortality rates in the world were heterogeneous and varied between 2% and 4.2% of those affected by the disease.[11,19,29] Among patients with worsening conditions and hospitalized in the Intensive Care Unit (ICU), these rates were much more expressive and changed from one health institution to another. Regarding mortality rates among hospitalized patients, there was a variation between 20.3% and 21.7% in the USA,[12,38] 24% in Europe and 25% in Africa.[22,23] In Spain and Italy, these rates were higher, respectively 42.4% and 44.3%.[21,26]

It was noted that, in outpatients, the mortality rate was 13% in the USA,[12,38] significantly lower than in patients in hospital. This discrepancy between the rates can be justified due to age. Outpatients were mostly younger than hospitalized patients. Furthermore, in the hospitalized group, there were people more likely to have pre-existing diseases (asthma, chronic obstructive pulmonary disease, hypertension, obesity, DM), changes

Chart 1. Articles included in the integrative review (n=25).

Author / place / year	Population and data source	Objective	Main findings
Donamou et al, Guinea, 2021.[22]	140 patients hospitalized with COVID-19 in the ICU. Secondary data extracted from medical records between March and July 2020.	Identify COVID-19-related mortality factors in ICUs in Guinea.	MR of 25% in intensive care. Mean age of patients who died was 65 years, prevalence of death among people with occupation in the informal sector (77%). There was a predominance of males in both subgroups.
Albitar O, et al, World, 2020.[10]	828 cases and 219 deaths due to COVID-19. Data collected at https:github.com/beoutbreakprepa-red/nCoV2019 until April 21, 2020.	Assess the risk factors for COVID-19 mortality in the world.	Male, advanced age, hypertension, DM and the region of America were the independent risk factors for death.
Baqui et al, Brazil, 2020.[20]	11,321 hospitalized patients positive for SARS-CoV-2 by May 4, 2020. Secondary data extracted from SIVEP-Grip.	Characterize the COVID-19 pandemic in Brazil and assess variations in mortality according to region, ethnicity, comorbidities and symptoms.	Brown ethnicity is more prone to death due to COVID-19 than other ethnicities, it appeared as the second variable more associated with mortality, being the first age. As for comorbidities, CVD was the most associated with death (77.4%). Pattern of increased deaths at a median age of 65.3 years and higher percentages of death in males (67.2%).
Sorci, Faivre, Morand. World, 2020.[11]	3,778 COVID-19 patients from 72 countries. Secondary Data by 11 June 2020 from the European Centre for Disease Prevention and Control (ECDC).	Analyze the factors that may cause variability in COVID-19 MR between countries.	Worldwide lethality rate due to COVID-19 was around 4%. Countries with the lowest CVD MR had the lowest fatality rate, and countries with the highest MR from smoking and people over the age of 70 years had the highest mortality.
Garcia et al, Europe, 2020.[23]	398 patients who completed their ICU stay for SARS-CoV-2 as of April 22, 2020. Data were collected in the RISC-19-ICU record.	Analyze the progression of COVID-19 in the first 7 days in the ICU and the prognostic factors of mortality in patients.	It showed moderate mortality in the ICU of 24%. It suggests that creatinine, d-dimer, lactate, potassium, and ischemic heart disease are predictors of mortality in these patients. Thus, 58 of mechanically ventilated patients died, with a predominance of males and ages ranging from 70 to 81 years.
Cao Y., Hiyoshi A., Montgomery S., World, 2020.[29]	10,445,656 confirmed COVID-19 cases and 511,130 deaths due to two hundred and nine countries and territories worldwide. Secondary data from the Our World in Data website.	Investigate the influence of demographic and socioeconomic factors on COVID-19 case fatality rate (CFR) globally.	The mean COVID-19 MR of countries and territories is about 2% to 3% worldwide. Risk factors associated with deaths were CVD and DM. SA: used spatial autocorrelation (Moran's Index), Pearson's correlation and multivariate linear regression. There were spatial clusters of deaths in Yemen (Asia), Western and Northern Europe and North America.
Kranjac AW; Karanjac D, World, 2021.[31]	4,098 deaths due to SARS-CoV-2 in 17 nations worldwide. Secondary data extracted from the ECDC between 13 January and 1 November 2020.	Examine the structural, sociodemographic and environmental factors of estimated MR in 17 nations affected by the COVID-19 pandemic.	The lethality rate of COVID-19 was higher in European and North American countries than that observed in Asia. The USA and the United Kingdom had high mortality (7.84%) compared to Japan and Singapore (1.54%). Obesity, DM and age are positively associated with MR. Ambient air pollution was a risk factor for higher lethality rates due to COVID-19.
Middya AI; Roy S; India, 2021.[33]	156,742 cumulative deaths related to COVID-19 until February 24, 2021. Data obtained from a public domain website: https:covidindia.org.br.	Explore the socioeconomic and demographic potential and environmental factors determining COVID-19 deaths.	The highest number of deaths due to COVID-19 was mainly in the western part of India. Associated factors were socioeconomic level and age greater than 50 years. SA: used the OLS (ordinary least square) and GWR (geographically-weighted regression) models and spatial correlation (Moran's Index) to verify associations of deaths. Significant clusters of deaths due to the disease were identified in the state of West Bengal.
Castro et al, Brazil, 2021.[34]	5,082,637 confirmed cases and 150,198 deaths in the period from February 23, 2020 to October 10, 2020. Secondary data from state health departments.	Understand, measure and compare the pattern of spread of COVID-19 cases and deaths in Brazil at thin spatial and temporal scales.	The first cluster of COVID-19 deaths was in May 2020 in Recife. Afterwards, five others emerged until June 2020. The clusters were around Fortaleza, Rio de Janeiro, Amazonas, Pará and Amapá. In January 2021, Manaus (the capital of Amazonas) had a cluster with significant cases and deaths, with collapse of the hospital network and death rates 39.8% higher than in 2020. SA: used spatiotemporal scanning and spatial correlation techniques (Moran's Index), presenting thematic maps with clusters of cases and deaths in Brazilian states by epidemiological weeks.

Mallipattu et al, USA (New York), 2020.[24]	1,325 patients with COVID-19, hospitalized between March 2 and May 11, 2020. Data were extracted from electronic medical records of patients at the Renaissance School of Medicine at Stony Brook University.	Identify predictors of length of stay and death in hospitalized patients with COVID-19.	Mean age 62 years, most were male (57%) with a history of hypertension (60%), obesity (41%), and diabetes (42%). SA: LASSO. The geospatial distribution of patients' homes in relation to population density was mapped by USA regions, and the analysis showed that geographic residences of patients hospitalized with COVID-19 were associated with greater population housing or were located in regions with clusters.
Mikami T et al., USA, 2021.[12]	6,493 COVID-19 patients between March 13 and April 17, 2020. Secondary data extracted from the medical records of Mount Sinai Health System.	Describe the clinical cha-racteristics and risk factors associated with mortality in a large population of patients in the USA.	858 patients died (13.2%), of which 52 were on an outpatient basis and 806 were hospitalized. There was an increased risk of in-hospital mortality over 50 years old, male, hypotension, tachypnea, hypoxia, impaired renal function, elevated D-dimer and elevated troponin. Asians had a higher MR than other ethnic groups.
Rosenthal, et al., USA, 2020.[38]	64,781 COVID-19 patients treated at 592 US hospitals between April 1 and May 31, 2020. Data extracted from the Premier Healthcare database.	Characterize COVID-19 patients in US hospitals and examine risk factors associated with in-hospital mortality.	The in-hospital MR was 20.3%. The use of hydroxychlo-roquine and azithromycin was associated with a higher chance of mortality. Common acute complications included acute respiratory failure, acute renal failure, and sepsis.
Grasselli et al, Italy, 2020.[26]	3,988 individuals with COVID-19 in the ICU. Data collected from records of the Ca Granda Coordination Center of COVID -19 between February 20 and April 22, 2020.	Assess risk factors associated with mortality among COVID-19 patients in ICUs in Lombardy, Italy.	60.5% of patients had at least one comorbidity. At ICU admission, 2,929 patients required invasive mechanical ventilation (IMV). Some independent factors associated with MR included advanced age (mean 63 years), male gender, history of COPD, type 2 DM, and hypercholesterolemia.
Berenguer et al., Spain, 2020.[21]	4,035 patients with COVID-19 hospi-talized in 127 Spanish centers. Data extracted from electronic medical records, until March 17, 2020.	Analyze the characteristics and predictors of death in hospitalized patients with COVID-19 in Spain.	High mortality in patients aged ≥80, who presented three or more comorbidities (47.7%) and in ICU patients (42.4%). Some factors independently associated with mortality were hypertension, CVD, DM, obesity and active cancer. Males accounted for 68% of deaths.
Harris R, England (London), 2021.[36]	20,283 deaths due to COVID-19 in the period from March 1 to April 17. Secondary data collected from the Office of National Statistics (ONS).	Explore neighborhood-level correlations of COVID-19 deaths in London, England.	Mortality was associated with Asian ethnic groups, blacks, socioeconomic disadvantages, and large families. SA: Pois-son spatial regression and Spearman spatial correlation. Neighborhoods with higher mortality were Faling, Merton and Croydon.
Kathe NJ, Wani RJ, USA, 2021.[30]	Cumulative confirmed cases (11,025,775) and deaths (199,170) due to COVID-19 in 3,011 US cities. Data extracted from The New York Times repository on February 27, 2021.	Assess ecological factors and clinical care associated with the United States COVID-19 lethality rate.	DM, age 65 years or older, reason for income inequality, social issues, were positively associated in some US cities with higher mortality. SA: Durbin spatial regression model and Moran's index were used, and clusters of high COVID-19 mortality in the border counties of the Phoenix area in Arizona were found.
Sousa, GJB et al. Brazil, 2020.[32]	2,070 cases and 131 deaths of people with COVID-19. Secondary data obtained from IntegraSUS until April 14, 2020.	Identify the risk factors as-sociated with mortality and survival due to COVID-19 in a state in northeastern Brazil.	6.3% died. Variables that potentiated MR were elderly, CVD, DM, neurological diseases and lung diseases. The difference between the sexes was not significant, but the male had a higher death (relative risk of 1.1, while for females, 1.0).
Contreras-Manzano, et al., Mexico, 2020.[35]	175,148 cases with 20,773 deaths due to COVID-19. Secondary data extracted from the General Directo-rate of Epidemiology of the Mexican Ministry of Health on June 20, 2020.	Analyze the factors at the municipal level associated with a high MR due to COVID-19 in Mexico.	At the municipal level, the prevalence of DM, obesity, population density and others influenced mortality. In 82 municipalities, MR was higher than expected, with 13.8 deaths/100,000 inhabitants. SA: the Poisson regression model was used to assess the binary outcome of death by COVID-19 and in the independent variables analyzed other characteristics and comorbidities.
Alamdari NM et al, Iran, 2020.[18]	It included 459 hospitalizations due to COVID-19 with 63 deaths. Data extracted from forms validated from electronic health records between January 30 and April 5, 2020.	Determine prognostic factors associated with COVID-19 mortality in patients admitted to a hospital in Tehran, Iran.	Older age, higher BMI, presence of lymphopenia, hypo-magnesemia and elevated creatinine on admission have a higher risk of mortality. Predominance of male patients in hospitalizations 69.7% and deaths 77.8%. The MR was higher in patients with comorbidities of DM, malignancy, CKD and obesity.

Souris, Gonzales, France, 2020.[37]	94,238 hospitalizations with 16,380 deaths due to COVID-19. Secondary data taken on the Santé Publique France website between March 19 and May 8, 2020.	Analyze the effectiveness of France's health system against COVID-19 and discuss differences in France's lethality rates with other countries.	The hospital MR in the period was 0.174. SA: spatial correlation (Moran's Index) at the district level showed no correlation between hospital capacity (number of beds per 100,000/inhab.) and the standardized lethality rate COVID-19 in France. High MR affect rural districts with low population density.
Yu C et al., China, 2020.[28]	1,464 patients hospitalized with COVID-19, with 212 deaths. Data extracted from electronic medical records between January 14 and February 28, 2020.	Examine the risk factors for mortality due to COVID-19 and establish a mortality risk prediction model.	Older age, males, hypertension, history of diabetes, lymphopenia and increased procalcitonin on admission were the variables associated with increased mortality.
Luo Y; Yan J; Clure S; USA, 2021.[1]	All daily COVID-19 deaths in 3,108 US counties between January 22 and June 26, 2020. Data collected on the USA FACTS and US Census Bureau websites.	Explore the variation in nonlinear relationships between multiple risk factors and the COVID-19 MR in different locations.	Risk factors related to socioeconomic levels were the ones that most correlated with COVID-19 mortality, other aspects highlighted were moving towards work, the environment, health status and climate. SA: GW-RF was used to estimate the nonlinear relationship between the COVID-19 MR and associated risk factors.
Surendra H et al., Indonesia, 2021.[27]	4,265 patients with COVID-19, hospitalized between March 2 and July 31, 2020, in 55 hospitals. Data collected from medical records extracted by the epidemiological investigation instrument.	Assess clinical characteristics and factors associated with in-hospital mortality of COVID-19 patients in Jakarta, Indonesia.	Higher MR due to COVID-19 was associated with age, male gender, pre-existence of hypertension, DM or CKD and immediate admission to the ICU or intubation. At all ages, the risk of death was higher for patients with more than one comorbidity.
Najera H; Ortega-Avila Ag, Mexico, 2020.[25]	515,090 cases with 55,963 deaths due to COVID-19. Secondary data extracted from the general direction of epidemiology data of the Government of Mexico until August 15, 2020.	Analyze how the interaction effects of noncommunicable diseases affect the mortality risk of patients with COVID-19 and estimate the risk variation between institutions with different comorbidity profiles.	Males, indigenous (speakers of the indigenous language) and older were more likely to die. Those with DM, obesity, CKD, hypertension and use of immunosuppressants had a higher risk of death. CVD were not associated with higher mortality. The interaction of DM with other comorbidities such as CKD and hypertension doubles the risk of COVID-19 mortality.
Alshogran OY et al, World, 2021.[19]	Confirmed cases and deaths due to COVID-19 in 113 countries that had more than 100 positive cases by April 13, 2020. Secondary data collected from the Johns Hopkins University coronavirus resource center.	Check the association of social, demographic, non-communicable diseases and health care factors with deaths due to COVID-19 worldwide.	The MR of COVID-19 varies between countries by 4.2 ± 3.8%, about half of the countries had a MR > 3.2%. There was no significant positive association at the country level between comorbidities hypertension and DM and deaths. SA: multivariate logistic regression and Spearman correlation. The analyses showed that the proportion of people over 60 years of age was positively correlated with fatal cases.

Source: own authorship. Caption: SA= spatial analysis; DM= diabetes mellitus; CVD = cardiovascular diseases; COPD = chronic obstructive pulmonary disease; CKD= chronic kidney disease; MR= mortality rates; ICU= Intensive Care Unit.

in vital signs [12] and more severe conditions, such as severe acute respiratory syndrome, requiring the use of mechanical ventilation.[23,38]

Specifically, regarding age, all studies that evaluated this variable demonstrated the association of higher death rates among older patients. A study that analyzed several countries found that 80% of deaths caused by COVID-19 occurred among adults aged ≥ 65 years.[10] Other studies showed similar results, thus showing that older adults aged 60 years and over had a higher risk of death.[18-20,22-24,26,28,31]

The greater vulnerability to COVID-19 in this age group may be associated with the weakening of the immune system in the fight against infections,[39,40] when the functions of T and B cells become potentially more defective with high production of type 2 cytokines, thus causing a deficiency in the control of viral replication, which is possibly related to the worse clinical prognosis in this age group.[28,41]

Gender was another factor that was associated with higher mortality due to COVID-19, with the male being the most prevalent.[10,12,18,21,22,24-28,38] In China, a retrospective study analyzing factors associated with mortality due to COVID-19 demonstrated, through multivariate logistic regression analysis, 2.75 more chances of mortality in men than in women.[28] Approximate value was verified in a survey conducted in a hospital unit in Iran, in which the odds ratio of mortality was three times higher in men.[18]

This higher mortality in men can be analyzed from some factors, such as higher prevalence of pre-existing

diseases in this group (coronary, chronic lung diseases and DM), more frequent risk behaviors such as smoking and alcohol habits, occupational exposure and sexual, genetic and hormonal differences.[42] Additionally, women generally produce a more effective and adaptive immune response to viruses, which favors a less severe evolution of COVID-19.[43]

Regarding the clinical manifestations of patients who progressed to death, the most frequent were dyspnea, fever, cough,[22,28] severe acute respiratory syndrome and consequent need for mechanical ventilation support.[18,23,26] This is justified due to the disease predominantly affecting the respiratory system, causing upper and/or lower airway infection.[44,45]

Among the comorbidities associated with deaths due to COVID-19, cardiovascular diseases (CVD) and DM stood out.[18,20,23,29-31] Patients with CVD have increased serum levels of angiotensin-converting enzyme 2, which binds to the Spike protein of SARS-CoV-2, which may contribute to more severe manifestations.[46] In diabetics, the higher concentration of glucose in monocytes can result in greater viral replication and production of pro-inflammatory cytokines, so they present a late hyperinflammatory response and a decrease in adaptive immunity.[47] Other studies have also shown other health conditions associated with deaths, such as neurological,[20,32] respiratory, kidney diseases[12,27,38] and obesity.[20,21,35]

In addition to biological and clinical factors, other factors that influenced mortality due to COVID-19 were socioeconomic, environmental and spatial distribution of the disease in the area of residence. Research conducted in 209 countries around the world,[29] in which spatial analysis techniques were used, such as global and local Moran's Index, in addition to multivariate logistic regression, identified the association of economic factors and population density related to mortality from the disease, establishing that mortality rates were associated with low economic level and higher population density in low- and middle-income countries. These data corroborate a study conducted in the United States, where it was found that income inequality and precarious housing conditions influenced the increase in mortality rates from the disease.[30]

Still in this perspective, in research that covered countries on the American, European and Asian continents, researchers reported that socioeconomic status can affect mortality due to COVID-19, because, as the number of severe cases increases and the public health system is overloaded, patients who need intensive care may not be able to receive care and do not have financially resources to provide another source of care.[11]

Socioeconomic and demographic risk factors, commuting route to work, environment, health status, and climate-related factors in the United States were associated with the COVID-19 mortality rate. It is also noteworthy that the concentration of benzene in the air showed a high correlation with death due to COVID-19, appearing as the main risk factor in 24% of the municipalities analyzed in this study.[1]

These findings are possibly related to the fact that SARS-CoV-2 spreads through the air; thus, walking to work reduces social distancing, which increases the risk of infection and dissemination. As for the influence of benzene concentration on increased mortality, it occurs due to the possible bonds of suspended particles that spread in the air, so an air with more pollutant particles is more favorable in viral propagation.[1]

Regarding the spatial distribution of COVID-19 deaths worldwide, until July 2, 2020, it was found that the highest concentration of deaths occurred in Yemen (27%), Western and Northern Europe (14% – 19%) and North America (9% – 12%). When employing Moran's analysis, a statistically significant spatial dependence relationship was found around countries/territories with high lethality due to the disease; thus, the areas considered to be at greatest spatial risk were North America and Western Europe.[29]

A study that investigated the association of multiple factors, including demographic, social, economic, health care, child health and non-communicable diseases with COVID-19 lethality worldwide, employed multivariate logistic regression and Spearman's correlation, revealed that, in April 2020, the three countries with the highest mortality rates from the disease were Zimbabwe, with a rate of 21.4% (Africa), Algeria with a rate of 17.6% (Africa) and Italy, with a rate of 15.6% (Europe).[19] In addition to this, it was also observed that the polio vaccine immunization coverage was related to a lower mortality due to COVID-19.

Research carried out in India using GWR techniques showed that the geographical distribution of deaths reported by COVID-19 did not occur randomly and was related to underlying factors, including demographics, socioeconomic and environmental variations related to pollution between different territories, with emphasis on regions with higher mortality rates linked to environmental pollution by $PM_{2.5}$ particles in the east of the country.[33]

It is also noteworthy that, through spatial scan statistic, significant clusters of high relative risk were detected statistically significant for the occurrence of deaths, and priority locations for health interventions were indicated by management and health services and systems, namely the city of Manaus, in the state of Amazonas (Brazil)[34], and in the states of Oaxaca, Yucatán and Sonora (Mexico).[35] This technique has been routinely used in several ecological studies carried out around the world dealing with communicable diseases, as it allows the identification of clusters, whether of low or high relative risk, of a given event in space and space, calculating radii in which values maximize the likelihood function related to the total number of cases observed.[49]

Other significant clusters for mortality were identified through spatial analysis of the global and local Moran's Indexes in border counties in the Phoenix area of Arizona (USA),[30] state of West Bengal (India).[33] Clusters with high lethality values were found in regions of high morbidity, especially in the state of Grand-Est (France).[37]

It is noteworthy that the global and local Moran methods incorporate information about the meaning of spatial patterns and identify spatial autocorrelation between ecological units of analysis.[50] In the case of the studies of this review that used them, it was possible to

identify and visualize, through LISA Maps, areas with higher mortality and lethality due to COVID-19, considered as priority areas for interventions aimed at monitoring the disease. This index provides a unique value as a measure of spatial association for the entire data set. This general measure of spatial association in the data set ranges from –1 to +1, in which values close to zero are related to the lack of spatial autocorrelation considering the values of the objects and their neighbors. Values close to 1 indicate positive autocorrelation, and negative values indicate negative autocorrelation.[50]

Thus, the use of geography in health through spatial analysis techniques in diseases is substantial, as it shows geographic patterns, detects spatial or spatial-temporal clusters of diseases and verifies their significance, pointing out which spatial correlations occur in the studied areas, as well as to make maps that allow visualizing disease mortality. Thus, in relation to COVID-19, in which spatial dissemination is an important factor, it assists in surveillance and control, by pointing out priority areas for necessary health and socio-spatial interventions.[29]

Among the limitations identified in the studies analyzed, the fact that they were carried out from secondary data (collections in databases, public domain websites or electronic patient records) stands out initially. Thus, the possibility of underreporting of pre-existing cases, deaths and comorbidities stands out, which interferes with the reliable determination of the disease's morbidity and mortality indicators, in addition to making it difficult to verify other variables of the clinical and epidemiological context associated with deaths due to the disease. Another limitation cited in studies on the spatial distribution of deaths was the so-called ecological fallacy, emphasizing that these findings should not have their results reproduced at the individual level, since they are population studies with interpretation at the group level of the regions analyzed.[48]

CONCLUSION

The studies analyzed demonstrated how some risk factors and geographic distribution affected COVID-19 mortality worldwide. Clinical, social and epidemiological conditions are crucial points in the outcome of the disease. Variables, such as age over 60 years, males and presence of comorbidities resulting from cardiovascular complications and DM, were predominantly associated with deaths due to COVID-19 and were listed as the main risk factors.

As for the spatial distribution of deaths, a heterogeneous distribution was observed in the different settings investigated. The use of different analysis techniques helped to identify geographic areas with higher population density, lower income, lower presence of sanitary sewage, higher environmental pollution and lower hospital capacity, associated with increased mortality.

These data indicate disparities in health, environmental and socioeconomic conditions that exist in different parts of the world. From this, the need to intervene on the identified risk factors emerges and to investigate, through additional studies, other factors associated with death in infected patients, as well as to know the spatial distribution of the disease in vulnerable territories, in order to contribute to the fight against the pandemic and to the elaboration of health strategies and policies that minimize mortality due to COVID-19.

REFERENCES

1. Luo Y, Yan J, MCClure S. Distribution of the environmental and socioeconomic risk factors on COVID-19 death rate across continental USA: a spatial nonlinear analysis. Environ Sci Pollut Res Int. 2021;28(6):6587-6599. doi: 10.1007/s11356-020-10962-2

2. Bourgonje AR, Abdulle AE, Timens W et al. A enzima conversora de angiotensina 2 (ACE2), SARS-CoV-2 e a fisiopatologia da doença coronavírus 2019 (COVID-19). J Pathol. 2020; 251(3): 228-248. doi: 10.1002%2Fpath.5471

3. Wang F, Kream RM, Stefano GB. Sequelas respiratórias e neurológicas de longo prazo de COVID-19. Med Sci Monit. 2020; (26): e928996. doi: 10.12659/msm.928996

4. World Health Organization – WHO. Coronavirus (COVID-19). 2021.https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey={adgroupsurvey}&gclid=CjwKCAjwwsmLBhACEiwANqtXMmrZcl2aKpHElX9an_qHYT41RpyIFKPZhMMyPgBwHStMc-DlwreaxoC-e8QAvD_BwE

5. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J. 2021;97(1147):312-320. doi: 10.1136/postgradmedj-2020-138577

6. Boban M. Atualização da nova doença coronavírus (COVID-19) sobre epidemiologia, patogenicidade, curso clínico e tratamentos. Jornal internacional de prática clínica. 2021; (75): 1-7. doi: 10.1111/ijcp.13868

7. Ministério da Saúde (BR). Boletim Epidemiológico Especial nº 86. Doença pelo coronavírus COVID 19. Semana Epidemiológica 42 (17 a 23/10) de 2021. https://www.gov.br/saude/pt-br/media/pdf/2021/outubro/29/boletim_epidemiologico_covid_86-final-_29out.pdf

8. Silva EA, Caetano, JM, Teixeira SHO. A distribuição desigual da COVID-19 no espaço intra-urbano. I Seminário Nacional-Urbanismo, Tempo e Espaço. Revista Políticas Públicas e Cidades. 2020;(1):1 https://rppc.emnuvens.com.br/urbanismo/article/view/457/323.

9. Guan W, Ni Z, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New england Journal of Medicine. 2020;(382):1708-1720. doi: 10.1056/nejmoa2002032

10. Albitar O, Ballouze R, Ooi JP et al. Risk factors for mortality among COVID-19 patients. Diabetes research and clinical practice. 2020;(166):108293-108297.doi: 10.1016/j.diabres.2020.108293

11. Sorci G, Faivre B, Morand S. Explicando a variação entre os países na taxa de letalidade do COVID-19. Relatórios Científicos. 2020;10(1):18909. doi: 10.1038/s41598-020-75848-2

12. Mikami T, Miyashita H, Yamada T et al. Risk factors for mortality in patients 22 with COVID-19 in new york city. J Gen Intern Med. 2020;36(1):17-26. doi: 10.1007/s11606-020-05983-z

13. Kang D, Choi H, Hunkim J et al. Spatial epidemic dynamics of the COVID-19 outbreak in China. International Journal of Infectious Diseases. 2020;(1):96-102. doi: 10.1016/j.ijid.2020.03.076

14. Mendes KDS, Silveira RCCP, Galvão CM. Use of the bibliographic reference manager in the selection of primary studies in integrative reviews. Texto & Contexto – Enfermagem. 2019;(28): e20170204. doi: 10.1590/1980-265X-TCE-2017-0204

15. Joanna Briggs Institute. Manual: Methodology for JBI Scoping Reviews. Edição suplementar. Austrália, 2015. https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Scoping-.pdf.

16. doi: Ouzzani M, Hammady H, Fedorowicz Z et al. Rayyan -a web and mobile app for systematic reviews. Systematic Reviews. 2016;(5):210. doi: 10.1186/s13643-016-0384-4

17. Page MJ, Mckenzie JE, Bossuyt PM et al. A declaração PRISMA 2020: uma diretriz atualizada para relatar revisões sistemáticas. Systematic Reviews. 2021;(372):71. doi: 10.1136/bmj.n71

18. Alamdari NM, Afaghi S, Rahimi FS et al. Risk factors for mortality among hospitalized PATIENTS COVID-19 in an important reference center in the Irã. The Tohoku Journal of Experimental Medicine. 2020;252(1):73-84. doi: 10.1620/tjem.252.73.

19. Alshogran OY, Altawalbeh SM, Al-Azzam SI, et al. Predictors of COVID-19 case fatality rate: Um estudo ecológico. Ann Med Surg. 2021;(65):102319. doi: 10.1016/j.amsu.2021.102319

20. Baqui P, Bica I, Marra V et al. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health. 2020;8(8):e1018-e1026. doi: 10.1016/S2214-109X(20)30285-0

21. Berenguer J, Ryan P, Rodríguez-Baño J et al. Characteristics and predictors of death among 4035 consecutively hospitalized patients with COVID-19 in Spain. Clin Microbiol Infect. 2020; 26(11):1525–1536. doi: 10.1016/j.cmi.2020.07.024

22. Donamou J, Touré A, Camara AY et al. Fatores preditivos de mortalidade em pacientes com COVID-19 na Guiné: análise dos primeiros 140 casos admitidos em unidade de terapia intensiva. The Pan African medical journal. 2021;(38):205. https://www.panafrican-med-journal.com/content/article/38/205/full/

23. Garcia WPD, Fumeaux T, Guerci P, et al. Prognostic factors associated with mortality risk and disease progression in 639 critically ill patients with COVID-19 in Europe: Initial report of the international RISC-19-ICU prospective observational cohort. EClinicalMedicine. 2020;(25):100449. doi: 10.1016/j.eclinm.2020.100449

24. Mallipattu SK, Jawa R, Moffitt R et al. Geospatial Distribution and Predictors of Mortality in Hospitalized Patients With COVID-19: A Cohort Study. Open Forum Infect Dis. 2020;7(10):ofaa436. doi: 10.1093/ofid/ofaa436

25. Najera H, Ortega-Avila AG. Health and Institutional Risk Factors of COVID-19 Mortality in Mexico, 2020. Am J Prev Med. 2021;60(4):471-477. doi: 10.1016/j.amepre.2020.10.015

26. Grasselli G, Greco M, Zanella A et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA internal medicine. 2020;180(10):1345-1355. http://jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2020.3539

27. Surendra H, Elyazar IR, Djaafara BA. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. Lancet Reg Health West Pac. 2021;(9):100-108. doi: 10.1016/j.lanwpc.2021.100108

28. Yu C, Lei Q, Li W et al. Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China. Am J Prev Med. 2020;59(2):168-175. doi: 10.1016/j.amepre.2020.05.002

29. Cao Y, Hiyoshi A, Montgomery S. COVID-19 case-fatality rate and demographic and socioeconomic influencers: worldwide spatial regression analysis based on country-level data. BMJ Open. 2020;10(11):e043560. doi: 10.1136/bmjopen-2020-043560

30. Kathe NJ, Wani RJ. Determinants of COVID-19 Case Fatality Rate in the United States: Spatial Analysis Over One Year of the Pandemic. J Health Econ Outcomes Res. 2021;8(1):51-62. doi: 10.36469/jheor.2021.22978

31. Kranjac WA, Kranjac D. Decomposing Differences in Coronavirus-related Case-Fatality Rates em Dezessete Nações. Patógenos e Saúde Global. 2021;115(2):100-107. doi: 10.1080/20477724.2020.1868824

32. Sousa GJB, Garces TS, Cestari VRF et al. Mortality and survival of COVID-19. Epidemiol Infect. 2020;(148):e123. doi: 10.1017/S0950268820001405

33. Middya AI, Roy S. Geographically varying relationships of COVID-19 mortality with different factors in India. Scientific reports. 2021;11(1):7890. doi: 10.1038/s41598-021-86987-5

34. Castro MC; KIM S; Barberia L et al. Spatiotemporal pattern of COVID-19 spread in Brazil. Science. 2021;(372):821-826. doi: 10.1126/science.abh1558

35. Contreras-Manzano A, Guerrero-López CM, Aguerrebere M et al. Municipality-Level Predictors of COVID-19 Mortality in Mexico: A cautionary Tale. Disaster Med Public Health Prep. 2020;(1):1-9. doi: 10.1017/dmp.2020.485

36. Harris R. Exploring the neighbourhood-level correlates of COVID-19 deaths in London using a difference across spatial boundaries method. Health Place. 2020;(66):102446. doi: 10.1016/j.healthplace.2020.102446

37. Souris M, Gonzalez JP. COVID-19: COVID-19: Spatial analysis of hospital case-fatality rate in France. Plos One. 2020;15(12):e0243606. doi: 10.1371/journal.pone.0243606.

38. Rosenthal N, Cao Z, Gundrum J et al. Factors Associated With In-Hospital Mortality in a US National Sample of Patients With COVID-19. JAMA Netw Open. 2020;3(12):e2029058. http://jamanetwork.com/article.aspx?doi=10.1001/jamanetworkopen.2020.29058

39. Granda EC, Cunha SGS, Silva MF et al. COVID-19 em idosos: por que eles são mais vulneráveis ao novo coronavírus?. Brazilian Journal of Development. 2021;(7):42572-42581. doi: 10.34117/bjdv7n4-630