COVID-19: A scoping review

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Abstract

Background: Globally, the novel coronavirus is a pandemic disease causing severe human infections. The severe acute respiratory syndrome 2 is causing severe and life-threatening complications.

Methods: A scoping review was conducted following the methodological framework. In this scoping review, 70 records as of May 21, 2020, were included and discussed to better understand the current updates of the virus. PubMed, BioRxiv, MedRxiv, Global Health and google scholars were searched comprehensively for articles, preprints, grey literature, reports, conference proceedings and expert information. Studies conducted in human and published in the English language were included in the review. All the findings and statements of the review regarding the outbreak are based on published data.

Results: We identified 408 records, of which 70 studies met the inclusion criteria. We synthesized the data from the included records and deep insights were extracted. The impact of the outbreak is worsening due to overcrowding, presence of asymptomatic carriers, scarcity of test kits, the immune escaping ability of the virus and lack of community awareness.

Conclusions and recommendations: Due to the fast-spreading nature of the severe acute respiratory syndrome 2 the prevention and control strategies become challenging. It is imposing social, psychological, and socio-economic impacts. Adherence to physical distancing, quarantining suspects, using personal protective equipment, health education and introducing appropriate handwashing practices, avoiding contact with animals, improved control, and prevention strategies are recommended.

Introduction

Globally, the novel coronavirus SARS-CoV-2 is causing a pandemic respiratory syndrome (COVID-19) that needs urgent attention [1]. Coronaviruses were not reported to cause serious and life-threatening respiratory complications in humans until the outbreak of severe acute respiratory syndrome (SARS-CoV) that occurred early in 2003 which had infected 8000 people, with a death rate of 9.5% [2]. This was followed by middle east respiratory syndrome (MERS-CoV) occurrence during 2012-2015 that infected 2500 people with a case fatality rate of 35% [2, 3]. COVID-19 is a new disease caused by the strain severe acute respiratory syndrome 2 (SARS-CoV-2) that has been identified to cause serious infection among humans [4] and has now become a pandemic with up to 4,789,205 confirmed cases and 318,789 deaths as of 20 May 2020 [5].

SARS-CoV-2 is a viral agent in the family of coronaviridae which are positive sense, enveloped, non-segmented RNA viruses. SARS-CoV-2 is classified under the genus of beta coronavirus that has a zoonotic origin whereby first isolated from humans in 1960s [1]. The origin of the virus is supported by a speculation during natural selection in an animal and human host before zoonotic transfer [6]. The novel coronavirus, previously designated 2019-nCoV, caused a cluster of pneumonia-like infections in China during late 2019. On 31 December 2019, four cases of an acute respiratory syndrome with unknown etiology were reported in China among people linked to a local seafood market [1, 3]. From 31 December

2019 to 3 January 2020, a total of 44 pneumonia cases with unknown etiology were reported to world health organization (WHO) from China. Within one month of the outbreak a total of 11, 791 confirmed cases and 213 deaths were reported from 19 countries [4, 5].

WHO declared SARS-CoV-2 as a global public health emergency [7] after about 118 598 confirmed cases reported from more than 100 countries [7, 8]. As of 21 May 2020, SARS-CoV-2 affected **213 countries and 2 territories** [9]. As per the report from a previous study the median age of the confirmed cases was 59 years (15 to 89 years) with the majority being males [8]. The incubation period of SARS-CoV-2 is from 2 to 14 days (sometimes ranging up to 27 days) [10, 11]. WHO and national guidelines have endorsed preventive strategies for the current outbreak. However, the current prevention and control strategy of SARS-CoV-2 is facing challenges. Hence, we conducted this scoping review to assess the epidemiology, transmission, treatment and current interventions, syndromes, factors associated with the pandemic, future prevention strategies and details of the immune system towards SARS-CoV-2 pandemic.

Methods

Methodological framework

We used the following methodological framework to conduct this scoping review. (1) Identification of review question, (2) Developing review objectives, (3) Developing search strategy and identification of search sources, (4) Screening records and data extraction and (5) Setting eligibility criteria.

Search strategy and searching sources

A search strategy was developed using MeSH terms in our research question: ((("SARS-CoV-2") OR ("nCoV-19") OR ("COVID-19"))). We comprehensively searched PubMed, Cochrane, Global Health and google scholars. To avoid missing relevant studies we included preprints and grey literature using BioRxiv, MedRxiv, World Health Organization and Centers for Disease Control and Prevention reports, conference proceedings and expert information.

Study selection and data extraction

After the literature search, all the references were imported to Zotero. Four researchers (BB, HD, HL and HN) independently screened studies for eligibility and relevance. A fifth researcher (GA) was consulted for discrepancies. We resolved differences in opinion through discussion.

Eligibility criteria

Articles, reports, preprints, expert opinions, articles conducted among human participants and records published in English language and records regarding SARS-CoV-2 were included.

Results And Discussion

Characteristics of the included studies and reports

Most of the records were retrieved from WHO, CDC reports and Global health. The 70 included articles summarized (**Figure 1**).

Global burden of SARS-CoV-2

The confirmed cases of SARS-CoV-2 are increasing. In the first two months, the numbers of cases were higher among countries in the west pacific Asian region than other regions with the lowest cases were reported in Africa. As of 21 May 2020, the number of cases was exponentially increased among countries in the European, American, and Eastern Mediterranean regions (**Figure 2**). Furthermore, the number of deaths was higher in the western pacific Asian region in January and February 2020. However, the reported deaths outnumbered among countries in the European region since March 2020 up to date (**Figure 3**).

Virology, pathogenesis, and the clinical syndrome of SARS-CoV-2

SARS-CoV-2 is an RNA virus, with a typical crown-like appearance under an electron microscope due to the presence of glycoprotein spikes [12]. Even though its origin remains vague, it was isolated in environmental samples of the Huanan seafood market by China centre for disease control and prevention, implying the origin of the outbreak [13]. SARS-CoV-2 was first isolated in the Bronchoalveolar lavage fluid of three suspects in Wuhan Jinyintan Hospital during the late 2019 and later determined as a member of β-CoVs [14, 15].

Genome phylogenetic analysis indicates that SARS-CoV-2 shares 79.5% and 50% sequence similarity to SARS-CoV and MERS-CoV, respectively [6, 14, 15]. The nucleocapsid is buried inside phospholipid bilayers and covered by spike proteins. The membrane and envelope proteins are located among the S proteins in the viral envelope [16].

Individuals infected with SARS-CoV-2 presented with early symptoms of high fever (39 ^{0}c), headache and abnormal respiratory findings such as cough, and difficult breathing. The virus is theorized to pass through the mucous membranes, especially nasal and laryngeal mucosa entering the lungs through the respiratory tract [17]. After the virus reaches in the lung it spreads to peripheral blood, causing viremia. Then the virus would adhere and express to the angiotensin-converting enzyme 2 (ACE2), of the organs like lungs, heart, renal, gastrointestinal tract. Patients infected with the virus have a higher number of leukocytes, and increased plasma pro-inflammatory cytokines [14, 18, 19]. The main pathogenesis of SARS-CoV-2 includes severe pneumonia, viremia, combined with the incidence of acute cardiac injury [13].

Manifestations of SARS-CoV-2 are milder in children compared with adults [20-22]. Although most infected individuals are asymptomatic, some children do require hospitalization and intensive care due to respiratory syndrome caused by SARS-CoV-2 [23-26]. Recent reports from Europe and North America have

described clusters of children and adolescents requiring admission to intensive care units with a multisystem inflammatory condition with symptoms like Kawasaki disease and toxic shock syndrome [27, 28].

Host immune response to SARS-CoV-2

The immune system is responsible for controlling, resolution and immunopathogenesis of Coronavirus (CoV) infections. The immune system recognizes the viral agent through pathogen-associated molecular patterns (PAMPs) and the pattern recognition receptors (PRRs). Usually, Toll-like receptor (TLR) 3, TLR7, TLR8, and TLR9 sense viral RNA in the endosome [29-32]. The most important recognition mechanisms of RNA viruses are viral RNA receptor (retinoic-acid inducible gene I), cytosolic receptor (melanoma differentiation-associated gene 5) and nucleotide transferase cyclic GMP-AMP synthase [31, 32]. This complex signalling recruits adaptors, including TLR domain-containing adaptor protein, mitochondrial antiviral-signalling protein [33] and stimulator of interferon genes protein [34] to trigger downstream cascade molecules. This will also be involved in adaptor molecule MyD88 and lead to the activation of the transcription factor nuclear factor-κB, interferon regulatory factor 3, the production of type I Interferons and a series of pro-inflammatory cytokines [35, 36].

Innate immunity

To mount an antiviral response, innate immune cells need to recognize the invasion of the SARS-CoV-2. The recognition is through PAMPs and PRRs. Innate immunity will be activated to limit the virus. A few plasma cytokines and chemokines like IL-1, IL-2, IL- 4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, macrophage colony-stimulating factor, IP-10, MCP-1, MIP-1α, hepatocyte growth factor, IFN-γ and TNF-α were abnormally high among SARS-CoV-2 infected individuals [13,37]. SARS-CoV-2 causes lung injury due to an inflammatory response in the lower respiratory tract that induces cytokine storm. This is associated with the critical and life-threatening conditions among cases [38].

Like SARS-CoV and MERS-CoV, early high rise in the serum levels of pro-inflammatory cytokines occurred among SARS-CoV-2 infected individuals [39], suggesting a cytokine storm-mediated disease severity [40, 41]. The effective innate immune response against SARS-CoV-2 involves the action of interferon responses and its downstream cascade that controls viral replication and induction of effective adaptive immune response [15]. The recognition site is present in a subset of lung cells called type 2 alveolar cells [14].

Adaptive immune response

SARS-CoV-2 is suggested to be neutralized by the antibodies produced against SARS-CoV in an in vitro plaque assay, suggesting a possible successful mounting of the humeral responses [14]. Although the antibody response against SARS-CoV-2 is currently under investigation, the previous study revealed that humoral immunity triggers the spike glycoproteins (S) and nucleoproteins (N). This humoral response reached peak and isotype switching to IgG 3 weeks of post symptoms onsets. After 3 weeks IgM

decreases and IgG increases [42]. Another study reported that CD8+ T cell responses were more frequently observed than CD4+ T cells. Generally, the virus-specific T cells were the central memory phenotypes with a significantly higher frequency of polyfunctional CD4+ T cells (IFNγ, TNFα, and IL-2) and CD8+ T cells (IFNγ and TNFα). Previously published report revealed that a strong T cell response was correlated significantly with higher neutralizing antibodies [43].

Immune Evasion Mechanisms

Current observations indicate that coronaviruses are particularly adapted to evade immune detection and dampen human immune responses. This partly explains why they tend to have a longer incubation period, 2-14 days [44]. Hence the viral antigen can escape host immune detection at the early stage. The immune evasion mechanism is potentially like SARS-CoV and MERS-CoV. The other immune escaping mechanism is inhibition of innate immune responses, inhibition of interferon recognition and signalling, immune modulation including membrane or nonstructural proteins (NS4a, NS4b, NS15), viral mutations and immune exhaustion [45-47]. Furthermore, in the adaptive immune response, the evasion mechanism is due to downregulation of antigen presentation via MHC class I and MHC class II [48].

Transmission, laboratory diagnosis and current treatment

Transmission: the virus has two main transmissions, zoonotic transmission like the outbreak of SARS-CoV in 2003 and MERS-CoV in 2012/2015 [49] and anthroponotic, via direct contact or through droplets spread while coughing or sneezing. Moreover, there is no evidence of congenital transmission for SARS-CoV-2 [16].

Laboratory diagnosis

The following laboratory diagnostic techniques are used to detect SARS-CoV-2.

A. Diagnostic laboratory tests

1. **Viral nucleic-acid test:** Is the routine confirmation test for COVID-19 based on detecting a unique sequence that shows the presence or absence of the virus. The sensitivity and specificity of real-time RT-PCR is greater than 90%. Some factors like contamination, mutations in the primer and probe-target regions of SARS-CoV-2 indicated to have false results [50, 51]. Another study revealed that RT-PCR is a gold standard with 100% sensitivity and specificity [52].
2. **Serology test:** Used for outbreak investigation. These serological tests play a role in research and surveillance which includes antigen and antibody testing. Serum antibody can be detected using ELISA coating a Specific antibody of SARS-CoV-2. Diagnosing SARS-CoV-2 with serology lies with 65-80% sensitivity and 93-100% specificity [53].
3. **Viral sequencing:** After the virus is detected by nucleic-acid test viral sequencing is important for monitoring genome mutation [54, 55].
4. **Viral culture:** It is not a routine test but used for further investigation [54, 55].

B. Supportive laboratory tests

1. **Haematological test:** Is a supportive test to the routine tests for screening the distribution of complete blood cells [54, 55].
2. **Chest CT Scan:** It aids as a supportive diagnostic method to show pneumonia. This test should be considered to confirm SARS-CoV-2 when we are under investigating of this virus [54, 55]. It has higher sensitivity (86-98%) and low specificity (25%) because the imaging features overlap with other viral pneumonia [56, 57].
3. **Blood oxygen saturation test:** This test also uncommon and not routinely applied as a confirmatory test rather used as further investigation of the virus [54].
4. **Detecting Indicators of the inflammatory response:** It is recommended to conduct tests of C-reactive protein, procalcitonin, ferritin, D-dimer, total and subpopulations of lymphocytes, IL-4, IL-6, IL-10, TNF-α, INF-γ and other indicators of inflammation and immune status, which can help evaluate clinical progress, alert severe and critical tendencies, and provide a basis for the formulation of treatment strategies [58].

Current treatment

Neither an effective vaccine nor anti-viral therapeutic agent is approved to treat SARS-CoV-2. Hence, we mostly focus on supportive care. Rapid public health interventions with antibodies, anti-viral or novel vaccine strategies are highly essential. As per previous reports, passive antibody therapy limits SARS-CoV-2 pandemic which can recognize epitope regions in the foreign virus particle and reduce the virus replication [56, 60]. A previous report suggested using some anti-bacterial, antimalarial, or antiviral drugs are important to limit the viral antigen by reducing viral shedding in the respiratory secretions [59]. Some of the antimicrobials which are suggested to have anti-SARS-CoV-2 activities are listed below.

Azithromycin: This antibacterial drug acts by regulating inflammatory responses and reduces the excessive cytokine production associated with respiratory viral infections [50].

Lopinavir and Ritonavir: These ant viral drugs act by binding to Mpro, a key enzyme for coronavirus replication [61].

Alpha interferon: It is used during immunomodulation as an adjuvant treatment [62].

Acetaminophen: It is used to manage fever [63].

Serum therapy: It is the use of monoclonal antibodies with serum therapy and intravenous immunoglobulins preparations as passive immunization [61, 64]. This can be achieved by using peptide fusion inhibitors, anti-SARS-CoV-2 neutralizing antibodies, anti- -ACE-2 and protease inhibitors. The spike protein present on the viral membrane plays a vital role in virus entry and is the principal antigenic component responsible for inducing immune response [62-65].

Antithrombotic treatment

SARS-CoV-2 has been associated with inflammation and a prothrombotic state, with increases in fibrin and fibrin degradation products which are currently added to the treatment guidelines. This treatment is recommended for careful monitoring, evaluating, and treating hospitalized patients with SARS-CoV-2 [66].

Drugs under investigation and trials

Remdesivir: This is not approved therapy by the Food and Drug Administration. However, it available through an FDA emergency use authorization for the treatment of hospitalized clients with COVID-19. It is suggested to be highly selective for viral polymerases, low toxicity and have a high genetic barrier to resistance with a long half-life that allows for once-daily dosing [66-68]. This drug is under trial (GS-5734) to evaluate its safety and antiviral activity among participants with moderate and severe coronavirus diseases comparing.

Immune globulin administration: Administration of convalescent plasma is recommended therapy which is currently under trial for SARS-CoV-2 treatment options [57, 66].

Interleukin inhibitors: To limit the cytokine storm following the immune response against SARS-CoV-2 interleukin inhibitors are undergoing phase trial for treatment option [57, 66].

Lenzilumab: This drug can alleviate the immune-mediated cytokine release syndrome and prevents respiratory failure. This is under clinical trial (CLS-20486775) [69].

Ravulizumab: This is also under clinical trial for safety and effectiveness with a registration number of CLS-20488594 [70].

The economical and psychological impact of SARS-CoV-2

Following the index case of SARS-CoV-2 infected individual in China by December 2019 it started to spread to the rest of the world. It is then declared as a pandemic outbreak by WHO. Since the declaration of the outbreak, it leads to several economical and psychological problems. Some of the impacts include disruption of the global chain supply due to the closing their border, a slowdown of the investment, loss of revenue due to debt, increment in health spending cost, shortage of food and drugs, decrement of business travel and tightening domestic financial markets [71, 72]. Additionally, the pandemic may be associated with increased fear, sadness, anxiety, and depression [73].

Risk groups: Individuals with obesity, cardiovascular disease, respiratory diseases, cancer, and diabetes are highly susceptible to SARS-CoV-2 due to the depletion of immunological barrier mechanisms and cellular dysfunction [62].

To minimize the risk of vulnerable individuals, preventative strategies like cleaning and disinfecting in-home and areas that people touch the most should be used. Furthermore, individuals should limit shared spaces when having guests and keeping recommended physical distancing [74].

Challenges and future prevention of SARS-CoV-2

Challenges: The challenges for the effective controlling of SARS-CoV-2 include absence validated vaccine and treatment [62, 75], the ability of the viral antigen to stay hours and even longer in the air, socio-cultural behaviour of people, lack of awareness, the viral capacity to stay in inanimate objects for weeks [76], overcrowding environment, presence of asymptomatic carriers [77], presence of wide host range [63], lack of adherence to the recommended physical distancing protocols, a variation of interpreting physical distancing, the unclear infective dose of the viral agent, unclear duration of infectiousness prior the onset of clinical manifestation and after recovery [67].

Future preventions and recommendations

At government level: International, National, regional governments should participate by allocating budget for training, isolation of suspects, testing and supportive cares and awareness creation.

At health institutions: Health institutions should also screen and early detection, giving supportive care and treatment, distributing medical protective equipment, give health education and introducing handwashing practices to customers and preparing isolation rooms [78].

At the community level: Creating community awareness on the transmission and early prevention, active case detection, distribution and preparing handwashing jars, utilization of hand sanitizers and respirators [78, 79], avoiding over-crowding [78], avoiding intimate contact with animals [79] and applying hand glove to protect touching different contaminates [78] should be practiced.

At churches and University levels: Minimizing conferences and Sunday schools, avoiding large group gatherings, avoiding class lectures are recommended. Alternative lecture methods like online lectures and video conferences have to be implemented.

For upcoming researchers: Researchers should develop validated vaccine and treatment.

Conclusion

Due to the rapidly spreading nature of SARS-CoV-2, the prevention and control strategies become challenging. Generally, the SARS-CoV-2 pandemic is imposing social, psychological, and socio-economic impacts. Curative treatments and vaccines are trying to be administered to humans and some are on clinical trials. Moreover, the most important preventing strategies for the pandemic up to date are physical distancing, isolation, and quarantine of suspects, using personal protective equipment, health education and improving handwashing practices, avoiding contact with animals. Hence, individuals have to strictly follow these prevention methods. Emphasis should be given to physical distancing as far as it is the most effective and approved preventive strategy than others. There are limitations in implementing prevention strategies.

List Of Abbreviations

ACE =Angiotensin converting enzyme, CD= Cluster of differentiation, CDC= Center of Disease Control, COPD = Chronic obstructive pulmonary disease, COVID-19= Novel corona virus-19, MERS-CoV=Middle East respiratory syndrome, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol, RNA= Ribonucleic acid, SARS-CoV= Severe acute respiratory syndrome, WHO= World health organization, TH= T helper cells TLR=Toll-like receptor

Declarations

Competing interests

The authors declare that they have no competing interests.

Declarations

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Not applicable

Consent for publication

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Availability of data and material

All data are incorporated into the manuscript.

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Authors' contributions

All authors contributed equally to conduct this review, read, and approved the final manuscript.

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Figures
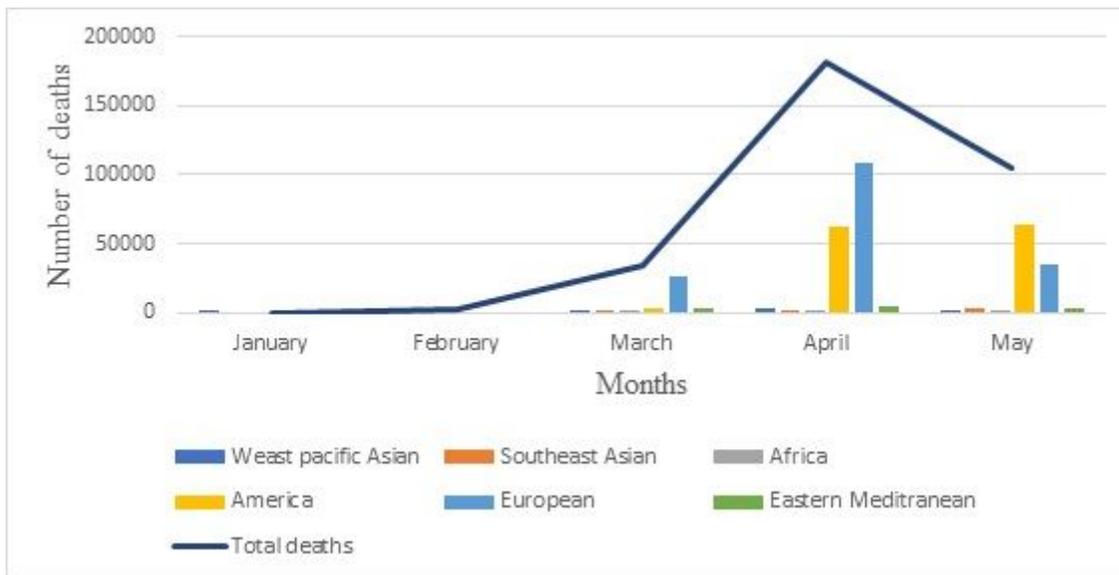
Figure 1

PRISMA diagram of included records
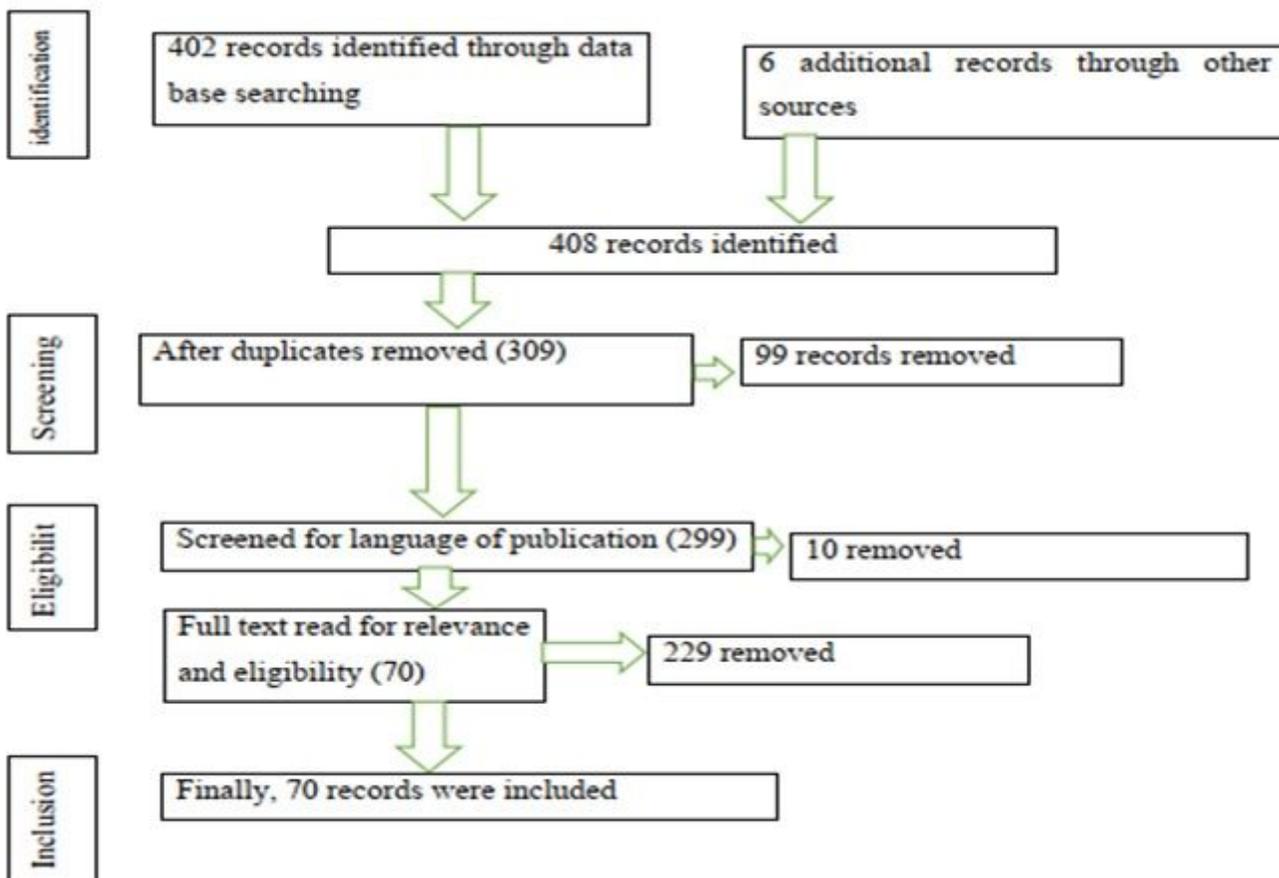
Figure 2

Distribution of confirmed SARS-CoV-2 cases in the recent five months in all WHO regions
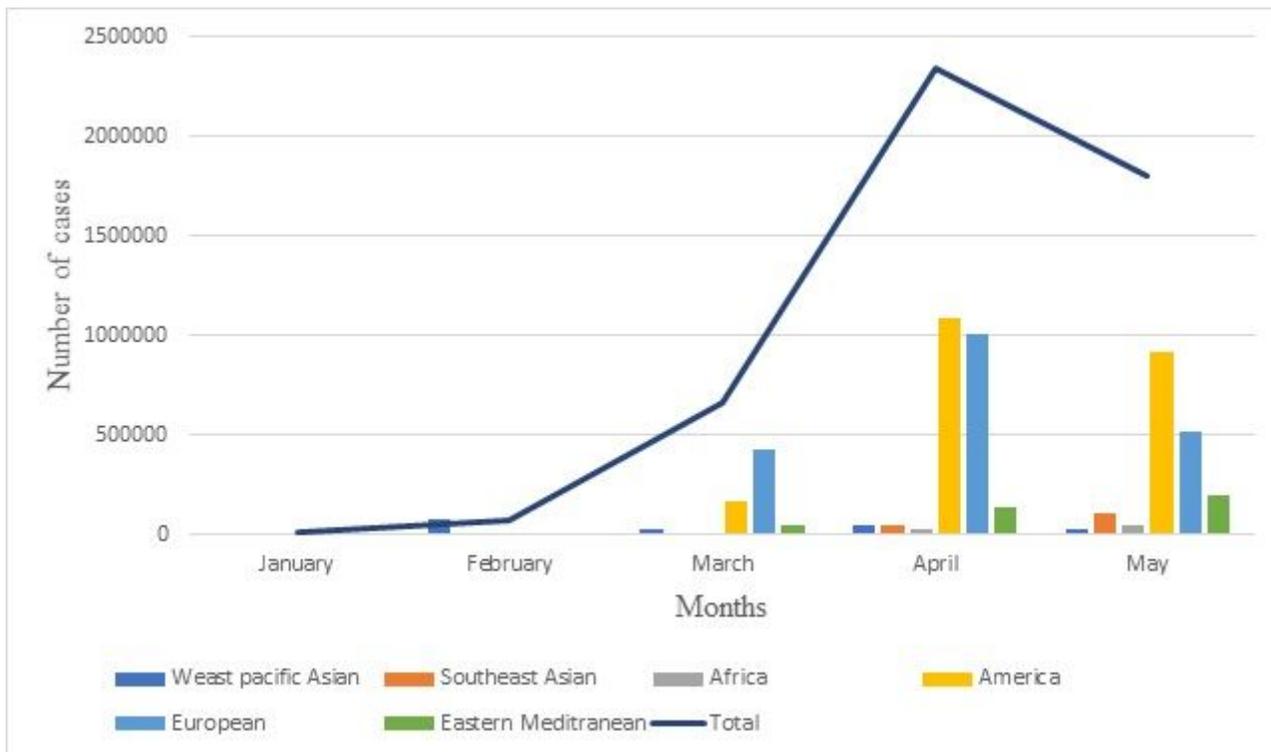
Figure 3

Total distribution of SARS-CoV-2 deaths in the recent five months with the WHO regions