A Systematic Review of Systematic Reviews on the COVID-19 Pandemic

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Abstract
COVID-19 a systemic inflammation involving multiple organs, affecting all age groups, with high mortality rate, severe adverse outcomes, and high economic burden need to be described. A systematic review of systematic reviews conducted. We searched PubMed, OVID Medline, Cochrane library, COVID-19 resource centers of N Engl. J Med, AHA, and LITCOVID. Certainty of evidences was evaluated by GRADE approach. Meta-analysis according to random effects model was conducted. Seventy-one eligible systematic reviews are included in the study. A total of 86.5% of them had high quality, and 13.5% had medium quality. Meta-analysis results are presented in tabular format, and the remaining results are presented in narration fashion. COVID-19 involves blood vessels, lung, heart, nervous system, liver, gastrointestinal system, kidney, eyes, and other organs and infects adult and children, neonates, pregnant women, and elderly, transmitted via air born and droplet. Comorbidities associated with COVID-19 are HTN 20.7%, CVD 9.6%, DM 9.5%, respiratory diseases 7%, and 9% of cigarette smoking. Prognostic factors for mortality among COVID-19 cases are acute cardiac injury, diagnosed CVD, DM, respiratory disease, and HTN. Prognostic factors for disease severity are CVD and HTN. Prognostic factors for disease progression were fever, shortness of breath, and smoking. There is no specific antiviral treatment. Preventive measures including physical distancing of 2 m and more, using PPE, avoiding social gatherings, quarantine, and isolation have been recommended. Encouraging telemedicine, online training, and homeschooling are highly recommended. Vaccine is approaching, and concerns exist about vaccine with a high efficacy. Modification of CVD and cardiometabolic risk became the cornerstone for sustainable control of pandemic.

Keywords Systematic reviews · COVID-19 · SARS-COV-2 · Natural history · Prevention · Treatment · Pandemic

Introduction
Global coronavirus disease 2019 (COVID-19) pandemic, which originated in Wuhan, China, has now about 41,189,939 confirmed cases as officially reported by the governments of 215 countries and territories around the world on October 21, 2020 with 1,131,527 deaths and case fatality rate of 2.74% which continues to change as the pandemic progresses [WORLDOMETER].

The global burden of COVID-19 disease could be accurately estimated based on a combination of population-based cohort studies in society, household, school base, and workplace rather than laboratory-based or hospital-based surveys, alone.

The COVID-19 pandemic can be precisely described as a communicable disease pandemic superimposed on the existence of non-communicable disease pandemic of CVD, DM, and obesity.

The clinical manifestation spectrum of infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) ranges from mild self-limited disease to life-threatening multiple organ involvement. It has initially been described as respiratory symptoms, pneumonia, and, in some cases, acute respiratory distress syndrome (ARDS) and shock [1]. Now, COVID-19 has presented as a systemic inflammation with multiple organ involvement including blood vessels, lung, heart, central nervous system, and other organs [2, 3].

Recent reports describing complement-mediated thrombotic microangiopathy-like syndrome in COVID-19 cases have complicated the pathophysiological feature of the disease.
We aimed to conduct a systematic review of published systematic reviews to provide comprehensive updated information on COVID-19.

Methods

Study design: we conducted a systematic review on COVID-19.

Types of included studies: systematic reviews on COVID-19.

Study population: confirmed cases of COVID-19.

Search Strategy

We searched PubMed, OVID Medline, Cochrane library, and COVID-19 resource centers of N Engl J Med and AHA, and LITCOVID up to June 10, 2020. Search was limited by published full-text article in English language. We searched for systematic reviews on COVID-19.

Data Extraction and Management

We screened titles and abstracts, retrieved published full-text articles, and extracted data based on PICOT algorithm. Accordingly, we extracted data on population/patients, interventions/indicators, comparators, outcomes, and time frame/type of study of included articles.

Risk of bias assessment included studies: Two independent reviewers critically appraised articles using standard method of appraising systematic reviews. Adherent to GRADE approach, we screened the valid evidences among retrieved articles of different databases [4]. Agreement ratio on critical appraisal topic in articles was 94% \( (p < 0.005) \), and disagreements were resolved by consensus. Systematic reviews on clinical trials have been critically appraised based on method evaluation in Cochrane Handbook for Systematic Reviews of Interventions and GRADE guideline.

Types of interventions: COVID-19 management including pharmaceutical and non-pharmaceutical interventions.

Types of outcomes: outcome of interest was efficacy of interventions and natural history of the COVID-19.

Data Synthesis

We extracted the certainty of evidences according to GRADE approach. GRADE approach was also used to present summary of evidence findings [4–13].

Homogenous results were managed by conducting meta-analysis.

Narrative synthesis was the best choice for summarizing systematic inference on various results of the included studies. We have also described data on tabular format.

Data Analysis

Meta-analysis method: Random-effects model was used. Pooled risk ratios, prevalence, and frequencies were estimated associated with 95% confidence intervals. Mantel-Haenszel test was used to estimate parameters. Statistical analysis has been planned and conducted using statistical package of IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Statistical relationships were considered significant at \( P < 0.05 \).

Funding resource: No funds, grants, or support was received.

Results

PRISMA flow diagram reported various studies assessed for further evaluation and including in the review (Fig. 1).

One hundred forty-eight full-text articles were assessed for inclusion based on the GRADE approach. Seventy-one systematic reviews were eligible to include in the systematic review. Critical appraisal assessed the quality of the included 71 systematic reviews; accordingly, 86.5% of studies evaluated as high/good quality, and the remaining 13.5% evaluated as medium quality.

Table 1 presents the included studies in the systematic review and meta-analysis based on PICOI items.

Mean age of COVID-19 cases in different studies was 58.05 ± 7.24. Gender distribution of COVID-19 cases demonstrated that 55.85% \( (45.24–64.39) \) were male.

Clinical Manifestations

Most frequent general symptoms are fever, cough, and fatigue [14] which is presented in Table 2. Dyspnea, anorexia, productive sputum, myalgia [15], sour throat, nausea, dizziness, diarrhea, headache, vomiting, and abdominal pain are other symptoms (with frequency of 82.2 to 2.2% in decreasing order) [16].

Organ-specific symptoms are pharyngodynia and nasal congestion with rare rhinorrhea [14]. Face pain and nasal obstruction were the most specific otorhinological symptoms, and olfactory and gustatory dysfunctions [15]. In a multinational European study, the prevalence of ageusia or dysgeusia was reported 49.8% [17]. The results of multivariate analysis presented in Table 3.
Cardiovascular presentations of SARS-COV-2 have been described as myocarditis [2], myocardial injury, arrhythmia, venous thrombosis [18], cardiogenic shock, and heart failure [1]. Cardiac injury is significantly associated with poor prognosis of COVID-19 patients and higher mortality rate [1, 19]. Circulatory biomarkers of myocardial injury increased in non-survivors of COVID-19 [20]. Another systematic review of 17 studies involving 5815 COVID-19 patients reported the most prevalent cardiovascular complication of COVID-19 as heart failure, cardiac injury, and arrhythmia [21].

Table 4 demonstrates the pooled prevalence of comorbidities associated with COVID-19.

Meta-analysis revealed pooled estimation of different COVID-19 outcomes and complications, which is presented in Table 5.

Coincidence of cardiovascular disease (CVD) and COVID-19 is associated with of 4.85 (95% CI 3.07–7.70) times in hospital mortality increase. Also, the presence of hypertension associated with COVID-19 will tend to in-hospital mortality of about 3.67 (95% CI 2.31–5.83) times [22].

Gastrointestinal symptoms of COVID-19 are vomiting, diarrhea, and abdominal pain or discomfort along with shedding viral RNA (in 48% of cases) in stool which could persist about 33 days after disease onset [23].

A systematic review of 35 studies involving 6686 COVID-19 patients demonstrated that prevalence of having three symptoms of nausea or vomiting, diarrhea, and loss of appetite was 15%. Abnormal liver tests were reported in 19% of COVID-19 cases. Gastrointestinal involvement compromised COVID-19 cases to disease complications [24].

A systematic review of 17 studies involving 2477 COVID-19 patients revealed that severe COVID-19 cases have reported abdominal pain seven times (OR = 7.17 95% CI 1.95–26.34) more than that of non-severe cases [25].

Clinical manifestation of COVID-19 in children [26] is described as fever, cough, and gastrointestinal symptoms. Lymphopenia has been reported in 32% of cases and severe lymphopenia in 9% of infected children.

COVID-19 presentation during pregnancy [27] confirmed cases of pneumonia was fever, cough, and dyspnea. Pregnancy outcome among infected patients reported miscarriage rate of 39.1%, preterm birth 24.3%, premature rupture of membrane 20.7%, pre-eclampsia 16.2%, and fetal growth retardation 11.7%.

Perinatal exposure to SARS-COV-2 in 222 newborns evaluated in 20 different studies resulted in 5.8% infection rate with a wide spectrum of clinical presentations [28]. Current knowledge regarding natural history of COVID-19 cannot confirm vertical transmission of SARS-COV-2 [28].

Eighty-four percent of deliveries were cesarean section. Perinatal death rate was 11.1%, and 57.2% of newborn babies were needed to be admitted in the neonatal intensive care unit [27]. Another study [29] reported 96% cesarean delivery rate, preterm birth of 39%, and median gestational age of 36.5 weeks. Another systematic review of nine studies did not demonstrate maternal mortality ration in pregnant COVID-19 patients. However, adverse events related to pregnancy such as C-section delivery, preterm labor, low birth weight, and NICU admission rate were reported at high a level [30].

A systematic review of 44 studies reported that children have accounted to 1–5% of symptomatic COVID-19 cases. So far, the disease in children was reported milder with better prognosis than adult COVID-19 cases [31].

Another systematic review of 24 studies suggested a similar attack rate of infection among children to adult patients; however, asymptomatic pattern or mild disease presentation tended to lower medical attention to COVID-19 in children [32].
| Title                                                                 | Types of Study design | Study population                        | Intervention                                      | Outcome(s)                                      | Date of publication | Country   | Author/authors                      |
|---------------------------------------------------------------------|-----------------------|------------------------------------------|--------------------------------------------------|-------------------------------------------------|---------------------|-----------|-------------------------------------|
| Quarantine alone                                                    | SR                    | People in quarantine                     | None                                             | Effectiveness of quarantine                     | 2020                | Austria   | Nussbaumer-Streit B et al.         |
| A Systematic Review of COVID-19 Epidemiology based on Current Evidence | SR                    | COVID-19 cases                           | Epidemiological modelling                        | Epidemiological parameters                      | March 18, 2020      | Singapore | Park M et al.                      |
| Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment | SR                    | 199 severe COVID-19 cases               | Antiretroviral drugs versus standard care         | Time to clinical improvement                     | March 20, 2020      | Switzerland | Ford N et al.                      |
| Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis | SR                    | COVID-19 patients with hypertension      | None                                             | Prevalence of hypertension                       | March 30, 2020      | Italy     | Zuin M et al                       |
| Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis | SR                    | Symptomatic COVID-19 patients            | Chest CT                                         | CT findings                                      | March 2020          | China     | Bao C et al.                       |
| Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: A meta-analysis | SR                    | 2389 severe COVID-19 cases              | Laboratory test for detection of myocardial injury | Mortality, ARDS                                  | April 14, 2020      | Indonesia | Santos A et al.                    |
| Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis | SR                    | Childhood cases of COVID-19              | None                                             | Clinical characteristic and diagnostic features  | April 9, 2020        | Taiwan    | Chang T et al.                     |
| Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults | SR                    | COVID-19 patients                        | None                                             | Prevalence and manifestation of the disease in adult and children | March 20, 2020      | Sweden    | Ludvigsson JF                     |
| Potential interventions for novel coronavirus in China: A systematic review | SR                    | COVID-19 patients                        | All available treatment options                  | Disease control                                  | February 4, 2020     | China     | Zhang L et al.                     |
| Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis | SR                    | 1576 COVID-19 patients                  | None                                             | Prevalence of comorbidities, clinical manifestation | March 5, 2020       | China     | Yang J et al.                      |
| COVID-19 and smoking: A systematic review of the evidence           | SR                    | COVID-19 patients                        | None                                             | Smoking rate                                     | March 20, 2020       | USA       | Vardavas CI et al.                 |
| Coronavirus Disease 2019 (COVID-19) Information for Cardiologists   | SR                    | COVID-19 patients                        | None                                             | Cardiovascular manifestations, cardiologists alert updates | April 29, 2020       | Japan/USA | Sugimoto T et al.                  |
| Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 - 19) during pregnancy: a systematic review and meta-analysis | SR                    | Pregnant COVID-19 cases                  | None                                             | Pregnancy related outcomes                       | May 23, 2020         | Italy     | Di Mascio D et al.                 |
| Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis | SR                    | 3600 COVID-19 cases                     | None                                             | Clinical and paraclinical characteristics of COVID-19 | March 15, 2020      | China     | Fu L et al.                        |
|                                                                        | SR                    | COVID-19 cases                           | None                                             |                                                  | March 26, 2020       | Hong Kong | Chenag KS et al.                   |
| Titles                                                                 | Types of Study design | Study population                               | Intervention                                                                 | Outcome(s)                                                                 | Date of publication | Country               | Author/authors         |
|----------------------------------------------------------------------|-----------------------|------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------|------------------------|------------------------|
| Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis | SR                    | COVID-19 patients using inhaled corticosteroids | Inhaled corticosteroids                                                      | Gastrointestinal manifestations of COVID-19                                 | March 2, 2020        | UK                     | Halpin DMG et al.       |
| Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective | SR                    | COVID-19 patients                              | Hydroxychloroquine and Azithromycin                                           | Outcomes of acute respiratory infection                                     | April 13, 2020       | India                  | Sarma P et al.          |
| Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis | SR                    | 4189 COVID-19 cases                            | Myocardial injury markers                                                     | COVID-19 infection outcomes                                                 | April 12, 2020       | China/ Australia/ UK/ US | Li JW et al.            |
| The impact of 2019 novel coronavirus on heart injury: A systemic review and Meta-analysis | SR                    | COVID-19 patients                              | Association of diabetes mellitus                                             | Mortality, severity of COVID-19 disease, ARDS and progression of the disease | April 13, 2020       | Indonesia              | Huang I et al.          |
| Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression | SR                    | 46959 COVID-19 patients                        | None                                                                        | Clinical manifestation and image findings                                   | March 30, 2020       | China                  | Cao Y et al.            |
| Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis | SR                    | COVID-19 patients with immunosuppression drugs | Imunosuppression drugs                                                        | Clinical outcomes of COVID-19                                                 | March 27, 2020       | UK                     | Russell B et al.        |
| Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence | SR                    | Sever COVID-19                                 | IL-6 level                                                                  | Mortality                                                                    | 2020                 | USA                    | Aziz M et al.           |
| Elevated Interleukin-6 and Severe COVID-19: A Meta-Analysis           | SR                    | 656 confirmed COVID-19 cases                   | Complete work up                                                             | Clinical and para-clinical findings, Case fatality rate, Clinical outcomes of COVID-19 | March 11, 2020       | Colombia               | Rodriguez-Morales AJ et al. |
| Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis | SR                    | COVID-19 patients                              | LOPINAVIR                                                                    | Efficacy and adverse effects                                                 | February 24, 2020    | China                  | Yao TT et al.           |
| A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus—A possible reference for coronavirus disease-19 treatment option | SR                    | COVID-19 patients                              | None                                                                        | Prevention of laboratory confirmed COVID-19                                  | April 1, 2020        | Canada                 | Bartoszko JJ et al.     |
| Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: A systematic review and meta-analysis of randomized trials | SR                    | Health care workers                            | Medical masks versus N95 respirators                                         | Clinical manifestation, image findings and outcome of patients               | April 16, 2020       | Lebanon                | Moujaess E et al.       |
| Cancer patients and research during COVID-19 pandemic: A systematic review of current evidence | SR                    | COVID-19 patients with cancer                  | None                                                                        | A comprehensive systemic review of current evidence                           |                      |                        |                        |
| A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 | SR                    | COVID-19 patients taking chloroquine           | Chloroquine                                                                  | In vitro effectiveness                                                       | 2020                 | Italy                  | Cortegiani A, et al.    |
| Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal | SR                    | General population at risk for COVID-19         | Prognostic and diagnostic models                                            | Decision making on diagnosis and management                                  | March 31, 2020       | Netherlands            | Wynants L et al.        |
| Titles                                                                 | Types of Study design | Study population                        | Intervention                                      | Outcome(s)                     | Date of publication | Country   | Author/authors                        |
|----------------------------------------------------------------------|-----------------------|-----------------------------------------|-------------------------------------------------|---------------------------------|----------------------|-----------|--------------------------------------|
| COVID-19 during pregnancy: a systematic review of reported cases     | SR                    | Pregnant COVID-19 female cases          | None                                            | Pregnancy outcomes            | April 7, 2020       | Italy     | Gatta AND et al.                     |
| COVID-19, Modern Pandemic: A Systematic Review From a Front-Line Health Care Providers’ Perspective | SR                    | COVID-19                               | Not special                                     | All aspects of the disease     | March 25, 2020      | USA       | Balla M et al.                       |
| Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis | SR                    | 3027 COVID-19 patients                 | Risk factors for COVID-19 progression           | Mortality reduction            | April 16, 2020      | China     | Zheng ZH et al.                      |
| Clinical Presentation of COVID-19: A Systematic Review Focusing on Upper Airway Symptoms supportive treatment with Tocilizumab for COVID-19: A Systematic Review | SR                    | 1556 hospitalized COVID-19 cases patients | None                                            | Upper airway symptoms and signs | March 30, 2020      | Italy     | Lovato A et al.                      |
| How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review | SR                    | 110 COVID-19 immunosuppressed patients  | Tocilizumab an IL-6 inhibitor                    | A supportive care for patients | April 19, 2020      | USA       | Alzghari SK et al.                   |
| The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis | SR                    | 5270 COVID-19 patients                 | Corticosteroid                                   | Mortality, clinical and para clinical outcomes | March 31, 2020      | China     | Yang ZH et al.                       |
| Survival rate in acute kidney injury superimposed COVID-19 patients: a systematic review and meta-analysis | SR                    | COVID-19 with acute kidney injury patients | Acute kidney injury management and Antiviral therapy | Survival rate                   | April 27, 2020      | UK        | Ali H et al.                         |
| Efficacy and safety of current therapeutic options for COVID-19 – lessons to be learnt from SARS and MERS epidemic: A systematic review and meta-analysis | SR                    | 4941 COVID-19 patients                 | Antiviral therapy                                | Mortality, clinical outcome and para clinical changes | April 24, 2020      | China     | Zhong H et al.                       |
| Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis | SR                    | 2473 confirmed COVID-19 cases          | COPD                                            | Disease severity and mortality | May 11, 2020        | India     | Alqahtani JS et al.                  |
| Taste Changes (Dysgeusia) in COVID-19: A systematic review and meta-analysis | SR                    | 817 COVID-19 patients                 | None                                            | Prevalence of disgeusia and ageusia | May 1, 2020         | USA       | Aziz M et al.                        |
| A systematic review on COVID-19: urological manifestations, viral RNA detection and special considerations in urological conditions | SR                    | 3714 COVID-19 patients                 | None                                            | Urological manifestations      | May 5, 2020         | UK        | Chan VWS et al.                      |
| A Rapid Systematic Review of Clinical Trials Utilizing Chloroquine and Hydroxychloroquine as a Treatment for COVID-19 | SR                    | COVID-19 patients                      | Chloroquine and hydroxychloroquine               | Efficacy and side effects      | April 28, 2020      | USA       | Chowdhury S et al.                   |
| Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis | SR                    | 25697 COVID-19 patients               | Preventive measures                             | Lowering infection rate        | June 1, 2020        | Canada    | Chu DK et al.                        |
| An Updated Systematic Review of the Therapeutic Role of Hydroxychloroquine in Coronavirus Disease-19 (COVID-19) | SR                    | 3543 COVID-19 patients                | Hydroxychloroquine                              | Efficacy and safety            | May 28, 2020        | India     | Das S et al.                         |
| Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis | SR                    | Non COVID-19 patients                 | Convalescent plasma                             | Efficacy                      | June 9, 2020        | Canada    | Devasenapathy N et al.               |
| Titles                                                                 | Types of Study design | Study population | Intervention | Outcome(s)                          | Date of publication | Country     | Author/authors              |
|----------------------------------------------------------------------|-----------------------|------------------|--------------|-------------------------------------|---------------------|------------|------------------------------|
| COVID-19 and newborn health: systematic review                        | SR                    | 222 newborn exposed to COVID-19 mother cases | None         | Neonatal outcomes                   | 2020                | USA        | Duran P et al.              |
| Efficacy of Remdesivir in patients with COVID-19: a protocol for systematic review and meta-analysis of randomized controlled trials | SR                    | Covid-19 patients | Remdesivir   | Efficacy                            | June 4, 2020        | Ethiopia   | Gebrie D et al.            |
| Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis | SR                    | Covid-19 patients | Lymphopenia  | Severity of disease                 | 2020                | Indonesia  | Huang I et al.              |
| Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis | SR                    | COVID-19 patients | Prognostic factors | Severity of disease and ICU admission rate | May 13, 2020 | UK         | Jain V et al.               |
| QT prolongation torsade de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review | SR                    | 1515 COVID-19 patients | Chloroquine and hydroxychloroquine | Efficacy and cardiac side effects | May 31, 2020 | USA/Canada | Jankelson L et al.         |
| Symptom burden and clinical profile of COVID-19 deaths: a rapid systematic review and evidence summary | SR                    | Hospitalized COVID-19 patients | Prognostic factors | Mortality                           | April 27, 2020    | UK         | Keely P et al.             |
| The role of biomarkers in diagnosis of COVID-19 – A systematic review | SR                    | COVID-19 patients | Prognostic biomarkers | Disease severity                    | May 13, 2020       | UK         | Kermali M et al.           |
| COVID-19, MERS and SARS with Concomitant Liver Injury—Systematic Review of the Existing Literature | SR                    | COVID-19 patients | None         | Hepatopathy                         | May 11, 2020       | Poland     | Kukla M et al.             |
| Markers of liver injury and clinical outcomes in COVID-19 patients: A systematic review and meta-analysis | SR                    | COVID-19         | Liver function tests | Hepatic injury                      | May 23, 2020       | UK         | Kumutsor SK et al.         |
| Co-infections in people with COVID-19: a systematic review and meta-analysis | SR                    | 3834 COVID-19 patients | None         | Bacterial and viral coinfections In hospital mortality rate | May 23, 2020       | UK         | Lansbury L et al.          |
| Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis | SR                    | COVID-19 patients | Cardiovascular disease and hypertension | Comorbidities | April 24, 2020 | China | Li X et al. |
| Comorbid Chronic Diseases are Strongly Correlated with Disease Severity among COVID-19 Patients: A Systematic Review and Meta-Analysis | SR                    | 10948 COVID-19 cases | Comorbidities | Diseases severity and ICU admission | May 2, 2020        | China      | Liu H et al.                |
| Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults | SR                    | Child COVID-19 cases | None         | Manifestation and outcomes | March 20, 2020 | Sweden | Ludvigsson JF              |
| SARS-CoV-2 (COVID-19): What do we know about children? | SR                    | COVID-19 child cases | None         | Manifestation and outcomes | March 20, 2020 | UK      | Mehta Ma, NS et al.        |
| Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review | SR                    | COVID-19 cases | None         | Neurological manifestation | May 15, 2020       | USA        | Montalvan V et al.         |
| Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis | SR                    | COVID-19 patients | Prognostic role of N-terminal pro-brain natriuretic peptide | Mortality | April 29, 2020 | Indonesia | Pranta R et al. |
| COVID-19 cases with cardiovascular and | SR                    | COVID-19 cases with cardiovascular and | None         | Mortality and severity of illness | May 6, 2020        | Indonesia | Pranta R et al. |

| Titles                                                                 | Types of Study design | Study population       | Intervention                        | Outcome(s)                      | Date of publication | Country      | Author/authors               |
|----------------------------------------------------------------------|-----------------------|------------------------|-------------------------------------|---------------------------------|---------------------|--------------|-----------------------------|
| Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19: systematic review, meta-analysis, and meta-regression |                       | cerebrovascular disease |                                     |                                 |                     |              | Pranta R et al.              |
| Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression | SR                    | 6560 COVID-19 cases    | Prognostic role of hypertension     | Poor outcomes                   | April /June 2020    | Indonesia    | Rogers JP et al.            |
| Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic | SR                    | COVID-19, SARS, MERS cases | None                              | psychiatrics and neuropsychiatrics presentation | May 18, 2020        | UK           | Rogers JP et al.            |
| Maternal and neonatal outcomes associated with COVID-19 infection: A systematic review | SR                    | Pregnant COVID-19 cases | None                              | Maternal and neonatal outcomes  | June 4, 2020         | Australia    | Smith V et al.               |
| Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19 | SR                    | 2477 COVID-19 cases    | None                              | Chest image findings            | April 30, 2020       | China        | Sun ZH et al.                |
| Obesity as a predictor for a poor prognosis of COVID-19: A systematic review | SR                    | COVID-19 cases          | Prognostic role of obesity         | Disease severity, advanced medical care need | May 9, 2020          | Indonesia    | Tamara A et al.              |
| COVID-19 and the Ocular Surface: A Review of Transmission and Manifestations | SR                    | 1875 COVID-19 cases    | None                              | Ocular presentation             | June 16, 2020        | Singapore    | Ho D et al.                  |
| Evidence from Cochrane systematic reviews for controlling the dissemination of COVID-19 infection. A narrative review | SR                    | COVID-19 prevention     | Non pharmaceutical intervention    | COVID-19 control                | 2020                | Brazil       | Flumignan RLG et al.        |

Table 1 (continued)
In a systematic review including 3714 COVID-19 patients, urological symptoms were not reported. However, urinary viral RNA shedding was reported among 5.74% of COVID-19 patients [33]. Also, acute kidney injuries in COVID-19 patients were associated with a mortality rate of 93.27% [33]. Age range of most cases is 30–79 years. Common comorbidities seen with COVID-19 infection consisted of hypertension (30.7%), diabetes mellitus (14.3%), cardiovascular diseases (11.9%), cerebrovascular disease (6.6%), malignancy (4.3%), chronic liver, lung and kidney disease (2.8%, 2.4%, 2.1% respectively), HIV (1.4%), and immunodeficiency (0.2%) [16].

Hypertension, cardiovascular disease (CVD), and chronic respiratory condition are accompanied with a severe form of COVID-19 infection [34].

A systematic review of 24 studies involving 10,948 COVID-19 patients reported that coincidence of diabetes mellitus (DM), CVD, coronary artery disease (CAD), and hypertension with COVID-19 was more common than chronic respiratory disease [35].

SARS-COV-2 receptors have been shown to present in nervous system. Consequently, the neurological manifestation of SARS-COV-2 virus infection is reported as non-focal signs of agitation, corticospinal tract sign, dys executive syndrome, and confusion [36, 37]. A systematic review of 67 different studies reported the most common symptoms as hyposmia, headache, weakness, and change in consciousness [38]. Furthermore, delirium (confusion) and agitation has been reported among patients admitted to ICU in a systematic review of 65 studies recruiting 3559 COVID-19 patients [39].

Summation of 43 studies revealed that hepatic involvement in COVID-19 could be explained as mild to moderate elevation of transaminases, hypoalbuminemia, and prolongation of prothrombin time [40].

A systematic review involving 1875 confirmed cases of COVID-19 reported that 4.3% of cases have shown ocular presentation, and 2.9% have viral nucleic acid in ocular swab. Conjunctivitis was reported as the main clinical manifestation of COVID-19 [41].

### Smoking Status and COVID-19 Infection

It has been reported that among the severe cases of COVID-19, 16% were current smokers versus 11.8% smoking rate among non-severe one [42]. Current smoking is associated with more severe complications and higher mortality rate [43].

### Infectious Agent

SARS-COV-2-virus is a single, positive-stranded RNA virus. Coronavirus family structural proteins have been described as spike protein (S), membrane protein (M), envelope (E), and nucleocapsid (N) [44].

Viral RNA is enveloped in a bilayer lipid crowned with two spike proteins (S-protein) [16]. The viral S1-protein binds with ACE2 protein receptors of human host cells, and then fuses host cells with S2 protein. Fusion with host cell

Table 2  Pooled prevalence of general clinical manifestations of COVID-19

| General manifestations of COVID-19 | Pooled prevalence | 95% confidence interval |
|-----------------------------------|------------------|-------------------------|
| Fever                            | 82.68            | 73.30–88.35             |
| Cough                            | 57.67            | 47.22–66.27             |
| Fatigue                          | 37.98            | 28.18–46.78             |
| Dyspnea                          | 35.32            | 26.36–44.75             |
| Gastrointestinal system          | 14.80            | 8.53–22.14              |
| Headache                         | 6.00             | 2.73–12.48              |

Table 3  Pooled prevalence of specific clinical manifestation of COVID-19

| Clinical manifestations          | Pooled prevalence | 95% confidence interval |
|---------------------------------|------------------|-------------------------|
| Shortness of breath             | 32.6             | 23.67–41.66             |
| Diarrhea                        | 7.8              | 3.43–13.75              |
| Ageusia or dysgeusia            | 49.8             | 39.42–58.65             |
| Polyneuropathy                  | 47               | 37.51–56.71             |
| Muscle soreness                 | 35.5             | 27.27–45.76             |
| Chest distress                  | 31.2             | 22.78–40.63             |
| Nasal congestion                | 3.7              | 1.57–9.84               |
| Pharyngodynia                   | 12.4             | 7.00–19.61              |
| Acute kidney injury             | 7.5              | 4.11–15                 |
| Nausea /vomiting                | 5.5              | 2.75–12.46              |
| Shock                           | 6.2              | 3.57–11.82              |
| ARDS                            | 30.80            | 21.89–39.58             |

ARDS acute respiratory distress syndrome

Table 4  Pooled prevalence of comorbidities associated with COVID-19 or risk factors

| Comorbidities                  | Pooled prevalence | 95% confidence interval |
|--------------------------------|------------------|-------------------------|
| Hypertension                   | 20.7             | 13.34–28.88             |
| Cardiovascular diseases        | 9.6              | 4.81–16.23              |
| Diabetes mellitus              | 9.55             | 5.52–17.44              |
| Respiratory diseases           | 7                | 3.84–12.57              |
| Cigarette smoking              | 9                | 6.13–21.43              |
membrane completes with lipid layers, and consequently, viral RNA releases into host cell cytoplasm [16].

N protein is responsible for viral pathogenesis, replication, and RNA packaging [44]. Ab against N protein has been detected among COVID-19-infected patients [44].

**Mode of Transmission**

The main route of transmission for rapidly spreading SARS-COV-2 is direct host-to-host contact.

Airborne transmission of viral small particles during a person-to-person contact over a distance of 2 m [45] could explain the rapid and massive spread of SARS-COV-2. Also, transmission of viral particles via droplet [16] and gas cloud emitted from sneeze and cough which can travel up to 6–8 m away [46] has been described.

Comprehensive understanding of SARS-COV-2 transmissibility is crucial for the prediction of the pandemic course and possibility of sustained transmission.

**Incubation Period**

Mean latency period lies between 3 and 9 days with a variation ranged from 0 to 24 days [16]. Serial interval mean is estimated 3–8 days, which can cause viral transmission by an infected person before symptom onset. This can describe 44% of transmissions during the pandemic course [16].

**Period of Communicability**

COVID-19, an emerging infectious disease, tends to be presented as asymptomatic in about 18%. Asymptomatic ones are mainly younger persons. In elderly, most infections are symptomatic with different severity measures. Symptoms are about to resolve after 10 days in 90% of cases and resolve after 15 days to onset in all cases [16]. However, viral RNA shedding via nasopharynx (18 days) and feces (19 days) persists after symptoms resolved and even longer in severe cases, which has been estimated about 25 days after disease onset. Viral load in severe cases is estimated to be 60 times more than mild cases [16].

US CDC and European CDC guidelines clearly stated that replication competent virus has been detected in most COVID-19 cases (mild to moderate severity cases) up to 10–15 days after symptom onset. However, in severe cases of COVID-19, the infectivity period remains longer and is estimated to be 10–20 days after symptom onset. Recovered

| Various clinical outcomes of COVID-19 | Pooled percentage | 95% confidence interval |
|-------------------------------------|------------------|------------------------|
| Complications                       | 36.2             | 26.36–44.75            |
| Mortality rate                      | 15.5             | 9.31–23.28             |
| Case fatality rate                  | 5.1              | 2.15–11.18             |
| Mortality rate of cigarette smoker COVID-19 patients | 38.5 | 29.10–47.79 |
| Mortality rate of COVID-19 patients with acute kidney injury | 93.27 | 86.25–95.57 |
| Coinfections (bacterial)            | 7                | 3.82–12.57             |
| Coinfection rate in ICU admitted COVID-19 patients | 14 | 8.53–22.14 |
| Viral coinfection                   | 3                | 1.03–8.45              |
| Low birth weight                    | 42.8             | 33.73–52.78            |
| Perinatal death                     | 7                | 1.71–7.05              |
| Preterm birth                       | 52.45            | 42.32–61.54            |
| NICU admission of neonates born with confirmed COVID-19 mothers | 67.06 | 57.31–75.44 |
| Cesarean section in COVID-19 pregnancies | 86.66 | 79.02–92.24 |
| Miscarriage                         | 39.1             | 31.49–49.80            |
| Preeclampsia                        | 6.2              | 3.78–11.84             |
| Growth restriction                  | 11.7             | 7–19.81                |
| Premature rupture of membrane       | 20.7             | 14.17–29.98            |
| ICU admission of COVID-19 cases     | 18.96            | 12.51–27.78            |
| Multiple organ dysfunction among COVID-19 cases | 14.25 | 8.53–22.14 |
| Invasive ventilation need           | 3.4              | 2.06–16.22             |
| Severe COVID-19 cases among all COVID-19 cases | 25.6 | 19.27–36.43 |

*ICU* intensive care unit
symptomatic persons continue to shed viral RNA in the upper respiratory system 3 months after disease onset.

**Diagnosis**

**Viral Tests**

The gold standard test for diagnosis of SARS-COV-2 is based on the detection of genetic materials of the virus. RT-PCR nucleic acid–based test tracks viral material from a respiratory tract swab specimen of the patients infected with SARS-COV-2 with minimum false-positive rate. Nasopharyngeal swab specimen is recommended in most cases. Lower respiratory tract samples are reserved for special occasions.

Nowadays, cell culture is not recommended [44]. Viral genome sequencing is impractical for diagnostic purposes [44].

Serological tests which focused on host immunological response to the infection with SARS-COV-2 determine IgM and IgG antibodies (Ab) to detect burden of COVID-19, asymptomatic cases, basic reproduction rate, and mortality rate (MR) [44].

Laboratory test findings: Blood sample tests revealed the following changes: decreased number of eosinophils 78.8%, lymphopenia 68.7%, elevated AST level 63.4%, high level of C-reactive protein 60.7%, elevated PT level 58.0%, high level of LDH 47.2%, elevated d-dimer level 46.4%, thrombocytopenia 36.2%, elevated ALT level 21.3%, and high HS-troponin level in 12.5% [16].

Immune system response translated to elevated CRP level, high IL-6 level and lymphopenia in mild to moderate severity cases, and increased level of IL-2, TNF-α, and IL-10 in severe cases of COVID-19 have been reported.

**Imaging**

Chest X-ray findings: bilateral pneumonia was more common than unilateral pneumonia.

Chest CT scan abnormalities: bilateral ground glass opacity at early stage of the disease and consolidations at advanced stage of the infection [16]. Validity of chest CT scan findings compared with RT-PCR results revealed a sensitivity of 84–94%, specificity of 25–80.5%, positive likelihood ratio of 1.17, and negative likelihood ratio of 0.84 [16].

A systematic review of 45 studies composed of 4410 COVID-19 patients reported consistently that the most common chest CT finding of COVID-19 was bilateral peripheral/subpleural ground glass opacity with or without consolidations [47].

Another systematic review of 55 studies confirmed the above common chest CT findings. Besides, this research reported 13.31% normal CT in COVID-19 patients with pneumonia [48].

Different paraclinical findings in meta-analysis have been presented in Table 6.

**Coinfections**

The most common bacterial and viral coinfections associated with COVID-19 are described as mycoplasma pneumonia (17.3%), chlamydia (11.9%), Legionella (8.82%), Influenza A (6.47%), Influenza B (5.76%), and respiratory syncytial virus (RSV) (1.44%) [16].

Another systematic review of 30 studies involving 3834 COVID-19 patients revealed that overall co-infection rate in hospitalized patients was 7%. In a mixed setting of hospital ward and intensive care unit (ICU), the most common germs were Mycoplasma pneumoniae, Pseudomonas aeruginosa, and Haemophilus influenzae. Viral co-infection reported as 3% comprises of RSV and Influenza A [49].

**Treatment**

Different treatment modalities have been recommended for COVID-19 around the world. Remdesivir, a nucleotide-analogue antiviral agent used for Ebola, is supposed to stop infection with SARS-COV-2 in a randomized placebo-controlled trial conducted on 1059 COVID-19 patients; 538 patients were allocated to receive intravenous Remdesivir arm (200 mg loading dose on first day followed by 100 mg daily for 9 days) versus placebo for 10 days. Remdesivir significantly shortened recovery time to 11 days versus 15 days of placebo, decreased mortality rate in 14 days to 7.1% compared with 11.9% of placebo administration, and lower adverse events of 21.1% versus 27% [50]. An ongoing systematic review of randomized controlled trials on efficacy of Remdesivir in COVID-19 patients will provide us with more features of the treatment effect of this drug [51].

A systematic review of 155 studies involving 9152 COVID-19 patients concluded that lopinavir/ritonavir use was associated with a significant shortening of hospital stay 11.7 days (± 1.09) or symptom resolution [52].

Another systematic review [53] of 11 retrospective studies involving 4941 COVID-19 patients has shown the superiority of LOPINAVIR and Ritonavir compared with other antiviral agents.

Current evidence derived from systematic reviews did not support the use of chloroquine and hydroxychloroquine in COVID-19 [54, 55]. A systematic review of 14 studies involving 1515 COVID-19 patients treated with these agents reported 10% incidence of QT interval prolongation which increases the risk of cardiac arrhythmia [56].

Quality of existence evidence on efficacy of convalescent plasma in COVID-19 is very low and non-conclusive [57].
Prognosis

Prognostic factors extracted from systematic reviews estimated in meta-analysis have been presented in Table 7.

A systematic review (SR) of 24 studies involving 3099 COVID-19 patients revealed a poor prognosis for those admitted with lymphopenia. Lower lymphocyte count was associated with severe COVID-19, progression toward ARDS, and higher mortality rate [58]. Another systematic review on prognostic biomarkers reported that decreased level of lymphocytes and platelets was associated with progression to severe COVID-19 [59].

An SR comprising seven studies recruiting 1813 COVID-19 patients has shown the prognostic value of dyspnea symptom for predicting severe COVID-19 and intensive care unit (ICU) admission [60].

Association of cerebrovascular diseases with COVID-19 will predict a higher mortality rate; an SR of 4448 patients evaluated in 16 studies also revealed that concomitant cardiovascular disease and COVID-19 resulted in both higher mortality rate and progression to severe COVID-19 [61].

An SR of six studies recruiting 967 patients reported higher levels of N-terminal pro-brain natriuretic peptide (NT pro BNP) in non-survivor of COVID-19 and predicted mortality with hazard ratio (HR) of 1.37 (95% CI 1.19–1.57) [62].

Hypertension (HTN) is a strong predictor of poor prognosis among COVID-19 patients including higher rates of

| Paraclinical findings in COVID-19 | Frequency (%) | 95% confidence interval |
|----------------------------------|---------------|------------------------|
| Lymphopenia                      | 67.3          | 57.31–75.44            |
| Leukopenia                       | 32.55         | 22.76–40.18            |
| Thrombocytopenia                 | 13            | 7.76–20.98             |
| **Chest CT findings in COVID-19:** |               |                        |
| Normal CT                        | 13.31         | 7.76–20.96             |
| Ground glass opacity             | 64.87         | 55.25–73.64            |
| Ground glass opacity with consolidations | 55.7   | 46.23–65.33            |
| Consolidation                    | 44.8          | 35.6–54.76             |
| Severe chest CT findings         | 88.5          | 81.3–93.75             |
| Change in chest CT               | 83            | 74.45–89.11            |
| Bilateral findings               | 78.92         | 70.02–85.83            |
| Peripheral                       | 71.15         | 61.64–78.90            |
| Central                          | 3.57          | 1.75–9.84              |
| Central associated with peripheral | 31.12         | 22.80–40.37            |
| Three or more lobe               | 70.8          | 61.46–78.99            |
| Right lower lobe                 | 87.21         | 79.02–92.24            |
| Left lower lobe                  | 81.04         | 72.22–87.49            |
| Bilateral lower lobes            | 65.22         | 55.25–73.64            |
| Right upper lobe                 | 64.23         | 52.25–71.38            |
| Right middle lobe                | 54.95         | 45.24–64.39            |
| Left upper lobe                  | 69.43         | 60.42–78.11            |
| Bilateral upper lobe             | 60.87         | 51.20–69.98            |
| **Viral RNA findings:**          |               |                        |
| Stool SARS-COV-2 RNA positive    | 56.96         | 47.22–66.27            |
| Urine SARS-COV-2RNA positive     | 5.74          | 2.78–12.48             |
| **Laboratory findings:**         |               |                        |
| (mean±95%CI) C-reactive protein (mg/L) | 52.26 | 48.1–56.40 |
| Viral SARS-COV-2 load (mean log<sub>10</sub> viral load calculated as copies per mL) | 5.1 | 2.15–11.16 |

CT computerized tomography, CI confidence interval
mortality, severe COVID-19, ARDS, need for ICU admission, and progressive illness [63].

Obesity is an independent prognostic factor for severity of the disease and fatal outcomes. COVID-19 patients with body mass index (BMI) greater than 35 kg/m² need more than seven times (OR = 7.36 95% CI 1.63–33.14) of use of mechanical ventilation compared with non-obese counterparts [64].

**Mode of Death**

Information regarding COVID-19 patient mode of death and end of life care should be improved.

The most common symptom described in dying patients is dyspnea [65].

A large cohort of 1145 confirmed COVID-19 cases with 67 days of follow up suggested the use of viral load as a risk assessment tool which can predict mortality with hazard ratio of 1.07, 95% CI (1.03–1.11). Mean \( \log_{10} \) viral load was reported 5.6 copies per mL, and the median \( \log_{10} \) viral load was calculated 6.2 copies per mL [66]. A fully adjusted multivariable model revealed a significant association between viral load and mortality in COVID-19 cases.

**Prevention**

**Non-pharmaceutical Preventive Measures**

At the present time, with no effective available vaccine and specific treatment modalities, prevention of COVID-19 should be focused on protection at individual and community level and contact tracing. We can descend transmission rate by implementing personal protection equipment (PPE) in all settings.

More effective distancing defined as distance of 2 m causes a significant lower infection rate compared with less than 2 m distancing. Protection probability will increase as length of distance increased by relative risk = 2.02 (RR) [67].

A systematic review of 172 studies and 25,697 cases demonstrated that effective social distancing of more than 1 m and wearing standard face mask and eye protection in public were reported to be associated with less SARS-COV-2 infection rate [67].

Optimum use of facemask in both public and health care setting has been associated with a significant reduction in infection rate. Superiority of N95 facemask compared with surgical and reusable 12–16 layers of cotton mask has been demonstrated [67].

Eye protection associated with using facemask and effective distancing has been shown to enhance protection against fatal SARS-COV-2 and resulted in significant decrease in infection rate [67].

A combination of social distancing, school closure, travel restriction, and quarantine can reduce the attack rate, mortality, and transmission rate [69]. Recent evidence reported that quarantine for people exposed to confirmed or suspected cases of COVID-19 will result in decreasing incidence rate about 44–81% and lowering mortality rate about 31–63% [70].

In addition to PPE use and population-based preventive measures, national and international action plan should be implemented on lifestyle intervention such as avoiding mass gathering, promotion of physical activity at home for entire family, group fitness class, adherence to healthy diet and reduction of calorie intake, massive quit smoking consultation, and coaching for stress management are crucial paces for pandemic control.

For effective control of an epidemic, we need evidences on number of mild cases, risk factors for infection, attack rates,
severity of illness, timing of transmission, and risk factors for severe outcomes and mortality among cases.

Therefore, contact tracing by improving surveillance system can lead to determine asymptomatic and mild diseases. Asymptomatic and mild to moderate cases could be found via household and school surveys by implementing seroepidemiological study and viral shedding assay. Besides, serological testing among individuals who are not suspected to infect with COVID-19 can guide to depict a more accurate feature of the disease severity spectrum.

Viral shedding studies can also detect disease severity, chain of transmission, and duration of patient isolation.

So, school and household surveys could help to find asymptomatic transmission to decide on social distancing, school and university closure, and mass gathering.

COVID-19 occurred in populations with a high burden of uncontrolled chronic diseases. Interaction between SARS-CoV-2 and CVD, DM, and obesity caused a high mortality and complication rate in different populations.

CVD and cardiometabolic risks should be controlled. CVD and cerebrovascular disease could be triggered by different infectious disease. Also, increased risk of CVD after an infection is highly possible. Among COVID-19 cases, cardiac damage is eminent.

From scientifically point of view, the COVID-19 pandemic highlighted an urgent need to invest on CVD prevention associated with control of DM, obesity, HTN, cigarette smoking, and high cholesterol level. It reminds us that essential fragility exists in health system infrastructures, which can reveal our vulnerability in the entire global community.

COVID-19 Vaccine

Vaccine development has a long-term process. So far, ten candidates of vaccine against SARS-CoV-2 have been introduced. They are in phase 1 and 2 of clinical trial, and the producers hope that phase 3 will be conducted in summer 2020. These vaccines deliver different viral components into the host cell to trigger immune system response for producing antibody [71]. Moderna and NIAID and BioNTech and Pfizer are working on mRNA vaccine. The University of Oxford and AstraZeneca are working on adenovirus vaccine in phase 2B/3. Inovio Pharmaceuticals is working on DNA vaccine, CanSino Biologics is working on adenovirus vaccine, Sinovac on inactivated virus plus adjuvant, Novavax on protein subunit, and Wuhan Institute of Biological Products and Sinopharm, and Beijing Institute of Biological Products and Sinopharm, Institute of Medical Biology, and Chinese Academy of Medical Sciences are working on inactivated virus in Phase 1/2 [71].

Despite global hunger for SARS-CoV-2 vaccine, scientific metrics in vaccine development should be carefully considered because ineffective vaccine products can enhance the disease burden and consequently escalate the pandemic situation.

Finally, it is highly recommended that we should avoid overtreatment during the current pandemic, which means unnecessary antibiotic use can cause unpredictable adverse outcomes.

Discussion

Tables 1, 2, 3, 4, 5, 6, and 7 have presented the results of meta-analysis of systematically reviewed articles. Seventy-one systematic reviews of COVID-19 included in the review with certainty of evidence were mostly in high- and good-quality score. This is the first systematic review of systematic reviews with meta-analysis focusing on confirmed cases of COVID-19 that provide comprehensive evidence available, so far.

The huge burden of adverse outcome following COVID-19 involvement has been exacerbated by comorbidities like hypertension, cardiovascular diseases, diabetes mellitus, cigarette smoking, respiratory diseases, and obesity. COVID-19 is superimposed on uncontrolled pandemic of cardiovascular disease and cardiometabolic risk factors. Now, we are facing to control the current emerging COVID-19 pandemic associated with managing the unfinished business of controlling CVD, DM, HTN, and obesity pandemic.

Results of meta-analysis precisely revealed prognostic factors associated with different outcomes in COVID-19 cases. We categorized the COVID-19 outcomes into three groups including mortality, severity of disease, and disease progression. The most powerful prognostic factors for mortality rate among COVID-19 cases were acute cardiac injury (RR = 10.89), previously diagnosed CVD (RR = 4.06), DM (RR = 3.68), respiratory disease (RR = 3.51), and HTN (RR = 2.86) (Table 7).

The most important prognostic factors for disease severity are CVD (RR = 2.83) and HTN (RR = 2.20). Finally, the most important prognostic factors for disease progression were determined as a combination of fever associated with shortness of breath with RR = 4.16 and cigarette smoking with RR = 2.19.

This is the first systematic review with meta-analysis reporting pooled details of different aspect of natural history of COVID-19 based on current published knowledge.

The most prevalent comorbidities associated with SARS-CoV-2 infection (Table 4) are HTN 20.7%, CVD 9.6%, DM 9.55%, respiratory diseases 7%, and prevalence of cigarette smoking among COVID-19 case reported as 9%. Therefore, effective long-term control of current pandemic and future threat of global community is crucially depended on controlling of CVD and cardiometabolic risk factors.

One percent of COVID-19 cases have cancer, mostly lung cancers. Mortality rate of these cases was reported as 28.3%
with adverse events of 53.6%. It is suggested that risk of discontinuation of cancer treatment is much higher than the risk of COVID-19 [72].

The COVID-19 global pandemic control depends on preventive measures at all four levels. At primary prevention level, PPE, social distancing, quarantine, isolation, effective distancing of 2 m and more [67–69], and effective vaccine prescription are approaching. Hand hygiene and disinfection of contaminated surfaces are also recommended.

Contact tracing based on precisely designed surveillance systems with serial nucleic acid testing will detect asymptomatic, pre symptomatic, and mild cases of COVID-19. Household, school-based, and workplace survey by using seroepidemiological study and viral shedding assay will accurately depict mode of transmission which can guide determining duration of patient isolation and reopening of schools, universities, and other public places. Current policies have acted based on symptomatic COVID-19 cases, which need to be developed. For enacting more effective preventive measure, it is suggested that decision-makers should broaden current policies to recommendations on asymptomatic and mild cases of COVID-19.

Symptom-based versus test-based approach for ending isolation is mainly dependent upon the resources available. For immunocompromised COVID-19 cases, test-based decision-making for ending isolation is preferred (US CDC guideline). COVID-19 cases that never developed symptoms in isolation can be discontinued 10 days after a positive RT-PCR test. Based on a fact that replication-competent virus has not been detected after 10–15 days after symptom onset, discontinuation of isolation for symptomatic patients is recommended after this time, mainly from a practical point of view.

Supplement use of vitamin D; low dose zinc; magnesium; vitamin A, B, E; and selenium has been shown to be efficacious in primary and also secondary prevention of SARS-COV-2 infection [73]. Probiotics might be a useful adjuvant recommendation based on the cross connection between lung and gastrointestinal tract [73].

Hospital care providers recommended using full isolation gun, N95 or higher facemask, eye protection, disposable gloves, and face shields.

So far, in secondary prevention, there is no effective anti-SARS-COV-2–specific viral agent. Available antiviral medication like remdesivir which shortened hospital stay and significantly lowered mortality rate [51] associated with supportive cares for each COVID-19 cases has been used. A systematic review reported the superiority of nucleoside analog with broad-spectrum antiviral activity of Remdesivir associated with interferon beta (IFN-β) to Lopinavir/Ritonavir and IFN-β [73]. Remdesivir may enhance protective host immune responses. This study has also reported that favipiravir was more effective than Lopinavir/Ritonavir [73]. An interventional study did not support the efficacy of lopinavir in COVID-19 cases [74].

Hydroxychloroquine has no significant effect on viral clearance, and there is no evidence about lowering mortality or preventing clinical worsening among COVID-19 cases, besides serious CVD complication reported which questioned the safety of this medication [75].

Steroids have delayed the viral clearance and should be limited to COVID-19 cases with ARDS.

Triage in hospital emergency room could be based on symptoms like fever, cough, shortness of breath, chest pain, headache, body pain, nasal congestion, travel history, and history of contact with confirmed cases of COVID-19 [73].

Interesting laboratory findings in narrative results were mean Hs-CRP level of 52.26 ± 17.85 g/dl in severe cases and mean level of 33.2 g/dl in non-severe COVID-19 cases [59].

Mean level of IL6 in severe COVID-19 patients was 56.8 Pg/mL and 17.3 Pg/mL for non-severe cases. Elevated level of IL6 was associated with higher mortality rate of COVID-19 cases [17].

Predictors of severe COVID-19 was presented in a systematic review as age, sex, chest CT findings, CRP level, LD level, and lymphocyte count [76]. Moreover, elevated level of pro-calcitonin will cause about fivefold increased risk of severe COVID-19 (OR = 4.76) [73]. Lymphopenia defined as lymphocyte count below 1100 μL demonstrated to be associated with severe COVID-19 presentations (OR = 3.27); it has been figured out that this relationship is stronger in COVID-19 cases under 55 years (OR = 5.32) [58].

Liver function tests revealed elevated transaminase, hypoalbuminemia, and prolonged PT time. Histopathological findings of liver in COVID-19 cases demonstrated a pattern compatible with nonspecific inflammation, mild steatosis, congestion, and massive necrosis [40].

So far, child COVID-19 cases were reported as 1–5% of the total COVID-19 cases [31]. This unexpected low rate of SARS-COV-2 infection among the younger population has been described in a systematic review as lower medical attention to the infection among children [32].

Narrative synthesis revealed the common neurological symptoms of COVID-19 in one systematic review including hyposmia, headache, weakness, and altered consciousness. Furthermore, COVID-19 has been associated with encephalitis, demyelination, neuropathy, and stroke [38].

Obesity (BMI > 35 kg/m²) has been associated with increased risk of mechanical ventilation in COVID-19 patients with an OR = 7.36, and also higher mortality rate [64].

A systematic review reported that enacting quarantine for people exposed to or suspected with SARS-COV-2 infection will decrease the incidence rate about 44–81% and lowering mortality rate about 31–63% [70].
Conclusion

Progressing global pandemic of COVID-19 is a systemic inflammation with multiple-organ involvement including blood vessels, lung, heart, central nervous system, liver, gastrointestinal system, kidney, eyes, and other organs. SARS-COV-2 infection involves adult and children, infant, neonates, pregnant women, and elderly people. Recent reports describing complement-mediated thrombotic microangiopathy-like syndrome in COVID-19 cases have complicated the pathophysiological feature of the disease. Rapidly spreading COVID-19, which is categorized as a highly infectious contagious disease, transmits via both air born and droplet.

The most prevalent comorbidities associated with SARS-COV-2 infection are HTN 20.7%, CVD 9.6%, DM 9.55%, respiratory diseases 7%, and prevalence of cigarette smoking among COVID-19 case reported as 9%.

The COVID-19 outcomes are categorized into three groups including, mortality, severity of disease, and disease progression. The most powerful prognostic factors for mortality rate among COVID-19 cases were acute cardiac injury, previously diagnosed CVD, DM, respiratory disease, and HTN. The most important prognostic factors for disease severity are CVD and HTN. Finally, the most important prognostic factor for disease progression determined is a combination of fever associated with shortness of breath and cigarette smoking.

All age groups are at risk for the disease with a higher susceptibility for patients with associated comorbidity. High case fatality rate is another aspect of the current pandemic. The coincidence of the COVID-19 pandemic and CVD and cardiometabolic risk pandemic exacerbated the adverse outcomes of SARS-COV-2 infection.

Authors’ Contributions Dr. Zinat Nadia Hatmi has designed, conducted, and statistically analyzed the data and prepared the manuscript.

Data Availability They are available.

Compliance with Ethical Standards

Conflict of Interest The author declare that she has no conflict of interest.

Ethical Approval Not applicable.

Consent of Participate Not applicable.

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Code Availability Statistical package of IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp has been used.

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