Review Article

Scoping Review of Six Retrospective Studies: Risk Factors Associated With the Case Fatality Rate of People Infected With Coronavirus (COVID-19)

Adel Sadeq[1], Asim Ahmed Elnour[2,3], Farah Hamad Farah[4,5], Azza Ramadan[6], Judit Don[7], Ahmed Ibrahim Fathelrahman[8], Maisoun Alkaabi[9], Mohammed Baraka[10,11], Abubakar B. Abubakar[12], Sasha Mohammed Elamin Suliman[13], Abdulla Al Amoodi[14], IsraaYousif Khidir[15], Khalid Awad Al Kubaisi[16], Nadia Al Mazroui[17]

[1]Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Al Ain, UAE, [2]Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Abu Dhabi Campus, Abu Dhabi, United Arab Emirates, [3]AAU Health and Biomedical Research Center, Al Ain University, Abu Dhabi, United Arab Emirates, [4]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman, UAE, [5]Center of Medical and Bio-Allied Health Sciences Research, Ajman University, Ajman, UAE, [6]Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Abu Dhabi Campus, UAE, [7]College of Pharmacy, Gulf Medical University, Ajman, UAE, [8]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Saudi Arabia, [9]New Medical Center (NMC), Abu Dhabi, UAE, [10]Clinical Pharmacy Department, College of Pharmacy, Al Ain University, Al Ain Campus, United Arab Emirates, [11]Clinical Pharmacy Department, College of Pharmacy, Al-Azhar University, Cairo, Egypt, [12]Department of Medical Imaging and Radiation Sciences, Monash University, Melbourne, Australia, [13]Clinical Pharmacy, College of Pharmacy, Riyadh Elm University Riyadh, Saudi Arabia, [14]Ambulatory Healthcare Services, Academic Affairs, Abu Dhabi Health Services (SEHA), UAE, [15]Clinical Pharmacist, Omdurman Islamic University, Omdurman, Sudan, [16]Department of Pharmacy Practice and Pharmacotherapeutics, College of Pharmacy, Sharjah University, Sharjah, UAE, [17]Department of Pharmacy Practice and Pharmacotherapeutics, Faculty of Pharmacy, University of Sharjah, United Arab Emirates

Submitted: 23-Jun-2021.
Accepted: 24-Sep-2021.
Published: 18-Jul-2022.

Access this article online

Quick Response Code:

Website: www.jpbsonline.org

DOI: 10.4103/jpbs.jpbs_460_21

ABSTRACT

Background: It would be rational to describe the pattern of the clinical characteristics of the survivors and the nonsurvivors during the critical intensive-infection era of coronavirus disease 2019 (COVID-19). The explicit objective of the current scoping review was to delineate the predictive risk factors associated with case fatality rate (CFR). Methods: Six retrospective studies of subjects infected with COVID-19 published between December 1, 2020, and March 30, 2020, describing nonsurvivors in Wuhan/Hubei, China, were identified. **Results:** There were 1769 subjects with a mean age of 52 years, and 65.9% were male. The highest comorbidity reported was cardiovascular diseases at 22.2% (393/1769). The overall number of cases admitted to the intensive care unit was 228 (12.9%). The reported overall CFR was 7.7% (136/1769), with the highest at 28.2% (54/191), and the lowest at 1.4% (15/1099). The mean duration of onset until death for nonsurvivors was 15.3 days. **Conclusion:** We have found that older age, male gender, the longer duration from onset till death (days), development of acute respiratory distress syndrome/shock, preexisting diabetes, and preexisting cardiovascular diseases were the major risk factors associated with high CFR.

KEYWORDS: *Case fatality rate, coronavirus disease 2019, nonsurvivors, predictive risk factors, survivors*

INTRODUCTION

The world is facing one of the most serious pandemic of coronavirus disease (COVID-19) crises. The percent of cases escalated worldwide resulting in rapid increase in death (case fatality rate [CFR]). The CFR increased sharply from 6000 cases in February 2020, to 11,868 on March 21, 2020, to 42,000 by the end of March 2020, to 46,252 on April 2, 2020, to 166,235 on April 20, 2020, to 199,272 on April 25, 2020, to 363,711 on May 28, 2020, and to 499,967 as of June 28, 2020; to 540,157 with a total of 11,694,766 infected cases as of July 8, 2020; (John Hopkins, 2020).[1]

Address for correspondence: Prof. Asim Ahmed Elnour, Program of Clinical Pharmacy, College of Pharmacy, Al Ain University, Abu Dhabi campus, Abu Dhabi-United Arab Emirates. AAU Health and Biomedical Research Center, Al Ain University, Abu Dhabi, United Arab Emirates.
E-mail: assahura2021@gmail.com

How to cite this article: Sadeq A, Elnour AA, Farah FH, Ramadan A, Don J, Fathelrahman AI, *et al.* Scoping review of six retrospective studies: risk factors associated with the case fatality rate of people infected with Coronavirus (COVID-19). J Pharm Bioall Sci 2022;14:81-92.

On 11th of February, the Chinese Center for Disease Control and Prevention published the largest case series of coronavirus disease 2019 (COVID-19) in mainland China. The overall case-fatality rate (CFR) was 2.3% (72,314 total recorded cases, 1023 deaths among 44,672 total confirmed cases).[2] The current data showed that the infection fatality rate in New York City (USA) as of the first of May 2020, was 1.4% (deaths/cases: [23,430/1,694,781 = 1.4%]) and mortality rate was 0.28% (deaths/population, 23,430/8,398,748 = 0.28%). In China, as of June 28, 2020, the CFR was 5.5% (4,641/84,745 = 5.5%) and the mortality rate was (4,641/1,439,282,831 = 0.32%).[3] The worldwide CFR was 5.0% (499,967/10,063,319 = 5.0%). The reported COVID-19 data has shown that, the CFR rises with the increasing age, males versus females, comorbidities (preexisting conditions such as cardiovascular diseases (13.2%, diabetes (9.2%), hypertension (8.4%), chronic respiratory disease (8.0%), and cancer (7.6%).[3]

A retrospective case series of 107 subjects with COVID-19 was conducted on February 10, 2020, from Zhongnan Hospital of Wuhan University in Wuhan and Xishui Hospital, Hubei Province, China. The independent risk factors for poor outcome for nonsurvivors were: Older age and male gender.[4] A single-center retrospective observational study of 145 hospitalized subjects with confirmed COVID-19 was performed between January 1, 2020, and March 11, 2020, at Taizhou Public Health Medical Center, Zhejiang, China. The average age was 47.5 years old (±14.6), and 54.5% were men. Hypertension (15.2%) and diabetes mellitus (9.7%) were the most common comorbidity.[5]

In a systematic review and meta-analysis of 14 retrospective and case series studies including 1,424 subjects, fever (89.2%), cough (67.2%), and fatigue (43.6%) were reported to be common.[6] An earlier study (between February 7 and 26, 2020) has described the epidemiological and clinical information of 205 subjects with COVID-19 admitted to a makeshift Fangcang hospital (Shanghai East Hospital, Shanghai, China). The median age was 51 years, 54.6% were males, 82.0% had fever, 69.8% had dry cough, 11.2% had hypertension, and 4.9% had diabetes.[7]

Another study has reviewed the electronic medical records of 140 hospitalized subjects with confirmed results of severe acute respiratory syndromes (SARS)-CoV-2 viral infection. The median age was 57 years and 50.7% were male. The most common clinical characteristics were: Fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal symptoms (39.6%). The most common comorbidities were: Hypertension (30.0%) and diabetes mellitus (12.1%). The onset of symptom to hospital admission median (interquartile range [IQR]) was 8 (6–11) days. The study concluded that older age and high number of comorbidities were associated with severe subjects.[8]

Despite the intensive published data about the Coronavirus 2019 disease, still there is a lack of clear epidemiological data on the risk factors for increased CFR. Hence the purpose of this study was to provide an overview of the predictive risk factors associated with COVID-19 case fatalities. Therefore, in the current scoping review of six retrospective studies, we have reported the clinical characteristics and potential risk factors associated CFR post-hospital admission in subjects with COVID-19 from Wuhan in China.

The research question in the current scoping review was: What are the clinical characteristics that were associated with death among patients with COVID-19?

The world continues to face one of the most serious pandemic COVID-19 crises with an escalated CFR climbing very rapidly from few thousands to nearly 400,000 in early June to more than 500,000 by June 28, 2020. In terms of the added value of the current review, screening the published literature for relevant articles published on the risk factors associated mortality rate or fatality cases at first inception of the COVID-19, may shed light into the clinical characteristics of the survivors and the nonsurvivors and inform about possible health-related preventive maneuvers, triaging and management of survivors as well as new infected cases. It is well known that the COVID-19 is responsible for acute respiratory distress syndrome (ARDS) that leads to death within a very short period of <2 weeks. Therefore, it would be rational to describe the pattern of the clinical characteristics of the survivors and the nonsurvivors during the critical intensive-infection era. The explicit objective of the current scoping review was to collate and report the published data on the clinical features of nonsurvivors. The main focus was on the inferences from the risk factors associated with the pattern of CFR.

Methods

The protocol for the current scoping review was developed prior to the commencement of the review. However, the protocol is not registered in platforms such as PROSPERO and Cochrane library due to various limitations for submission of protocols for systematic reviews.

We conducted our search on Google Scholar for specific and relevant articles with the inclusion criteria: English published articles, subjects with

COVID-19, adults, reported risk factors for CFR, survivors, nonsurvivors, intensive care unit (ICU), and the mortality rate reported from December 1, 2019, to March 30, 2020. The search was repeated on May 1, 2020, with the same MeSH (Medical Subject Headings) terms, and we have extended the duration of retrieved articles to cover till May 30, 2020. Articles from well-reputed journals were included. The PRISMA guidelines were used to screen and include articles relevant for the study.

We have limited the Google Scholar search strategy to the following MeSH terms: China, Wuhan, Coronavirus, COVID-19, novel Coronavirus (2019-nCoV), adult subjects, admission to ICU, death, infection, mortality rate, pneumonia, retrospective studies, risk factors, SARS-CoV2, survivors/non-survivors. We have also retrieved published articles in the reputed Journals that included robust relevant-articles reporting cases from December 1, 2019, to March 30, 2020). We have contacted the relevant authors to identify additional sources.

The authors of the current scoping review have reviewed published articles of studies mainly conducted in Wuhan city in China between January 2020 and May 30, 2020. We have included retrospective studies conducted in Wuhan hospitals, published in English, and reporting survivors, nonsurvivors, mortality-risk factors, and the mortality rate.

The full electronic search strategy for articles retrieval from Google Scholar with the previously mentioned specified MeSH terms has been illustrated in the PRISMA chart [Figure 1]; which includes the number of articles included and excluded. We have screened the collected articles for eligibility of the relevant papers included in the scoping review and have followed a strict strategy based on the developed criteria in our protocol. For instance, four authors have conducted the search, followed by other four authors repeating the search, and further other four authors rescreened the articles as per our protocol. All authors further retrieved the included articles, and in case of dispute, an external expert professor has been invited to resolve the conflict with prior discussions on ZOOM meeting platform.

Initially, we have collected 25 studies and reviewed 23 studies (2 duplicates), 14 studies were excluded (did not met 100% inclusion criteria) and 9 were eligible. The 14 articles that were excluded were case studies, case series studies, and case–control studies. Of the 9 included, six studies were qualified as per our inclusion criteria[9-14] [Table 1], and three studies were excluded with very specific reasons indicated in Appendix 1.[15-17] We have used predefined and pretested forms for charting data with independent checking and data confirmation. The main form for data charting that was developed by AAE, was reviewed and tested by the research team before its implementation (AAE; FH, ABE, WK, and SMAL).

The data charting was then conducted by four independent authors, followed with another different five authors (IYK, JD, KG, WK and SAB), and finally double-checked for the third approach by different six authors (NA, AAL, AIF, SMM, SASA, and ASQ). An external professor inspected the final data charted, and consensus was generated among all authors.

We have used a clear, comprehensive data charting form and have extracted relevant information from the included articles. The items selected for charting were specified on a checklist, and the protocol process mentioned-above has been strictly followed for highly quality reporting and precision of collected data items. We have used a pretested specific standard form to ease the process between the team members (authors), and the completed final form was agreed upon and unified for data calibration.

The relevant studies have been collected by (AAE; FH, ABE, and SMAL), double-checked by (Azza R, IYK, JD, KG, and SAB). The discrepancies and redundancies were removed and rechecked by another four authors (NA, AAL, AIF, AAB, SMM, SASA, and ASQ), whereby disputed statements were resolved by further double-check, and consensus among the authors was obtained as appropriate.

We have applied the PICO concept (population, intervention, comparison and outcome) to each selected and screened article, to assess the validity, results, and relevance ahead of the final informed decision. This has included and acknowledged the various sources of evidence suitable to the current scoping review.

We have abstracted data from the six relevant articles, which included: (a) demographics, (b) times/durations, for example, duration of the study, duration of onset to dyspnea, hospital length of stay, time from first symptom to date of hospitalization, duration of onset to hospital admission, duration of time in ICU and duration of onset till death, (c) comorbidities, (d) complications, and (e) signs and symptoms of admitted patients. We calculated CFR using the mortality rate reported in the studies for more rigorous inferences.

The reporting of the scoping review was guided by the PRISMA-ScR checklist.

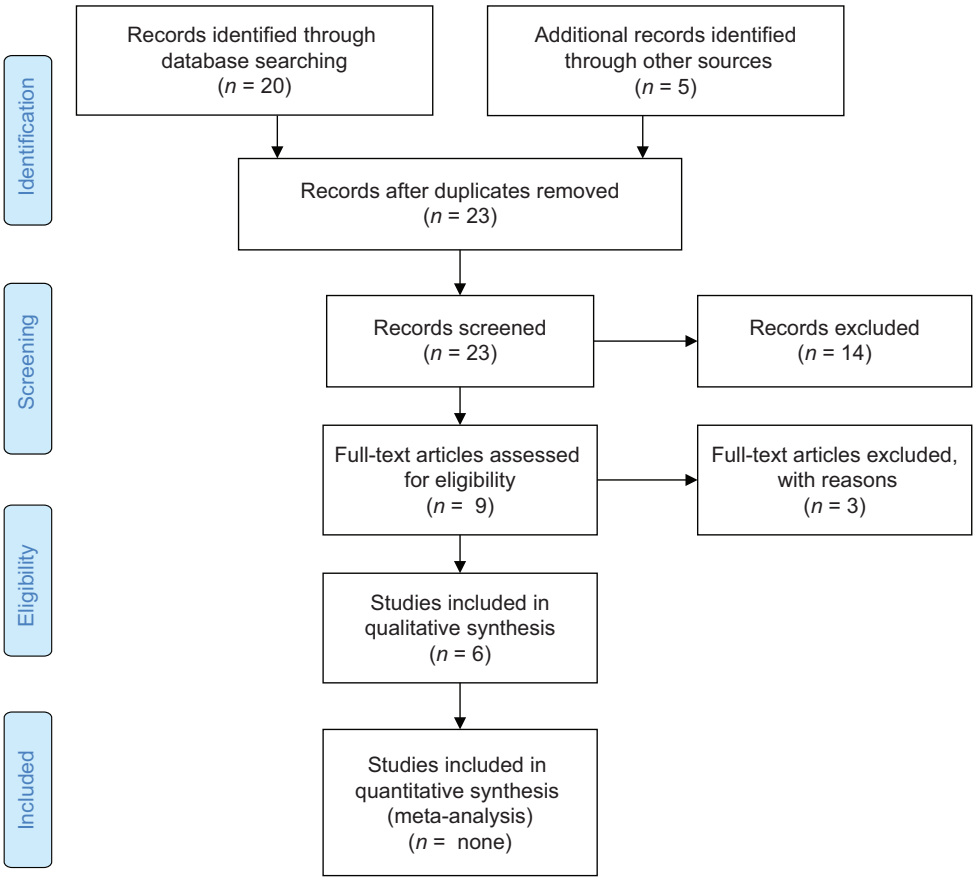

Figure 1: PRISMA 2009 flow diagram

Statistical analysis

There were no statistical tests performed as we have relied on reported data and comparison of published mortality rates between studies. We have included the main relevant summarized data as mean and range as appropriate. The clinical characteristics that were relevant to the outcome of CFR have been well presented. The outcome events or summary measures were presented as a percentage of the clinical risk factors for increased CFR.

Results

We have screened six retrospective studies, duplicates were removed and the full-text documents were accessed. We have used the original PRISMA flow diagram template as a guide [Figure 1]. There were 1769 subjects included from six retrospective studies, with over all mean age of 52 (range 35–67) years and majority were males (65.9%). The CFR was 7.7% (136/1769) mainly in Jin Yintan Hospital (5 studies), in Wuhan-Hubei province, China, [Table 1]. The mean duration of the six retrospective studies was 24.7 days, the duration of onset to dyspnea was 8.7 days, and the mean hospital length of stay was 11.7 days. The mean duration of time from first symptom to date of hospitalization was 5.7 days. The mean duration of time in the ICU was 8.2 days and the mean duration of onset till death was 15.3 days. The main reported complications were: ARDS, shock, acute kidney injury, and acute cardiac disease,[9-14] [Table 2]. The majority of the complications occur in the highest percent in the earlier dated study by Huang *et al*.,[9] except for shock where the highest percent (20.0%) was reported in the study by Zhou *et al*.[13]

The overall preexisting medical conditions (comorbidities) were reported in the current scoping review from the six retrospective studies in descending pattern: Cardiovascular diseases (injuries), diabetes, chronic liver disease, chronic respiratory diseases, and cancer. The highest comorbidity reported was cardiovascular diseases at 22.2% (393/1769, [Table 3].

The major reported symptoms/signs of the cohorts were: Fever, cough, myalgia/fatigue, dyspnea, and respiratory distress syndrome. The most commonly prevailing symptom in the six compared studies was fever in nearly all cases (98.0%, 82.0%, 98.6%, 94.0%, 88.7%, and 93.5%).[9-14] A high incidence of diarrhea was reported in 10.1% (14) by Dawei *et al*. study.[11] The overall percent of the symptom of cough was (70.8%) which

Table 1: The six retrospective studies case fatality rate from Hubei province in China (136/1769=7.7%)

The study author/ month/year/ reference/journal	Title of article	DOI	Correspondence	Study design (citations)	Population sample (*n*)	City/ province/ hospital	CFR reported (%)
Huang *et al*., January 24, 2020[9] Lancet	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	10.1016/ S0140-6736 (20) 3018 3-5	Prof Bin Cao, Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing 100029, China Email: caobin_ ben@163.com	Retrospective (9501)	41	Wuhan/ Hubei Jin Yintan Hospital	(15.0) 6/41
Chen *et al*., January 29, 2020[10] Lancet	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	10.1016/ S01406736 (20) 30211-7	Prof Li Zhang, Tuberculosis and Respiratory Department, Wuhan Jinyintan Hospital, Dongxihu District, Wuhan 430023, China Email: zhangli080806@163. com	Retrospective (5020)	99	Wuhan/ Hubei Jin Yintan Hospital	(11.1) 11/99
Wang *et al*., February 7, 2020[11] Corrected on February 20, 2020 JAMA	Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China	10.1001/jama. 2020.1585	Zhiyong Peng, MD, Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan 430071, Hubei, China Email: Pengzy5@ hotmail.co m.	Retrospective (5618)	138	Wuhan/ Hubei Zhongnan Hospital	(4.3) 6/138
Guan *et al*., February 28, 2020[12] NEJM	Clinical characteristics of coronavirus disease 2019 in China	10.1056/ NEJMoa2002032	Dr. Zhong at the State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Rd., Guangzhou, Guangdong, China, Email: nanshan@ vip. 163.com.	Retrospective (5830)	1099	Wuhan/ Hubei: Jinyintan Hospital Data outside Hubei province: National Health Commission	(1.4) 15/1099
Zhou *et al*., March 9, 2020[13] Lancet	Clinical course and risk factors for mortality of adult inpatients with coronavirus disease 2019 in Wuhan, China: A retrospective cohort study	10.1016/ S01406736 (20) 30566-3	Prof Bin Cao, Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing 100029, China Email: caobin_ ben@163.com	Retrospective (4575)	191	Wuhan/ Hubei Jinyintan Hospital and Wuhan Pulmonary Hospital	(28.2) 54/191

Contd...

Table 1: Contd...

The study author/ month/year/ reference/journal	Title of article	DOI	Correspondence	Study design (citations)	Population sample (*n*)	City/ province/ hospital	CFR reported (%)
Chaomin MD *et al*., March 13, 2020[14] Corrected on May 11, 2020 JAMA Intern Med	Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 Pneumonia in Wuhan, China	10.1001/ jamainternmed. 2020.0994	Yuanlin Song, MD, Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, 180 Fenglin Rd, Shanghai 200032, China Email: ylsong70_02@163.com Junhua Zheng, MD, Department of Urology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, 85 Wujin Rd, Shanghai 200080, China Email: zhengjh0471@ sina.com.	Retrospective cohort study (1360)	201	Wuhan/ Hubei Jinyintan Hospital	(21.9) 44/201

CFR: Case fatality rate, DOI: Digital object identifier, N: Population sample

continues to dominate in later dated studies, (81.1%)[14] as compared to earlier dated ones, (82%),[10] [Table 4].

The overall number of cases admitted to the ICU was (12.9%) 228/1769. However, there were very minor discrepancies aligned between the six studies, except for the study by Guan *et al*.; (5%),[13] [Table 4]. The overall CFR was 136/1769 (7.7%) with the highest CFR of 28.2%, (54/191) reported by Zhou *et al.* in Jinyintan Hospital and Wuhan Pulmonary Hospital at Wuhan city.[13] While the lowest CFR was 15/1099 (1.4%) reported from 552 hospitals in 30 provinces in China.[12] The mean duration of onset until death for nonsurvivors was 15.3 days.

The first study included in the current scoping review was for subjects admitted to Jin Yin-tan Hospital in Wuhan. The investigators have collected and analyzed data from electronic medical records of 41 subjects with laboratory-confirmed COVID-19 infection by real-time polymerase chain reaction (RT-PCR) and next-generation sequencing. The majority of cases were men (30, [73.0%]) with median age of 49·0 years (IQR 41·0–58·0). From overall 41 cases, 13 (32.0%) were admitted to ICU and six were nonsurvivors (15.0%).[9]

The single-center retrospective study of 99 cases of 2019-nCoV in Jin Yin-tan Hospital in Wuhan, has confirmed all the infected cases by RT-PCR and has analyzed epidemiological, demographic, clinical, and radiological features and laboratory data. The average age of the subjects was 55·5 years (standard deviation 13·1), including 67 men and 32 women. Eleven (11.1%) cases worsened in a short period of time and died of multiple organ failure.[10]

The largest retrospective, single-center study has reported 138 consecutive hospitalized cases with confirmed 2019-nCoV infected pneumonia at Zhongnan Hospital of Wuhan University in Wuhan, China. The median age was 56 years (interquartile range; [42–68] range [22–92] years) with slightly more than half were males (54.3%). The study reported overall CFR of 4.3% (n = 6).[11]

The fifth study of 1099 subjects with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, in China revealed the results of primary composite endpoint (6.1%, 67/1099) of admission to ICU (5.0%), the use of mechanical ventilation (2.3%), or CFR death (1.4%). The median age of the subjects was 47 years; 41.9% of them were females.[12]

The retrospective, multicenter cohort study, for subjects (191) with laboratory-confirmed COVID-19 from Jinyintan Hospital (135) and Wuhan Pulmonary Hospital (56) in Wuhan-China has compared between survivors and nonsurvivors and has explored the risk factors associated with in-hospital death. The in

Table 2: The time/duration (study duration, duration of onset dyspnea, hospitalization, time from first symptoms to date of hospitalization, ICU admission and death), complications and total case fatality rate

Clinical parameter	The six retrospective studies						
	Huang *et al*. Lancet., 2020[9] (*n*=41)	Chen *et al*., 2020[10] (*n*=99)	Wang *et al*. 2020[11] (*n*=138)	Guan *et al*., 28 February, 2020[12] (*n*=1099)	Zhou *et al*., 2020[13] (*n*=191)	Chaomin *et al*., 2020[14] (*n*=201)	Mean duration (days)
Duration of the study (days)	24	25	25	NA	NA	NA	24.7
Duration of onset to dyspnea (days/IQR)	8 (5-13)	NA	5 (1-10)	NA	13 (9-16·5)	NA	8.7
Hospital length of stay (days/median/IQR)	NA	NA	10 (7-14)	12 (10-14)	11·0 (7-14)	13 (10-16)	11.5
Time from first symptom to date of hospitalization (days) (duration of onset to hospital admission)	7	5	5	NA	NA	NA	5.7
Duration of time in ICU (days)	10.5	7	7	NA	8 (4-12)	NA	8.2
Duration of onset till death (days) (IQR) mean	17	10 (9–11)	13	NA	21 (17-25)*	NA	15.3
Complications frequency (%)							
ARDS	12 (29.3)	17 (17.2)	27 (19.6)	37 (3.4)	103 (54.0)*	84 (41.8)	280/1769 (15.8)
Shock	3 (7.3)	4 (4.0)	12 (8.7)	12 (1.1)	38 (20.0)*	NA	69/1769 (3.9)
Acute cardiac diseases (injury)	5 (12.2)*	NA	10 (7.2)	1 (0.1) (disseminated intravascular coagulation)	15 (8.0)	NA	31/1769 (1.8)
Acute kidney injury	3 (7.3)*	3 (3.0)	5 (3.6)	6 (0.5)	2 (1.0)	NA	19/1769 (1.1)
Total case fatality rate frequency (%)	6/41 (15.0)	11/99 (11.1)	6/138 (4.3)	15/1099 (1.4)	54/191 (28.2)*	44/201 (21.9)	136/1769 (7.7)

*The highest percent achieved in a row. ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit, IQR: Interquartile range, N: Population, NA: Not available

hospital CFR was 28.2% (54/191), associated with older age (odds ratio 1·10, 95% confidence interval 1·03–1·17, per year increase; $P = 0·0043$), higher sequential organ failure assessment (SOFA) score (5·65, 2·61–12·23; $P < 0·0001$), and d-dimer greater than 1 μg/mL (18·42, 2·64–128·55; $P = 0·0033$) on admission.[13]

The last retrospective cohort study in the current scoping review in Jinyintan Hospital in Wuhan-China has described the clinical characteristics and outcomes of 201 subjects with confirmed COVID-19 pneumonia who have developed ARDS or died. The median age was 51 years (interquartile range, 43–60 years), and 128 (63.7%) subjects were males, of which eighty-four (41.8%) had developed ARDS, and of which, 44 (52.4%) had died. The bivariate Cox regression analysis, risk factors associated with the development of ARDS and progression from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI 2.08–5.11; and HR, 6.17; 95%CI, 3.26–11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09–1.19; and HR, 1.08; 95%CI, 1.01–1.17, respectively), and organ and coagulation dysfunction (e.g, higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44–1.79; and HR, 1.30; 95% CI, 1.11–1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01–1.04; and HR, 1.02; 95% CI, 1.01–1.04, respectively]). High fever (≥39°C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11–2.84) and lower likelihood of death (HR, 0.41; 95% CI, 0.21–0.82). Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20–0.72).[14]

The current global data according to the frequency of infected subjects and the CFR (percent of death from total) was presented on Figures 2 and 3.

Discussions

The explicit objective of the current scoping review was to collate and report the published data on the clinical features of nonsurvivors for COVID-19. We have reported the clinical characteristics of subjects with confirmed COVID-19 from six retrospective studies with 1769 cases admitted to Wuhan hospitals in Hubei

Table 3: The age, gender, preexisting medical conditions (comorbidities) and case fatality rate in the six retrospective studies (n=1769)

Respective study author/year/ population (*n*) →	Huang *et al*. Lancet., 2020[9] (*n*=41)	Chen *et al*., 2020[10] (*n*=99)	Wang *et al*. 2020[11] (*n*=138)	Guan *et al*., 28 February, 2020[12] (*n*=1099)	Zhou *et al*., 2020[13] (*n*=191)	Chaomin *et al*., 2020[14] (*n*=201)
Age (years), range	49 (41-58)	55.5 (SD 13.1)	56 (42-68)	56 (46-67)	47 (35-58)	51 (43-60)
Gender (male: female) frequency (%)	30 (73.2):11 (26.8)	67 (67.7):32 (32.3)	75 (54.3): 63 (45.7)	119 (62.0):72 (38.0)	560 (51.9):539 (49.1)	128 (63.7):73 (36.3)
Comorbidities						
Cardiovascular frequency (%)	6 (14.6)	40 (40.0)	20 (14.5)	Hypertension: 58 (30.0)	Hypertension: 165 (15.0)	Hypertension: 39 (19.4)
Total: 393/1769 (22.2)**	Hypertension: 6 (14.6) Total: 12 (29.2)	Including cerebrovascular disease	Hypertension: 43 (31.2) Total: 53 (45.7)*	CHD: 15 (8.0) Total: 73 (38.0)	CHD: 27 (2.5) Total: 92 (17.5)	Cardiovascular disease: 8 (4.0) Total: 47 (23.4)
Chronic respiratory disease frequency (%)	1 (2.0)	1 (2.0)	4 (2.9)	COPD: 6 (3.0)*	COPD: 12 (1.1)	CLD: 5 (2.5)
Total: 29/1769 (1.63)						
Cancer frequency (%)	1 (2.0)	1 (1.0)	10 (7.2)*	2 (1.0)	10 (0.9)	Tumor: 1 (0.5)
Total: 25/1769 (1.4)						
Diabetes frequency (%)	8 (20.0)*	None	14 (10.1)	36 (19.0)	81 (7.4)	22 (10.9)
Total: 161/1769 (9.1)						
Chronic liver disease frequency (%)	1 (2.0)	Endocrine system diseases: 13 (13.0)*	4 (2.9)	Missing data	Hepatitis B: 23 (2.1)	7 (3.5) Endocrine system disease: 2 (1.0)
Total: 35/1769 (1.97)						
Other specify frequency (%)	Missing data	Digestive system diseases: 11 (11.0) Nervous system diseases: 1 (1.0)	CKD: 4 (2.9) Cerebrovascular disease: 7 (5.1) HIV infection: 2 (1.4)	CKD: 2 (1.0) Others: 22 (12.0)*	CKD: 8 (0.7) Cerebrovascular disease: 15 (1.4) Immunodeficiency: 2 (0.2)	CKD: 2 (1.0) Nervous system disease: 7 (3.5)
Total CFR, per each study frequency (%)	6/41 (15.0)	11/99 (11.1)	6/138 (4.3)	54/191 (28.2)*	15/1099 (1.4)	44/201 (21.9)
Total: 136/1769 (7.7)						

*The highest percent achieved in a row, **The highest comorbidity. CFR: Case fatality rate, CHD: Coronary heart disease, CKD: Chronic kidney disease, CLD: Chronic lung disease, COPD: Chronic obstructive pulmonary disease, HIV: Human immune virus, NA: Not available, N: Population, SD: Standard deviation

Province, mainland China. The main predictive risk factors associated with the increased pattern of CFR were: Older age, male gender, longer duration of onset till death (days), development of ARDS/shock, preexisting diabetes, and preexisting cardiovascular diseases.

The main finding of the current scoping review has revealed that the development of ARDS as complication (103, [54.0%] and 84 [41.8%]) was associated with higher CFR (54/191 [28.2%] and 44/201 [21.9%]) in two of the reviewed studies,[13,14] respectively. Furthermore, shock (38, 20.0%) and acute cardiac diseases (15, 8.0%) were associated with higher CFR in one study.[13] The CFR reported from the reviewed studies was 7.7%.

We highly lend support to the findings from retrospective study of medical records of (59,883) subjects with

Table 4: The symptoms and signs of the subjects in the current reviewed three studies (Wuhan-Hubei province)

Signs and symptoms	Study details						
	Huang *et al.* Lancet., 2020[9] (*n*=41) frequency, *n* (%)	Chen *et al*., 2020[10] (*n*=99) frequency, *n* (%)	Wang *et al.* 2020[11] (*n*=138) frequency, *n* (%)	Guan *et al*., 28 February, 2020[12] (*n*=1099) frequency, *n* (%)	Zhou *et al*., 2020[13] (*n*=191) frequency, *n* (%)	Chaomin *et al*., 2020[14] (*n*=201) frequency, *n* (%)	Mean percent (*n*=1769) frequency, *n* (%)
Dyspnea	22 (55.0)*	31 (31.0)	43 (31.2)	205 (18.7)	NA	80 (39.8)	(11.9) 211/1769
Cough	31 (76.0)	81 (82.0)*	82 (59.4)	745 (67.8)	151 (79.0)	163 (81.1)	(70.8) 1253/1769
Fever	40 (98.0)	82 (83.0)	136 (98.6)*	975 (88.7)	180 (94.0)	188 (93.5)	(90.5) 1601/1769
Diarrhea	1 (3.0)	2 (2.0)	14 (10.1)*	42 (3.8)	9 (5.0)	NA	(3.8) 68/1769
Respiratory rate breath per minute (IQR)	12 (29.0) had >24	NA	20 (19–21)	NA	56 (29.0) had>24	NA	(5.0) 88/1769
Blood pressure	Systolic pressure (mmHg): 125.0 (119.0-135.0)	NA	Mean arterial pressure (mmHg), IQR: 90 (84-97)	NA	1 (1.0) had SBP<90 mmHg	NA	Not applicable
Organ failure	-	11 (11.0)	36 (26.1)*	NA	NA	NA	(2.7) 47/1769
Myalgia or fatigue	18 (44.0)*	11 (11.0)	48 (34.8), fatigue: 96 (69.6)	164 (14.9) Fatigue: 419 (38.1)	29 (15.0)	65 (32.3)	(13.3) 235/1769
Nausea or vomiting	Missing data	1 (1.0)	14 (10.1)* Vomiting: 5 (3.6)	55 (5.0)	7 (4.0)	NA	(4.4) 77/1769
Admission to ICU	13 (32.0)*	23 (23.0)	36 (26.1)	53 (5.0)	50 (26.0)	53 (26.4)	(12.9) 228/1769

*The highest percent achieved in a row (the descending trend in severity of symptoms was observed). IQR: Interquartile range, N: Population, NA: Not available, ICU: Intensive care unit

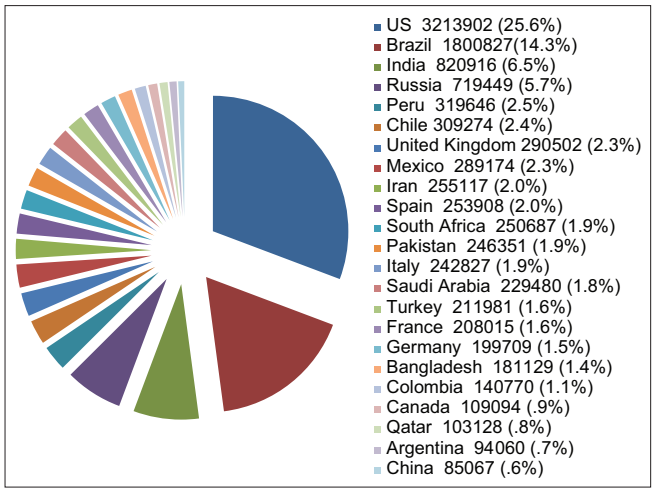

Figure 2: The Frequency and respective percent (%) of the confirmed infected cases per country (global cases 12,573,041 (100.0%) (as of 12th July 2020) (Johns Hopkins Center for Systems Science and Engineering (2020) Coronavirus COVID-19 global cases. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda759474 0fd40299423467b48e9ecf6. [Last acessed on 2020 Jun 13]

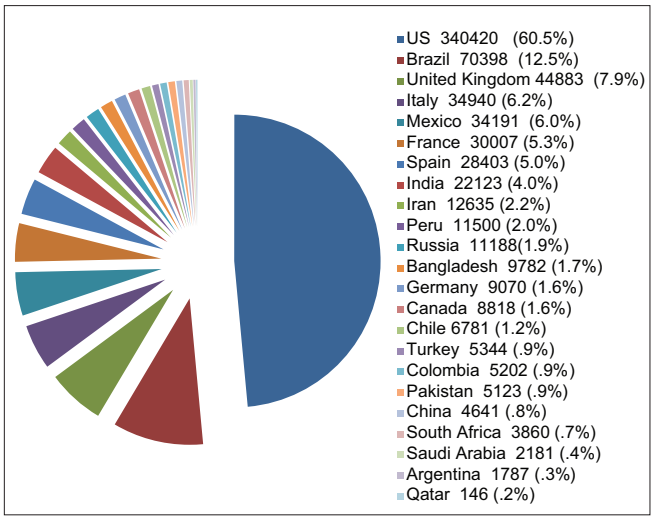

Figure 3: Frequency and respective percent (%) of the death cases (case fatality rate) per country (global cases 562137(4.5%) (as of 12th July 2020). (Johns Hopkins Center for Systems Science and Engineering (2020) Coronavirus COVID-19 global cases. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. [Last accessed on 2020 Jun 13]

confirmed COVID-19 at Renmin Hospital of Wuhan University (from January 14, to February 13, 2020). The authors reported that ARDS was reported in 25 non survivors. In line with our findings the most significant associated comorbidity diseases were: Hypertension 64.0%, (16/25), followed by diabetes (10/25, 40%) and heart diseases (8/25, 32%). Similar to our findings the most important risk factors for death caused by COVID-19 were age and the preexisting medical condition.[18] The

major preexisting comorbidities reported in the current scoping review were cardiovascular diseases, diabetes, cancer and chronic respiratory diseases, which was in line with the main clinical characteristics in the descriptive study conducted on the non-survivors by Xun.[18] The age of subjects reported in the current six retrieved studies was (<60 years) which was far less than that reported by Xun.[18] The study by Xun did not report the number of the clinical records reviewed from which the non-survivors were retrieved and has not reported any CFR.

Another study from Taiwan conducted by Chih-Cheng Lai and colleagues, have reported a pooled data analysis from the three studies[9-11] which have been included in our current scoping review. The pooled data contains in depth epidemiological information, laboratory data, clinical manifestation, radiological findings and treatment options.[19]

In the current scoping review we did not find any relevant information regarding the severity of pneumonia assessment using CURB-65 score (Confusion, blood urea nitrogen (BUN >19 mg/dL), respiratory rate ≥30 breaths/min, Systolic Blood pressure <90 mmHg or Diastolic blood pressure ≤60 mmHg, Age ≥65), or SOFA for the ICU cases (except in one study).[13] Therefore, it is imperative to include the CURB-65 score at the initial phase of hospital admission and SOFA at the initial intention to admit to the ICU, as planned triaging, ventilation maneuvers and treatment levels will accordingly differ.

A recently published study of 1859 subjects with confirmed COVID-19 from seven centers in Wuhan city (from January 20 to April 4, 2020) has shown CFR of 11.2% (208/1859). The study has revealed 8 risk factors associated with in-hospital death including older age (HR = 1.04; 95% Confidence Interval [CI], 1.03, 1.06 per year increase; $P < 0.001$).[20]

The findings of our current scoping review were highly supported by the Open SAFELY platform revealed data on 17,425,445 adults from United Kingdom (Time period February 1, 2020–April 25, 2020). The primary outcome of this cohort study was in-hospital death among people with confirmed COVID-19. The reported CFR was 5683 subjects, which was associated with: Being male (hazard ratio 1.99, 95% CI 1.88–2.10); older age and deprivation; uncontrolled diabetes (HR 2.36 95% CI 2.18–2.56).[21]

Our findings lend support to the data reported from Tongji Hospital in Wuhan, China. This study cohort of 799 subjects diagnosed with COVID-19, whereby the deceased subjects have had a median age of 68 years, male gender (83; 73%), chronic hypertension (54 (48%) and median time from disease onset to death was 16 (IQR 12.0–20.0) days. Furthermore, similar to our findings common complications were more frequently reported in the deceased subjects have included ARDS (113; 100%), sepsis (113; 100%), acute cardiac injury (72/94; 77%), heart failure (41/83; 49%). However, the CFR reported was 113 (14.1%), which was double what was reported in our current scoping review of 7.7%.[22]

The summary of the main findings were:

1. The main findings from the current scoping review were the associated predictive risk factors for increased CFR. We have found that older age, male gender, the longer duration of onset till death (days), development of ARDS/shock, pre-existing diabetes, and pre-existing cardiovascular diseases were the major risk factors associated with high CFR
2. The major comorbidities in descending order reported in the six retrieved studies were: Cardiovascular diseases (393/1769 [22.2%]), diabetes (161/1769 [9.1%]), chronic liver disease 35/1769 [1.97%]), chronic lung disease (29/1769 [1.63%]) and cancer (25/1769 [1.4%])
3. The main complications reported in the current review were: ARDS, shock and acute cardiac disease
4. The CFR was high in two of the reported studies (28.2% and 11.0%) which have decreased in the later dated study to 3.4%. The reported overall CFR was 7.7% (136/1769), with the highest at 28.2%, (54/191) in the study by Zhou *et al*. 2020,[12] and the lowest at 1.4% (15/1099) in the study by Guan *et al*. 2020.[13]

The study is with limitations. One of the limitations was the lack of access to the individual data of cases to conduct pooled analyses or subgroup analyses. Also, while we utilized google scholar and reputable journals for article searches, which provides a wealth of publications from various databases, we may not have identified all the scoping reviews since we did not utilize specific electronic databases and the grey literature. To overcome this limitation, we used multiple Mesh terms during the google scholar search to retrieve many publications to be as comprehensive as possible. Furthermore, while Wuhan city was front and center for the COVID outbreak during the early stages of the pandemic, its specific selection and not other cities may have introduced report biasing.

On the other hand, the scoping review had multiple strengths. The compilation of the scoping review was carried out with rigorous selection standards and transparent methods. Also, the study reporting was guided by the PRISMA-ScoR checklist. Furthermore, articles' search and selection, the data charting were

reviewed by multiple reviewers. The current study identified a comprehensive outline of the risk factors that may increase mortality due to COVID-19 infection postadmission to hospitals. The potential implications of determining the clinical characteristic of the COVID-19 nonsurvivors, put forth by this review, will enable risk stratification of newly infected subjects and improve the CFR. Deploying a risk stratification strategy for high CFR will influence the prognosis and improve the clinical outcomes of survivors.

Conclusion

In conclusion, we have collated the main clinical characteristics from six retrospective studies which have been reported during the first 3 months of COVID-19 pandemic of 2020 in Wuhan city-China. The collated features male gender, older age, having preexisting cardiovascular diseases, diabetes and ARDS were found to be at an increased risk of high CFR. Regarding the implications of the findings, the identified clinical characteristics of nonsurvivors will assist healthcare professionals in triaging the subjects at high risk of CFR for prompted care and timely interventions. Furthermore, the predicted risk factors for in hospital death can predict the outcomes in persons with COVID-19. Further research via systematic review and metanalysis into the association of the reported risk factors is therefore required.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Johns Hopkins Center for Systems Science and Engineering (2020) Coronavirus COVID-19 Global Cases. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. [Last accessed on 2020 Jun 28].
2. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) – China, 2020. China CDC Wkly 2020;2:113-22.
3. Available from: https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/. [Last accessed on 2020 Jun 28].
4. Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, *et al.* Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care 2020;24:1-9.
5. Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, *et al.* Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection 2020;48:1-9.
6. Ji W, Zhang J, Bishnu G, Du X, Chen X, Xu H, *et al*. Comparison of severe and non-severe COVID-19 pneumonia: Review and meta-analysis. [doi: 10.1101/2020.03.04.20030965]. Not Peer-Reviewed. Available from: https://www.medrxiv.org/content/100.1101/2020.03.04.20030965v1. [Last accessed on 2020 Jul 13].
7. Hua J, Chen R, Zhao L, Wu X, Guo Q, He C, *et al.* Epidemiological features and medical care-seeking process of patients with COVID-19 in Wuhan, China. ERJ Open Res 2020;6:00142-2020.
8. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. China. Allergy 2020;75:1730-41.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
10. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
11. Wang D, Hu BO, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus – Infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
12. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. For the China medical treatment expert group for COVID-19. N Eng J Med 2020;382:1708-20.
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395:1054-62.
14. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-43.
15. Ai J, Chen J, Wang Y, Liu X, Fan W, Qu G, *et al*. The cross-sectional study of hospitalized coronavirus disease 2019 patients in Xiangyang, Hubei province. MedRxiv 2020. [doi: 10.1101/2020.02.19.20025023].
16. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
17. Cao W, Shi L, Chen L, Xu X, Wu Z. Clinical features and laboratory inspection of novel coronavirus pneumonia (COVID-19) in Xiangyang, Hubei. medRxiv 2020. [doi: 10.1101/2020.02.23.20026963].
18. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, *et al*. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. medRxiv 2020. [doi: 10.1101/2020.02.19.20025239].
19. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020;55:105924.
20. Chen L, Yu J, He W, Chen L, Yuan G, Dong F, *et al*. Risk factors for death in 1859 subjects with COVID-19. Leukemia 2020;34:1-11.
21. Esai Selvan M. Risk factors for death from COVID-19. Nat Rev Immunol 2020;20:407.
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al*. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020;368:m1091.

Appendix 1: The detail of studies excluded with reasons

Study author/year/ reference	Title of the article	DOI	Correspondence	Study design	Population (*n*) case fatality rate reported (%) and reasons for exclusion
Ai J *et al*., 2020[15]	The cross-sectional study of hospitalized coronavirus disease 2019 patients in Xiangyang, Hubei province	10.1101/2020.02.19.20025023	Professor Bin Pei, Evidence-Based Medicine Center, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, 15 Jiefang Road, Fancheng District, Xiangyang 441000, Hubei Province, China. Tel: +86 18995678520; E-mail: xyxzyxzx@163.com Or Guoxin Huang, Evidence-Based Medicine Center, Xiangyang No. 1 People's Hospital, Hubei University of Medicine, 15 Jiefang Road, Fancheng District, Xiangyang 441000, Hubei Province, China. Tel: +86 17671174060: E-mail: xzyxhgx@163.com	Cross-section	*n*=102 (3.0) Data for cases from other regions in Hubei Province Xiangyang second biggest city in Hubei with a large number of labor-force migrant to Wuhan
Yang *et al*., 2020[16]	Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study	10.1016/S2213-2600(20) 30079-5	Prof You Shang, Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China; Email: you_shang@ yahoo.com	Retrospective	32 (61.5) 52 critically ill patients out of 710 admitted Highly, critically ill
Cao W *et al*., 2020[17]	Clinical features and laboratory inspection of novel coronavirus pneumonia (coronavirus disease 2019) in Xiangyang, Hubei	10.1101/2020.02.23.20026963	Weiliang Cao. Clinical Laboratory of Xiangyang No. 1 hospital, The fourth affiliated hospital of hubei medicine university, Number 15 of Jiefang Road, xiangyang, Hubei, China. Tel.: 18371013627; E-mail: 790561571-@qq.com	Case series study	*n*=128 No mortality rate laboratory study findings

DOI: Digital object identifier, N: Population