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Clinical characteristics of hospitalized patients with covid-19 in the first hundred days of Covid 19 pandemic. What do we know so far? An analysis of the first 100 days of covid19 pandemic, lessons which we learnt and the future direction

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Abstract

Background & Aims: Coronavirus disease 2019 (COVID-19) outbreak has rapidly become a pandemic.

We conducted this study to appraise the current data on the disease by meta-analysis and meta-regression methods.

Methods: We conducted a comprehensive search of several databases for the first hundred days of COVID19 from inception to March 25 2020 to include studies reporting clinical characteristics and outcomes of hospitalized patients with COVID-19. The pooled rate of occurrence of various clinical symptoms, clinical work-up, complications, and death were calculated. Random effects model was used and heterogeneity was assessed by I^2% values and 95% prediction interval.

Results: A total of 27 studies including 4077 patients were included in our final analysis. Based on our analysis, the pooled rates of fever, cough and myalgia/fatigue were 82.6% (CI 74.5-88.5), 63% (CI 57.4-68.2) and 29.5% (CI 22.3-37.9). Lymphopenia was noted in 57.5% (CI 44.5-69.5) and elevated CRP in 66.4% (CI 55.4-75.8). Ground glass opacities were seen in 62.8% (CI 52.3-72.2) and bilateral pneumonia in 75.8% (CI 66.6-83). Based on meta-regression analysis, supplemental oxygen use, and increased antiviral use with minimal steroids seem to reduce rate of death.

Conclusion: Fever, cough and fatigue are the most common symptoms of COVID-19. Lymphopenia and elevated CRP are the most common laboratory findings. Diffuse ground glass opacities and bilateral pneumonia are the most common radiological findings. Supplemental oxygen therapy and antivirals with cautious use of steroids seem to reduce the rate of death.

Keywords: Covid-19

1. Introduction

A novel coronavirus resulted in an outbreak of pneumonia of unknown cause in Wuhan city, China. Initially termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the condition was renamed as coronavirus disease 2019 or COVID-19 by the World Health Organization on February 11th, 2020.[1]

COVID-19 outbreak has rapidly become a pandemic and cases continue to increase across the world. While we now know that fever and cough are the most common symptoms of COVID-19, robust data on the overall clinical features, laboratory values and radiological findings are emerging.[1]

In terms of medical management of patients with COVID-19, data regarding need for supplemental oxygen including mechanical ventilation, need for antibiotic, antiviral, glucocorticoid and intravenous immunoglobulin (IVIG) therapy continues to emerge.[1]

The prevalence of hypoxic respiratory failure in affected patients is estimated to be about 19% and although the true incidence is not clear, it appears that around 14% patients will develop severe disease requiring oxygen therapy, and 5% will require ICU admission and mechanical ventilation.[2]

It remains unclear whether patients with certain clinical and/ or laboratory and/ or radiological abnormalities have worse clinical outcomes. We aimed at reviewing the published literature on hospitalized patients with COVID-19 and quantitatively summarize the clinical outcomes, characteristic radiological findings and disease outcomes in the first hundred days of COVID19 by meta-analysis methods. In addition, we aimed to study any predictors of outcomes by meta-regression methods.

2. Methods

2.1. Search strategy

Four physicians, with experience in systematic reviews (SP, SC, BPM, VM), searched the literature independently for studies reporting on the clinical characteristics of patients with SARS-CoV-2 infection/ COVID-19. Searches were run in Google-Scholar, Ovid Embase (1974+), Ovid Medline (1946+ including epub ahead of print, in-process & other non-indexed citations), Scopus (1970+) and Web of Science (1975+). There were no language restrictions and Google Translator function was used to extract data. Literature search was conducted up to March 25, 2020.

Key words used for the search were as follows: "COVID-19", "SARS-CoV-2", "Wuhan Coronavirus", "Coronavirus 2019", and "COVID pandemic". Literature search strategy key words and Boolean terms are provided in Appendix-1. We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines, the checklist of which is available as Appendix-2. Reference lists of evaluated studies were examined to identify other studies of interest.

2.2. Study selection

In this meta-analysis, we included studies that reported on the epidemiologic, clinical, investigational (including laboratory and radiological) data of patients with a confirmed diagnosis of SARS-CoV-2 infection/ COVID-19. Studies were included irrespective of the publication language, study design and/ or type, study sample-size, follow-up time, and geography as long as they provided the appropriate data needed for the analysis.

Authors decided not to have strict exclusion criteria due to the nature of the disease and the ongoing COVID pandemic, except for sample size (studies with 5 and less number of patients were excluded). In cases of multiple publications from a single research group reporting on the same patient same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained. The retained studies were decided by two authors (BPM, SC) based on the publication timing (most recent) and/ or the sample size of the study (largest). In situations, where a consensus could not be reached, possible overlapping studies were included in the final analysis and any potential effects were assessed by sensitivity-analysis of the pooled outcomes by leaving out one study at a time.

2.3. Data abstraction and quality assessment

Data on study-related outcomes from the individual studies were abstracted independently onto a standardized form by multiple authors (SP, SRK, GK, OJC, MF, RO, GVP, SC, BPM) simultaneously using Google cloud services. Authors VM, RK cross-verified the collected data for possible errors and two authors (SRK, SC) did the quality scoring independently.

The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies.[3] This quality score consisted of 8 questions, the details of which are provided in supplementary Table 1.

2.4. Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by Der Simonian and Laird using the random-effects model.[4] When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis.[5]

We assessed heterogeneity between study-specific estimates by using Cochran Q statistical test for heterogeneity, 95% prediction interval (PI), which deals with the dispersion of the effects, and the I^2 statistics.[5-7] In this, values of <30%, 30% - 60%, 61% - 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.

Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test.[8] When publication bias was present, further statistics using the fail-Safe N test and Duval and Tweedie's 'Trim and Fill' test was used to ascertain the impact of the bias.[9] Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there were no bias. The impact was reported as minimal if both versions were estimated to be same, modest if effect size changed substantially but the final finding would still remain the same, and severe if basic final conclusion of the analysis is threatened by the bias.[10]

Meta-regression analysis was carried out to assess the effect of a clinical variable on the outcomes of interest. The Knapp-Hartung 2-tailed p-value was used to assess statistical significance and a p-value of <0.05 was set as the level of significance. Scatter plots were generated in cases of statistical significance to study the direction of the effect. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

3. Results

3.1. Search results and population characteristics

From an initial total of 304 studies, 62 full-length articles were reviewed and 27 studies[11-37] were included in the final analysis. The study selection PRISMA flowchart is provided in supplementary materials (supplementary figure-1).

Data from the 27 studies consisted of 4077 confirmed and/ or suspected hospitalized patients being treated for SARS-CoV-2 infection. Confirmation of the disease was based on a positive RT-PCR viral RNA testing and/ or CT evidence of typical findings. Mean/ median age ranged between 34 years to 70 years and 56% were males. 1829 patients (45%) had a known history of exposure to COVID-19. Underlying comorbidities of hypertension was recorded in 9.4%, cardio-cerebro-vascular disease in 5% and diabetes in 4.9%. Chronic obstructive pulmonary disease (COPD) was noted in less than 1% of cases (0.86%).

From the reported data, 27.4% of hospitalized patients received intravenous antibiotic treatment, 22.8% received

some form of antiviral therapy and about 10% of patients received intravenous steroids. The mean/ median length of hospital stay for patients with favorable outcome was 7.5 to 23.2 days. Further information on study population characteristics are summarized in supplementary table-1, information on laboratory values and treatments rendered are summarized in supplementary table-2, information on radiological findings are summarized in supplementary table-3 & information on hospital outcomes are summarize in supplementary table-4.

3.2. Characteristics and quality of included studies

Four studies[20, 21, 25, 33] were population based and eleven studies were multicenter based. Due to the acute nature of the disease being studied, authors scored follow-up information as 1 (max score=1, minimum score=0), as not all studies reported on the adequacy of follow-up. It was assumed that the studies accounted for all patients due to the short duration of study period. Based on the New-Castle Ottawa scoring system, twenty-four studies[11, 12, 14-18, 20-36] were considered to be of high quality and three studies to be of medium quality. The details of the scoring system are available as supplementary table-5.

3.3. Meta-analysis outcomes

Clinical characteristics

Fever, cough, myalgia/fatigue, dyspnea and headache were the most commonly reported symptoms. The pooled rate of fever was 82.6% (95% CI 74.5-88.5), cough was 63% (95% CI 57.4-68.2), myalgia/fatigue was 29.5% (95% CI 22.3-37.9), dyspnea was 18.6% (95% CI 12.7-26.4) and headache was 7.2% (95% CI 5.3-9.8). The pooled rate of diarrhea was 7.3% (95% CI 4.8-11) and that of nausea/vomiting was 5% (95% CI 3.3-7.7). Supplementary table-1.

Other infrequently reported symptoms were sore throat (5.4%), and chest discomfort (1.6%).

Laboratory findings

The pooled rate of leukocytosis was 11.1% (95% CI 6.4-18.5), leucopenia was 21.2% (95% CI 16.2-27.3), lymphopenia was 57.5% (95% CI 44.5-69.5) and elevated LDH was 52.8% (95% CI 41.2-64.1).

The pooled rate of elevated d-dimer was 31.5% (95% CI 22.4-42.2), elevated CRP levels was 66.4% (95% CI 55.4-75.8) and elevated procalcitonin was 11.8% (95% CI 6.1-21.6).

The pooled rate of elevated creatinine was 7% (95% CI 2.6-17.4), and elevated Urea/Nitrogen was 8.5% (95% CI 4.4-15.8).

The pooled rate of decreased albumin was 38.5% (95% CI 9.8-78.4), elevated aspartate aminotransferase (AST) was 26.4% (95% CI 17.4-37.9), elevated alanine aminotransferase (ALT) was 22.6% (95% CI 14.7-33.2) and elevated bilirubin was 8.5% (95% CI 4.4-15.8). Laboratory values are summarized in supplementary table-2.

Radiological findings

In terms of characteristic radiological findings, the overall pooled rate of ground glass/patchy opacities was 62.8% (95% CI 52.3-72.2), consolidations was 38.4% (95% CI 21.6-58.4), unilateral and bilateral pneumonia were 38.4% (95% CI 21.6-58.4) and 75.8% (95% CI 66.6-83), respectively. Pooled rate of pleural effusion was 9% (95% CI 5.3-15) and normal radiograph was 10.9% (95% CI 6.2-18.7). Radiological findings are summarized in supplementary table-3.

Complications

Acute respiratory distress syndrome (ARDS), septic shock and acute kidney injury (AKI) were the most frequently encountered complications of SARS-CoV-2 infection. The pooled rate of ARDS was 21.9% (95% CI 10.4-40.4), septic shock was 5.3% (95% CI 2.3-11.5), and AKI was 5.9% (95% CI 2.5-13.6).

Other complications reported infrequently were as follows: cardiomyopathy, secondary infections, acute liver failure, acute cardiac injury, arrhythmias, seizure, pneumothorax, and disseminated intravascular coagulation. Supplementary table-4.

Hospital course and Death

In our analysis, we found that the pooled rate of discharge was 38.2% (95% CI 23.6-55.3) and ongoing hospitalization was 47.2% (95% CI 29.4-65.7). The pooled rate of reported death was 5.5% (95% CI 2.7-10.9), forest plot figure-1.

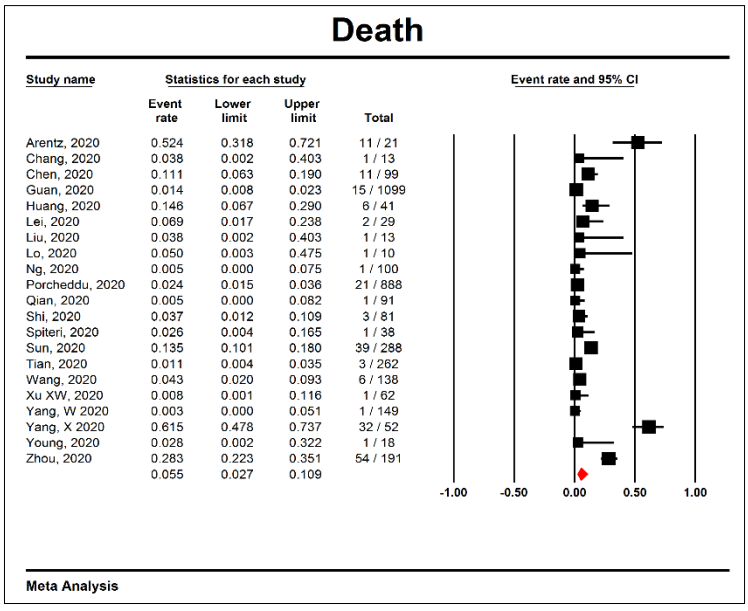

Fig 1

3.4. Meta-regression outcomes

Meta-regression analysis was conducted to study the effects of comorbid variables, radiological variables and treatment variables on the calculated pooled rates of SARS-CoV-2 infection related complications and death.

Supplemental oxygen therapy seemed to have significant beneficial effect on the pooled rate of death (2-tailed p-value = 0.03, R^2=0.68), scatter-plot figure-2.

Additionally, we noticed a trend towards significance with antiviral treatment on the pooled outcomes of death (p-value = 0.08, R^2=0.62), scatter-plot figure-3.

Bivariate regression analysis of antiviral treatment along with steroids seemed to have significant influence on the pooled rate of death (2-tailed p-value = 0.02, R^2=0.66; scatter-plot figure-4). Scatter plot analysis seemed to suggest a linear association with the use of antivirals reducing the rate of death. On the other hand, use of steroids seemed to suggest increasing rate of death (2-tailed p-value=0.04, R^2=0.66; scatter-plot figure-5).

Furthermore, univariate regression assessment of Oseltamivir and Lopinavir/ Ritonavir did not seem to have any significant effects on the pooled rate of death (2-tailed p-value=0.2 & 0.9, respectively).

Patient characteristics like smoking, hypertension (HTN); diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), cardio-cerebro-vascular disease (CCVD), chronic liver disease (CLD), and any cancers did not have any influence on the pooled rates of complications and/ or death.

Laboratory values of leucocytosis, leukopenia, lymphopenia, elevated d-dimer, elevated LDH, elevated CRP, elevated procalcitonin, elevated creatinine, and decreased albumin levels did not reveal any influence on the pooled rates of complications and/ or death.

Administration of antibiotics, antifungals, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), supplemental oxygen support, intravenous immunoglobulin did not show any influence on the outcomes of complications and/ or death.

Radiological presence of ground glass opacities, consolidations, bilateral pneumonia, and pleural effusion did not reveal any effects on the pooled complications and/ or death. Treatment of a patient in ward setting, ICU setting, use of non-invasive and invasive mechanical ventilation did not have any effects on the outcomes of complications and/ or death.

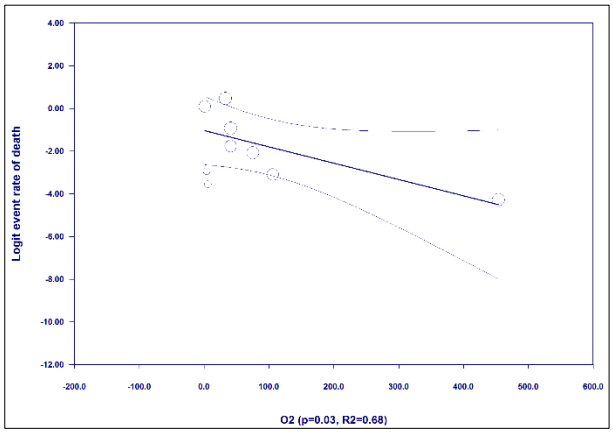

Fig 2: Univariate regression of Logit event rate on O2

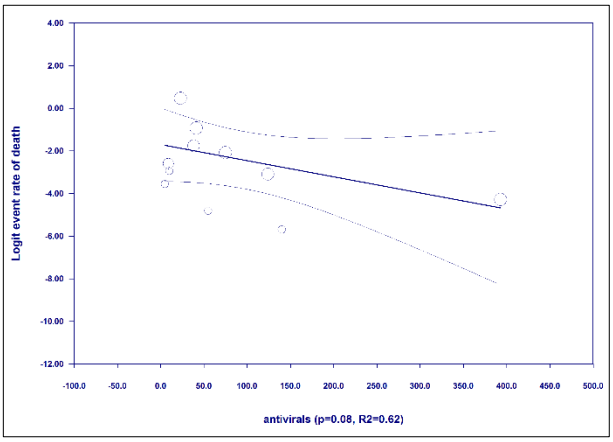

Fig 3: Univariate regression of Logit event rate on antivirals

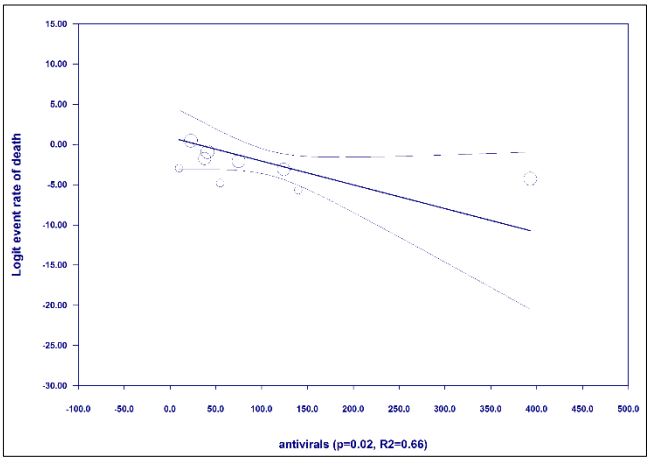

Fig 4: Bivariaet Regression of Logit event rate on antivirals with steroids

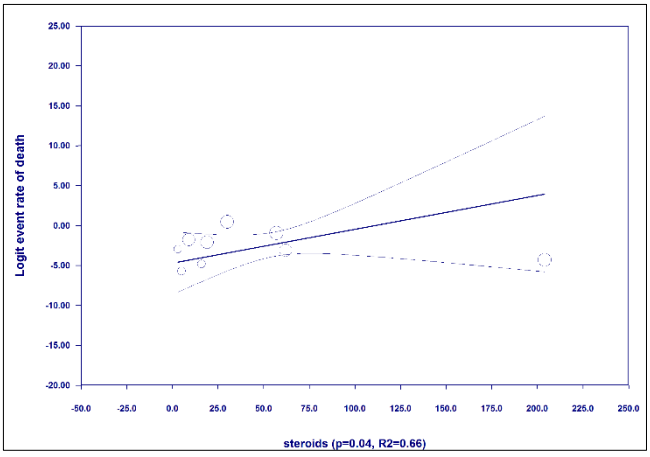

Fig 5: Bivariaet Regression of Logit event rate on steroids with antivirals

4. Validation of meta-analysis results

4.1. Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. In this analysis, no single study significantly affected the outcome or the heterogeneity.

4.2. Heterogeneity
We assessed dispersion of the calculated rates using the prediction interval (PI) and I^2 percentage values. The PI gives an idea of the range of the dispersion and I^2 tells us what proportion of the dispersion is true vs chance. The calculated PIs are reported with the pooled rates in Table-1. Overall, substantial to considerable heterogeneity was noted in the analysis.

4.3. Publication bias
Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was no evidence of publication bias (Eggers 2-tailed p-value=0.2).

5. Discussion
New data is being reported every day as COVID-19 continues to grip the world. SARS-CoV-2 appears to be more easily transmissible and lethal than seasonal influenza. Specifically, an early estimate of the reproductive number (R0) of SARS-CoV-2 (defined as the average number of people an infected person subsequently infects another, owing to the biological properties of the pathogen in combination with social and environmental factors) is 2.3. By comparison, the estimated average R0 for the 1918 influenza pandemic that results in an estimated 50 million deaths globally was 1.8, and the estimated average R0 for seasonal influenza is 1.28.[38] In our study, a history of exposure was noted in 45% of patients and the time to hospitalization from symptom onset ranged from a mean of 3.5 to 11 days.

In terms of the disease symptomatology, we report 82.6% of patients present with fever, 63% with cough, 29.5% with symptoms of myalgia/ fatigue/ weakness, 18.6% with dyspnea, and 7.2% with headache. Gastrointestinal symptoms like diarrhea can be present in 7.3% and nausea/ vomiting in 5% of patients. We noticed a pooled proportion of 66.4% with elevated CRP levels followed by 57.5% of patients with lymphopenia and 52.8% of patients were noted to have an elevated LDH. Our study demonstrated a decreased albumin levels in 38.5% of patients and an increased d-dimer in 31.5%.

Diffuse ground glass opacity was the most frequently observed radiological finding. The pooled rate was 62.8%. Bilateral pneumonia was noted in 75.8% and unilateral findings were noted in 20.1% of patients. Pleural effusion was noted in 9% and 10.9% of the patient population had a clear radiograph at presentation. Peripherally located opacities with adjacent pleural thickening were reported as well.

ARDS in 21.9% of patients, AKI in 5.9% and septic shock in 5.3% can complicate the clinical course of SARS-CoV-2 infection. Death was noted in 5.5% of patients. The mean/ median length of hospital stay was 7.5 to 23.2 days. Based on our meta-regression analysis, CRRT treatment, non-invasive and/ or invasive mechanical ventilation did not seem to affect the outcomes. 38.2% of patients have been successfully discharged with 47.2% of patients currently under treatment based on the reported data at the time of this study.

We conducted meta-regression to study the effects of multiple variables on the calculated rates of disease complications and death. None of the patient characteristics, laboratory variables, radiological features or treatment strategies had an influence on the pooled rates of complications. The use of oxygen therapy, antivirals and steroids however seemed to demonstrate thought provoking findings.

Based on the scatter plot, increased use of oxygen therapy seemed to reduce the death events. The surviving sepsis campaign guidelines on the management of critically ill adults with COVID-19, suggest starting supplemental O2 if the peripheral oxygen saturation (SPO2) is < 90% and be maintained not higher than 96%.[38] In critically ill patients hyper-oxygen therapy has been shown to be detrimental and associated with poor outcomes.[38] The panel utilized indirect evidence from critically ill population to make recommendations since the effect of supplemental oxygen therapy on clinical outcomes in COVID-19 patients remains largely unclear.[38]

This study reports a possible linear association demonstrating less risk of death with O2 supplementation in SARS-CoV-2 patients and therefore is a key finding of this study. This information however has to be interpreted with caution, as we do not have data on the actual peripheral oxygen saturation targets and/ or the arterial blood gas values with alveolar to arterial (A-a) oxygen gradient and/ or the oxygen delivery method. Rather, we can only comment that more people getting supplemental Oxygen seems to be beneficial in terms of reducing the pooled death rate.

Bivariate regression scatter plot, with antivirals and steroids, seemed to suggest that the use of antivirals might reduce the chances of the rate of death when administered in the presence of steroids. However, data was limited to ascertain the specific type of antiviral medication. The studies that employed antiviral therapy used oseltamivir as single agent in 648 patients (15.8%), Ganciclovir in 14 patients (0.3%), Lopinavir single agent in 7 patients (0.2%), Lopinavir/ Ritonavir combination in 111 patients (2.7%), and a combination of Oseltamivir, Ganciclovir, and Lopinavir/Ritonavir in 75 patients (2%). An additional 149 patients (3.6%) were administered some form of antivirals the details of which are unknown. Furthermore, the ideal duration of antiviral treatment is unknown.

Univariate regression analysis of Oseltamivir and Lopinavir/ Ritonavir did not demonstrate statistical significance (2-tailed p-value = 0.2 and 0.9, respectively). This finding is in line with a recently published randomized controlled study that showed Lopinavir-Ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability. However, during the SARS epidemic, Ritonavir and Lopinavir, with or without Ribavirin, have shown some success.[39] Based on our analysis, it seems that Oseltamivir and Lopinavir/ Ritonavir are likely of no benefit in the treatment of COVID-19.

The bivariate regression plot data of steroids, when used along with antivirals, is worrisome. The scatter plot data seems to suggest an increase in the risk of death with increased use of steroids. We do not have direct data to explain this finding and information on the duration and/ or dosage of steroids is lacking. However data exists in patients with SARS and MERS that suggest increased use of steroids delays virus particle clearance and might prolong virus-induced cell damage. Furthermore, current guidelines recommend avoiding corticosteroids in patients with COVID-19 for treatment of viral pneumonia and to use low-dose steroids in patients with shock, based on indirect evidence in critically ill patients in general.[1, 38]

Our meta-regression analysis on steroids is based on COVID-

19 data and results seem to suggest that IV steroids should be used minimally. It should however be noted that meta-regression is considered a weak statistic with regards to the predictive effects of a variable on the reported outcomes. In addition, it is important to note that a higher percentage of patients with severe disease received these therapies. With the ongoing pandemic and staggering mortality numbers worldwide, we are inclined to take any weak data as potentially usable.

COVID19 has a thromboembolic phenomenon. In a meta-analysis by Guru etal (42) the pooled rate of major VTE was 12.5% in hospitalized patients and 17.2% in intensive care unit patients. Many societies and experts recommend routine prophylactic anticoagulation with heparin for VTE prevention in hospitalized COVID-19 patients.

There are several meta-analyses published on this topic thus far and the reported pooled rates of clinical features and radiological findings are comparable.[40, 41] This study differs primarily in the overall number of studies included, pooled rate of death and the meta-regression findings. We report the 95% prediction intervals that give the readers an idea on the range within which the pooled outcomes could fall in the real world.

This study has limitations, the majority of which are inherent to any meta-analysis. We were unable to assess the regression results to the type of antiviral medication. We were unable to ascertain a plausible cause for the study heterogeneity. Due to the nature of the disease and the population based reporting of data, we do not think we have avoided patient overlap with absolute certainty. However, we have assessed the effects of this in our sensitivity analysis. Based on which, we believe, despite potential overlapping patients, our pooled results would not be different if all possible patient overlaps were to be avoided. The rapidly progressing nature of the disease is a major limitation to the applicability of our results.

In conclusion, based on a meta-analysis of 27 studies, fever (82.6%), cough (63%) and weakness/ myalgia (29.5%) are the most common symptoms. Lymphopenia (57.5%) is the most frequently encountered laboratory abnormality followed by elevated CRP levels (66.4%) and elevated LDH (52.8%). Diffuse ground glass opacities (62.8%) and bilateral pneumonia (75.8%) are the most frequently noted radiographic findings. In terms of treatment, supplemental oxygen and administration of antivirals with cautious use of steroids seem to demonstrate reduced death rates by regression analysis. Oseltamivir and Lopinavir/ Ritonavir seem to have no benefit in the treatment of COVID-19. Future well-conducted and adequately powered studies are warranted to verify our findings and to establish the specific type of antiviral medication that might cure SARS-CoV-2 infection.

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Supplementary Materials

Supplementary Table -1: Study, population characteristic & symptomatology
Supplementary Table-2: Summary of laboratory values and treatments
Supplementary Table-3: Summary of radiological findings
Supplementary Table-4: Summary of hospital related outcomes.
Supplementary Table-5: Study quality assessment.
Supplementary Figure-1: Study selection flow chart
Appendix-1: Literature search strategy
Appendix-2: MOOSE checklist

Supplementary Table 1: Study, population characteristic & symptomatology

Study	Design, country	N (Total)	Age	History of exposure	M/F	Comorbidities	Signs & symptoms		Time to hospitalization (days)
						SM - Smoking, HTN - Hypertension, DM - Diabetes, Ca-cancer, CLD - Chronic liver disease, CCVD - Cardio-cerebero-vascular disease, CKD - Chronic kidney disease	Non GI Symptoms: Asymp: asymptomatic, f - fever, c - cough, dys - dyspnea, m - muscle soreness, h-headache, ARDS, ct, cc - critical condition, Fa - Fatigue	GI Symptoms (d - Diarrhea, n/v - Nausea/Vomiting)	
Arentz, 2020	Retrospective, Single center, Feb 20 to Mar 5 2020, Washington - USA.	21	70 (43-92)	-	11/10	CKD - 12 , CHF - 9 , COPD - 7 , Chronic pulmonary disease (Asthma) - 2 , Solid organ transplant - 2, CLD - 1, Immunosuppressed - 3, Rheumatologic disease - 1, OSA - 6	dys - 17, c - 11, f - 11	0	3.5
Chan, 2020	Prospective Case series, Jan 10 to Jan 15, 2020, Single center, Single family cases, Shenzhen, Guangdong province - China.	6	10, 36, 37, 63, 65, 66	6	3/3	HTN - 2, DM - 1, Chronic sinusitis - 1, Ca - 1	f - 5, c - 3, Sputum -1, Weakness - 3, Nasal congestion - 1, Rhinorrhoea - 1, Sneezing - 1, Sore throat -1, Chest pain - 1,	d - 2	6-10
Chang, 2020	Retrospective, Multicenter (07), January 16, 2020, to January 29, 2020, Beijing - China.	13	34 (34-48) Adult - 11 / Children - 2 (aged 2 years and 15 years)	12	10/3	NR	f - 12, c - 6, Sputum - 2, m - 3, Upper airway congestion - 8 , h - 3, Rhinorrhea - 1	d - 1	8.33 (4.16)
Chen, 2020	Retrospective, Single center, Jan 1 to Jan 20, 2020, Wuhan - China.	99	55·5 (21–82)	49	67/32	CCVD - 40, Digestive - 11, Chronic pulmonary disease - 1, Endocrine - 13, Neuro 1, Ca - 1	f - 82, c - 81, dys - 31, m - 11, Confusion - 9, h - 8, Sore throat - 5, Rhinorrhoea - 4, Chest pain - 2	d - 2, n/v - 1	NR
Guan, 2020	Retrospective, Multicenter (552), December 11, 2019, and January 29, 2020; the data cutoff for the study was January 31, 2020, 30 provinces China.	1099	47.0 (35.0–58.0)	794	637/459 {1096n}	Current SM - 137 , Former SM - 21 , HTN - 165 , DM - 81, Ca - 10, COPD - 12 , CKD - 8, CCVD - 42, HBV - 23 , Immunodeficiency 2	f 473, Conjunctival congestion - 9, c - 745 , Sore throat - 153, Sputum - 370, h - 150, Nasal congestion - 53, Fa - 419, Hemoptysis - 10, dys - 205, m - 164, Chills - 126	d - 42, n/v - 55	4.0 (2.0-7.0)
Huang, 2020	Prospective, Single center, Dec 16, 2019, to Jan 2, 2020, China.	41	49·0 (41·0–58·0)	27	30/11	DM - 8, HTN - 6, CCVD - 6, COPD - 1, CLD - 1, Ca 1	f - 40, c - 31, m - 31, Sputum - 11, h - 3, Hemoptysis - 2, dys - 22	d - 1	7·0 (4·0–8·0)
Lei, 2020	Single center, Jan 14-29, 2020; China.	29	56 (26-79)	-	21/8	SM - 2 , HTN - 8, DM - 5, Ca 1, CLD - 2	f - 28, c - 21, dys -17, m - 12, h - 2	d - 4	-
Liu, 2020	Retrospective, Multicenter, December 8, 2019, and February 25, 2020, China.	13	22 - 36	12	0/13	-	f - 10, Fa - 4, dys - 3, c - 2 , Sore throat - 1	0	NR
Lo, 2020	Retrospective, Single center, January 21st and February 16th, 2020.	10	54 (27 – 64)	-	3/7	HTN - 3, HLD - 3, Former SM - 3	f - 8, c - 5, dys - 5, Fa - 3	d - 8, n - 5	5 (1 – 11)
Ng, 2020	Population based, as of Feb 2020, Singapore.	100	41 (34-54)	-	60/40	-	-	-	5 (2-8)
Porcheddu, 2020	Population based, Italy.	888	-	-	-	-	-	-	-
Qian, 2020	Retrospective, Multicenter (05), 20 January 2020 to 11 February 2020, Zhejiang province, China.	91	50 (36.5 - 57.0)	90	37/54	HTN - 15, DM - 8, CCVD - 3	f - 65, c - 55 , Fa - 40, dys - 13, h - 7, Sputum - 30, Anorexia - 23, Chest distress - 17, m - 5, Back discomfort - 3	d - 21, n - 11, v - 6	6 (3-8)
Shi, 2020	Retrospective, Multicenter (02),	81	49·5 (25–81)	31	42/39	Chronic pulmonary disease - 9, DM - 10,	f - 59, dys - 34, Chest tightness - 18,	d - 3, v - 4	NR

	Dec 20, 2019, and Jan 23, 2020, Wuhan China.					HTN - 12 , CKD - 3, CCVD - 14, Ca - 4, CLD - 7	c - 48, h - 5, Sputum - 15, Rhinorrhea - 21, Anorexia - 1, Dizziness - 2, Weakness - 7		
Song, 2020	Retrospective, Single center, January 20, 2020, to January 27, 2020, Shanghai, China.	51	49 (16)	50	25/26	DM - 3, HTN - 5, CLD - 1, CCVD - 1, COPD - 1	f - 49, c - 24, Sputum - 10, Fa - 16, h/Dizzines - 8, dys/Chest pain - 7, Sore throat - 3, Rhinorrhea - 2, Loss of appetite - 9	d - 5, n/v - 3	-
Spiteri, 2020	Population based, as of 21 Feb 2020, WHO European region	38	42 (2-81)	38	25/13	-	f - 20, c - 14, Fa - 8 , h - 6, Sore throat - 2, Rhinorrhea - 2, Asymp - 2, dys - 2	0	2.5 - 4.6
Sun, 2020	Multicenter, Jan 20, 2020 and Jan 30, 2020, China	288	49 (2-89)	-	172/116	-	-	-	0 (0-9)
Tian, 2020	Retrospective, Multicenter (57), Jan 20 to Feb 10, 2020, , Beijing China.	262	47.5 (1 – 94)	241	127/135	-	f 215, c - 120, Fa - 69, dys - 18, h - 17	0	6.83 (5)
Wang, 2020	Retrospective, Single center case series, Jan 1 to Jan 28 2020, Wuhan - China	138	56 (22 - 92)	12	75/63	HTN - 43, DM - 14, Ca 10, CCVD - 27, COPD - 4, CKD - 4, CLD - 4, HIV - 2	f - 136, Fa - 96, c - 82, Anorexia - 55, m - 48, dys - 43, Sputum - 37, Pharyngalgia - 24, Dizziness - 13, h - 9	d - 14, n - 14, v - 5, abd pain - 3	7 (4-8)
Xu XW, 2020	Retrospective Case series study, Multicenter (07), 10 January 2020 to 26 January 2020, Zheizang province - China	62	41	23	35/27	CLD - 7, HTN - 5, DM - 1 , COPD - 1, CCVD - 1, CKD - 1	c - 50, f - 48, m/Fa - 32, Sputum - 35, Hemopysis - 2, h - 2, dys - 2	d - 3	2 (1-4.3)
Xu X, 2020	Retrospective, single center, January 24 to February 4, 2020, Guangzhou, Guangdong Province - China	90	50 (18-86)	86	39/51	HTN - 17, DM - 5, CCVD - 3, COPD - 1, TB - 2, Ca - 2, Others - 15	f - 70, c - 57, Sputum - 11, Fa/Weakness - 19, m - 25, Sore throat - 23, Chills - 6, h - 4, Asymp - 6	d - 5, n - 5 , v - 2	NR
Yang, W 2020	Retrospective, Multicenter, January 17th to February 10th, 2020, Wenzhou, Zhejiang - China.	149	45.11 (13.35)	134	81/68	CCVD - 28, Digestive - 8, Endocrine - 9, Ca - 2, Chronic pulmonary disease - 1	f - 114, c - 87, Sputum - 48, m - 5, dys - 2, Chest pain - 5, h - 13, Chest tightness - 16, Chills - 21, Sore throat - 21 Snotty - 5	d - 11, n/v - 2	6.83 (5)
Yang, X 2020	Retrospective, Single center, December, 2019, and Jan 26, 2020, Wuhan - China	52	59.7 (13-3)	27	35/17	SM - 2, Ca - 2, DM - 9, Chronic pulmonary disease - 4, CCVD - 7, Chronic cardiac disease - 5, Dementia - 1, Malnutrition - 1	f - 51, c - 40, dys - 33, m - 6, Malaise - 18, Rhinorrhoea - 3, Arthralgia - 1, Chest pain - 1, h - 3	v - 2	9.5 (7-12.5)
Young, 2020	Population based, Case series, Jan 23 to Feb 3 2020, Singapore	18	47 (31-73)	-	9/9	HTN - 4, DM - 1, HLD - 1	f - 13, c - 15, dys - 2, Sore throat - 11	d - 3	-
Zhang, 2020	Retrospective, single center, January 16 to February 3, 2020, Wuhan - China	140	57 (25-87)	18	71/69	HTN - 42, DM - 17, CCVD - 7, COPD - 2, CKD - 2, SM - 9	f - 110, c - 90, Fa - 90, dys - 44	d - 18, n - 24, v - 7, abd pain - 8	8 (6-11)
Zhao, 2020	Retrospective, multicenter, Hunan - China	101	43 (17–75)	96	56/45	CCVD - 16, Digestive - 6, Chronic pulmonary disease - 5, Endocrine - 3, None - 71	f - 79, c - 63, m - 17, dys - 1	d - 3, n/v - 2	-
Zhou, 2020	Retrospective, Multicenter, Dec 29, 2019 and Jan 31, 2020, Wuhan - China.	191	56·0 (46·0–67·0)	73	119/72	HTN - 58, DM - 36, CCVD - 15, COPD - 6, Ca 2, CKD - 2	f - 180, c - 151, m - 29	d - 9, n/v - 7	11·0 (8·0–14·0)
Zhu, 2020	Single Center, Guangdong - China	6	27-63	5	0/6	-	-	-	-