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Systematic Literature Review of Covid-19: Quality and Source of Primary Clinical Data

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Abstract

Importance: As of April 10, 2020, there were 1.7 million confirmed cases of COVID-19 worldwide and 496,500 cases in the US, with an ongoing surge in the number of reported cases and deaths. It is important to know the strengths and weaknesses, quality, and source of clinical data that was available at an important time point in the surge to help physicians caring for patients with COVID-19.

Objective: We performed a systematic literature review of all clinical studies published in Pubmed® regarding COVID-19. We included all articles identified from a search of the keywords "COVID-19" or "COVID 19" from January 1, 2020 to April 10, 2020. We identified the type of study, number of patients studied, country of origin, whether multivariate regression was used, and other characteristics.

Findings: Of 3337 articles, only 490 (15%) were clinical studies that analyzed primary patient clinical information. Of the 490, there were 310 (63%) retrospective cohort studies, 136 (28%) case reports, 16 (3%) prospective cohort studies, 24 (5%) cross-sectional studies, and 4 prospective clinical trials (1%). Of the 490 studies, 74% were from China, 15 (3%) from the US, and 111 (23%) from other countries. Chinese patients accounted for 31,050 (79%) of the 39,477 individuals studied. Excluding a letter to the editor that included 3,615 patients, there were only 81 patients from the US included in publications at a time when there were 496,500 affected individuals in the US. While papers were accepted for publication rapidly (mean time from submission to acceptance 9.4 ± 9.6 days), they were primarily descriptive, statistical analysis was limited, and publications did not address the critical clinical questions facing clinicians and public health officials at a critical time during the pandemic.

Conclusions and Relevance: As cases of COVID-19 reached 1.7 million worldwide and 496,500 in the US, almost all clinical studies were published by Chinese authors studying individuals in China affected with COVID-19. Studies were in general small and accepted quickly, with limited statistical analysis. With rapidly emerging infectious outbreaks and pandemics, the US and other countries must be better prepared to quickly publish clinically important studies that will improve insights and improve patient care.

Introduction

As of April 10, 2020, there were 1.7 million reported cases of COVID-19 worldwide and almost 500,000 cases in the US [1]. Despite the very large number of cases, there were unanswered clinical questions that were critical to the care of COVID-19 patients. For example, a validated multi-center risk score for hospitalization and mortality was critically needed to help triage patients and identify healthcare workers at high risk for infection who might need to avoid direct patient contact. Other critical questions at this time included whether individuals who have received hydroxychloroquine and azithromycin had a better outcome than other affected individuals [2-8], and whether individuals who were receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers had better or worse outcomes [9-11].

Unlike early observational epidemiologists like John Snow and Florence Nightingale, investigators today have access to computer capabilities that facilitate communication, data collection and analysis through databases that can be easily built in programs like REDCap (Research Electronic Data Capture) [12], and the ability to perform more advanced statistical analysis such as multivariate regression with statistical programs such as SAS (Cary, NC) and free software such as The R Project for Statistical Computing [13]. However, clinical researchers must also comply with investigational review boards and data sharing agreements between academic centers and nations. Clinical researchers may also have additional clinical responsibilities.

The purpose of this investigation was to determine how the knowledge base regarding COVID-19 was formed at a critical time point during the pandemic and to determine how clinical researchers around the world responded to the COVID-19 pandemic and potential obstacles. This study is a historical document but also provides insight into the course of action for the months ahead as the pandemic continues to evolve. In order to analyze currently published knowledge on COVID-19, we reviewed manuscripts that were published in PubMed with the keyword “COVID_19” as of April 10, 2020.

Materials and Methods

All studies that included the keyword “COVID-19” or “COVID 19” were identified using PubMed®. We chose PubMed® because it is used almost exclusively by clinicians for clinical information and because we were not studying basic science articles that may be represented in other databases. PubMed® includes the following search terms when “COVID-19” is searched: COVD-2019, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS-CoV-2, 2019nCoV, Wuhan combined with coronavirus, or the term coronavirus occurring after December 2019. To be included in this study, each reference required a title, English abstract, and, if an abstract was not available, a link to an article in English that provided the information collected (see below). An initial review was manually performed by reviewing each abstract to limit the database to articles that provided primary clinical information regarding COVID-19. Primary clinical information was defined as research that included information collected directly about individuals with COVID-19. We excluded all studies that were basic science

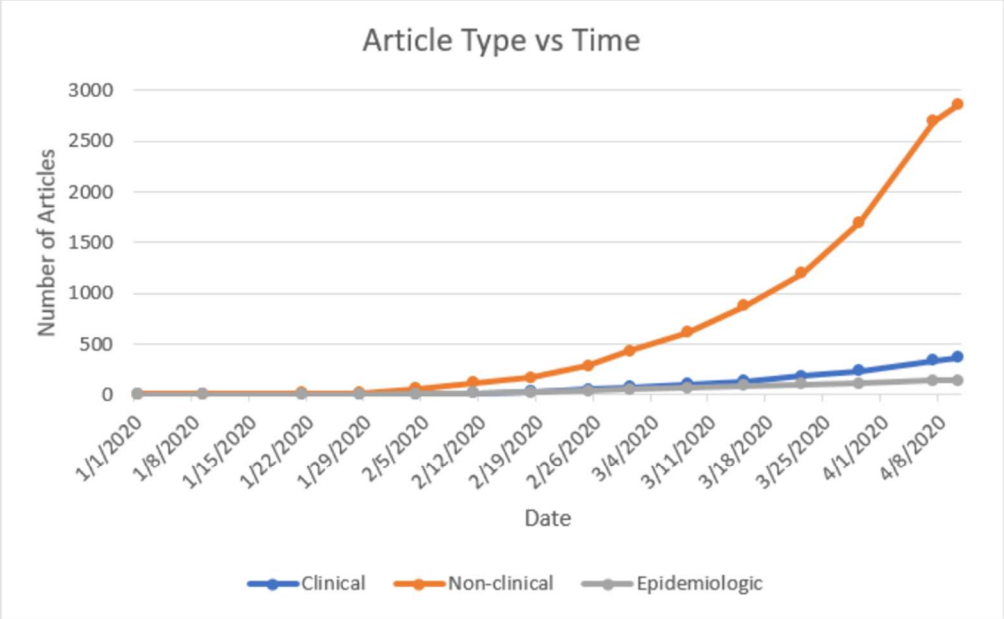
articles (defined as articles studying COVID-19 in the laboratory and not including patient specimens, reviews, editorials, or clinical guidelines on the COVID-19 pandemic. We also excluded studies that did not directly concern COVID-19 (e.g. population attitudes about COVID-19). Clinical studies were classified as follows: Case reports included all studies of a single individual affected with COVID-19. Retrospective cohort studies included studies with at least two patients that collected information from at least two time points. Prospective cohort studies were non-interventional studies that collected pre-defined data prospectively. Cross-sectional studies were observational descriptions of patients at a single point in time. Epidemiologic studies were defined as studies that provided limited or no patient-specific information and focused almost exclusively on temporal or geographic trends related to COVID-19 spread. We defined studies as meta-analyses or systematic reviews if they were described as such in the title or abstract, and this was verified on review of the publication. The country of origin was identified as the country in which all or most of the cases occurred. As a marker of the analytical complexity of studies, we analyzed how many clinical studies performed multivariate regression. We determined how many studies were focused on radiologic, obstetric/gynecologic, and pediatric findings. Radiologic studies were tabulated because of the large number of such studies noted upon initial review. Obstetric/gynecologic and pediatric studies were tabulated because of interest in the specific subgroups. For each clinical article, we obtained the date of publication from PubMed® and attempted to obtain the dates of submission and acceptance by manuscript review; these dates were not always available. Due to the vast majority of studies originating from China and concerns regarding multiple publications on the same patient population, a closer examination of the origin of these studies was performed. We determined from which hospitals the patient population originated and reviewed the number of authors who contributed more than one manuscript. There were two studies that used the same database of 1590 individuals from China [14, 15]. Both studies were included in our analysis, but we included the number of patients in our calculations only one time. Each abstract was reviewed by one of the co-investigators, with review of the entire article as needed for the collection of data. Studies analyzing primary data on clinical subjects were reviewed by two faculty members. We used data from the Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University website [1] to calculate the number of affected individuals in affected regions by date.

Statistical analysis: Data was entered in Microsoft Excel, with subsequent analysis performed by SAS statistical software (Cary, NC), using standard analytic techniques for discrete and continuous variables.

Results

There were 3380 studies reviewed, of which 43 were excluded for insufficient data. There were 3,337 articles reviewed and published online from January 1, 2020 to April 10, 2020 for which there was adequate data available (including title, abstract (or link to text), and date of publication). There were 2563 (77%) articles that were classified as basic science articles, editorials, narratives, clinical recommendations, ethical reports, and other opinion pieces that were not included in further review. There were 144 (4%) epidemiologic articles, 16 meta-analyses (<1%) and 7 systematic reviews (<1%). Fig

118 1 shows the publication of articles over time. The publication of narratives, editorials, reviews, and
119 similar articles increased rapidly, while there has been only a slow increase in clinical articles.



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121 **Fig 1. Cumulative publication of articles by type and date. Non-clinical articles have increased much**
122 **more rapidly than clinical articles.**

123 There were 490 articles that analyzed primary patient data, accounting for only 15% of all
124 articles. Of the 490 clinical studies, there were 310 (63%) retrospective cohort studies, 136(28%) case
125 reports, 16 (3%) prospective cohort studies, 24 (5%) cross-sectional studies, and 4 prospective clinical
126 trials (1%). Of these 490 studies, 74% were from China, 15 (3%) from the US, and 111 (23%) from other
127 countries). Fig 1 shows the increase over time in the number of articles published and the publication
128 type. Fig 2 shows the increase over time of different clinical articles.

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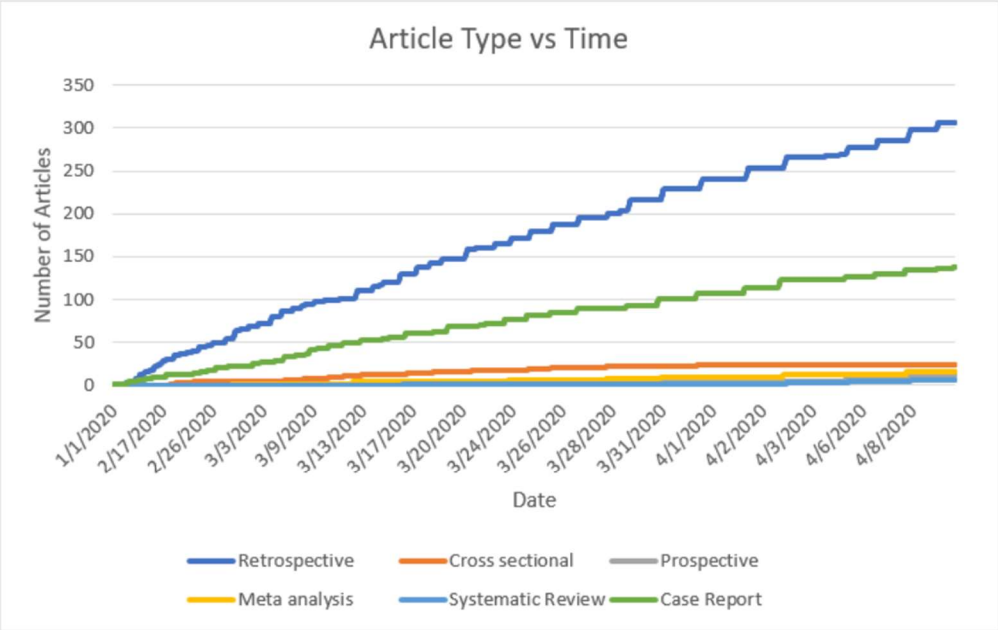

Fig 2. Cumulative publication of articles by type and date of clinical articles.

Study quality: The level of evidence of clinical studies is shown in Table 1. The majority of the studies provided a low level of evidence. There were four prospective clinical trials. One was a well-executed and designed trial of 199 patients that found lopinavir-ritonavir was not beneficial in severe COVID-19 [16]. Another study [17] from France was an open-label non-randomized clinical trial showing 20 patients treated with hydroxychloroquine and azithromycin had a significantly faster decrease in viral load. There was another study of chloroquine [18], in which 22 patients were randomized into two groups with 10 treated with chloroquine 500 mg orally twice per days for 10 days and 12 patients receiving lopinavir/ironavir. The percentage of patients whose COVID-19 viral load became negative in the chloroquine group was slightly higher at day 7, 10, and 14. There was also a prospective non-randomized trial of ACE2-mesenchymal stem cells in patients with COVID-19 pneumonia. (7 treated and 3 controls).

Table 1. Level of quality for clinical studies.

Type	Description	N (percent)	China (5)	US (%)	Other (%)
1	Properly powered randomized trial	1 (0%)	1(100%)		
	Systematic review	7(1%)	4(57%)		3(43%)
	Meta-analysis	16(3%)	14(88%)	1(6%)	1(6%)
2	Prospective cohort study	16 (3%)	12(75%)		4(25%)
	Prospective nonrandomized trials	3(0%)	2(67%)		1(33%)
3	Retrospective cohort studies	310 (60%)	263(85%)	5(2%)	42(13%)
4	Cross-sectional studies	24 (5%)	19(79%)		5(21%)
5	Case Reports	136 (27%)	67(49%)	10(7%)	59(44%)

Table 2 shows the number of patients included in clinical studies. There were only 13 studies that included more than 500 patients, and 10/13 (77%) were from China. Twenty-nine percent of studies were case reports and 72% included less than 50 individuals. The total number of patients included in studies from China were 31,050, in the US 3,696, and from other countries 4,731. There was one US study that was a letter to the editor[19] that included 3,615 patients and looked at weight and age associated with hospital admission and ICU admission only. Excluding this study, there were only 81 patients in the US studies, a time when nearly 500,000 individuals were affected with COVID-19. There were 454 clinical studies from which the number of centers could be determined (see table 2). Eighty-three percent of Chinese, 100% of US, and 94% of studies from other countries were single center studies. China had 17 studies including more than 5 centers.

Table 2. Number of patients in Clinical studies

Class	Number	China	US	Other
Case reports	138	69(50%)	10(7%)	59(43%)
2 to <50	207	165(78%)	4(2%)	38(18%)
2 to <100	62	58(94%)	0	4(6%)
100 to <500	62	56(90%)	0	6(10%)
500 to <1,000	5	4(80%)	0	1(25%)
>= 1,000	8	6(75%)	1(13%)	1(13%)

The time from submission to study acceptance was very short in most cases. From 227 publications with data available, 31 (14%) were accepted on the day of submission and 80 (35%) were accepted within three days of submission. Statistical analysis was cursory in most instances with only 36% of studies with > 100 patients having multivariate analysis. 11% of studies were pediatric, 19% radiologic, and 5% obstetric. 75% of studies included information about diagnosis and 49% about prognosis.

Of the 490 studies, 364 (74%) were from China (see Table 3). Chinese patients accounted for 80% of the patients who were studied, though this analysis was limited by the possibility of Chinese patients being included in multiple reports and possible inaccurate reporting of the number of affected individuals in China [20]. As of April 10, 2020, there were 82,900 reported affected individuals in China, suggesting inclusion of a significant number of patients in these observational studies. As of April 10, 2020, there were 496,500 patients infected in the US, with only 84 individuals reported in full articles. As of April 10, 2020, with Italy having 147,600 patients, there were 22 studies including 2,024 patients, including one study with 1,591 patients [21]. Fig 3 shows the rate of publication of clinical studies for the US, Italy, and China, together with the number of reported cases from each country. Chinese studies were published earlier and included more centers and individuals. As of April 10, 2020, Italy had reached 500 cases of COVID-19 43 days ago. At this time point, China had 112 publications with 7,542 patients vs. 22 publications and 2,024 patients from Italy. As of April 10,202, the US had reached 500 patients 32 days previously and had 14 full publications of 81 patients vs. 50 publications with 1,610 patients from China at a similar time point.

Table 3. Number of centers in clinical studies.

Number of centers	Number	China	US	Other
1	392	283(72%)	13(3%)	96(25%)
2	23	21(91%)	0	2(9%)
3	14	13(93%)	0	1(7%)
4	6	5(83%)	0	1(17%)
5 or greater	19	17(89%)	0	2(2%)

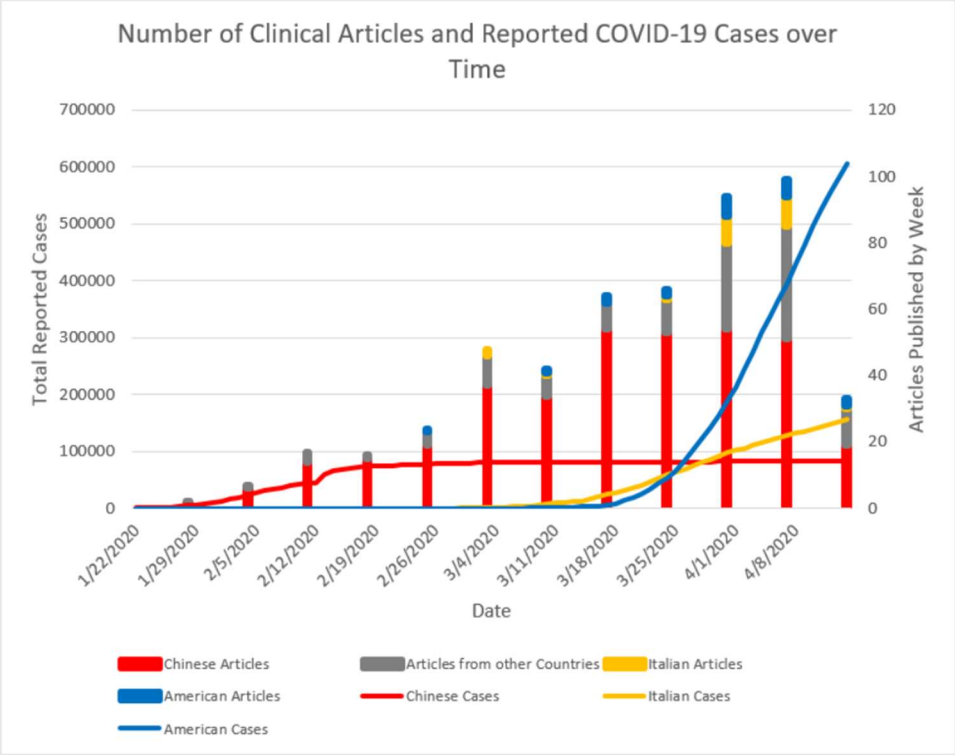

Fig 3. Number of reported COVID-19 affected individuals by country (China, US, and Italy) and number of articles published by country.

We then specifically examined the clinical studies from China that collected and analyzed primary data. Of 357 with clinical data available, 171 (48%) were from Wuhan province and included 20,208 patients. There were 186 studies from other provinces and included 10,581 individuals. The three most common centers from which patients were studied included Tongji Hospital of Tongji Medical College, (46 (9%)), Union Hospital of Tongji Medical College (29 (6%)) and Wuhan Children's hospital (13 (3%)). In general, studies appeared to come from many different authors, multiple medical centers, and many different geographic areas of China.

Studies of clinical relevance:

There were several larger studies that identified the relative importance of risk factors associated with increased severity of COVID-19 infection. Liu et al [22] studied 78 individuals admitted to three regional hospitals and identified factors associated with progression to severe disease. Multivariate logistic analysis indicated that age (odds ratio [OR], 8.54; 95% confidence interval [CI]: 1.63-44.86; P = 0.011), history of smoking (OR, 14.3; 95% CI: 1.58-25.0; P = 0.018), maximum body temperature at admission (OR, 9.0; 95% CI: 1.04-78.147, P = 0.046), respiratory failure (OR, 8.7, 95% CI:

1.9-40; P = 0.016), serum albumin (OR, 7.35, 95% CI: 1.1-50; P = 0.003), and serum C-reactive protein (OR, 10.5; 95% CI: 1.2-34.7, P = 0.028) as risk factors for disease progression. In a large study, Guan et al [15] studied 1590 patients with COVID-19 and evaluated the risk of severe adverse outcomes, with a composite endpoint of admission to intensive care unit, invasive ventilation, or death, which occurred in 131 patients (8.3%). After adjusting for age and smoking status, the following risk factors were of highest significance in a multivariate model: COPD (hazards ratio (HR) 2.7, 95% confidence interval (95%CI) 1.4-5.0], diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64). The HR was 1.79 (95%CI 1.16-2.77) among patients with at least one comorbidity and 2.59 (95%CI 1.61-4.17) among patients with two or more comorbidities. Grasselli et al. [21] reported on 1,591 patients admitted to intensive care units in Italy. These authors found that the majority of patients admitted to the intensive care unit were older men, and a large proportion required mechanical ventilation with positive end-expiratory pressure, with an ICU mortality of 26%. This study did not develop a risk score and was descriptive in nature. In a letter to the editor [19], a US study of 3,615 reported that patients with a body mass index between 30 and 34 were 2.0 times (95%CI 1.6-2.6, P<0.001) more likely to be admitted and 1.8 (1.2-2.7, P=0.006) times more likely to be admitted to acute and critical care units. The authors did not control for diabetes, hypertension, or other comorbidities.

There had been a number of editorials regarding the potential effects of angiotensin converting enzyme inhibitors or angiotensin receptor blockers [9, 23-32], but little data had been obtained in this regard. In a study by Peng et al. [33] of 112 patients admitted to Union Hospital, with a group of 16 critical patients, the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers was not associated with an increased incidence of poor outcomes. Meng et al.[34] studied 417 patients with COVID-19 admitted to the hospital, including 17 patients treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and 25 who did not receive these medications. During hospitalization 12 (48%) of the patients not receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers developed severe disease vs. 4 patients (24%) in the patients receiving these medications.

Similarly, there had been numerous editorials [10, 17, 18, 35-40] regarding the benefits and risks of hydroxychloroquine, but there have only been two very small studies (see above).

Discussion

This investigation summarizes the state of medical knowledge regarding COVID-19 as of April 10, 2020. At this time point, there were 496,500 cases in the US, with 34 days since 500 cases reported (3/7/2020). Clinical knowledge from the US was based on 15 US manuscripts describing 3,696 patients. Excluding a letter to the editor [19] regarding 3,615 patients, clinical judgement was based on 14 articles describing 81 of the 496,500 individuals affected with COVID-19. As of April 10, 2020, there were 147,600 cases in Italy, with 43 days since 500 cases reported. There were 22 studies of 2,024 patients at this time. The majority of clinical information regarding COVID-19 stemmed from China, where 89,200 patients were reported with COVID-19 and 80 days had elapsed since 500 cases were reported

(1/21/2020). Chinese publications accounted for 74% of the publications, with 80% of the patients studied. While the duration of the COVID-19 pandemic was significantly longer than in other countries, publications lagged at similar time points for the US and Italy compared to China.

Chinese investigators, primarily from Wuhan province and Tongji Medical College, published a large number of manuscripts, which provided the basis for clinical understanding of the COVID-19 pandemic. A number of the studies from China were multi-center, and authorship did not appear to be concentrated at one hospital. There was a focus on radiologic studies, accounting for 21% of clinical studies. Studies were published quickly, with many studies accepted within several days of submission. However, study quality appeared to have been limited by the haste of editors to publish. The lack of more advanced statistical analysis (such as multivariate regression) was a hindrance to our understanding of risks associated with COVID-19 infection.

Data to answer critical questions remained unavailable (see Table 4). Given the large number of affected patients, a multivariate risk score to predict patients at increased risk of admission and death could have been developed but was not. Such risk scores would have been useful in the admissions process, in determining which healthcare personnel should not interact with patients, and in assisting in determining individuals who were at very low risk and might be able to return to work. A single-center study in the US [19] identified a body mass index greater than 30 as a significant risk factor for severity of disease. A study from China [15] with multivariate regression identified smoking status, age, COPD, diabetes, hypertension, and malignancy as important risk factors, as well as an increased number of comorbidities. Validation of these results, together with inclusion of race as a covariate, is critical to our understanding of individuals at risk from COVID-19.

Table 4. Critical unanswered questions regarding coronavirus as of April 10, 2020:

1) Is there a risk score that would help identify individuals at increased risk of hospitalization for COVID-19 infection?
2) Is there a risk score that would help identify individuals at increased risk of death from COVID-19 infection?
3) Is hypertension an independent risk factor for death?
4) Is African American race an independent risk factor for death?
5) Are gender and obesity independent risk factors for death?
6) Is the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers beneficial or disadvantageous to survival after COVID-19 infection.?
7) Is consumption of commonly used medications such as non-steroidal anti-inflammatory agents a risk factor for death?
8) Does administration of hydroxychlorquine and azithromycin improve outcomes?
9) Why is mortality so high in Italy?
10) Are healthcare workers at increased risk of death from coronavirus?
11) Is there a clinical score that could predict futility of outcome?
12) Is influenza vaccination beneficial to survival?

Early studies of hydroxychloroquine that included less than 50 patients were used to guide treatment for over 500,000 patients. Retrospective case control studies of the more than 100,000 individuals who have received this medication would have been helpful to detect adverse effects and identify potential benefit. An observational study of 1,446 patients from a single medical center was published on May 7, 2020 [41], showing no association of hydroxychloroquine use with intubation or death (hazard ratio 1.04, 95% confidence interval 0.82-1.32). This analysis was published after there were already 1.25 million patients diagnosed with COVID-19, many of whom had received hydroxychloroquine as a therapy. Similarly, the identification of hypertension as a risk factor needed further explanation. The binding of COVID-19 to ACE2 receptors in the lungs pointed to possible effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on patient survival. Similarly, case control studies could have been performed to resolve this issue.

While there were a large number of editorials and reviews reflecting interest in COVID-19 in the US and other countries, primary data analysis was limited. Whereas, historically, early epidemiologic studies focused on infectious diseases, more recently, epidemiologic studies have focused on large aggregations of data and chronic diseases. Such data collection is not time-sensitive, and protection of individual privacy, especially with genetic information, has been a priority. This environment has fostered the slow, methodical collection of data that has multiple safeguards for participants, academic centers, and countries involved in research. Patients are protected by institutional review board approval at each site, and the Health Insurance Portability and Accountability Act (HIPAA) further complicates data sharing. Academic centers are protected by data sharing agreements between sites, and countries are protected by a variety of laws overseeing research. Unfortunately, this structure is likely providing critical obstacles in the study of a rapidly emerging epidemic. The very limited number of multicenter studies pointed to an environment that did not foster rapid collaboration. In addition, the ability to obtain funding quickly to perform these studies is extremely limited.

Living in an environment which allows the rapid movement of individuals worldwide results in the possibility of rapid spread of new viruses. To counter these pandemics, real-time epidemiology is required, with the development and utilization of tools that are similar to those used in industry to obtain real-time collection of data and data analysis. The tools for such data collection are available, but administrative obstacles must be overcome for their use.

Real-time collection of basic data including demographics, comorbid conditions, medications, and outcomes should be performed at individual centers. This real-time collection of data at individual centers will help each center in their response to viral outbreaks and collectively could provide answers to critical questions in a rapid manner. However, even the real-time collection of data is not as important as well performed clinical trials, which require time to design and execute.

A primary weakness of this article was the lack of inclusion of more databases. We chose PubMed® because it is the most common database used by academic clinicians and includes publications from all major clinical journals. Other weaknesses include the possible inaccurate reporting of the number of cases in China, which would make their publication record appear more favorable. We could not ascertain how many patients were included in more than one study from China, though

we showed that there was data available from many academic centers. We also included only articles in PubMed® and did not explore other methods of publication. In addition, the rapid publication of articles may result in changes in trends of publication and analysis.

While we have looked at general trends in COVID-19 publication, it is important to also point out the importance of primarily literature from China in providing us information about subsets of our patient population. For example, studies in children [42], pregnant women [43], hemodialysis patients [44], and cancer patients [45] provide important guidance even though they are descriptive and have small patient numbers.

In summary, clinically reported data on COVID-19 as of April 10, 2020 were limited and primarily from China. While articles were accepted quickly, data analysis was poor, and the vast majority of publications did not address the critical issues facing patients, clinicians, and public health officials at this time. Clinical researchers and leaders of medical centers and governments must identify obstacles to collection and dissemination of data and overcome them quickly. We must overcome administrative obstacles and develop a real-time approach to the collection of data and its analysis to help prevent morbidity and mortality during pandemics.

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