Background
COVID-19 is now well-established as a global pandemic, contributing to thousands of deaths while SARS-CoV2 has infected millions of people across the globe.1 As the disease evolves, it is important to explore the underlying determinants and the epidemiologic pattern of COVID-19. There has been an explosion of COVID-19-related publications, both as preprints and in peer-reviewed journals.2 Therefore, it is important that evidence is synthesized on specific aspects of the epidemiology of COVID-19 for informing existing targeted public health strategies, which may have been impacted by the current pandemic. One such determinant is smoking, which is associated with a higher smoking prevalence and an increased risk of smoking history on both SARS-CoV2 infection and on COVID-19 severity.3 Therefore, any potential association between smoking and COVID-19 would be a public health opportunity for tackling both the current pandemic and the tobacco epidemic toward population health and well-being.

Evidence to date on the potential association between smoking and COVID-19 is patchy and mixed.4,5 In the early days of the pandemic, the evidence available to the global audience was mostly from China. The first systematic review on smoking and COVID-19 was published in March 2020 which included studies from China but were mostly preprints.5,6 A rapid “living” systematic review is also available – initially as a pre-print.8 The Lancet has acknowledged the importance of preprints but reiterated quality.9 A recent review of systematic reviews on smoking and COVID-19 has highlighted several methodological limitations of the systematic reviews published to date, such as small sample size, selection bias, and the lack of generalisability.10 Therefore, we set out to address few of these potential gaps through a comprehensive literature review of smoking and COVID-19 including only cohort studies from settings outside of China which are peer-reviewed journal publications in English.

The overarching research question was “Are individuals with a smoking history at an increased risk of developing SARS-CoV2 infection, COVID-19 disease severity or mortality compared to those without a smoking history?”

Methods
Search strategy and selection criteria
A search was conducted in the PubMed database for studies published between January 1, 2020, to August 30, 2020. The Zotero 5.0.85 software was used to manage the selected studies. A comprehensive search was designed for the purpose of this study (Appendix 1). Only full-text studies were included in
The evidence synthesis. The studies identified by this search were further analyzed for their eligibility. Study characteristics of the selected studies (n = 8) are shown in Table 1. The PRISMA flowchart is available as Figure 1.

**Narrative synthesis of evidence**

The final number of cohort studies (both prospective and retrospective) included for narrative synthesis were 7 (all outside of China). Depending on the outcome of each study, the data presented in Table 2 reflects the heterogeneity of each study. The 3 outcomes presented for the exposure of interest (a smoking history – either a former smoker or a current smoker, as defined in each study) were: (1) smoking prevalence by subgroups; (2) severity of SARS-CoV2 infection (as demonstrated in each study of being hospitalized); (3) mortality (COVID-19-related deaths). If information on gender is available in any of the studies related to the above 3 outcomes, Table 2 also captures this. No quality appraisal was undertaken because of the nature of this literature review.

**Results**

A comprehensive search of PubMed between January 1, 2020 and August 30, 2020 yielded 40 peer-reviewed publications in non-Chinese population settings in alignment with our eligibility criteria of including only cohort studies. Of these 40 eligible, only 7 were finally included following full-text reviewing by 2 independent reviewers (AF & MN), and any conflicts were resolved by a third reviewer (ZK).

Two of these 7 studies were from the United States,\(^1\)\(^{15}\) \(^1\) from Turkey\(^1\)\(^4\) and the remaining 4 were from the United Kingdom.\(^1\)\(^2\)-\(^1\)\(^6\)-\(^1\)\(^7\) The sample populations in all these 7 studies were individuals who tested positive for COVID-19 from a target population. The population sample ranged from 200 (Bronx, US) to 502,640 (UK) patients. All the studies included were cohort studies (Table 2).
Table 2. Study characteristics.

| Title | Setting | Population | Study-Design and Time-Horizon | Outcomes | Smoking Rates by Outcome |
|-------|---------|------------|--------------------------------|----------|-------------------------|
| Jehi et al10 | Development and validation of a model for individualized prediction of hospitalization risk in 4536 patients with COVID-19 | >220 outpatient locations and 18 hospitals in Ohio and Florida | Retrospective cohort study of patients with COVID-19 applying a least absolute shrinkage and selection operator (LASSO) logistic regression algorithm. Between March 8, 2020 and June 5, 2020. | Disease severity: Development Cohort-Non-hospitalized = 2270 Hospitalized = 582 Validation Cohort-Non-hospitalized = 1308 Hospitalized = 376 | Smoking history for hospitalized patients [n (%): Current smoker = 37 (21.4), Former smoker = 221 (25.6)] P-value of association between smoking history and hospitalization = 0.001 |
| Lassale et al11 | Ethnic disparities in hospitalization for COVID-19 in England: The role of socioeconomic factors, mental health, and inflammatory and proinflammatory factors in a community-based cohort study | England | Prospective cohort study, From 16th March to 26th April 2020 | Disease vulnerability: Participants who tested positive for COVID-19 were older and more likely to be male, and current/former smokers, compared to those who did not have a positive COVID-19 test | Smoking history for patients testing positive for COVID-19: Non-smokers: 49% (n = 642) tested positive/Current/previous smoker: 51% (n = 669) tested positive. |
| McQueenie et al12 | Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort | England, Scotland and Wales | A longitudinal population-based cohort study from 2006 to 2010 | Disease severity: Non-hospitalized = 427,594 Hospitalized = 900 | Smoking history for hospitalized patients [%]: Current smokers = 11.4, Past smokers = 41.9 P-value of association between smoking history and hospitalization = 0.001 |
| Senkal et al13 | A association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19 | Istanbul | A retrospective cohort study carried out between March 9th and May 11th, 2020 | Disease severity: Non-Hospitalized: N = 165 (27%). Hospitalized: N = 446 (73%) | Smoking history in non-severe patients: 11% (n = 48), Smoking history in severe patients: 13% (n = 21). Smoking being a predictor of severe disease had an odds ratio higher than 1. |
| Palaiodimos et al14 | Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York | The Bronx, New York | A retrospective cohort study of the first 200 patients who presented to the emergency room (ER) and were admitted to the inpatient medicine service or the intensive care unit (ICU) with laboratory-confirmed COVID-19. | The in-hospital mortality was 24% with severe obesity (BMI⩾35 kg/m²), increasing age, and male sex linked to more severe outcomes. | Smoking was found to be a significant predictor of increasing oxygen requirements during hospitalization. |
| Raisi-Estabragh et al,15 Renin-Angiotensin-Aldosterone System Blockers Are Not Associated With Coronavirus Disease 2019 (COVID-19) Hospitalization: Study of 1439 UK Biobank Cases | England | 7099 participants from the UK Biobank who had been tested for COVID-19 in hospital. 1439 tested positive and 5660 tested negative. | Prospective cohort study, From 16th March to 14th of June, 2020 | Smoking association to a positive COVID19 test: Non-smoker: Of 5660 non-smokers, 51.8% (n = 2931) tested positive for COVID19. Current/former smoker: Of 1439 smokers, 50.9% (n = 1439) tested positive. The odds ratio by predictor found smoking to have a statistical significance when testing positive for COVID19. | Smoking association to a positive COVID-19 test: Non-smoker: Of 5660 non-smokers, 51.8% (n = 2931) tested positive for COVID19. Current/former smoker: Of 1439 smokers, 50.9% (n = 1439) tested positive. The odds ratio by predictor found smoking to have a statistical significance when testing positive for COVID19. |
| Woolford et al17 | COVID-19 and associations with frailty and multimorbidity: a prospective analysis of UK Biobank participants | England, Scotland and Wales | A prospective community-based cohort analysis from 16th March 2020 to 1st June, 2020 | no differences for frailty status or number of morbidities when comparing those who tested positive for COVID-19 and those who tested negative. Suggesting associations compared to background population influence disease progression for admission to hospital rather than COVID19 | Association between smoking and COVID-19: Non-smokers: 49% (643) of non-smokers were positive for COVID19 with 48.3% (n = 1526) of non-smokers testing negative. Current/former smokers: 50.52% tested positive with 51.35% testing negative. |
The findings of this review are summarized below. We also report adjusted odds ratios where available.

Jehi et al\(^\text{11}\) in the US of 4536 patients reported significant higher smoking rates (\(P < .001\)) among those hospitalized (\(n = 958\)) across 2 cohorts (development and validation) – 8.6\% were current smokers and 36.4\% were former smokers compared to 6.9\% and 26.3\%, respectively, among those who were not hospitalized.

Lassele et al\(^\text{12}\) in England studying 428,494 individuals using the UK Biobank study reported a similar trend as Jehi et al study: significantly higher smoking rates among those hospitalized (\(n = 900\)) compared to those not hospitalized (\(n = 427,594\)), 41.9\% former smokers and 11.4\% current smokers as against 34.6\% former and 10\% current smokers, respectively. The same study reported significantly higher odds of hospitalizations among former and current smokers compared to non-smokers (1.30; 95\% CI:1.10-1.55 and 1.25; 95\% CI: 0.96-1.62), respectively, following multivariable regression.

Another UK Biobank Study (McQueenie et al\(^\text{13}\)) reported smoking prevalence among those who tested COVID-19 positive (\(n = 1324\)) and those who tested negative or were not tested (\(n = 426,875\)), 51\% were ever smokers (current and former combined) as against 44.6\% among those who were negative, respectively. The same study also reported that ever-smokers had an increased risk of testing COVID-19 positive in individuals with no multimorbidity (1.26; 95\% CI: 1.02-1.57) in the multivariable analysis.

A retrospective cohort study in Istanbul,\(^\text{14}\) Turkey of 611 in-patients (Şenkal et al) reported a higher smoking rate (13\%) among those defined as "non-severe" (11\%), and this was not significant (\(P = 0.56\)).

The smallest study (Palaiodimos et al\(^\text{15}\)) in this review (\(n = 200\)) of all COVID-19 in-patients from Bronx, New York reported an ever-smoking rate of 32.5\%, which is certainly higher than the smoking rate in general population of New York City. The same study reported in the univariate analyses that ever-smokers had higher odds of in-patient mortality (1.19; 95\% CI: 0.60-2.36) but in multivariable analyses ever-smoking was found to be protective of inpatient mortality (0.83; 95\% CI: 0.37-1.87) albeit not a significant association. However, this study showed that COVID-19 in-patients who were ever-smoking had an increased odds of oxygen requirements in a multivariable analysis (2.10; 95\% CI:1.07-4.10).

Another UK Biobank study\(^\text{16}\) of 7099 participants (Raisi-Estabhagh et al) reported that 1439 tested COVID-19 positive. Of these, 50.9\% were ever-smokers compared to 51.8\% ever-smokers among those who tested negative. The same study reported a higher odds (1.26; 95\% CI: 1.13, 1.40) of testing COVID-19 positive among ever-smokers when compared to those who were COVID-19 test negative and were not tested (\(n = 494,838\)) in the multivariable analyses, but did not reach statistical significance when the untested populations were excluded from the model (1.02; 95\% CI: 0.90, 1.15).

The largest study\(^\text{17}\) in this review included 502,640 participants from the UK Biobank (Woolford et al.). 4510 of the participants were tested for COVID-19 and 1326 tested positive. 40\% of those who tested positive were former smokers as opposed to 37.8\% among those who tested negative. However, 11\% were currently smoking among those who tested positive as against 14\% among those who tested negative. All these findings were significant when compared with the background population (\(P < .001\)).

In summary, all the 7 studies included show an apparent higher risk of COVID-19 among the ever-smoking population, and more pronounced among former smokers.

**Discussion**

This review of cohort studies outside of China examining the relationship of smoking and COVID-19 is an explorative narrative synthesis following a systematic approach, with predefined eligibility criteria and search strategy. The conclusion across all these 7 studies are broadly in the same direction, pointing toward a potential harmful effect of smoking on COVID-19 severity and being more susceptible to contracting SARS-CoV-2 infection. However, the observation of an increased risk of COVID-19 among former smokers is intriguing. This observation is consistent across several studies both included in this review and few of those which did not qualify for this review.\(^{18,19}\) This observation needs careful attention and deeper exploration, especially related to timing of quitting smoking, because it is probable that those smokers with morbidity conditions could have quit smoking once they were diagnosed with COVID-19.

Some of the strengths of this review include the robustness of eligibility criteria of not including pre-prints and to include only cohort studies. Pre-defined eligibility criteria and a comprehensive search strategy also lends support to the rigor of this review. A systematic approach to include studies outside of Chinese population settings may add to the strength of this review for several reasons. First, a systematic review of initial 5 Chinese studies have already been published in March 2020.\(^7\) Second, several systematic reviews post this first systematic review have also been published, majority of these reviews did include studies from China and were preprints.\(^{5,6}\) Third, the evolution and the epidemiology of COVID-19 adds to the complexity of reproducibility – and this was evident from the studies published in the initial stage of the pandemic which were mainly from Chinese hospitals and had small population sample.\(^7\) Therefore, these initial studies from China and elsewhere were either cross-sectional or hospital-based and were methodologically weak: selection bias, the lack of generalizability, confounding, and relatively of small sample size. We aimed to address these limitations in our current review by including only cohort studies.
Our review has some methodological limitations. We did not undertake a systematic review or a meta-analysis because of the heterogeneity of the papers. Our limit to only published peer-reviewed literature instead of including gray literature may have influenced our search strategy. We searched only 1 database, the PubMed, which is otherwise considered one of the most comprehensive peer-reviewed medical literature databases to date. Finally, not all studies included in this review had all the parameters that we were interested in examining. Examples include, self-reported smoking history (some had no specific distinction between current and former smokers), the lack of adjusted estimates for the specific outcomes of interest, no gender breakdowns, no unified operational definition of “severity” of COVID-19 across the studies reviewed, and the inability to capture “infectiousness” of SARS-CoV2 owing to the nature of the currently COVID-19 diagnostic tests widely employed across these countries. All these methodologically inherent limitations need to be addressed in future research to infer a more concrete conclusion on smoking and COVID-19 progression.

Furthermore, the epidemiology and the natural history of this pandemic is evolving. Therefore, it would be premature to speculate on the probable causal mechanism of this observation between a smoking history and SARS-CoV2 infection and its sequelae. Several potential mechanisms have been postulated, especially in relation to upregulation of ACE2 receptors and smoking, and also the role of nicotine on anti-cholinergic path-way.20,21 However, the totality of evidence in terms of the global tobacco epidemic remains unaltered, smoking kills 8 million individuals every year globally, and any additional attribution of smoking to SARS-CoV2 infection quite naturally will increase the burden on the current pandemic. Therefore, smoking cessation and avoidance of secondhand smoke exposure must remain the cornerstone of population health and well-being, despite the lingering uncertainty.

Ethical Considerations
No personal data were used, therefore no ethical approval was sought.

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Appendix 1. The PICO.

| POPULATION | ALL COVID-19 CASES |
|------------|-------------------|
| Intervention/Exposures | Smoking history (current/former smokers) |
| Comparison | Non-smokers |
| Outcomes | Smoking prevalence; SARS-CoV2 infection; Severity & mortality of COVID-19 (hospitalizations/deaths) |
## Appendix 2: Detailed search strategy in PubMed using Boolean operators.

| SEARCH NUMBER | QUERY | SEARCH DETAILS | RESULTS |
|---------------|-------|----------------|---------|
| 3             | (((smoking) AND (Covid-19)) AND (severity)) AND (sex) | ((((((("smoke"[MeSH Terms] OR "smoke"[All Fields]) OR "smoke s"[All Fields]) OR "smoked"[All Fields]) OR "smokes"[All Fields]) OR "smoking"[MeSH Terms]) OR "smoking"[All Fields]) OR "smokings"[All Fields]) OR "smoking s"[All Fields]) AND ((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields] OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR ("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) AND (((((("sever"[All Fields] OR "severe"[All Fields]) OR "severed"[All Fields]) OR "severely"[All Fields]) OR "severer"[All Fields]) OR "severes"[All Fields]) OR "severing"[All Fields]) OR "severities"[All Fields]) OR "severity"[All Fields]) OR "severs"[All Fields]) AND ("sex"[MeSH Terms] OR "sex"[All Fields]) | 40 |
| 2             | (ismoking) AND (Covid-19) AND (severity) | ((((((("smoke"[MeSH Terms] OR "smoke"[All Fields]) OR "smoke s"[All Fields]) OR "smoked"[All Fields]) OR "smokes"[All Fields]) OR "smoking"[MeSH Terms]) OR "smoking"[All Fields]) OR "smokings"[All Fields]) OR "smoking s"[All Fields]) AND ((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields] OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR ("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) AND (((((("sever"[All Fields] OR "severe"[All Fields]) OR "severed"[All Fields]) OR "severely"[All Fields]) OR "severer"[All Fields]) OR "severes"[All Fields]) OR "severing"[All Fields]) OR "severities"[All Fields]) OR "severity"[All Fields]) OR "severs"[All Fields]) | 214 |
| 1             | (smoking) AND (Covid-19) | ((((((("smoke"[MeSH Terms] OR "smoke"[All Fields]) OR "smoke s"[All Fields]) OR "smoked"[All Fields]) OR "smokes"[All Fields]) OR "smoking"[MeSH Terms]) OR "smoking"[All Fields]) OR "smokings"[All Fields]) OR "smoking s"[All Fields]) AND ((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields] OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR ("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))) | 327 |