Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Combined and interactive effects of alcohol drinking and cigarette smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19: a multicentre retrospective cohort study

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ABSTRACT

Objectives: Cigarette smoking is an established risk factor for illness severity and adverse outcomes in patients with COVID-19. Alcohol drinking may also be a potential risk factor for disease severity. However, the combined and interactive effects of drinking and smoking on COVID-19 have not yet been reported. This study aimed to examine the combined and interactive effects of alcohol drinking and cigarette smoking on the risk of severe illness and poor outcomes in patients with COVID-19.
Study design: This was a multicentre retrospective cohort study.
Methods: This study retrospectively reviewed the data of 1399 consecutive hospitalised COVID-19 patients from 43 designated hospitals. Patients were grouped according to different combinations of drinking and smoking status. Multivariate mixed-effects logistic regression models were used to estimate the combined and interactive effects of drinking and smoking on the risk of severe COVID-19 and poor clinical outcomes.
Results: In the study population, 7.3% were drinkers/smokers, 4.3% were drinkers/non-smokers and 4.9% were non-drinkers/smokers. After controlling for potential confounders, smokers or drinkers alone did not show a significant increase in the risk of severe COVID-19 or poor clinical outcomes compared with non-drinkers/non-smokers. Moreover, this study did not observe any interactive effects of drinking and smoking on COVID-19. Drinkers/smokers had a 62% increased risk (odds ratio = 1.62, 95% confidence interval: 1.01-2.60) of severe COVID-19 but did not have a significant increase in the risk for poor clinical outcomes compared with non-drinkers/non-smokers.
Conclusions: Combined exposure to drinking and smoking increases the risk of severe COVID-19, but no direct effects of drinking or smoking, or interaction effects of drinking and smoking, were detected.

Introduction

The COVID-19 pandemic is rapidly evolving worldwide.[1,2] The clinical spectrum of COVID-19 appears to be wide, ranging from mild, moderate and severe to critical illnesses.[3] Severe and critical cases are more likely to present with multiple organ dysfunction syndrome, acute respiratory distress syndrome (ARDS) and shock, thus contributing to intensive care unit (ICU) admission, mechanical ventilation (MV) and even death, and posing a serious threat to public health.[4,5] Therefore, the risk factors for severe COVID-19 and

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poor outcomes should be identified to improve the management of COVID-19 in clinical practice.

Several studies have investigated factors related to the severity of COVID-19 and its adverse outcomes. Smoking has received special attention as this is a well-established modifiable risk factor for many diseases.[6] In relation to COVID-19, although the results are contradictory,[7,8] smoking seems more likely to be associated with disease severity, negative progression and adverse outcomes of COVID-19.[9–13] The results from a recent meta-analysis involving 22,939 COVID-19 patients reported that smoking is an independent risk factor for COVID-19 progression, including mortality.[13] Drinking alcohol, a factor closely related to cigarette smoking, has been reported to be associated with poor outcomes of pneumonia patients and critically ill patients.[14–16] However, little attention has been paid to the effects of drinking alcohol on the severity and clinical outcomes of COVID-19.

Alcohol drinking and smoking can cause damage to nearly all body organs and are globally the two most important preventable health risk factors, with an important impact on public health.[17] Based on the report of the Global Burden of Disease study, drinking accounted for nearly 10% of global deaths among populations aged 15–49 years, while smoking accounted for 11.5% of global deaths.[18,19] Furthermore, alcohol drinking and cigarette smoking, as two closely related factors, have various detrimental effects. Alcohol drinking and cigarette smoking have an interactive or combined effect on the treatment of pulmonary tuberculosis, the risk of lung cancer and many digestive malignancies and on all-cause and premature mortality.[17,20–22] However, the association between combined smoking and drinking and COVID-19 has not yet been reported. Therefore, this study aimed to evaluate the combined and interactive effects of alcohol drinking and smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19, thereby providing a better understanding of the effects of alcohol drinking and smoking exposure in COVID-19 patients.

Methods

Study design and participants

Data from patients with COVID-19 from Sichuan Province and Wuhan City, China, were used in this multicentre retrospective cohort study. All patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were admitted to one of 43 designated hospitals in Sichuan and Wuhan between 14 January and 22 March 2020 were enrolled in the study. All patients with COVID-19 enrolled in this study were diagnosed according to the World Health Organisation (WHO) interim guidelines.[23] SARS-CoV-2 infection was confirmed by laboratory tests using real-time reverse-transcription polymerase chain reaction or high-throughput sequencing. Confirmed cases referred to patients who had positive results on nasal and pharyngeal swab tests.[24]

Clinical data collection

All clinical data on demographic characteristics, underlying comorbidities, laboratory and radiological findings, and treatment and outcome information were retrospectively extracted from the medical records by members of the trained research team. A standardised form, a modified version of the International Severe Acute Respiratory and Emerging Infection Consortium forms, was used for data collection.[25] The confidentiality of the information was maintained by removing personal identifiable information. After careful review of medical records, detailed information on patients' demographic characteristics, pre-existing chronic comorbidities, computed tomographic (CT) images of the chest, laboratory indicators on admission, treatment and outcomes were collected. Data were abstracted and entered into a Microsoft Excel spreadsheet by trained researchers, and the results were then cross-checked by two researchers.

Exposure

Information on the smoking and alcohol drinking history of patients was collected from the electronic medical records. In terms of smoking status, patients were classified as smokers (including former smokers and current smokers) and non-smokers based on the self-reported information. Similarly, in terms of alcohol drinking status, patients were classified as drinkers (including current drinkers and former drinkers) and non-drinkers according to their self-reported information.

Patients were divided into four groups as follows: group one included drinkers/smokers; group two included drinkers/non-smokers; group three included non-drinkers/smokers; and group four included non-drinkers/non-smokers.

Outcomes

The primary outcomes included two important events, one of which was severe illness of COVID-19, and the other was a composite endpoint of all-cause death, ICU admission or invasive/non-invasive MV occurring during hospitalisation. These events were combined into a binary coded composite adverse outcome variable, indicating that at least one of the events occurred during the period of hospitalisation. This composite measure was adopted because all individual components were considered as serious outcomes in a previous study of COVID-19.[26] The disease severity of COVID-19 was evaluated based on the WHO living guidance for COVID-19 management.[27] The clinical classification was as follows:

Critical cases: Defined as patients with ARDS, sepsis, septic shock or other conditions requiring life-sustaining therapies, such as MV or vasopressor therapy.

Severe cases: Defined as patients who met any of the following criteria: (1) respiratory distress ($\geq$30 breaths/min) for adults; (2) oxygen saturation of $\leq$90% at room air; and (3) signs of severe respiratory distress.

Non-severe cases: Defined as patients who did not meet the criteria for diagnosing severe or critical cases.

In line with previous studies,[28] 'severe COVID-19' in our study was defined as patients with severe or critical COVID-19.

The secondary outcomes were defined as the individual events of the primary composite outcome: namely, death (all-cause death after COVID-19 diagnosis), ICU admission and invasive/non-invasive MV during the period of hospitalisation.

Statistical analyses

Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]), as appropriate. Categorical variables were expressed as counts and percentages. Continuous variables were compared using the one-way analysis of variance or Kruskal–Wallis test; categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Bonferroni's correction was used for multiple comparisons. Multivariate mixed-effects logistic regression models were used to explore the association of alcohol drinking and cigarette smoking with outcomes. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated. The details

regarding the statistical methods used are shown in the online Supplementary Material.

Results

Demographic and clinical characteristics

Patients aged <18 years, pregnant women, patients who died on admission to hospital and patients with missing information on smoking and alcohol status were excluded. In total, 1399 patients were included in the final analysis (Fig. 1). As shown in Table 1, the median age of the cohort was 55 years (IQR: 41, 66); 47.9% of patients were men, 60.9% patients were from Wuhan, 56.3% had at least one comorbidity, and the median duration from onset of illness to hospital admission was 10 days (IQR: 5, 16).

Drinkers/smokers, drinkers/non-smokers, non-drinkers/smokers and non-drinkers/non-smokers accounted for 7.3% (n = 103), 4.3% (n = 61), 4.9% (n = 69) and 82.7% (n = 1166) of the total study participants, respectively. Notably, compared with non-drinkers/non-smokers, drinkers/smokers were more likely to be men, younger, live in the epidemic centre region (Wuhan) and have a shorter time from illness onset to hospitalisation. In addition, drinkers/smokers were more likely to show lower CURB-65 (confusion, uraemia, respiratory rate, blood pressure, age ≥65 years) scores on admission, with a higher incidence of hepatic dysfunction complications. Drinkers/non-smokers were less likely to receive antibiotic treatment (39.3% vs. 59.8%; $P = 0.002$) than non-drinkers/non-smokers.

Laboratory and radiological findings

After Bonferroni's correction, the median eosinophil count ($P = 0.006$) and median platelet count ($P = 0.005$) were lower in the drinkers/non-smokers group than in the non-drinkers/non-smokers group. Compared with non-drinkers/non-smokers, the other three groups (drinkers/smokers, drinkers/non-smokers and non-drinkers/smokers) had higher levels of haemoglobin ($P < 0.001$, $P < 0.001$ and $P = 0.001$, respectively) and serum creatinine ($P < 0.001$, $P = 0.005$ and $P = 0.004$, respectively). Moreover, drinkers/smokers had higher levels of creatine kinase ($P < 0.001$) and albumin ($P < 0.001$) than patients in the non-drinkers/non-smokers group. With regard to markers of coagulation function, drinkers/smokers and drinkers/non-smokers showed a slightly longer activated partial thromboplastin time ($P < 0.001$ and $P < 0.001$, respectively) than non-drinkers/non-smokers. In addition, patients in the drinkers/smokers group were more likely to show abnormal findings on radiological CT images (Supplementary Table S1).

Severity and clinical outcomes

The incidence of severe COVID-19 was significantly higher in drinkers/smokers than in non-drinkers/non-smokers (40.8% vs. 29.4%; $P = 0.016$) after Bonferroni's correction. However, no significant difference was observed in the composite outcome (comprised of MV, ICU admission and in-hospital death) or in any of these three outcomes alone (Fig. 2).

Mixed-effects logistic regression analyses

Compared with non-smokers, current smokers and/or former smokers did not have significant associations with severe COVID-19 or composite outcomes. Moreover, current and/or past alcohol consumption were not significant predictors of severe COVID-19 or composite outcomes. By adding the interaction term to the regression models, no interaction effects were observed between smoking and alcohol consumption and severe COVID-19 and poor outcomes (*P*-values of the interaction term of drinking and smoking were 0.30 and 0.10, respectively). With regard to the different combinations of smoking and alcohol drinking status, the present study shows that smoking alone or drinking alone was not associated with severe COVID-19 and composite outcomes. Furthermore, the results show no significant association between drinkers/smokers and an increased risk of composite outcomes. In contrast, drinkers/smokers were more likely to have severe COVID-19 compared with non-drinkers/non-smokers (OR = 1.62; 95% CI: 1.01, 2.60), after adjusting for all potential confounders, including age, sex, Carlson Comorbidity Index, CURB-65 scores, time from illness onset to hospital admission, level of hospital and using centre as a random effect (Tables 2 and 3). However, no significant associations were found between smoking and drinking and any of the secondary outcomes (ICU admission, MV and in-hospital death; Supplementary Tables S2, S3 and S4).

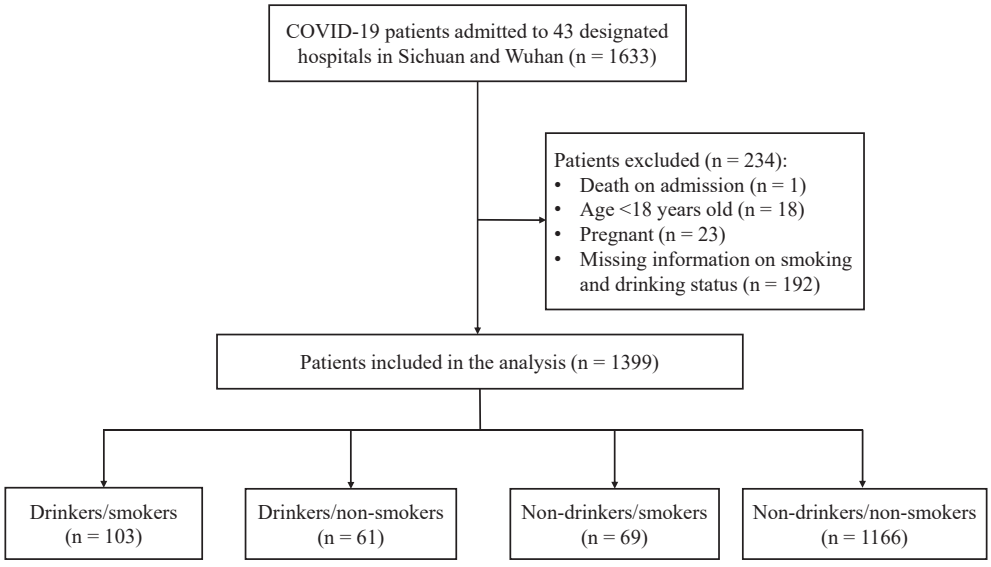

Fig. 1. Flowchart of participants with COVID-19 in this study. The study cohort was divided into four groups based on different combinations of alcohol drinking and smoking status.

Table 1
Demographics and clinical characteristics of COVID-19 patients.[a]

Variables	Drinkers/smokers	Drinkers/ non-smokers	Non-drinkers/ smokers	Non-drinkers/ non-smokers	Total	χ2/H	*P*-value[b]
Total	103 (7.3)	61 (4.3)	69 (4.9)	1166 (82.7)	1399		
Age (years)	48.00 (38.00, 62.00)[c]	48.00 (34.00, 61.00)[c]	56.00 (34.00, 63.50)	56.00 (42.00, 66.00)	55.00 (41.00, 66.00)	16.106	0.001
Male	77 (74.8%)[c]	48 (78.7%)[c]	58 (84.1%)[c]	487 (41.8%)	670 (47.9%)	106.666	<0.001
Region						39.388	<0.001
Sichuan	21 (20.4%)[c]	7 (11.5%)[c]	31 (44.9%))	488 (41.9%)	547 (39.1%)		
Wuhan	82 (79.6%)[c]	54 (88.5%)[c]	38 (55.1%)	678 (58.1%)	852 (60.9%)		
Allergic history	6 (5.8%)	3 (4.9%)	5 (7.2%)	94 (8.1%)	108 (7.7%)	1.404	0.705
CURB-65[d]	0.36 (0.73)[c]	0.43 (0.74)	0.48 (0.72)	0.52 (0.74)	0.50 (0.74)	8.626	0.035
Any comorbidity	53 (52.0%)	32 (52.5%)	36 (52.9%)	662 (57%)	783 (56.3%)	1.701	0.637
CCI[d]	1.37 (2.23)	1.05 (1.53)	1.90 (2.592)	1.51 (2.03)	1.50 (2.06)	4.052	0.256
Complications	62 (60.2%)	30 (49.2%)	39 (56.5%)	679 (58.2%)	810 (57.9%)	2.232	0.526
ARDS	5 (4.9%)	4 (6.6%)	3 (4.3%)	91/1166 (7.8%)	103 (7.4%)	2.261	0.520[e]
Pneumonia	59 (57.3%)	25 (41.0%)	33 (47.8%)	554 (47.5%)	671 (48.0%)	4.869	0.182
Hepatic dysfunction	23 (22.3%)[c]	11 (18.0%)	12 (17.4%)	129 (11.1%)	175 (12.5%)	14.507	0.002
Treatment							
Antiviral treatment	98 (95.1%)	57 (93.4%)	60 (87.0%)	1070 (91.8%)	1285 (91.9%)	3.920	0.270
Antibiotics	54 (52.4%)	24 (39.3%)[c]	39 (56.5%)	697 (59.8%)	814 (58.2%)	11.596	0.009
High-flow oxygen therapy	5 (4.9%)	4 (6.6%)	6 (8.7%)	85 (7.3%)	100 (7.1%)	1.074	0.787[e]
Corticosteroids	17 (16.5%)	11 (18.0%)	23 (33.3%)	307 (26.3%)	358 (25.6%)	8.802	0.032
Time from illness onset to ICU admission, days	14.00 (8.00, 16.00)	6.00 (5.00, 7.00)	23.00 (14.50, 24.00)	11.00 (7.50, 15.50)	11.00 (7.00, 16.00)	3.607	0.307
Time from illness onset to hospital admission, days	6.50 (3.00, 11.00)[c]	7.00 (3.00, 16.00)	9.00 (4.00, 14.00)	10.00 (5.75, 16.00)	10.00 (5.00, 16.00)	22.415	<0.001
Hospital length of stay, days	16.00 (9.25, 21.00)	16.00 (13.00, 23.50)	16.00 (10.00, 24.00)	18.00 (10.00, 27.00)	17.00 (10.00, 26.00)	5.048	0.168
Duration of viral shedding, days	15.00 (9.00, 23.75)	14.50 (11.75, 22.00)	15.00 (9.50, 26.50)	18.00 (12.00, 29.00)	17.00 (11.00, 28.00)	6.374	0.095
Duration of corticosteroids treatment, days	3.00 (1.75, 4.00)	3.00 (2.00, 11.50)	4.00 (1.50, 10.00)	5.00 (3.00, 8.00)	4.00 (3.00, 8.00)	3.403	0.334

CCI, Carlson Comorbidity Index; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years.
[a] Data are expressed as median (IQR) or n (%), n/N (%), where N is the total number of patients with available data.
[b] *P*-values comparing four groups are from χ^2, Fisher's exact test or Kruskal–Wallis test. There are post-hoc comparisons.
[c] Indicates $P < 0.017$. Bonferroni's correction was used for multiple comparison with the non-drinkers/non-smokers group.
[d] Shown as mean (standard deviation) because the median of CURB-65 and CCI was '0'.
[e] Fisher's exact test.

Discussion

Following a review of the medical literature, to the best of the authors' knowledge, this is the first multicentre, retrospective, cohort study to explore the combined and interactive effects of alcohol drinking and smoking on the risk of severe illness and poor clinical outcomes in patients with COVID-19. In this study, it was observed that patients who smoked and consumed alcohol were more likely to experience severe illness when diagnosed with COVID-19 compared with patients who did not smoke or drink alcohol. However, smoking alone or drinking alone, or the co-existence of both, was not associated with poor clinical outcomes. In addition, we did not observe any interactive effects of drinking and smoking on the severity and poor clinical outcomes of COVID-19.

Smoking is a well-established risk factor for many diseases and is the leading cause of death among middle-aged and older men.[19] However, the association between smoking and COVID-19 has never been clearly evaluated. The results from existing studies are inconsistent, with most studies reporting smoking as a risk factor for severe COVID-19.[11,29,30] A possible explanation for this phenomenon might be the different distribution of important social and clinically relevant variables between smokers and non-smokers. Hence, in this study, we used multivariable mixed-effects logistic regression models to minimise the potential bias. No significant association was found between smoking and severe COVID-19 and poor clinical outcomes. This result is consistent with Ho et al.,[31] who did not observe a significant association between smoking (current or former) and the risks of in-hospital mortality, ICU admission or invasive MV. Conversely, the results from Dai et al.[32] and Adrish et al.[33] show that smoking is associated with a higher risk for developing critical illness and death in hospitalised COVID-19 patients. It is worth emphasising that the results, so far, mainly come from cross-sectional studies or retrospective studies, with relatively small sample sizes. The non-significant correlations obtained might be associated with other uncontrolled factors. The inconsistent results of existing studies may be due, at least partially, to differences in the study participants, study design, follow-up duration and data analysis, in addition to other unknown reasons. However, the exact duration and number of cigarettes smoked per day have not been reported in most studies. The inconsistent results are partially attributed to the difference in exposure dose and duration. To explain the association between smoking and COVID-19, further well-designed and population-based prospective studies are necessary. In addition, the hypothesis that nicotine may be protective against severe COVID-19 makes the association between smoking and COVID-19 more complex.[34] To better understand the relationship between smoking and COVID-19, clinical trials on nicotine are warranted.

In terms of alcohol drinking, to the best of the authors' knowledge, only a few studies have explored the association of alcohol consumption with severe COVID-19 and poor clinical outcomes in COVID-19 patients.[32,35,36] Similar to the findings in the present study, Liu et al.[35] and Dai et al.[32] show that drinking alcohol is not related to the severity of COVID-19. The current finding, that drinking is not related to the severity of COVID-19, is consistent with results from previous studies. In addition, we observed that alcohol consumption was equally unrelated to poor clinical outcomes, including in-hospital death, MV and ICU admission of hospitalised COVID-19 patients, although some important confounding factors were adjusted. Considering the amount of alcohol

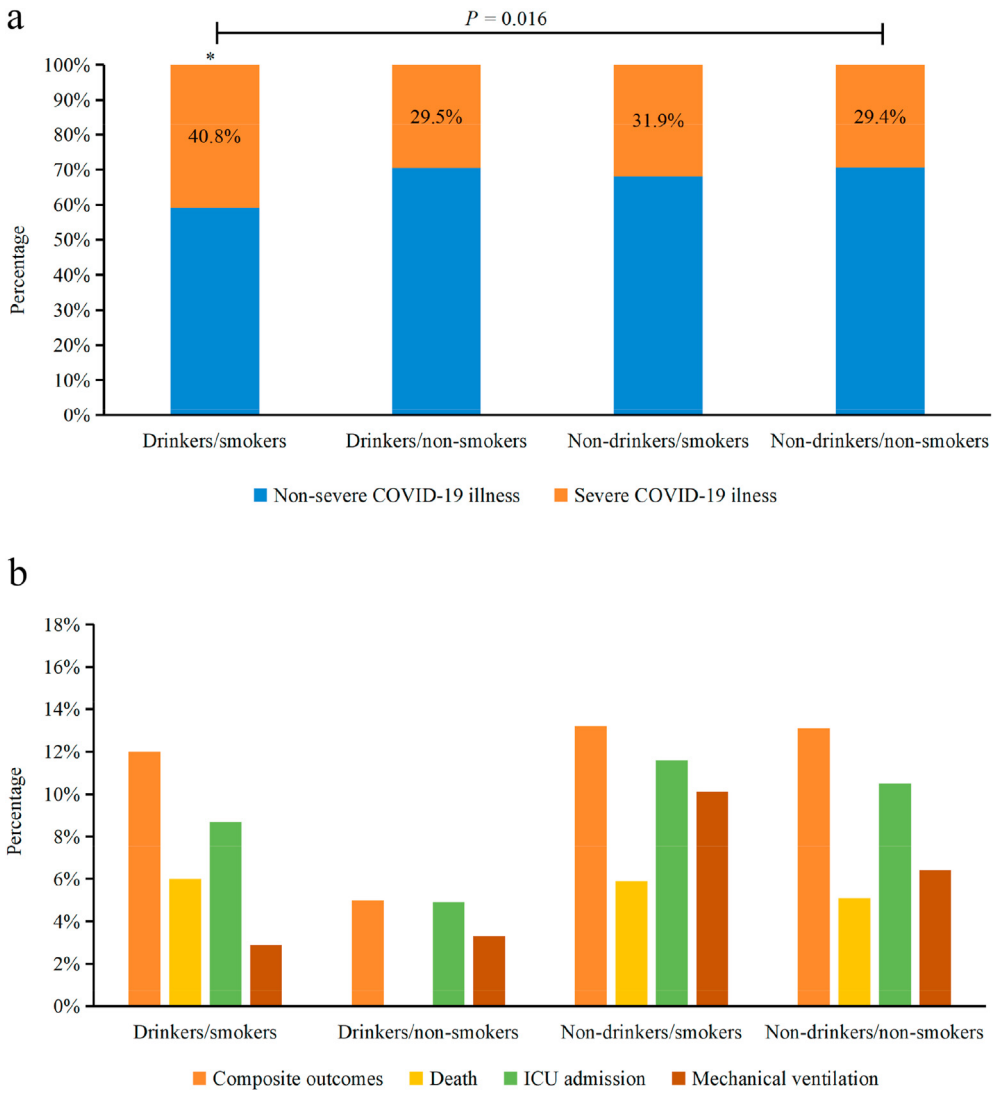

Fig. 2. (a) Disease severity of COVID-19, grouped by alcohol drinking and smoking status. (b) Outcomes of COVID-19 grouped by alcohol drinking and smoking status. There are post-hoc comparisons. * $P < 0.017$. Bonferroni's correction was used for multiple comparison with the non-drinkers/non-smokers group. ICU, intensive care unit.

consumed, the results from Fan et al.'s study, based on a larger sample size, show that heavy drinkers with obesity were more likely to have worse COVID-19 clinical outcomes.[36] Existing evidence demonstrating the association between alcohol consumption and COVID-19 is limited; it remains unclear whether alcohol drinking increases the risk of severe COVID-19 and poor clinical outcomes in COVID-19 patients. In the future, researchers should pay more attention to exploring whether alcohol drinking volume and time are associated with the severity and poor clinical outcomes of COVID-19.

Patients who smoke and drink alcohol are more vulnerable to COVID-19. Smoking can alter the structure of the respiratory tract and decrease the immune response, both systemically and locally within the lungs, increasing the risk of infections.[37] Furthermore, smoking has been shown to upregulate the expression of angiotensin-converting enzyme two receptor in the lungs,[38] which is associated with increased SARS-CoV-2 attachment and entry into the alveolar epithelial cells,[39] indicating a possible high-risk factor for COVID-19. Similarly, alcohol consumption, another important health risk factor, has been shown to alter the release of cytokines and functions of the barrier and ciliary fibres, thereby changing the defence capabilities of the airway epithelial host.[40] Alcohol can also change the function of alveolar macrophages, affect the recruitment of neutrophils, weaken the phagocytosis of neutrophils to pathogens, and reduce the production and release of neutrophils into the circulating blood. Previous studies confirmed that consumption of alcohol causes an increased susceptibility to airway bacterial and viral infections, regardless of the exact underlying mechanism.[41] Although the specific mechanism is not clear, it is likely that alcohol consumption also plays an important role in SARS-CoV-2 infection. In addition, both alcohol consumption and smoking trigger the production of the following substances, leading to oxidant stress: nitric oxide, carbon monoxide and phenolic free radicals, which have proven proinflammatory[42–44] and could increase the likelihood of adverse clinical outcomes of COVID-19. Therefore, given their adverse effects on the lungs and immune system, as well as based on the results of previous studies on other bacterial and viral lung infections, it is reasonable to believe that, despite the lack of data, alcohol consumption and smoking may contribute to the COVID-19-related risk. Although the present study did not find interactive effects between smoking and drinking on COVID-19, combined exposure to drinking and smoking

Table 2
Mixed-effects logistic regression models with centre as a random effect for severe COVID-19.

Variables	Severe COVID-19[a]		Unadjusted	Adjusted
	No, *n* (%)	Yes, *n* (%)	OR (95% CI)	OR (95% CI)
Drinking[b]				
Non-drinkers	361 (29.5)	863 (70.5)	1.00 (reference)	1.00 (reference)
Current drinkers	38 (35.5)	69 (64.5)	1.33 (0.76, 2.34)	1.00 (0.52, 1.92)
Former drinkers	22 (38.6)	35 (61.4)	1.28 (0.84, 1.97)	1.15 (0.67, 1.95)
Drinkers (current/former)	60 (36.6)	104 (63.4)	1.30 (0.91, 1.86)	1.09 (0.69, 1.72)
Smoking[c]				
Non-smokers	357 (29.4)	859 (70.6)	1.00 (reference)	1.00 (reference)
Current smokers	43 (35.0)	80 (65.0)	1.68 (0.93, 3.02)	1.68 (0.84, 3.38)
Former smokers	21 (42.9)	28 (57.1)	1.27 (0.85, 1.89)	1.24 (0.76, 2.03)
Smokers (current/former)	64 (37.2)	108 (62.8)	1.38 (0.98, 1.93)	1.35 (0.87, 2.10)
Combined drinking and smoking[d]				
Non-drinkers/non-smokers	339 (29.4)	816 (70.6)	1.00 (reference)	1.00 (reference)
Drinkers/non-smokers	18 (29.5)	43 (70.5)	0.95 (0.53, 1.69)	0.89 (0.48, 1.64)
Non-drinkers/smokers	22 (31.9)	47 (68.1)	1.13 (0.67.1.91)	1.12 (0.64, 1.99)
Drinkers/smokers	42 (40.8)	61 (59.2)	1.56 (1.02, 2.40)	1.62 (1.01, 2.60)
Interaction of drinking and smoking				
P for interaction[e]			0.39	0.30

CI, confidence interval; CCI, Carlson Comorbidity Index; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years; OR, odds ratio.
[a] Severe COVID-19: including severe subtype and critical subtype.
[b] Adjusted for age, sex, smoking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[c] Adjusted for age, sex, drinking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[d] Adjusted for age, sex, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[e] The *P* value represents the multiplicative interaction of drinking and smoking.

Table 3
Mixed-effects logistic regression models with centre as a random effect for composite poor outcome.

Variables	Composite poor outcome[a]		Unadjusted	Adjusted
	No, *n* (%)	Yes, *n* (%)	OR (95% CI)	OR (95% CI)
Drinking[b]				
Non-drinkers	1077 (87.2)	158 (12.8)	1.00 (reference)	1.00 (reference)
Current drinkers	100 (93.5%)	7 (6.5)	1.29 (0.59, 2.84)	0.90 (0.35, 2.30)
Former drinkers	49 (86.0)	8 (14.0)	0.53 (0.24, 1.18)	0.45 (0.18, 1.13)
Drinkers (current/former)	149 (90.9)	15 (9.1)	0.78 (0.44, 1.38)	0.61 (0.30, 1.25)
Smoking[c]				
Non-smokers	1075 (87.6)	152 (12.4)	1.00 (reference)	1.00 (reference)
Current smokers	110 (89.4)	13 (10.6)	1.41 (0.64, 3.08)	1.37 (0.53, 3.54)
Former smokers	41 (83.7)	8 (16.3)	0.94 (0.51, 1.73)	1.07 (0.52, 2.22)
Smokers (current/former)	151 (87.8)	21 (12.2)	1.08 (0.66, 1.77)	1.16 (0.62, 2.18)
Combined drinking and smoking[d]				
Non-drinkers/non-smokers	1017 (87.2)	149 (12.8)	1.00 (reference)	1.00 (reference)
Drinkers/non-smokers	58 (95.1)	3 (4.9)	0.38 (0.12, 1.26)	0.29 (0.08, 1.03)
Non-drinkers/smokers	60 (87.0)	9 (13.0)	1.02 (0.49, 2.10)	0.81 (0.27, 1.82)
Drinkers/smokers	91 (88.3)	12 (11.7)	1.04 (0.55, 1.99)	0.91 (0.45, 1.84)
Interaction of drinking and smoking				
P for interaction[e]			0.20	0.10

CI, confidence interval; CCI, Carlson Comorbidity Index; CURB-65, confusion, uraemia, respiratory rate, blood pressure, age ≥65 years; ICU, intensive care unit; OR, odds ratio.
[a] Composite poor outcome: including death, ICU admission or mechanical ventilation.
[b] Adjusted for age, sex, smoking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[c] Adjusted for age, sex, drinking status, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[d] Adjusted for age, sex, level of hospital, the duration from illness onset to hospital admission, CCI and CURB-65 scores on admission.
[e] The *P* value represents the multiplicative interaction of drinking and smoking.

significantly increased the risk (OR = 1.62; $P < 0.05$) for severe COVID-19, indicating that drinkers/smokers may be prone to developing severe COVID-19. However, the role of combined exposure to smoking and alcohol drinking as risk factors for severe COVID-19 among hospitalised COVID-19 patients is a preliminary finding; hence, further investigation of these results is necessary.

The present study has several notable strengths. To the best of the authors' knowledge, this is the first study to investigate the interaction and combined effects of alcohol drinking and smoking on severe COVID-19 and the clinical outcomes of COVID-19 patients in China. In addition, this was a multicentre study, with a relatively large number of patients. The results reveal that drinkers/smokers had a higher risk of developing severe COVID-19 than non-drinkers/non-smokers.

The present study also has some limitations. First, the status of cigarette smoking and alcohol consumption was self-reported by the patients. Therefore, it is prone to recall bias. Second, the study had a retrospective observational design. Thus, the observed findings should be interpreted carefully because residual confounding cannot be entirely ruled out. For instance, obesity has been confirmed as an important risk factor for the severity and prognosis of COVID-19 patients;[45] however, the information required to determine obesity was not collected, as body mass index data were missing. Third, exposure levels to alcohol and smoking were not provided; therefore,

the dose–response relationship with COVID-19 cannot be explored. Fourth, a previous study has shown that the smoking rate in hospitalised patients with COVID-19 was lower than that of the general population.[46] The present study only included a hospital-based population, which likely led to a greater imbalance between the number of patients in each group, thus possibly affecting the results and limiting the generalisation of results to other populations. Finally, because of the rapid and strict measures taken by the Sichuan provincial government to combat COVID-19, the sample size of most designated hospitals in Sichuan was relatively small. This limited the ability to control for hospital variability using hospital as a random effect. Therefore, further data are required that are more representative of the global population to validate these preliminary findings.

Conclusions

In conclusion, combined exposure to alcohol drinking and smoking is linked to severe COVID-19; however, drinking alone or smoking alone had no direct effects, and both drinking and smoking had no interaction effects. Intervention strategies for alcohol consumption and smoking are recommended to decrease the risk of severe COVID-19.

Author statements

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Ethical approval

This study was approved by the Biological and Medical Ethics Committee of West China Hospital (approval number: 2020-304 and 2020-126) and the Ethic Committee of Renmin Hospital of Wuhan University (approval number: WDRY2020-K068). Administrative permission to access the raw data was granted by administrators of each hospital. The study was a retrospective cohort design, and the data used in the study were anonymous, so the requirement for informed consent was waived.

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.01.013.

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