Open Peer Review on Qeios

The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review (version 4)

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Abstract

Background: SARS-CoV-2 is the causative agent of COVID-19, an emergent zoonotic disease which has reached pandemic levels and is designated a public health emergency of international concern. It is plausible that former or current smoking status is associated with infection, hospitalisation and/or mortality from COVID-19.

Objective: We aimed to estimate the association of smoking status with rates of i) infection, ii) hospitalisation, iii) disease severity, and iv) mortality from SARS-CoV-2/COVID-19 disease.

Methods: This is a living evidence review with frequent updates. We adopted recommended practice for rapid evidence reviews, which involved limiting the search to main databases and having one reviewer extract data and another verify. Published articles and pre-prints were identified via Ovid MEDLINE, medRxiv and expertise within the review team. We included observational or experimental studies with community-dwelling or hospitalised adults aged 16+ years who had received a test for SARS-CoV-2 infection or a diagnosis of COVID-19, providing that data on smoking status were reported. Studies were judged as 'good' quality if they: i) had low levels of missing data on smoking status (i.e. <20%) and used a reliable self-report measure that distinguished between current, former and never smoking status, ii) used biochemical verification of smoking status, and iii) adjusted smoking and COVID-19 analyses for covariates that are likely to confound these associations (e.g. age, non-smoking related comorbidities).

Results: Version 4 with searches up to 3 June 2020 included 102 studies, 36 of which were conducted in China, 25 in the US, nine in the UK, six in Mexico, six in Spain, five in France, four in Italy, three across multiple international sites, two in Israel, and one each from Finland, Iran, Korea, Kuwait, Saudi Arabia and Switzerland. Twenty-one (20.6%) studies reported current, former and never smoking status. Twenty-seven studies explicitly reported the proportion missing data on smoking status, which ranged from 0.08% to 96.3%. Notwithstanding recording uncertainties, compared with adult national prevalence estimates, recorded current and former smoking rates were generally lower than expected, but similar to expected in studies conducted in the UK. In seven 'fair' quality studies, current smokers were at reduced risk of testing positive for SARS-CoV-2 compared with never smokers (RR = 0.73, 95% CI = 0.54-0.99, p = .046, I2 = 93%). No significant difference was observed between former and never smokers (RR = 1.02, 95% CI = 0.88-1.18, p = .80, I2 = 84%). In five 'fair' quality studies, there was no significant difference between current and never (RR = 1.12, 95% CI = 0.74-1.69, p = .48, I2 = 84%) or former and never smokers (RR = 1.21, 95% CI = 0.82-1.79, p = .24, I2 = 81%) in the risk of requiring admission to hospital with COVID-19 among those testing positive in the community. In four 'fair' quality studies, current smokers admitted to hospital were at increased risk of greater disease severity compared with never smokers (RR = 1.39, 95% CI = 1.09-1.77, p < .01, I2 = 0%). No significant difference was observed between former and never smokers (RR = 1.40, 95% CI = 0.76-2.59, p = .28, I2 = 74%). In two 'fair' quality studies, there was no significant difference between current and never (RR = 1.41, 95% CI = 0.91-2.20, p = .12, I2 = 40%) or former and never smokers (RR = 0.98, 95% CI = 0.65-1.48, p = .93, I2 = 0%) in the risk of in-hospital mortality from COVID-19.

Conclusions: Across 102 studies, there is substantial uncertainty about the associations of smoking with COVID-19 outcomes. The recorded smoking prevalence in the included studies was generally lower than overall adult national estimates. There was no evidence of reduced risk of admission to hospital in current compared with never smokers among those testing positive in the community from five 'fair' quality studies. There was some evidence from 'fair' quality studies that current compared with never smoking is associated with reduced risk of testing positive in the community but greater disease severity in those hospitalised for COVID-19.

Implications: Unrelated to COVID-19, smokers are at a greater risk of a range of serious health problems. Given uncertainty around the association of smoking with COVID-19 outcomes, smoking cessation remains a public health priority and high-quality smoking cessation advice including recommendations to use alternative nicotine products should form part of public health efforts during this pandemic. High quality, smoking-specific research is needed to resolve these mixed findings.

Introduction

COVID-19 is a respiratory disease caused by the emerging SARS-CoV-2 virus. Large age and gender differences in case severity and mortality have been observed in the ongoing COVID-19 pandemic[1]; however, these differences are currently unexplained. SARS-CoV-2 enters epithelial cells through the ACE-2 receptor[2]. Some evidence suggests that gene expression and subsequent receptor levels are elevated in the airway and oral epithelium of current smokers[3,4], thus putting smokers at higher risk of contracting SARS-CoV-2. Other studies, however, suggest that nicotine downregulates the ACE-2 receptor[5]. These uncertainties notwithstanding, both former and current smoking is known to increase the risk of respiratory viral[6,7] and bacterial[8,9] infections and is associated with worse outcomes once infected. Cigarette smoke reduces the respiratory immune defence through peri-bronchiolar inflammation and fibrosis, impaired mucociliary clearance and disruption of the respiratory epithelium[10]. There is also reason to believe that behavioural factors (e.g. regular hand-to-mouth movements) involved in smoking may increase SARS-CoV-2 infection and transmission in current smokers. However, early data from the COVID-19 pandemic have not provided clear evidence for a negative impact of current or former smoking on SARS-CoV-2 infection or COVID-19 disease outcomes, such as hospitalisation or mortality[11]. It has also been hypothesised that nicotine might protect against a hyper-inflammatory response (or "cytokine storm") to SARS-CoV-2 infection, which may lead to adverse outcomes in patients with COVID-19 disease[12.]

There are several reviews that fall within the scope of smoking and COVID-19[11,13–17]. We aimed to produce a rapid synthesis of available evidence pertaining to the rates of infection, hospitalisation, disease severity and mortality from SARS-CoV-2/COVID-19 stratified by smoking status. Given the increasing availability of data on this topic, this is a living review with regular updates. As evidence accumulates, the review will be expanded to include studies reporting COVID-19 outcomes by alternative nicotine use (e.g., nicotine replacement therapy or e-cigarettes).

Methods

Study design

This is a living evidence review which is updated as new evidence becomes available[18]. We adopted recommended practice for rapid evidence reviews, which involved limiting the search to main databases and having one reviewer extract the data and another verify[19].

Eligibility criteria

Studies were included if they:

1) Were primary research studies using experimental (e.g. randomised controlled trial), quasi-experimental (e.g. pre- and post-test) or observational (e.g. case-control, retrospective cohort, prospective cohort) study designs;
2) Included adults aged 16+ years;
3) Recorded as outcome i) results of a SARS-CoV-2 diagnostic test (including antibody assays), ii) clinical diagnosis of COVID-19, iii) hospitalisation with COVID-19, iv) severity of COVID-19 disease in those hospitalised or v) mortality from COVID-19;
4) Reported any of the outcomes of interest by self-reported or biochemically verified smoking status (e.g. current smoker, former smoker, never smoker);
5) Were available in English;
6) Were published in a peer-reviewed journal, as a pre-print or a public health report by reputable agents (e.g. governments, scientific societies).

Search strategy

The following terms were searched for in Ovid MEDLINE as free text or Medical Subject Headings:

1) Tobacco Smoking/ or Smoking Cessation/ or Water Pipe Smoking/ or Smoking/ or Smoking Pipes/ or Cigar Smoking/ or Smoking Prevention/ or Cigarette Smoking/ or smoking.mp. or Pipe Smoking/ or Smoking, Non-Tobacco Products/ or Smoking Water Pipes/
2) Nicotine/ or nicotine.mp. or Electronic Nicotine Delivery Systems/ or Nicotine Chewing Gum/

3) vaping.mp. or Vaping/

4) 1 or 2 or 3

5) Coronavirus/ or Severe Acute Respiratory Syndrome/ or Coronavirus Infections/ or covid.mp.

6) 4 and 5

The following terms were searched for in titles, abstracts and full texts in medRxiv:

1) covid smoking

2) covid nicotine

3) covid vaping

Additional articles/reports of interest were identified through mailing lists, Twitter, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), the Intensive Care National Audit & Research Centre (ICNARC) and the US Centers for Disease Control and Prevention (CDC).

Where updated versions of pre-prints or public health reports were available, old versions were superseded.

Selection of studies

One reviewer screened titles, abstracts and full texts against the inclusion criteria.

Data extraction

Data were extracted by one reviewer and verified by a second on i) author (year); ii) date published; iii) country; iv) study design; v) study setting; vi) sample size; vii) sex; viii) age; ix) smoking status (e.g. current, former, never, not stated, missing); x) SARS-CoV-2 infection; xi) diagnosis of COVID-19; xii) hospitalisation with COVID-19; xiii) disease severity in those hospitalised with COVID-19; and xiv) mortality.

Quality appraisal

In previous review versions, we used the National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies to determine the quality of included studies[20]. However, we decided against applying the entire tool in the current review version. The appraisal is challenging to apply when studying an emerging disease with unknown pathology. For example, it is not possible to determine what proportion of eligible participants/patients are included in the studied populations when the total number of infections in a given region/city is unknown. With a largely unknown disease process, it is also difficult to determine whether the time between the exposure and outcome is sufficient. We therefore focused on three of the 14 criteria to determine whether studies were of sufficient quality to warrant inclusion in meta-analysis. Studies were judged as 'good' quality if they: i) had low levels of missing data on smoking status (i.e. <20%) and used a reliable self-report measure that distinguished between current, former and never smoking status, ii) used biochemical verification of smoking status, and iii) adjusted smoking and COVID-19 analyses for covariates that are likely to confound these associations (e.g. age, non-smoking related comorbidities). Studies were rated as 'fair' if they fulfilled criterion i) and were otherwise rated as 'poor'. The quality appraisal was conducted by one reviewer and verified by a second.

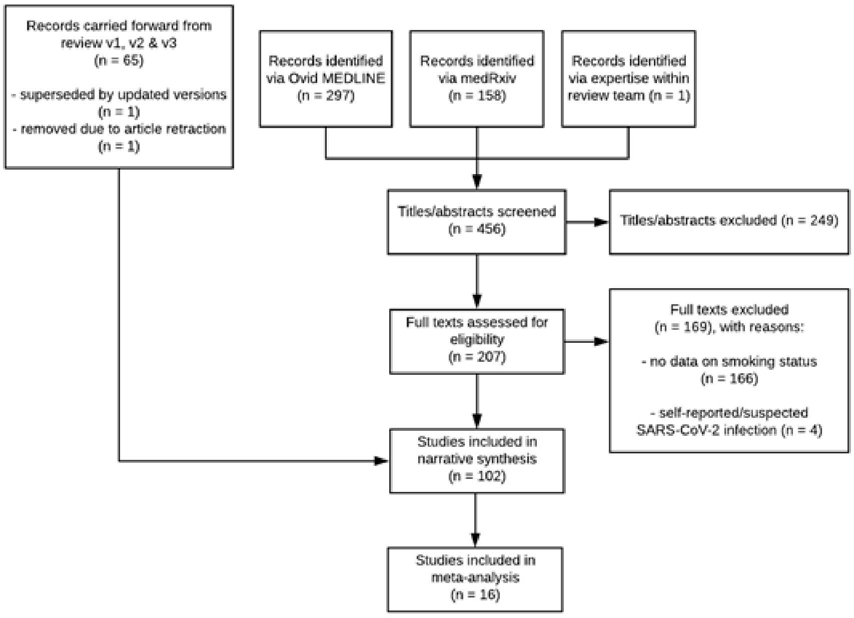
Evidence synthesis

A narrative synthesis was conducted. Where possible, data were pooled in R v.3.6.3[21] with the Mantel-Haenszel or inverse variance method using random or fixed effects, depending on heterogeneity, and presented as risk ratios (RRs)[22]. Heterogeneity between study outcomes was assessed using the I^2 statistic, suitable for smaller meta-analyses[23].

To aid in the visualisation of smoking prevalence in the included studies, 95% bootstrap percentile confidence intervals were calculated. We performed 1,000 bootstrap replications, with the 2.5th and 97.5th percentiles of the empirical distribution forming the 95% bootstrap percentile confidence intervals[24]. Prevalence estimates in the included studies were not adjusted for age, sex or socioeconomic position.

Results

In the current review version (v4), a total of 456 new records were identified, with 102 studies included in a narrative synthesis and 16 studies included in meta-analyses (see Figure 1).



Study characteristics

Characteristics of included studies are presented in Table 1. Thirty-six studies were conducted in China, 25 in the US, nine in the UK, six in Mexico, six in Spain, five in France, four in Italy, three across multiple international sites, two in Israel, and one each in Finland, Iran, Korea, Kuwait, Saudi Arabia and Switzerland. Eighty-one studies were conducted in hospital settings. Sixteen studies included a community component in addition to hospitalised patients. Three studies were conducted in the community, one in a quarantine centre and one did not state the study setting. Studies had a median of 310 (interquartile range = 95-1,006) participants.

Smoking status

Categorisation of smoking status was heterogeneous (see Table 1). Sixty-two studies collected data on smoking status through routine electronic health records, 25 studies used a bespoke case report form for COVID-19 and 15 studies did not state the source for information on smoking status. None of the studies verified smoking status biochemically. Notably, only 22 (21.6%) studies reported current, former and never smoking status, with a further seven studies reporting current/former and never smoking status. The remaining 73 studies reported current, current/former or current and former smoking status but did not explicitly state whether remaining participants were never smokers or if data were missing on smoking status. Twenty-seven studies explicitly reported the proportion missing data on smoking status, which ranged from 0.08% to 96.3%. One study[25] reported that 91.4% of former smokers had been quit ≥6 months prior to COVID-19 disease onset; the remaining studies did not report time since quitting in former smokers.

Use of alternative nicotine products

Two studies recorded the use of alternative nicotine products in current and/or former smokers but did not report COVID-19 outcomes stratified by nicotine use.

Quality appraisal

Nineteen studies were rated as 'fair' quality due to having low levels of missing data and distinguishing between current, former and never smoking status (see Appendix 1). The remaining 83 studies were rated as 'poor' quality.

Table 1. Characteristics of included studies.

Reference	Lead author	Date published	Country	Sample size	Study setting	Median age (IQR)	Female %	Current smokers %	Current/former smokers %	Never smokers %	Never/unknown smokers %	Missing %	Overall rating (poor, fair, good)
[1]	Guan, Ni	2020-02-28	China	1,099	Hospital	47 (35-58)	41.90	12.47	-	84.35	-	1.27	Fair
[26]	Guan, Liang	2020-03-26	China	1,590	Hospital	49 (33-64)	42.70	-	6.98	93.02	-	0.00	Poor
[27]	Lian	2020-03-25	China	788	Hospital	-	38.50	6.85	-	-	-	93.15	Poor
[28]	Jin	2020-03-24	China	651	Hospital	46 (32-60)	49.20	6.30	-	-	-	93.70	Poor
[29]	Chen	2020-03-26	China	548	Hospital	62 (44-70)	37.60	4.38	-	-	-	93.07	Poor
[30]	Zhou, Yu	2020-03-11	China	191	Hospital	56 (46-67)	38.00	5.76	-	-	-	94.24	Poor
[31]	Mo	2020-03-16	China	155	Hospital	54 (53-66)	44.50	3.87	-	-	-	96.13	Poor
[32]	Zhang, Dong	2020-02-19	China	140	Hospital	57^ (25-87)	46.30	1.43	-	-	-	93.57	Poor
[33]	Wan	2020-03-21	China	135	Hospital	47 (36-55)	46.70	6.67	-	-	-	93.33	Poor
[34]	Liu, Tao	2020-02-28	China	78	Hospital	38 (33-57)	50.00	-	6.41	-	-	93.59	Poor
[35]	Huang, Wang	2020-01-24	China	41	Hospital	49 (41-58)	27.00	7.32	-	-	-	92.68	Poor
[36]	Zhang, Cai	2020-03-20	China	645	Hospital	-	49.10	6.36	-	-	-	93.64	Poor
[37]	Guo	2020-03-27	China	187	Hospital	59 (45-73)	51.30	9.63	-	-	-	90.37	Poor
[38]	Liu, Ming	2020-03-12	China	41	Hospital	39 (30-48)	58.50	9.76	-	-	-	90.24	Poor
[35]	Huang, Yang	2020-03-05	China	36	Hospital	69 (60-78)	30.60	-	11.11	-	-	88.89	Poor
[39]	Xu	2020-03-08	China	53	Hospital	-	47.20	11.32	-	-	-	88.68	Poor

[40]	Li	2020-02-12	China	17	Hospital	45 (33-57)	47.10	17.65	-	-	-	82.35	Poor
[41]	Rentsch	2020-04-14	USA	3,528	Community and Hospital	66 (60-70)	4.60	27.18	-	36.92	-	5.30	Fair
[42]	Hu	2020-03-25	China	323	Hospital	61^ (23-91)	48.60	-	11.76	-	-	88.24	Poor
[43]	Wang, Pan	2020-03-24	China	125	Hospital	41 (26-66)	43.20	-	12.80	-	-	87.20	Poor
[44]	Petrilli	2020-04-11	USA	4,103	Community and Hospital	52 (36-65)	47.90	5.17	-	-	78.60	0.00	Poor
[45]	Chow (US CDC)	2020-03-31	USA	7,162	Community and Hospital	-	-	1.34	-	-	-	96.36	Poor
[46]	Dong, Cao	2020-03-20	China	9	Hospital	44 (30-46)	66.70	11.11	-	-	-	88.89	Poor
[47]	Kim	2020-04-01	Korea	28	Hospital	43 (30-56)	46.40	17.86	-	-	-	82.14	Poor
[48]	Shi, Yu	2020-03-18	China	487	Hospital	46 (27-65)	46.80	-	8.21	-	-	91.79	Poor
[49]	Yang, Yu	2020-02-24	China	52	Hospital	60 (47-73)	37.00	3.85	-	-	-	96.15	Poor
[50]	Argenziano	2020-04-22	USA	1,000	Hospital	63 (50-75)	40.40	4.90	-	77.20	-	0.00	Fair
[51]	Solis	2020-04-25	Mexico	650	Hospital	46	42.10	9.38	-	-	-	90.62	Poor
[52]	Richardson	2020-04-22	USA	5,700	Hospital	63 (52-75)	39.70	-	9.79	52.79	-	37.42	Poor
[53]	Fontanet	2020-04-23	France	661	Community and Hospital	37 (16-47)	62.00	10.44	-	-	89.56	0.00	Poor
[54]	Zheng, Gao	2020-04-19	China	66	Hospital	47^	25.80	12.12	-	-	-	87.88	Poor
[55]	Liao, Feng	2020-04-24	China	1,848	Hospital	55 (48-61)	54.70	-	0.43	-	-	99.57	Poor
[56]	Rodriguez-Cola	2020-04-24	Spain	7	Hospital	68 (34-75)	28.60	-	42.86	57.14	-	0.00	Poor
[57]	Magagnoli	2020-04-16	USA	368	Hospital	69 (59-75)	0.00	-	14.13	-	-	85.87	Poor
[58]	Shi, Ren	2020-04-23	China	134	Hospital	46 (34-58)	51.50	-	10.45	-	-	89.55	Poor
[59]	Hadjadj	2020-04-23	France	50	Hospital	55 (50-63)	22.00	2.00	-	80.00	-	0.00	Fair
[60]	Niedzwiedz	2020-04-30	UK	1,474	Community and Hospital	-	-	9.98	-	55.04	-	0.59	Fair
[61]	Gold (US CDC)	2020-04-20	USA	305	Hospital	-	50.50	5.25	-	-	-	94.75	Poor
[62]	Yu, Cai	2020-04-27	China	95	Hospital	-	44.21	8.42	-	-	-	91.58	Poor
[63]	Zheng, Xiong	2020-04-30	China	73	Hospital	43^	45.20	-	10.96	89.04	-	0.00	Poor
[25]	Miyara	2020-05-09	France	479	Community and Hospital	-	44.70	6.68	-	59.71	-	1.88	Fair
[64]	de la Rica	2020-05-11	Spain	48	Hospital	66^ (33-88)	33.00	-	20.83	-	-	79.17	Poor
[65]	Yin, Yang	2020-05-10	China	106	Hospital	73 (61-85)	39.60	-	16.98	-	-	83.02	Poor
[66]	Gaibazzi	2020-05-10	Italy	441	Hospital	71 (62-80)	38.00	4.76	-	85.26	-	0.00	Fair
[67]	Shi, Zuo	2020-05-10	USA	96	Hospital	63^ (44-82)	41.00	-	30.21	-	-	69.79	Poor
[68]	Cho	2020-05-11	UK	1,331	Community and Hospital	-	49.20	19.01	-	54.02	-	0.00	Fair
[69]	Allenbach	2020-05-08	France	152	Hospital	77 (60-83)	31.10	-	6.58	-	-	93.42	Poor
[70]	Robilotti	2020-05-08	USA	423	Hospital	-	50.00	2.13	-	58.63	-	1.65	Fair
[71]	The Opensafely Collaborative	2020-05-07	UK	17,425,445	Community and Hospital	-	50.10	17.00	-	45.91	-	4.16	Fair
[72]	Borobia	2020-05-06	Spain	2,226	Hospital	61 (46-78)	52.00	7.05	-	-	-	92.95	Poor
[73]	Giacomelli	2020-05-06	Italy	233	Hospital	61 (50-72)	31.90	-	30.04	69.96	-	0.00	Poor

[74]	Shah	2020-05-06	USA	316	Hospital	63 (43-72)	48.10	16.46	-	42.09	-	23.73	Poor
[75]	Bello-Chavolla	2020-05-06	Mexico	62,489	Community and Hospital	-	49.40	-	9.94	-	-	90.06	Poor
[76]	Kolin	2020-05-05	UK	1,474	Community and Hospital	58 (49-67)	46.60	14.45	-	44.57	-	0.81	Fair
[77]	Lubetzky	2020-05-08	USA	54	Hospital	57 (29-83)	62.00	-	22.22	-	-	77.78	Poor
[78]	Goyal	2020-04-17	USA	393	Hospital	62.2 (49-74)	39.30	5.09	-	-	-	94.91	Poor
[79]	Feng	2020-04-10	China	476	Hospital	53 (40-64)	43.10	9.24	-	-	-	90.76	Poor
[80]	Yao	2020-04-24	China	108	Hospital	52 (37-58)	60.20	3.70	-	-	-	96.30	Poor
[81]	Sami	2020-05-15	Iran	490	Hospital	56.6 (41-71)	39.00	14.08	-	-	85.92	0.00	Poor
[82]	Almazeedi	2020-05-15	Kuwait	1,096	Hospital	41 (25-57)	19.00	4.01	-	-	95.99	0.00	Poor
[83]	Carrillo-Vega	2020-05-14	Mexico	10,544	Community and Hospital	46.5^ (30-62)	42.30	8.88	-	-	-	91.12	Poor
[84]	Yanover	2020-05-13	Israel	4,353	Community and Hospital	35 (22-54)	44.50	11.81	-	85.23	-	0.00	Fair
[85]	Hamer	2020-05-13	UK	387,109	Hospital	56.2 (48-64)	55.10	9.67	-	55.50	-	0.00	Fair
[86]	Regina	2020-05-14	Switzer land	200	Hospital	70 (55-81)	40.00	4.50	-	-	-	95.50	Poor
[87]	de Lusignan	2020-05-15	UK	3,802	Community	58 (34-73)	57.60	10.86	-	29.59	-	13.44	Fair
[88]	Targher	2020-05-13	China	339	Hospital	48.4^ (NA)	52.80	8.26	-	-	-	91.74	Poor
[89]	Valenti	2020-05-18	Italy	789	Community	40.7^ (NA)	34.98	25.86	-	-	-	74.14	Poor
[90]	Feuth	2020-05-18	Finland	28	Hospital	56 (47-72)	46.00	10.71	-	60.71	-	0.00	Fair
[91]	Ge	2020-05-18	China	51	Hospital	70 (58-79)	27.50	13.73	-	-	-	86.27	Poor
[92]	Parrotta	2020-05-18	USA	76	Community and Hospital	44.9 (13-71)	61.80	2.63	-	68.42	-	2.63	Fair
[93]	Shekhar	2020-05-18	USA	50	Hospital	55.5 (20-85)	54.00	48.00	-	-	-	52.00	Poor
[94]	Mejia-Vilet	2020-05-16	Mexico	329	Hospital	49 (41-60)	36.00	-	6.99	-	-	93.01	Poor
[95]	Chen, Jiang	2020-05-16	China	135	Hospital	-	42.20	-	9.63	-	-	90.37	Poor
[96]	Li	2020-05-16	China	1,008	Hospital	55 (44-65)	43.60	5.65	-	-	-	94.35	Poor
[97]	Rimland	2020-05-19	USA	11	Hospital	59 (48-65)	18.20	9.09	-	-	-	81.82	Poor
[98]	Palaiodimos	2020-05-15	USA	200	Hospital	64 (50-73.5)	51.00	-	32.50	67.50	-	0.00	Poor
[99]	Ip	2020-05-25	USA	2,512	Hospital	64 (52-76)	37.62	3.07	-	64.49	-	14.61	Fair
[100]	Heili-Frades	2020-05-25	Spain	4,712	Hospital	62 (47-77)	50.50	4.94	-	-	66.49	11.16	Poor
[101]	Vaquero-Roncero	2020-05-24	Spain	146	Hospital	66^ (59-72)	32.20	-	6.85	-	-	93.15	Poor
[102]	Kim, Garg	2020-05-22	USA	2,491	Hospital	62 (50-75)	46.80	6.02	-	-	68.13	0.08	Poor
[103]	Wu	2020-05-21	Italy	174	Hospital	61.2^ (50-71)	30.46	-	33.33	-	-	66.67	Poor
[104]	Shi, Zhao	2020-05-20	China	101	Hospital	71 (59-80)	40.60	-	4.95	-	-	95.05	Poor
[105]	Kimmig	2020-05-20	USA	60	Hospital	64 (50-68)	41.67	-	36.67	-	-	63.33	Poor
[106]	Al-Hindawi	2020-05-20	UK	31	Hospital	61	12.90	3.23	-	25.81	-	0.00	Fair
[107]	Basse	2020-05-19	France	141	Hospital	62 (52-72)	72.00	17.73	-	-	-	82.27	Poor
[108]	Freites	2020-05-19	Spain	123	Hospital	59.88^ (44-74)	69.92	3.25	-	-	-	96.75	Poor

[109]	Alshami	2020-05-19	Saudi Arabia	128	Quarantine Centre	39.6^ (24-55)	53.90	15.62	-	-	-	82.03	Poor
[110]	Russell	2020-05-19	UK	106	Hospital	67^ (52-81)	45.30	6.60	-	39.62	-	29.25	Poor
[111]	Berumen	2020-05-26	Mexico	102,875	Hospital	-	49.08	-	9.64	-	90.36	0.00	Poor
[112]	Gianfrancesco	2020-05-29	Multiple	600	Community and Hospital	56 (45-67)	71.00	-	21.50	64.83	-	13.67	Poor
[113]	Li, Long	2020-05-28	China	145	Not Stated	49^ (13-80)	61.00	-	5.52	-	-	94.48	Poor
[114]	Batty	2020-06-01	UK	908	Hospital	57.27^ (48-66)	44.27	11.23	-	-	-	88.77	Poor
[115]	Israel	2020-06-01	Israel	24,087	Community and Hospital	43.4^ (24-62)	48.70	17.08	-	69.88	-	0.00	Fair
[116]	del Valle	2020-05-30	USA	1,484	Hospital	62 (52-72)	40.60	5.53	-	-	-	71.16	Poor
[117]	Zuo, Zuo	2020-05-29	USA	44	Hospital	57^ (45-69)	18.18	-	27.27	-	-	72.73	Poor
[118]	Chaudhry	2020-05-29	USA	40	Community and Hospital	52 (45.5-61)	60.00	-	15.00	-	-	85.00	Poor
[119]	Louis	2020-06-28	USA	22	Hospital	66.5^ (55-77)	36.40	-	45.45	-	-	54.55	Poor
[120]	Soto-Mota	2020-05-27	Mexico	400	Hospital		30.00	-	12.00	-	-	88.00	Poor
[121]	Patel	2020-05-26	USA	104	Hospital	60.66^ (47-74)	47.00	41.35	-	-	49.04	9.62	Poor
[122]	Garibaldi	2020-05-26	USA	832	Hospital	63 (49-75)	47.00	5.53	-	-	-	71.88	Poor
[123]	Docherty	2020-05-22	Multiple	20,133	Hospital	72.9 (58-82)	40.00	4.23	-	44.54	-	29.55	Poor
[124]	Boulware	2020-03-06	Multiple	821	Community	40 (33-50)	51.60	3.29	-	-	-	96.71	NA

Note. – Age not provided for total sample; ^ Denotes mean (SD).

Smoking prevalence by country

Unadjusted smoking prevalence in community and hospital studies compared with overall estimates for national adult smoking prevalence split by country is presented in Figure 2a and 2b. Lower than expected current and former smoking prevalence was generally observed, with similar to expected prevalence reported in studies conducted in the UK. Variability in prevalence estimates was observed across studies conducted in the US.

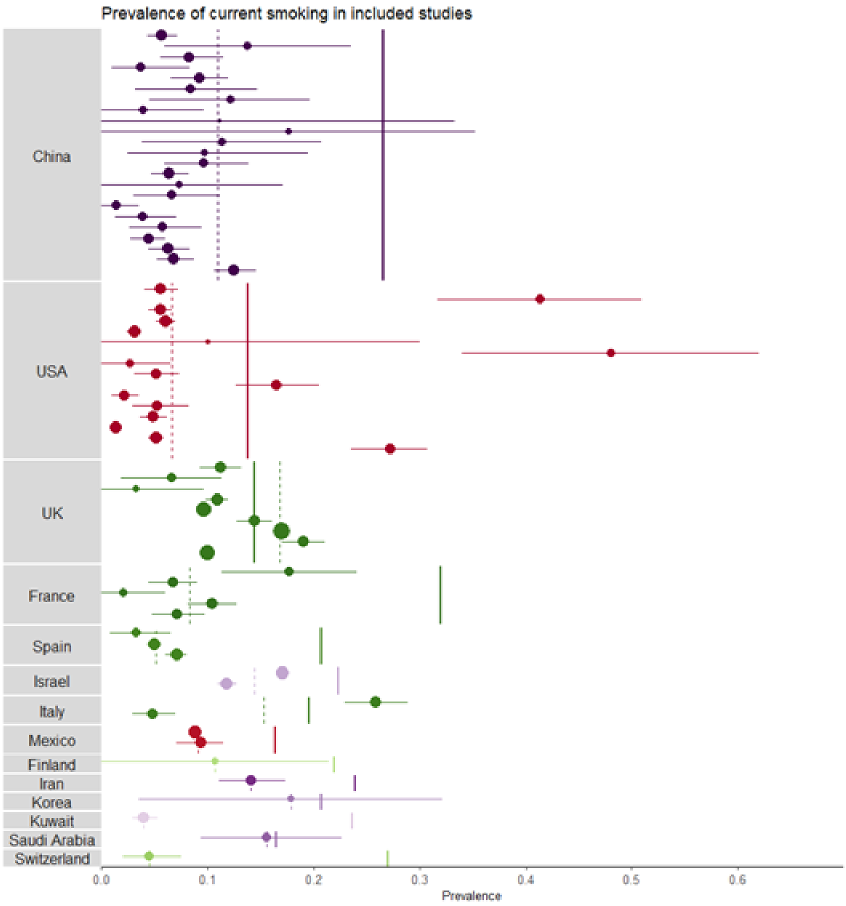


Figure 2a. Weighted average of current smoking prevalence in included studies (dashed lines) with 95% bootstrap confidence intervals compared with national current smoking prevalence (solid lines), split by country. Dot size corresponds to study sample size.

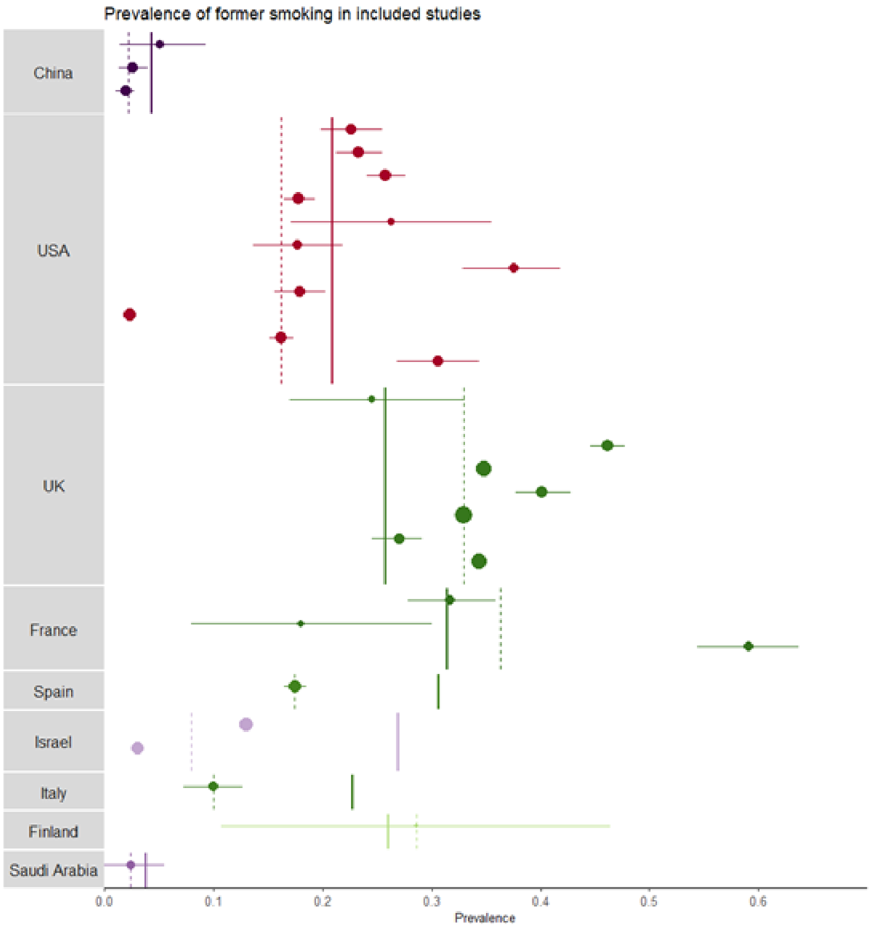


Figure 2b. Weighted average of former smoking prevalence in included studies (dashed lines) with 95% bootstrap confidence intervals compared with national former smoking prevalence (solid lines), split by country. Studies conducted in Mexico, Iran, Korea, Kuwait and Switzerland did not report former smoking prevalence. Dot size corresponds to study sample size.

SARS-CoV-2 infection by smoking status

Thirteen studies provided data on SARS-CoV-2 test results for people meeting local testing criteria by smoking status (see Table 2). Meta-analyses were performed for seven 'fair' quality studies (see Figure 3 and 4). Current smokers were at reduced risk of testing positive for SARS-CoV-2 compared with never smokers (RR = 0.73, 95% CI = 0.54-0.99, p = .046, I^2 = 93%). No significant difference was observed between former and never smokers (RR = 1.02, 95% CI = 0.88-1.18, p = .80, I^2 = 84%).

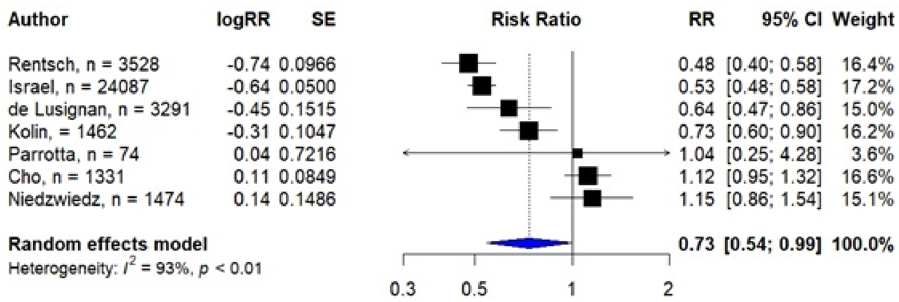


Figure 3. Forest plot for risk of testing positive for SARS-CoV-2 in current vs. never smokers.

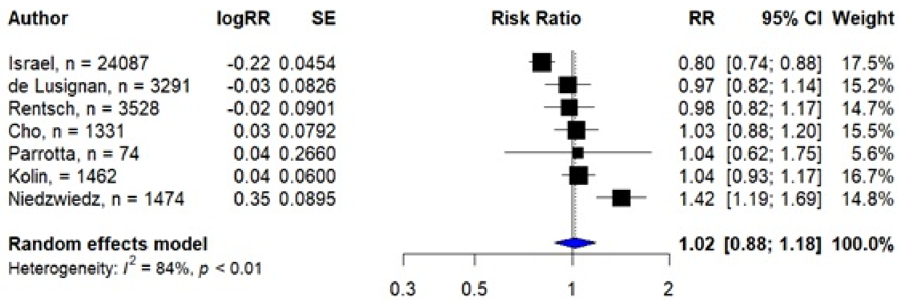


Figure 4. Forest plot for risk of testing positive for SARS-CoV-2 in former vs. never smokers.

Hospitalisation for COVID-19 by smoking status

Fourteen studies examined hospitalisation for COVID-19 disease stratified by smoking status (see Table 3). Meta-analyses were performed for five 'fair' quality studies (see Figure 5 and 6). There was no significant difference between current and never (RR = 1.12, 95% CI = 0.74-1.69, p = .48, I^2 = 84%) or former and never smokers (RR = 1.21, 95% CI = 0.82-1.79, p = .24, I^2 = 81%) in the risk of requiring admission to hospital with COVID-19.

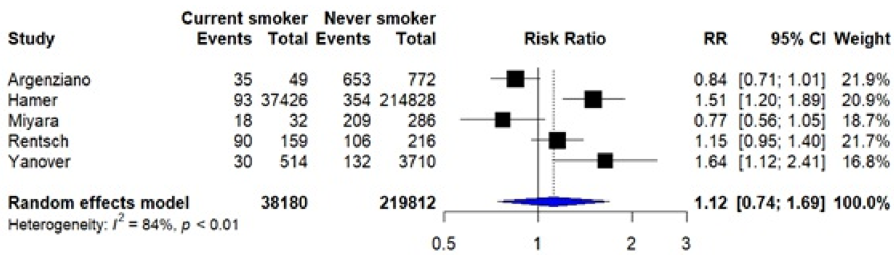


Figure 5. Forest plot for risk of hospitalisation in current vs. never smokers.

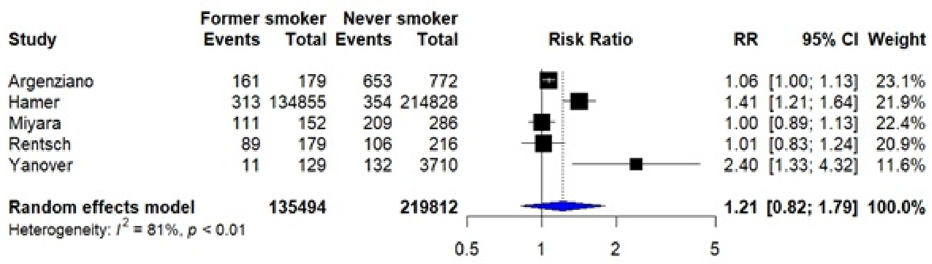


Figure 6. Forest plot for risk of hospitalisation in former vs. never smokers.

Disease severity by smoking status

Thirty-three studies reported disease severity in hospitalised patients stratified by smoking status (see Table 4). Severe (as opposed to non-severe) disease was broadly defined as requiring ITU admission, requiring oxygen as a hospital inpatient or in-hospital death (where this had not already been disaggregated into disease severity vs. mortality). Meta-analyses were performed for four 'fair' quality studies (see Figure 7 and 8). Current smokers were at increased risk of greater disease severity compared with never smokers (RR = 1.39, 95% CI = 1.09-1.77, p < .01, I^2 = 0%). No significant difference was observed between former and never smokers (RR = 1.40, 95% CI = 0.76-2.59, p = .28, I^2 = 74%).

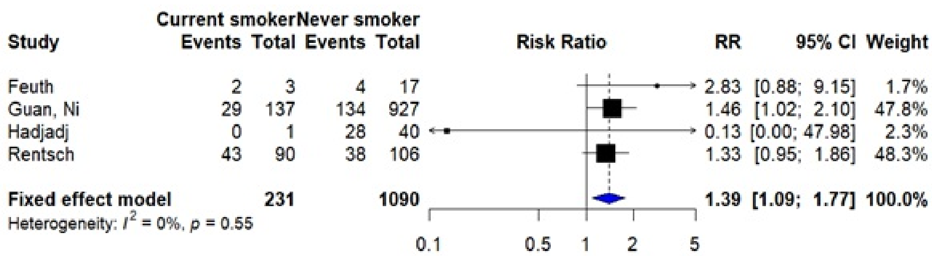


Figure 7. Forest plot for the risk of severe disease in current vs. never smokers.

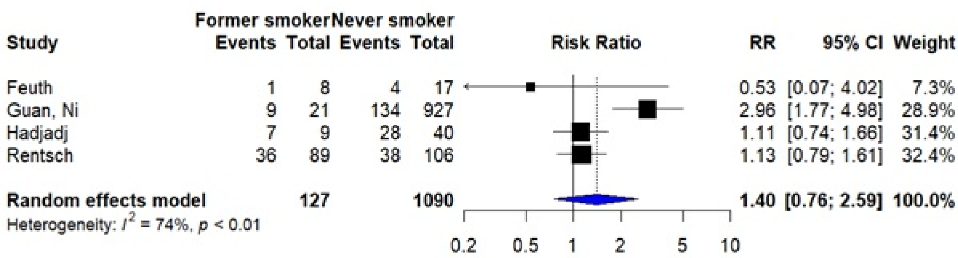


Figure 8. Forest plot for the risk of severe disease in former vs. never smokers.

Mortality by smoking status

Seventeen studies reported mortality from COVID-19 by smoking status (see Table 6), with three 'fair' quality studies. Meta-analyses were performed for two 'fair' quality studies with event data (see Figure 9 and 10). There was no significant difference between current and never (RR = 1.41, 95% CI = 0.91-2.20, p = .12, I^2 = 40%) or former and never smokers (RR = 0.98, 95% CI = 0.65-1.48, p = .93, I^2 = 0%) in the risk of mortality from COVID-19. The third 'fair' quality study reported hazard ratios adjusted for age and sex, suggesting an increased hazard of death in current (HR = 1.25, 95% CI = 1.12-1.40) and former (HR = 1.80, 95% CI = 1.70-1.90) compared with never smokers. In the adjusted primary analysis, the hazard in former smokers remained heightened (HR = 1.25, 95% CI = 1.18-1.33) but reversed in current smokers (HR = 0.88, 95% CI = 0.79-0.99). The result was not robust in unplanned sensitivity analyses including further adjustment for ethnicity, early censoring and complete data for smoking and BMI.

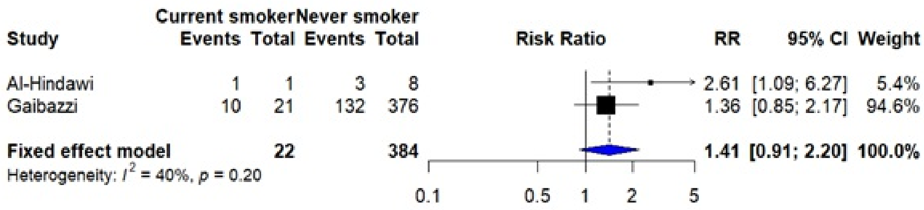


Figure 9. Forest plot for the risk of mortality in current vs. never smokers.

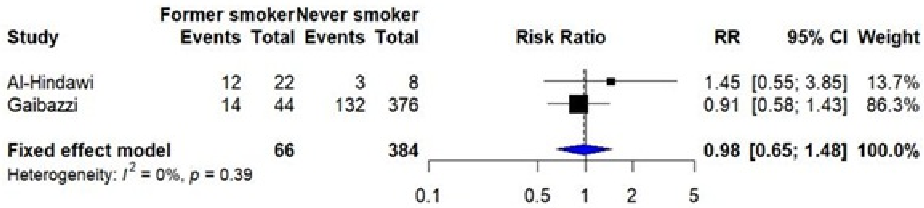


Figure 10. Forest plot for the risk of mortality in former vs. never smokers.

Table 2. SARS-CoV-2 infection by smoking status.

Author	Total population tested	SARS-CoV-2 negative N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Not stated (%)	SARS-CoV-2 positive N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Not stated (%)
Rentsch	3528*	2974* (84.30%)	1444 (48.55%)	704 (23.67%)	-	826 (27.77%)	-	554* (15.70%)	159 (28.70%)	179 (32.31%)	-	216 (38.99%)	-
Fontanet	661	490 (74.13%)	64 (13.06%)	-	-	426 (86.94%)	-	171 (25.87%)	5 (2.92%)	-	-	166 (97.08%)	-
Cho	1331	793 (59.58%)	142 (17.91%)	214 (26.99%)	-	437 (55.11%)	-	538 (40.42%)	111 (20.63%)	145 (26.95%)	-	282 (52.42%)	-
Shah	243**	212 (87.24%)	52 (24.53%)	47 (22.17%)	-	113 (53.30%)	-	29 (11.93%)	0 (0.00%)	9 (31.03%)	-	20 (68.97%)	-
Bello-Chavolla	62489	46960 (75.15%)	-	-	4835 (10.30%)	-	42125 (89.70%)	15529 (24.85%)	-	-	1374 (8.85%)	-	14155 (91.15%)
Kolin	1474***	805 (54.61%)	141 (17.52%)	307 (38.14%)	-	354 (43.98%)	3 (0.37%)	669 (45.39%)	72 (10.76%)	285 (42.60%)	-	303 (45.29%)	9 (1.35%)
de Lusignan	3291^	2740 (83.26%)	366 (13.36%)	1450 (52.92%)	-	924 (33.72%)	-	551 (16.74%)	47 (8.53%)	303 (54.99%)	-	201 (36.48%)	-
Valenti	789	689 (87.33%)	197 (28.59%)	-	-	-	492 (71.41%)	40 (5.07%)	7 (17.50%)	-	-	-	33 (82.50%)
Parrotta	76	39 (51.32%)	1 (2.56%)	10 (25.64%)	-	27 (69.23%)	1 (2.56%)	37 (48.68%)	1 (2.70%)	10 (27.03%)	-	25 (67.57%)	1 (2.70%)
Berumen	102875	71353 (69.36%)	-	-	7173 (10.05%)	64180 (89.95%)	-	31522 (30.64%)	-	-	2748 (8.72%)	28774 (91.28%)	-
Israel	24087	20076 (83.35%)	3711 (18.48%)	2670 (13.30%)	-	13695 (68.22%)	-	4011 (16.65%)	403 (10.05%)	471 (11.74%)	-	3137 (78.21%)	-
del Valle	1108`	143 (12.91%)	27 (18.88%)	53 (37.06%)	-	-	63 (44.06%)	965 (87.09%)	55 (5.70%)	293 (30.36%)	-	-	617 (63.94%)

Note. Niedzwiedz et al. reported on SARS-CoV-2 infection by smoking status in multivariable analyses but did not present raw data; * Data on smoking status were missing for 261 participants; ** Data on smoking status were missing for 75 participants; *** Data on smoking status were missing for 12 participants; ^ Data on smoking status were missing for 511 participants; ` Data on smoking status were missing on 376 participants.

Table 3. Hospitalisation for COVID-19 by smoking status.

Author	Population with outcome	Community N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	Hospitalised N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Rentsch	554	269 (48%)	69 (25.65%)	90 (33.46%)	-	110 (40.89%)	-	-	285 (51%)	90 (31.58%)	89 (31.23%)	-	106 (37.19%)	-	-
Petrilli	4103	2104 (51%)	108 (5.13%)	250 (11.88%)	-	-	1746 (82.98%)	-	1999 (48%)	104 (5.20%)	416 (20.81%)	-	-	1479 (73.99%)	-
Chow (US CDC)	6637	5143 (77%)	61 (1.19%)	80 (1.56%)	-	-	-	5002 (97.26%)	1494 (22%)	27 (1.81%)	78 (5.22%)	-	-	-	1389 (92.97%)
Argenziano	1000	151 (15%)	14 (9.27%)	18 (11.92%)	-	119 (78.81%)	-	-	849 (84%)	35 (4.12%)	161 (18.96%)	-	653 (76.91%)	-	-
Miyara	470	139 (29%)	14 (10.07%)	41 (29.50%)	-	77 (55.40%)	-	7 (5.04%)	340 (72%)	18 (5.29%)	111 (32.65%)	-	209 (61.47%)	-	2 (0.59%)
Lubetzky	54	15 (27%)	-	-	4 (26.67%)	-	-	11 (73.33%)	39 (72%)	-	-	8 (20.51%)	-	-	31 (79.49%)
Carrillo-Vega	9946	3922 (39%)	408 (10.40%)	-	-	-	-	3514 (89.60%)	6024 (60%)	486 (8.07%)	-	-	-	-	5538 (91.93%)
Yanover	4353	4180 (96%)	484 (11.58%)	118 (2.82%)	-	3578 (85.60%)	-	-	173 (3%)	30 (17.34%)	11 (6.36%)	-	132 (76.30%)	-	-
Hamer	387109	386349 (99%)	37333 (9.66%)	134542 (34.82%)	-	214474 (55.51%)	-	-	760 (0%)	93 (12.24%)	313 (41.18%)	-	354 (46.58%)	-	-
Heili-Frades	4712	1973 (41%)	121 (6.13%)	222 (11.25%)	-	-	1630 (82.62%)	1630 (82.62%)	2739 (58%)	112 (4.09%)	598 (21.83%)	-	-	2029 (74.08%)	-
Freites	123	69 (56%)	1 (1.45%)	-	-	-	-	68 (98.55%)	54 (43%)	3 (5.56%)	-	-	-	-	51 (94.44%)
Berumen	102875	18832 (18%)	-	-	1546 (8.21%)	-	17286 (91.79%)	-	12690 (12%)	-	-	1202 (9.47%)	-	11488 (90.53%)	-
Gianfrancesco	600	323 (53%)	-	-	61 (18.89%)	-	-	262 (81.11%)	277 (46%)	-	-	68 (24.55%)	-	-	209 (75.45%)
Chaudhry	40	19 (47%)	-	-	0 (0.00%)	-	-	19 (100.00%)	21 (52%)	-	-	6 (28.57%)	-	-	15 (71.43%)

Note. * Data on smoking status were missing for 31 participants; ** Data on smoking status were missing for 9 participants; ^ 22 individuals died in the emergency department and were thus not hospitalised but are included in the community sample; ‘Data on outcomes were missing for 525 participants.

Table 4. Disease severity by smoking status.

		Non severe disease							Severe disease						
Author	Population with severity	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Guan, Ni	1085[a]	913 (84%)	108 (11.83%)	12 (1.31%)	-	793 (86.86%)	-	-	172 (15%)	29 (16.86%)	9 (5.23%)	-	134 (77.91%)	-	-
Zhang, Dong	9[b]	3 (33%)	0 (0.00%)	3 (100.00%)	-	0 (0.00%)	-	-	6 (66%)	2 (33.33%)	4 (66.67%)	-	0 (0.00%)	-	-
Wan	9[c]	8 (88%)	8 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	1 (11%)	1 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-
Huang, Wang	3[d]	3 (100%)	3 (100.00%)	0 (0.00%)	-	0 (0.00%)	-	-	0 (0%)	0 (-)	0 (-)	-	0 (-)	-	-
Rentsch	285	168 (58%)	47 (27.98%)	53 (31.55%)	-	68 (40.48%)	-	-	117 (41%)	43 (36.75%)	36 (30.77%)	-	38 (32.48%)	-	-
Hu	323	151 (46%)	-	-	12 (7.95%)	-	139 (92.05%)	-	172 (53%)	-	-	26 (15.12%)	-	146 (84.88%)	-
Wang, Pan	125	100 (80%)	-	-	9 (9.00%)	-	91 (91.00%)	-	25 (20%)	-	-	7 (28.00%)	-	18 (72.00%)	-
Petrilli	1278	932 (72%)	62 (6.65%)	175 (18.78%)	-	-	391 (41.95%)	-	650 (50%)	28 (4.31%)	145 (22.31%)	-	-	477 (73.38%)	-
Kim	27[e]	21 (77%)	3 (14.29%)	-	-	-	18 (85.71%)	-	6 (22%)	2 (33.33%)	0 (0.00%)	-	-	4 (66.67%)	-
Shi, Yu	474[f]	425 (89%)	-	-	34 (8.00%)	-	391 (92.00%)	-	49 (10%)	-	-	6 (12.24%)	-	43 (87.76%)	-
Liao, Feng	148[g]	92 (62%)	-	-	5 (5.43%)	-	-	87 (94.57%)	56 (37%)	3 (5.36%)	-	-	-	-	53 (94.64%)
Shi, Ren	134	88 (65%)	-	-	8 (9.09%)	-	-	80 (90.91%)	46 (34%)	-	-	6 (13.04%)	-	-	40 (86.96%)
Hadjadj	50	15 (30%)	1 (6.67%)	2 (13.33%)	-	12 (80.00%)	-	-	35 (70%)	0 (0.00%)	7 (20.00%)	-	28 (80.00%)	-	-
Zheng, Xiong	73	43 (58%)	-	-	6 (13.95%)	37 (86.05%)	-	-	30 (41%)	-	-	2 (6.67%)	28 (93.33%)	-	-
de la Rica	48	26 (54%)	-	-	6 (23.08%)	-	-	20 (76.92%)	20 (41%)	-	-	4 (20.00%)	-	-	16 (80.00%)
Yin, Yang	106	47 (44%)	-	-	6 (12.77%)	-	-	41 (87.23%)	59 (55%)	-	-	12 (20.34%)	-	-	47 (79.66%)
Allenbach	147[h]	100 (68%)	-	-	9 (9.00%)	-	-	91 (91.00%)	47 (31%)	-	-	0 (0.00%)	-	-	47 (100.00%)
Goyal	393	263 (66%)	14 (5.32%)	-	-	-	-	249 (94.68%)	130 (33%)	6 (4.62%)	-	-	-	-	124 (95.38%)
Feng	454[i]	333 (73%)	27 (8.11%)	-	-	-	-	306 (91.89%)	121 (26%)	17 (14.05%)	-	-	-	-	104 (85.95%)
Yao	108	83 (76%)	1 (1.20%)	-	-	-	-	82 (98.80%)	25 (23%)	3 (12.00%)	-	-	-	-	22 (88.00%)
Sami	490	400 (81%)	53 (13.25%)	-	-	-	-	347 (86.75%)	90 (18%)	16 (17.78%)	-	-	-	-	74 (82.22%)
Regina	200	163 (81%)	9 (5.52%)	-	-	-	-	154 (94.48%)	37 (18%)	0 (0.00%)	-	-	-	-	37 (100.00%)
Feuth	28	21 (75%)	1 (4.76%)	7 (33.33%)	-	13 (61.90%)	-	-	7 (25%)	2 (28.57%)	1 (14.29%)	-	4 (57.14%)	-	-
Mejia-Vilet	329	214 (65%)	-	-	13 (6.07%)	-	-	201 (93.93%)	115 (34%)	-	-	10 (8.70%)	-	-	105 (91.30%)
Chen, Jiang	135	54 (40%)	-	-	4 (7.41%)	-	-	50 (92.59%)	81 (60%)	-	-	9 (11.11%)	-	-	72 (88.89%)
Vaquero-Roncero	146	75 (51%)	-	-	4 (5.33%)	-	-	71 (94.67%)	71 (48%)	-	-	6 (8.45%)	-	-	65 (91.55%)
Kim, Garg	2490[j]	1692 (67%)	112 (6.62%)	395 (23.35%)	-	-	1185 (70.04%)	-	798 (32%)	38 (4.76%)	247 (30.95%)	-	-	512 (64.16%)	-
Wu	174	92 (52%)	-	-	47 (51.09%)	-	45 (48.91%)	-	82 (47%)	11 (13.41%)	-	-	-	71 (86.59%)	-
Russell	106	87 (82%)	6 (6.90%)	22 (25.29%)	-	35 (40.23%)	-	24 (27.59%)	19 (17%)	1 (5.26%)	4 (21.05%)	-	7 (36.84%)	-	7 (36.84%)
Chaudhry	40	34 (85%)	-	-	5 (14.71%)	-	-	29 (85.29%)	6 (15%)	-	-	1 (16.67%)	-	-	5 (83.33%)
Patel	104	67 (64%)	25 (37.31%)	-	-	-	36 (53.73%)	6 (8.96%)	37 (35%)	18 (48.65%)	-	-	-	15 (40.54%)	4 (10.81%)
Garibaldi	832	532 (63%)	25 (4.70%)	107 (20.11%)	-	-	-	400 (75.19%)	300 (36%)	21 (7.00%)	81 (27.00%)	-	-	-	198 (66.00%)

Note. a Data on smoking status were missing for 14 participants; b Data on smoking status were missing for 131 participants; c Data on smoking status were missing for 126 participants; d Data on smoking status were missing for 38 participants; e Data on smoking status were missing for 1 participant; f Data on smoking status were missing for 13 participants; g Data on smoking status were missing for 1700 participants; h Data on smoking status were missing for 5 participants; i Data on smoking status were missing for 21 participants; j Data on smoking status were missing for 1 participant; * Patients with disease requiring hospital (but not ITU) admission.

Table 5. Mortality by smoking status.

		Recovered							Died						
Author	Population with mortality	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)	N (%)	Current smoker (%)	Former smoker (%)	Current/former smoker (%)	Never smoker (%)	Never/unknown smoker (%)	Not stated (%)
Chen	274*	161 (58%)	5 (3.11%)	5 (3.11%)	-	-	-	151 (93.79%)^	113 (41%)	7 (6.19%)	2 (1.77%)	-	-	-	104 (92.04%)
Zhou, Yu	191	137 (71%)	6 (4.38%)	-	-	-	-	131 (95.62%)	54 (28%)	5 (9.26%)	-	-	-	-	49 (90.74%)
Yang, Yu	52	20 (38%)	2 (10.00%)	-	-	-	18 (90.00%)	-	32 (61%)	-	-	-	-	32 (100.00%)	-
Gaibazzi	441	285 (64%)	11 (3.86%)	30 (10.53%)	-	244 (85.61%)	-	-	156 (35%)	10 (6.41%)	14 (8.97%)	-	132 (84.62%)	-	-
Borobia	2226	1766 (79%)	113 (6.40%)	-	-	-	-	1653 (93.60%)	460 (20%)	44 (9.57%)	-	-	-	-	416 (90.43%)
Giacomelli	233	185 (79%)	-	-	53 (28.65%)	132 (71.35%)	-	-	48 (20%)	-	-	17 (35.42%)	31 (64.58%)	-	0 (0.00%)
Yao	108	96 (88%)	1 (1.04%)	-	-	-	-	95 (98.96%)	12 (11%)	3 (25.00%)	-	-	-	-	9 (75.00%)
Carillo-Vega	9946**	8983 (90%)	795 (8.85%)	-	-	-	-	8188 (91.15%)	963 (9%)	99 (10.28%)	-	-	-	-	864 (89.72%)
Heng	51	39 (76%)	6 (15.38%)	-	-	-	-	33 (84.62%)	12 (23%)	1 (8.33%)	-	-	-	-	11 (91.67%)
Heili-Frades	4712	4086 (86%)	210 (5.14%)	659 (16.13%)	-	-	3217 (78.73%)	-	626 (13%)	23 (3.67%)	161 (25.72%)	-	-	442 (70.61%)	-
Kim, Garg	2490	2070 (83%)	128 (6.18%)	481 (23.24%)	-	-	1461 (70.58%)	-	420 (16%)	22 (5.24%)	161 (38.33%)	-	-	236 (56.19%)	-
Al-Hindawi	31	15 (48%)	0 (0.00%)	10 (66.67%)	-	5 (33.33%)	-	-	16 (51%)	1 (6.25%)	12 (75.00%)	-	3 (18.75%)	-	-
Louis	22	16 (72%)	-	-	7 (43.75%)	-	-	9 (56.25%)	6 (27%)	-	-	3 (50.00%)	-	-	3 (50.00%)
Soto-Mota	400	200 (50%)	-	-	23 (11.50%)	-	-	177 (88.50%)	200 (50%)	-	-	25 (12.50%)	-	-	175 (87.50%)
Garibaldi	747***	634 (84%)	36 (5.68%)	129 (20.35%)	-	-	-	469 (73.97%)	113 (15%)	6 (5.31%)	36 (31.86%)	-	-	-	71 (62.83%)
Docherty	13364`	8199 (61%)	370 (4.51%)	1832 (22.34%)	-	4179 (50.97%)	-	1818 (22.17%)	5165 (38%)	214 (4.14%)	1350 (26.14%)	-	2105 (40.76%)	-	1496 (28.96%)

Note. Solis et al. and the OpenSAFELY Collaborative reported on mortality by smoking status in a multivariable analysis but did not present raw data on both exposure and outcome; * Data on smoking status were missing for 274 participants; ** Data on smoking status were missing for 598 participants; *** Data on smoking status were missing for 85 participants; ` Data on smoking status were missing for 6769 participants; ^ No smoking history defined as <30 pack-years of smoking.

Discussion

This rapid review of 102 studies found substantial uncertainty arising from the recording of smoking status. Notwithstanding these uncertainties, compared with overall adult national prevalence estimates, recorded current and former smoking rates in most countries were lower than expected. From available data, there was insufficient evidence to conclude that current and/or former smoking status is associated with hospitalisation or mortality. There was some evidence from 'fair' quality studies that the risk of SARS-CoV-2 infection is reduced, and disease severity in those hospitalised for COVID-19 is greater, in current but not former smokers compared with never smokers.

Infection by smoking status

In seven 'fair' quality studies, evidence suggest that current (but not former) smokers in the community are less likely to test positive for SARS-CoV-2 compared with never smokers. It should be noted that criteria for accessing testing will vary during the course of the epidemic. It is possible that current and former smokers are more likely to receive a test due to increased prevalence of cough or altered sense of smell or taste[125], which are used as screening criteria. Infection positivity rates estimated among random samples will be more informative than currently available data. Smoking status is being collected in at least one large representative infection and antibody survey in the UK[126].

Hospitalisation and disease severity by smoking status

As reported elsewhere16, smoking prevalence among multiple hospital and community cohorts was consistently lower than national estimates from China, USA, France, Spain, Israel, Italy, Mexico, Finland, Iran, Kuwait and Switzerland. In a single study conducted in Korea and nine studies of varying quality conducted in the UK, however, current and former smoking rates were similar to those expected.

In five 'fair' quality studies across four countries, there was no evidence that current or former smokers are at lower risk of hospitalisation for COVID-19 compared with never smokers among those identified as testing positive. There was some evidence from four 'fair' quality studies that current smokers are at increased risk of greater disease severity compared with never smokers.

Mortality by smoking status

In three 'fair' quality studies, there was inconsistent evidence on the association of smoking status and the risk of death from COVID-19. Given lack of knowledge of the disease progression and long-term outcomes of COVID-19 disease, it is unclear whether studies conducted thus far in the pandemic have monitored patients for a sufficient time period to report complete survival outcomes or whether this reflects early censoring.

Issues complicating interpretation

Interpretation of these early studies is complicated by several factors (see Figure 11). First, exposure to SARS-CoV-2 is heterogeneous with different subgroups being at heightened risk of infection at different stages of the pandemic. This will likely introduce bias in studies assessing the rate of infection by smoking status conducted early on. Second, as mentioned above, current and former smokers may be more likely to meet local criteria for community testing due to increased prevalence of symptoms consistent with SARS-CoV-2 infection, such as cough, increased sputum production or altered sense of smell or taste125. Third, testing for acute infection requires swabbing of the mucosal epithelium, which may be disrupted in current smokers, potentially altering the sensitivity of assays[87].

Fourth, most included studies relied on electronic health records (EHRs) as the source of information on smoking status. Research shows large discrepancies between EHRs and actual behaviour[127]. Known failings of EHRs include implausible longitudinal changes, such as former smokers being recorded as never smokers at subsequent hospital visits[127]. Misreporting on the part of the patient (perhaps due to perceived stigmatisation) has also been observed, with biochemical measures showing higher rates of smoking compared with self-report in hospitalised patients in the US128. It is hence possible that under-reporting of current and former smoking status occurred across the included studies. Fifth, individuals with severe COVID-19 symptoms may have stopped smoking prior to admission to a care facility and may therefore not have been recorded as current smokers (i.e. reverse causality).

Sixth, smokers with COVID-19 may be less likely to receive a SARS-CoV-2 test or present to hospital due to lack of access to healthcare and may be more likely to die in the community from sudden complications (i.e. self-selection bias) and thus not be recorded. Seventh, if there is a protective effect of nicotine on COVID-19 disease outcomes, abrupt nicotine withdrawal upon hospitalisation may lead to worse outcomes[12]. Eight, during periods of heightened demand of limited healthcare resources, current smokers with extensive comorbidities may have reduced priority for intensive care admission, thus leading to higher in-hospital mortality.

Another important issue is that the reason for hospitalisation varies by country and time in the pandemic. For example, early cases may have been hospitalised for isolation and quarantine reasons and not due to medical necessity. It is plausible that this may have skewed early data towards less severe cases. In addition, the observed association between current smoking and disease severity may be explained by collider bias129, where conditioning on a collider (e.g. testing or hospitalisation) by design or analysis may introduce a spurious association between smoking (a potential cause of testing or hospitalisation) and SARS-CoV-2 infection/adverse outcomes from COVID-19 (potentially exacerbated by smoking)[130].

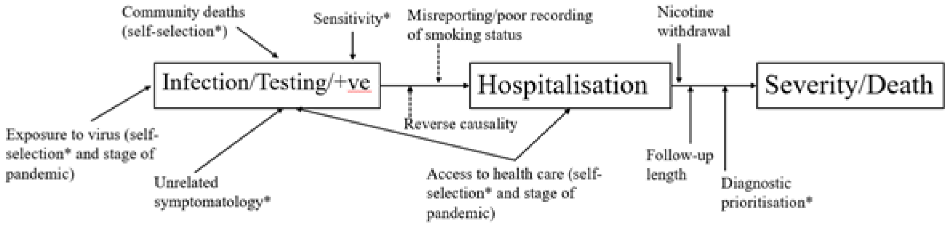


Figure 11. A schematic of some of the interpretation issues for the association of smoking and SARS-CoV-2/COVID-19. * Indicates potential confounding with smoking status.

Limitations

This rapid review was limited by not having two independent reviewers extracting data, limiting the search to one electronic database and one pre-print server and by not including at least three large population surveys due to their reliance on self-reported SARS-CoV-2 infection (which means they are not meeting our eligibility criteria)[125,131,132]. Population surveys – particularly with linked health data – will be included in future review versions to help mitigate some of the limitations of healthcare based observational studies. The comparisons with national estimates of smoking prevalence did not adjust observed prevalence for the demographic profile of those admitted/tested. Other reviews focused on this comparison have applied adjustment for sex, and continue to find lower than expected prevalence – notwithstanding the issues complicating interpretation described above[16].

Implications for research, policy and practice

Further scientific research is needed to resolve the mixed findings summarised in our review. First, clinical trials of the posited therapeutic effect of nicotine could have important implications both for smokers and for improved understanding of the SARS-CoV-2 virus. Such trials should focus on medicinal nicotine (as smoked tobacco is a dirty delivery mechanism that could mask beneficial effects) and potentially differentiate between different modes of delivery (i.e. inhaled vs. not) since this can affect pharmacokinetics[133] and potential therapeutic effects. A second research priority would be a large, representative (randomly sampled) population survey with a validated assessment of smoking status which distinguishes between recent and long-term ex-smokers – ideally biochemically verified – and assesses seroprevalence and links to health records.

In the meantime, public-facing messages about the possible protective effect of smoking or nicotine are premature. In our view, until there is further research, the quality of the evidence does not justify the huge risk associated with a message likely to reach millions of people that a lethal activity, such as smoking, may protect against COVID-19. It continues to be appropriate to recommend smoking cessation and emphasise the role of alternative nicotine products to support smokers to stop as part of public health efforts during COVID-19. At the very least, smoking cessation reduces acute risks from cardiovascular disease and could reduce demands on the healthcare system[134]. GPs and other healthcare providers can play a crucial role – brief, high-quality and free online training is available at National Centre for Smoking Cessation and Training.

Conclusion

Across 102 studies, there is substantial uncertainty arising from the recording of smoking status on whether current and/or former smoking status is associated with SARS-CoV-2 infection, hospitalisation or mortality. There is some evidence that current smoking compared with never is associated with reduced risk of testing positive in the community but greater disease severity in those hospitalised for COVID-19.

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Declaration of conflicts of interest

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Appendix 1

We used the following three criteria from the NIH National Heart, Lung and Blood Institute quality assessment tool for observational cohort and cross-sectional studies to assess study quality.

8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?

9: Were the exposure measures (independent variables) clearly defined, valid, reliable and implemented consistently across all study participants?

14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Lead Author	8.	9.	14.	Missing data	Overall rating (Poor, Fair, Good)
Guan, Ni	Yes	Yes	No	1.27%	Fair
Guan, Liang	No	No	Yes	0.00%	Poor
Lian	No	No	No	93.15%	Poor
Jin	No	No	No	93.70%	Poor
Chen	No	No	No	93.07%	Poor
Zhou, Yu	No	No	No	94.24%	Poor
Mo	No	No	No	96.13%	Poor
Zhang, Dong	No	No	No	93.57%	Poor
Wan	No	No	No	93.33%	Poor
Liu, Tao	No	No	No	93.59%	Poor
Huang, Wang	No	No	No	92.68%	Poor
Zhang, Cai	No	No	No	93.64%	Poor
Guo	No	No	No	90.37%	Poor
Liu, Ming	No	No	No	90.24%	Poor
Huang, Yang	No	No	No	88.89%	Poor
Xu	No	No	No	88.68%	Poor
Li	No	No	No	82.35%	Poor
Rentsch	Yes	Yes	Yes	5.30%	Fair
Hu	No	No	Yes	88.24%	Poor
Wang, Pan	No	No	No	87.20%	Poor
Chow (US CDC)	No	No	No	96.36%	Poor
Petrilli	No	No	Yes	0.00%	Poor
Dong, Cao	No	No	No	88.89%	Poor
Kim	No	No	No	82.14%	Poor
Shi, Yu	No	No	No	91.79%	Poor
Yang, Yu	No	No	No	96.15%	Poor
Argenziano	Yes	Yes	No	0.00%	Fair
Solis	No	No	No	90.62%	Poor
Richardson	No	No	No	37.42%	Poor
Fontanet	No	No	Yes	0.00%	Poor
Zheng, Gao	No	No	No	87.88%	Poor
Liao, Feng	No	No	No	99.57%	Poor
Rodriguez	No	No	No	0.00%	Poor
Magagnoli	No	No	No	85.87%	Poor
Shi, Ren	No	No	No	89.55%	Poor
Hadjadj	Yes	Yes	No	0.00%	Fair
Niedzwiedz	Yes	Yes	Yes	0.59%	Fair
Gold (US CDC)	No	No	No	94.75%	Poor
Yu, Cai	No	No	No	91.58%	Poor
Zheng, Xiong	No	No	No	0.00%	Poor
Miyars	Yes	Yes	Yes	1.88%	Fair
de la Rica	No	No	Yes	79.17%	Poor
Yin, Yang	No	No	No	83.02%	Poor
Gaibazzi	Yes	Yes	Yes	0.00%	Fair
Shi, Zuo	No	No	No	69.79%	Poor
Cho	Yes	Yes	Yes	0.00%	Fair
Allenbach	No	No	No	93.42%	Poor
Robilotti	Yes	Yes	No	1.65%	Fair

The Opensafely Collaborative	Yes	Yes	Yes	4.16%	Fair
Borobia	No	No	No	92.95%	Poor
Giacomelli	No	No	No	0.00%	Poor
Shah	Yes	No	No	23.73%	Poor
Bello-Chavolla	No	No	No	90.06%	Poor
Kolin	Yes	Yes	No	0.81%	Fair
Lubetzky	No	No	No	77.78%	Poor
Goyal	No	No	No	94.91%	Poor
Feng	No	No	No	90.76%	Poor
Yao	No	No	No	96.30%	Poor
Sami	No	No	No	0.00%	Poor
Almazeedi	No	No	Yes	0.00%	Poor
Carillo, Vega	No	No	No	0.00%	Poor
Yanover	Yes	Yes	No	0.00%	Fair
Hamer	Yes	Yes	Yes	0.00%	Fair
Regina	No	No	No	95.50%	Poor
de Lusignan	Yes	Yes	Yes	13.44%	Fair
Targher	No	No	No	91.74%	Poor
Valenti	No	No	No	74.14%	Poor
Feuth	Yes	Yes	No	0.00%	Fair
Heng	No	No	No	86.27%	Poor
Parrotta	Yes	Yes	No	2.63%	Fair
Shekhar	No	No	No	52.00%	Poor
Megia-Vilet	No	No	No	93.01%	Poor
Chen, Jiang	No	No	No	90.37%	Poor
Li, Chen	No	No	No	94.35%	Poor
Rimland	No	No	No	81.82%	Poor
Palaiodimos	No	No	No	0.00%	Poor
Ip	Yes	Yes	No	14.61%	Fair
Heili-Frades	No	No	Yes	11.16%	Poor
Vaquero-Roncer	No	No	No	93.15%	Poor
Kim, Garg	No	No	Yes	0.08%	Poor
Wu	No	No	No	66.67%	Poor
Shi, Zhao	No	No	No	95.05%	Poor
Kimmig	No	No	No	63.33%	Poor
Al-Hindawi	Yes	Yes	No	0.00%	Fair
Basse	No	No	No	82.27%	Poor
Freites	No	No	Yes	96.75%	Poor
Alshami	No	No	No	82.03%	Poor
Russell	Yes	No	Yes	29.25%	Poor
Berumen	No	No	Yes	0.00%	Poor
Gianfrancesco	No	No	No	13.67%	Poor
Li, Long	No	No	No	94.48%	Poor
Batty	No	No	No	88.77%	Poor
Israel	Yes	Yes	Yes	0.00%	Fair
del Valle	Yes	No	Yes	71.16%	Poor
Zuo, Zuo	No	No	No	72.73%	Poor
Chaudhry	No	No	No	85.00%	Poor
Louis	No	No	No	54.55%	Poor
Soto-Mota	No	No	No	88.00%	Poor
Patel	No	No	No	9.62%	Poor
Garibaldi	No	No	No	71.88%	Poor
Docherty	Yes	No	Yes	29.55%	Poor
Boulware	NA	NA	NA	96.71%	NA