


ORIGINAL



Nicotine patches in patients on mechanical ventilation for severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial

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Abstract

Purpose: Epidemiologic studies have documented lower rates of active smokers compared to former or non-smokers in symptomatic patients affected by coronavirus disease 2019 (COVID-19). We assessed the efficacy and safety of nicotine administered by a transdermal patch in critically ill patients with COVID-19 pneumonia.

Methods: In this multicentre, double-blind, placebo-controlled trial conducted in 18 intensive care units in France, we randomly assigned adult patients (non-smokers, non-vapers or who had quit smoking/vaping for at least 12 months) with proven COVID-19 pneumonia receiving invasive mechanical ventilation for up to 72 h to receive transdermal patches containing either nicotine at a daily dose of 14 mg or placebo until 48 h following successful weaning from mechanical ventilation or for a maximum of 30 days, followed by 3-week dose tapering by 3.5 mg per week. Randomization was stratified by centre, non- or former smoker status and Sequential Organ Function Assessment score (< or ≥ 7). The primary outcome was day-28 mortality. Main prespecified secondary outcomes included 60-day mortality, time to successful extubation, days alive and free from mechanical ventilation, renal replacement therapy, vasopressor support or organ failure at day 28.

Results: Between November 6th 2020, and April 2nd 2021, 220 patients were randomized from 18 active recruiting centers. After excluding 2 patients who withdrew consent, 218 patients (152 [70%] men) were included in the analysis: 106 patients to the nicotine group and 112 to the placebo group. Day-28 mortality did not differ between the two groups (30 [28%] of 106 patients in the nicotine group vs 31 [28%] of 112 patients in the placebo group; odds ratio

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The members of the COVID-REA Trial Group are listed in the Acknowledgement section.

1.03 [95% confidence interval, CI 0.57–1.87]; $p=0.46$). The median number of day-28 ventilator-free days was 0 (IQR 0–14) in the nicotine group and 0 (0–13) in the placebo group (with a difference estimate between the medians of 0 [95% CI -3–7]). Adverse events likely related to nicotine were rare (3%) and similar between the two groups.

Conclusion: In patients having developed severe COVID-19 pneumonia requiring invasive mechanical ventilation, transdermal nicotine did not significantly reduce day-28 mortality. There is no indication to use nicotine in this situation.

Keywords: Acute respiratory failure, Nicotine, Nicotinic receptor, COVID-19, Intensive care units, Randomized trial, Ventilation, Artificial

Introduction

The world population remains at risk for coronavirus disease 2019 (COVID-19), especially with the emergence of genetic variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with increase in transmissibility, potential for more severe disease and significant reduction in neutralization by antibodies generated during previous infection or vaccination [1, 2]. Thus, there is still an urgent need for effective, easy-to-use and safe medications for patients who develop severe forms of COVID-19.

Early epidemiologic studies documented lower rates of active smokers compared to former or non-smokers in symptomatic COVID-19 patients [3–9], although more severe forms of the disease were reported among smokers or former smokers once infected [10, 11]. It was hypothesized that nicotine may interact with SARS-CoV-2 entry in human cells by downregulating the expression of angiotensin converting enzyme 2 (ACE2), the principal receptor for the virus [12–15]. SARS-CoV-2 may also interact with the nicotinic cholinergic system, particularly with $\alpha 7$ nicotinic acetylcholine receptors (nAChRs), leading to an increased inflammatory response that might be mitigated by nicotine, a competitive agonist of these receptors [14, 16–20]. Nicotine may likewise mediate cholinergic anti-inflammatory effects by decreasing pro-inflammatory cytokine production through the activation of nAChRs, which are expressed on human bronchial epithelial and endothelial cells, macrophages and other immune cells [14, 15, 17, 18, 20]. Favourable effects of nicotine have indeed been reported in inflammatory syndromes such as Behcet's disease or ulcerative colitis [21].

We designed a multicentre, randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of nicotine administered by a transdermal patch in critically ill patients with COVID-19 pneumonia who were receiving invasive mechanical ventilation.

Take-home message

Early epidemiologic studies documented lower rates of active smokers compared to former or non-smokers in symptomatic patients affected by coronavirus disease 2019 (COVID-19). It was hypothesized that nicotine may interact with SARS-CoV-2 entry in human cells by downregulating the expression of angiotensin converting enzyme 2, and might mitigate the inflammatory response induced by the virus through activation of the nicotinic cholinergic system. This multicentre, randomized, double-blind, placebo-controlled trial aimed to determine the efficacy and safety of nicotine administered by a transdermal patch in critically ill patients with COVID-19 pneumonia who were receiving invasive mechanical ventilation. The results show that transdermal nicotine did not significantly reduce day-28 mortality. 60-Day mortality, time to successful extubation, days alive and free from mechanical ventilation, renal replacement therapy, vasopressor support or organ failure were also not modified by nicotine.

Methods

Trial design and oversight

This multicentre, double-blind, placebo-controlled randomized trial was sponsored by the Direction de la Recherche Clinique et de l'innovation (DRCI), Assistance Publique—Hôpitaux de Paris, France, with a research grant from the French Ministry of Health (Programme Hospitalier de Recherche Clinique, PHRC). An independent data and safety monitoring committee periodically reviewed trial outcomes. The members of the writing committee wrote all drafts of the manuscript. All authors approved the final version of the manuscript, and agreed to submit it for publication. They also verified the data and vouched for the completeness of the data, the accuracy of the analyses, and the fidelity of the trial to the protocol.

Pierre Fabre (Paris, France) provided nicotine patches (Nicopatchlib®). Neither Pierre Fabre nor the study sponsors participated in the study design, data collection, analysis and interpretation, or in the writing or submission of the study report. Additional information is provided in the Supplementary Appendix.

Ethical aspects

The study protocol was approved by the independent ethics committees (Comité de Protection des Personnes CPP SUD-EST VI, Clermont-Ferrand, on September 28 2020, #AU 1650) and the competent French Health Authorities (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM, on October 2 2020, #EudraCT 2020-003723-42). Informed consent was obtained from a close relative or surrogate prior to inclusion. In accordance with French law, when such a person was absent, the patient was randomized using deferred consent whereby the patient was asked to give consent for continuation of the trial when his/her condition allowed. The trial was registered on October 22, 2020, before the inclusion of the first patient at Clinicaltrials.gov (identifier# NCT04598594).

Patients

Patients were eligible for enrolment if they were endotracheally intubated and receiving ventilation for <72 h, had proven COVID-19 infection and were non-smokers, non-vapers or had quit smoking/vaping for at least 12 months.

Exclusion criteria were age < 18 years; anticipated duration of mechanical ventilation \leq 48 h; pregnant or lactating women; long-term chronic respiratory insufficiency with baseline PaCO₂ > 60 mmHg or treated with oxygen therapy or non-invasive ventilation, with the exception of CPAP/BiPAP for sleep apnoea; malignancy or severe disease with life expectancy < 1 year; patient moribund on the day of randomization or with a Simplified Acute Physiology Score [22] (SAPS II) > 90; cerebral deficiency with dilated areactive pupils or irreversible neurological pathology. Other exclusion criteria are reported in the Supplement.

Trial procedures

Randomization was stratified by centre, smoker status (former or non-smoker) and Sequential Organ Function Assessment (SOFA) score (< or \geq 7). Allocation concealment was assured through a centralized, secure, Web-based randomization system.

Patients received transdermal patches containing either nicotine at a daily dose of 14 mg (determined after an extensive review of the literature of the use of transdermal nicotine in non- or former smokers [16]) or placebo until 48 h following successful weaning from mechanical ventilation or for a maximum of 30 days, followed by 3-week dose tapering by 3.5 mg per week. The study protocol provided guidance for drug adjustment or cessation in case of suggestive signs of overdose, adverse events or the occurrence of severe renal or hepatic failure. Treatments for smoking cessation such as varenicline,

bupropion or other nicotine substitute were not permitted. All the patients were treated according to local [24] and international standards [25] of care for COVID-19, which included dexamethasone, antibiotic agents, anticoagulants, remdesivir and tocilizumab, as appropriate. Patients were assessed daily while hospitalized in the intensive care unit. Follow-up visits occurred on days 28 and 60 post-randomization and 2 and 8 weeks after the first day of nicotine tapering. Prespecified reasons for permanent discontinuation of the trial intervention are described in the protocol.

Endpoints

The primary endpoint was day-28 mortality. Other endpoints included mortality at day 60; time to successful extubation, i.e. without reintubation or death in the following 48 h and for tracheotomized patients, alive and not ventilated for 48 h (with death and therapeutic limitations as competitive risks); the number of ventilator-free days between inclusion and day 28, defined as the number of days alive and free from mechanical ventilation (patients were only considered as free from mechanical ventilation if they had a successful extubation, defined as being free from mechanical ventilation for at least 48 consecutive hours and non-survivors were considered to have no ventilator-free days). Other secondary endpoints, safety outcomes related to nicotine use and health-related quality of life outcomes are detailed in the Supplement.

Statistical analysis

The expected 28-day mortality rate was 35% for the placebo group [27, 28]; to demonstrate a decrease to 20% for those receiving nicotine, for 80% power and one-sided $\alpha=0.05$, 110 participants per group had to be included. A non-binding futility analysis was planned after 50% of inclusions to stop recruitment if the probability of showing a difference in 28-day mortality greater than 15 points at the final analysis was less than 10%. Alpha and beta spending were low so no sample size inflation was needed. The futility analysis was not performed because inclusion rate was faster than expected and almost all patients were randomized before futility analysis results.

Baseline characteristics are reported as proportions (%) for categorical variables and as means (\pm standard deviations, SD) or medians (interquartile range, IQR) for continuous variables, as appropriate. Efficacy endpoints were analysed according to intention-to-treat principles. Safety endpoints were analysed in all patients who received at least one transdermal patch. The primary endpoint of death at day 28 was compared with the chi-square test. The ranked composite score incorporating death and days free from mechanical ventilation among

survivors through day 60 were compared using Mann–Whitney test and measured with net benefit (see appendix pp 9) [30]. Two planned sensitivity analyses were performed: the first used logistic regression analysis to adjust for stratification parameters, the second regarded the per-protocol population (excluding patients receiving treatment for less than 72 h). Pre-specified subgroup analyses were also conducted (see the Supplement).

Analyses were conducted at the one-sided α risk of 5% for the primary outcome and the two-sided α risk of 5% for all other outcomes. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria), version 3.5.1.

Results

Study population

Between November 6th 2020 and April 2nd 2021, 220 patients were randomized from 18 active recruiting centres. After excluding 2 patients who withdrew consent, 218 patients (152 [70%] men) were included in the analysis: 106 patients to the nicotine group and 112 to the placebo group (Fig. 1). In the placebo group, one patient did not receive the transdermal treatment and another died within less than 72 h after randomization. Baseline demographic and disease characteristics were similar between groups (Table 1). The mean (SD) age was 60 ± 12 years in the nicotine group and 62 ± 12 years in the placebo group. The mean time between symptom onset and initiation of invasive mechanical ventilation was 10 ± 5 days in both groups. The comorbidities, severity of critical illness and acute respiratory distress syndrome (ARDS) were similar between the two groups, as indicated by the absence of difference for the SAPS II and SOFA scores, vasopressor support, lung compliance, and $\text{PaO}_2/\text{FiO}_2$ ratio on admission to the intensive care unit (ICU) (Table 1). The ventilator settings did not differ between the two groups, nor did the use of corticosteroids, angiotensin conversion enzyme inhibitors or angiotensin receptor blockers and tocilizumab (Table 1). There was no missing data for the primary endpoint and very few for secondary endpoints (Table S1 in the Supplement).

Primary endpoint

The mortality rate at day 28 in the intention-to-treat population did not differ between the two groups (30 [28%] of 106 patients in the nicotine group vs 31 [28%] of 112 patients in the placebo group; odds ratio 1.03 [95% confidence interval, CI, 0.57–1.87]; $p = 0.459$; Table 2, Fig. 2). Adjusting for stratification parameters did not change this result (odds ratio, 1.01 [95% CI 0.54–1.89], $p = 0.973$). The per-protocol sensitivity analysis (odds ratio 1.03 [95% CI 0.56–1.87], $p = 0.466$) and the pre-specified subgroup analyses (Fig. 3) were consistent with the main result and

did not show any beneficial effect of nicotine. Noticeably, no difference in nicotine effect existed for patients included before or after Feb 17th, 2021, when the median number of patients enrolled in the trial was reached and a few days before the alpha variant of SARS-CoV-2 became dominant in France.

Secondary endpoints

The ranked composite endpoint, incorporating death and days free from mechanical ventilation through day 60, was not significantly different between treatment groups (table S1 in the Supplement). The median number of ventilator-free days at day 28 was 0 (IQR 0–14) in the nicotine group and 0 (0–12) in the placebo group (with a difference estimate between the medians of 0 [95% CI –2–7; Table 2, figure S2 in the Supplement). The median numbers of vasopressor- and renal failure-free days and the number of patients supported by extracorporeal membrane oxygenation (ECMO) during the ICU stay were not different between the 2 groups. The rate of extubated patients at day 28, the time to successful extubation (figure S3, in the Supplement) and the median duration of invasive mechanical ventilation, length of intensive care unit and hospital stays were also similar between the two groups (Table 2).

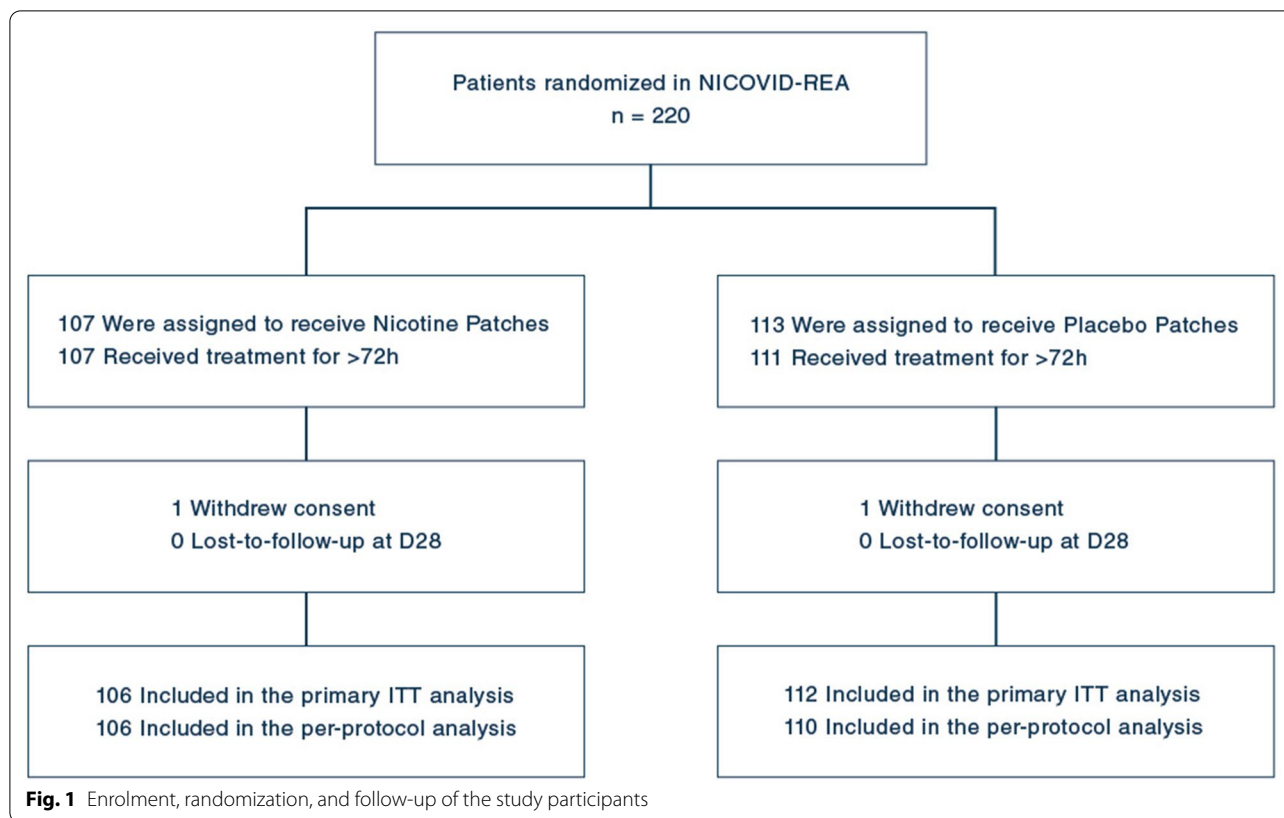
Safety endpoints

The median number of days under nicotine in the ICU was 18 [12–29] with a median daily dose of 14 mg (IQR 14–14). Nicotine was tapered over 19 [10–21] days. The number of adverse events related to nicotine was low (3%) and similar between the two groups (Table 3). There was no difference in the occurrence of ventilator-acquired pneumonia, bacteraemia, pneumothorax, need for renal replacement therapy and thromboembolism between the two groups (Table 3).

Follow-up at weeks 2 and 8 after initiation of nicotine tapering was available for 93 and 100 patients. No patient reported smoking, vaping or taking nicotine substitutes. The scores of desire to smoke, and nicotine withdrawal symptoms were not different between groups, as were the scores evaluating anxiety, depression, PTSD symptoms and insomnia (table S2, appendix p 13–14).

Discussion

In this randomized, double-blind, placebo-controlled phase 3, clinical trial involving hospitalized patients with COVID-19 pneumonia receiving invasive mechanical ventilation, transdermal nicotine did not significantly reduce mortality at day 28. No significant difference existed in any secondary outcomes evaluated, including mortality at day 60, durations of invasive mechanical



ventilation, renal and cardiovascular failures, ICU and hospital stays.

The “nicotine hypothesis” linking lower than expected COVID-19 cases among active smokers to putative preventive and therapeutic effects of nicotine against SARS-CoV-2 emerged early in the course of the pandemic [3]. In the weeks following the pre-print publication of these data, social media platforms like Twitter relayed thousands of messages about the benefits of smoking or vaping in the context of COVID-19 [31, 32]. However, the effects of nicotine and cigarette smoke on SARS-CoV-2 replication and the expression of its entry receptor ACE2 remain highly controversial with recent reports of both increased [33, 34] and decreased [35] ACE2 levels. Alternatively, cumulative smoking exposure (in former or current smokers) was constantly associated with worse outcomes for COVID-19 [11, 36–38].

Our results demonstrate the absence of effect of nicotine in patients who had developed the most severe forms of COVID-19 pneumonia requiring invasive mechanical ventilation. Demographics, disease progression, and severity markers of our patients were in line with those of previous cohorts of mechanically ventilated COVID-19 ARDS. The 36% mortality rate at day 60 we observed is similar to that reported in the large epidemiologic French COVID-ICU cohort [27] (March to July 2020) and the

ICAR randomized trial [39] (April to October 2020) evaluating intravenous immunoglobulins in COVID-19 mechanically ventilated patients, but lower than that of other large European cohorts [28, 40, 41]. It should however be noted that the SAPS II [39] and SOFA [27] scores were higher in our patients, as were the rate of patients on vasopressor [27] and ECMO [27, 41, 42] support at randomization. The trajectory of our patient during ICU stay was also similar to other recent cohorts [28, 40, 41], with long ICU and hospital stays and frequent ventilator-associated pneumonia. Reassuringly, adverse events related to nicotine patches were rare and no sign of nicotine addiction was reported in the 8 weeks following ICU discharge.

Our trial has several limitations. First, the day 28 mortality we observed was lower than the hypothesis we had made based on preliminary data on COVID-19 patients’ outcomes [27, 28, 43]. However, the complete absence of difference between the outcomes of nicotine- and placebo-treated patients argue against any effect of the molecule in this context. Second, the study was conducted when the original SARS-CoV-2 virus and its alpha variant were dominant in France. Still, our results can be extended to the latest delta and omicron variants, for which virus entry into cells and pathophysiological mechanisms of the disease has not changed.

Table 1 Characteristics of the patients at randomization*

Characteristic	Nicotine (n = 106)	Placebo (n = 112)
Age, years	59.9 ± 11.7	61.8 ± 11.5
Male—no.	71 (67%)	81 (72%)
Body mass index, kg/cm ²	32.8 ± 7.7	31 ± 6.8
SAPS II	50.1 ± 15.7	52.5 ± 16.3
SOFA score	9.8 ± 2.6	9.3 ± 2.6
Comorbidities		
Hypertension	60 (57%)	68 (61%)
Diabetes	36 (34%)	54 (48%)
Ischemic cardiomyopathy	8 (8%)	10 (9%)
COPD	4 (4%)	3 (3%)
Other chronic respiratory disease	2 (2%)	2 (2%)
Former smoker	43 (41%)	41 (37%)
Immunocompromised	6 (6%)	7 (6%)
Time from		
1st symptoms to hospital admission, days	7 ± 3	7 ± 4
1st symptoms to ICU admission, days	8 ± 4	9 ± 4
1st symptoms to intubation, days	10 ± 5	10 ± 5
Treatments before or at randomization		
Anticoagulants	18 (17%)	18 (16%)
Antibiotic agent	10 (9%)	10 (9%)
Remdesivir	0 (0%)	0 (0%)
Tocilizumab	1 (1%)	0 (0%)
Dexamethasone	58 (55%)	58 (52%)
Other glucocorticoids	13 (12%)	11 (10%)
ACE inhibitors or ARB	40 (45%)	49 (54%)
Vasopressor support	62 (58%)	56 (50%)
Concomitant bacterial pneumonia	3 (3%)	11 (10%)
Mechanical ventilation settings		
Tidal volume, ml/kg PBW	6 ± 1.2	5.9 ± 1
Respiratory rate, /min	26 ± 5	26 ± 5
Plateau pressure, cmH ₂ O	25 ± 5	24 ± 4
PEEP, cmH ₂ O	12 ± 3	12 ± 3
Driving pressure, cmH ₂ O	13 ± 4	12 ± 3
Compliance, ml/cmH ₂ O	33 ± 14	34 ± 13
Arterial blood gases		
pH	7.39 ± 0.08	7.38 ± 0.08
PaCO ₂ , mmHg	44 ± 13	43 ± 9
PaO ₂ , mmHg	93 ± 36	93 ± 38
Bicarbonate, mmol/l	26 ± 4	25 ± 5
PaO ₂ /FiO ₂	155 ± 79	163 ± 78
Laboratory results		
Creatinine, micromol/l	89 ± 61	98 ± 64
Platelet, × 10 ³ /mm ³	263 ± 107	286 ± 110
Haemoglobin, g/dL	12 ± 1.9	11.6 ± 1.9
Lymphocyte count per mm ³	0.99 ± 1.03	0.96 ± 1.36
White blood cells per mm ³	11.1 ± 5.4	11.7 ± 8.6
Fibrinogen, mg/L	6.6 ± 1.7	6.1 ± 1.8
Adjuvant ARDS therapy		
Prone positioning	46 (43%)	47 (42%)

Table 1 (continued)

Characteristic	Nicotine (n = 106)	Placebo (n = 112)
Inhaled Nitric oxide or prostacyclin	7 (7%)	3 (3%)
ECMO	10 (9%)	9 (8%)
Renal replacement therapy	0 (0%)	3 (3%)
Pneumothorax	1 (1%)	3 (3%)

* Plus-minus values are means \pm SD

SAPS II Simplified Acute Physiology Score, SOFA Sequential Organ Function Assessment, COPD chronic obstructive pulmonary disease, ICU intensive care unit, ACE angiotensin conversion enzyme, ARB angiotensin receptor blocker, PBW predicted body weight, PEEP positive end-expiratory pressure, PaCO₂ partial pressure of arterial carbon dioxide, PaO₂ partial pressure of arterial oxygen, FIO₂ the fraction of inspired oxygen, PaO₂/FIO₂ the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, ARDS acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation

No significant differences were observed between the groups among characteristics evaluated at randomization

Table 2 Endpoints

Endpoint	Nicotine (n = 106)	Placebo (n = 112)	Odds ratio, sub-hazard ratio or difference (95% CI)*	P value
Primary endpoint				
Day 28 mortality—no.	30 (28%)	31 (28%)	1.03 (0.57–1.87)	0.459
Secondary endpoint				
Day 60 mortality [†]	38/101 (38%)	40/112 (37%)	1.09 (0.62–1.90)	
Time to successful extubation, days [‡]	23 [12–31]	27 [13–39]	1.01 [0.74; 1.39]	
ICU length of stay, days	17 [11–30]	21 [11–30]	– 4 [– 8; 2]	
Hospital length of stay, days	24 [15–42]	28 [18–55]	– 4 [– 10; 5]	
Day 1–28 ventilation-free days	0 [0–14]	0 [0–12]	0 [– 2; 7]	
Day 1–28 vasopressor-free days	9 [0–18]	8 [0–16]	2 [– 6; 9]	
Day 1–28 renal failure-free days	1 [0–15]	0 [0–12]	1 [– 3; 5]	
Prone position—no.	87 (82%)	87 (78%)	1.32 [0.68; 2.59]	
iNO or prostacyclin—no.	25 (24%)	32 (29%)	0.77 [0.42; 1.41]	
ECMO—no. (%)	14 (13%)	14 (13%)	1.07 [0.40; 2.37]	

Data are median [25th–75th percentile] or number (%)

ICU intensive care unit, iNO inhaled nitric oxide, ECMO extracorporeal membrane oxygenation

* The width of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment differences

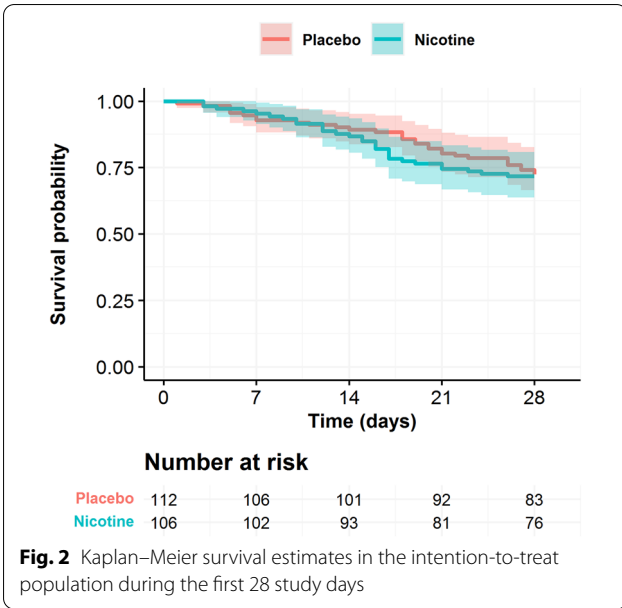
[†] At day 60, one patient in the nicotine group was lost to follow-up and four had withdrawn consent between day 28 and day 60

[‡] Treatment effect was measured with sub-Hazard ratio provided by Fine and Gray model with death and active therapies limitation as competitive events

Free-days were calculated assigning zero free-days to patients who died during the follow-up period

Third, we did not include current smokers in this trial. Although it may be speculated that an acute deprivation of nicotine in smokers may be associated with worse outcomes in COVID-19 patients (for example, due to an acute upregulation of ACE2 and increased secretion of proinflammatory cytokines) that may be reversed by nicotine replacement therapy, including

current smokers may have introduced a major bias in the interpretation of the impact of nicotine in severe COVID-19. Additionally, nicotine replacement therapy is sometimes recommended in ICU patients to prevent withdrawal syndrome [44]. Fourth, we cannot exclude a preventive effect of nicotine, if administered earlier, on contamination by SARS-CoV-2 or on the progression



to severe forms of the disease. Pertinently, the effect of remdesivir [45] administered very early after symptoms onset was associated with a larger clinical benefit than if given to patients already hospitalized for severe forms. Fourth, although transdermal nicotine has been used successfully in other populations of ICU patients [44, 46], we cannot exclude inconstant absorption of the drug, especially in septic patients treated with vaso-pressors and having subcutaneous vasoconstriction and oedema. Inhalation of nicotine or its administration through an oral or nasal spray may potentially be more effective. Lastly, further research is urgently needed to find drugs or strategies for patients who have developed the most severe forms of COVID-19 requiring mechanically ventilation, since, as of today, only corticosteroids [47, 48] administered after hospitalization significantly improved the survival of these patients.

In conclusion, this randomized trial showed that transdermal nicotine did not significantly improve the outcomes of patients having developed severe COVID-19 pneumonia requiring invasive mechanical ventilation. Therefore, there is no indication to use nicotine in this situation.

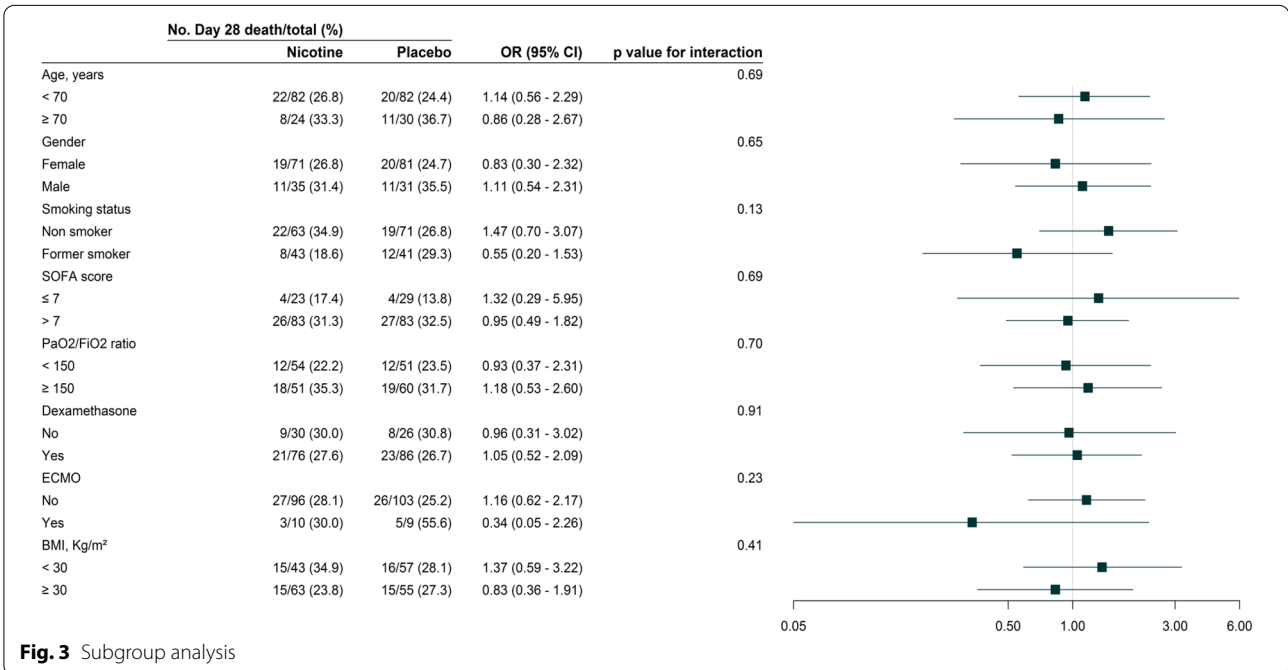


Table 3 Adverse events potentially related to nicotine and other events

Variable	Nicotine	Placebo	Difference (95% CI)*
Adverse events potentially related to trial treatment[†]	<i>n</i> = 106	<i>n</i> = 111	
Nausea or vomiting	1 (1%)	1 (1%)	0.03 (− 2.65; 2.71)
Skin rash	1 (1%)	1 (1%)	0.03 (− 2.65; 2.7)
Tachycardia	0	3 (3%)	− 2.78 (− 6.25; 0)
Total adverse events related to treatment	3 (3%)	3 (3%)	0.08 (− 4.41; 4.61)
Smoked/vaped in the 8 weeks following randomization	0	0	0
Other events during ICU stay[†]	<i>n</i> = 106	<i>n</i> = 112	
Pneumothorax—no.	7 (7%)	9 (8%)	− 1.43 (− 8.42; 5.5)
VAP treated with antibiotics—no.	57 (54%)	72 (64%)	− 10.51 (− 23.37; 2.14)
Bacteraemia—no.	22 (21%)	21 (19%)	2 (− 8.41; 12.55)
Renal replacement therapy—no.	20 (19%)	23 (21%)	− 1.67 (− 12.06; 9.17)
Thromboembolism	10 (9%)	18 (16%)	− 6.64 (− 15.28; 2.05)

* The width of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment differences

[†] *n* = population at risk

VAP ventilator-associated pneumonia, ICU intensive care unit

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-022-06721-1>.

Abbreviations

ACE2: Angiotensin converting enzyme 2; nAChRs: Nicotinic acetylcholine receptors; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; MV: Mechanical ventilation; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

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Declarations

Conflicts of interest

RG has received compensation as a member of the scientific advisory board of Janssen, Lundbeck, Roche, SOBI, Takeda. He has served as consultant and/or speaker for Astra Zeneca, Boehringer-Ingelheim, Pierre Fabre, Lilly, Lundbeck, LVMH, MAPREG, Novartis, Otsuka, Pileje, SANOFI, Servier and received compensation, and he has received research support from Servier. Co-founder and stock shareholder: Regstem. AC reported receiving grants and personal fees from Maquet, Xenios and Baxter outside the submitted work. No other disclosures were reported.

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References

- Centers for Disease Control and Prevention: SARS-CoV-2 Variant Classifications and Definitions <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Concern>; Last accessed, January 1st, 2022
- Del Rio C, Omer SB, Malani PN (2021) Winter of omicron—the evolving COVID-19 pandemic. *JAMA* 2:2
- Miyara M, Tubach F, Pourcher V et al (2022) Low rate of daily smokers in patients with symptomatic COVID-19: a monocentric self-report of smoking habit study. *Front Med*. <https://doi.org/10.3389/fmed.2021.668995>
- Farsalinos K, Barbouni A, Niaura R (2020) Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? *Intern Emerg Med* 15:845–852
- Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 382:1708–1720
- Simons D, Shahab L, Brown J et al (2021) The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). *Addiction* (Abingdon, England) 116:1319–1368
- Fontanet A, Tondeur L, Grant R, et al. (2021) SARS-CoV-2 infection in schools in a northern French city: a retrospective serological cohort study in an area of high transmission, France, January to April 2020. *Euro surveillance* : bulletin Européen sur les maladies transmissibles = European communicable disease bulletin 26
- Paleiron N, Mayet A, Marbac V et al (2021) Impact of tobacco smoking on the risk of COVID-19: a large scale retrospective cohort study. *Nicotine Tobacco Res* 23:1398–1404
- González-Rubio J, Navarro-López C, López-Nájera E et al (2020) A systematic review and meta-analysis of hospitalised current smokers and COVID-19. *Int J Environ Res Public Health* 17:2
- Reddy RK, Charles WN, Sklavounos A et al (2021) The effect of smoking on COVID-19 severity: a systematic review and meta-analysis. *J Med Virol* 93:1045–1056
- Lowe KE, Zein J, Hatipoglu U et al (2021) Association of smoking and cumulative pack-year exposure with COVID-19 outcomes in the Cleveland clinic COVID-19 registry. *JAMA Intern Med* 181:709–711
- Yan R, Zhang Y, Li Y et al (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* 367:1444–1448
- Oakes JM, Fuchs RM, Gardner JD et al (2018) Nicotine and the renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol* 315:R895–r906
- Changeux JP, Amoura Z, Rey FA et al (2020) A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. *CR Biol* 343:33–39
- Tizabi Y, Getachew B, Copeland RL et al (2020) Nicotine and the nicotinic cholinergic system in COVID-19. *FEBS J* 287:3656–3663
- Dautzenberg B, Levi A, Adler M et al (2021) Transdermal nicotine in non-smokers: a systematic review to design COVID-19 clinical trials. *Respir Med Res* 80:100844
- Wang H, Yu M, Ochani M et al (2003) Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 421:384–388
- Fujii T, Mashimo M, Moriwaki Y et al (2017) Expression and function of the cholinergic system in immune cells. *Front Immunol* 8:1085
- Farsalinos K, Eliopoulos E, Leonidas DD et al (2020) Nicotinic cholinergic system and COVID-19: in silico identification of an interaction between SARS-CoV-2 and nicotinic receptors with potential therapeutic targeting implications. *Int J Mol Sci* 21:2
- Gonzalez-Rubio J, Navarro-Lopez C, Lopez-Najera E et al (2020) Cytokine release syndrome (CRS) and nicotine in COVID-19 patients: trying to calm the storm. *Front Immunol* 11:1359
- Gomes JP, Watad A, Shoenfeld Y (2018) Nicotine and autoimmunity: The lotus' flower in tobacco. *Pharmacol Res* 128:101–109
- Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* 270:2957–2963
- Lameire N, Levin A, Kellum JA et al (2021) Harmonizing acute and chronic kidney disease definition and classification: report of a kidney disease: improving global outcomes (KDIGO) Consensus Conference. *Kidney Int* 2:2
- Base documentaire de l'APHP sur la COVID-19: <http://covid-documentation.aphp.fr/>; Last accessed, January 1st 2022
- IDSA Guidelines on the Treatment and Management of Patients with COVID-19: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>; Last accessed, January 11st 2022
- Beitler JR, Sarge T, Banner-Goodspeed VM et al (2019) Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 321:846–857
- (2021) COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators, Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 47: 60–73
- Grasselli G, Zangrillo A, Zanella A et al (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 323:1574–1581
- Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94:496–509
- Buyse M (2010) Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. *Stat Med* 29:3245–3257
- Kamiński M, Muth A, Bogdański P (2020) Smoking, vaping, and tobacco industry during COVID-19 pandemic: twitter data analysis. *Cyberpsychol Behav Soc Netw* 23:811–817
- Kavuluru R, Noh J, Rose SW (2021) Twitter discourse on nicotine as potential prophylactic or therapeutic for COVID-19. *Int J Drug Policy* 99:103470
- Ghosh A, Girish V, Yuan ML et al (2021) Combustible and electronic cigarette exposures increase ACE2 activity and SARS-CoV-2 spike binding. *Am J Respir Crit Care Med* 2:2

34. Masso-Silva JA, Moshensky A, Shin J et al (2021) Chronic E-cigarette aerosol inhalation alters the immune state of the lungs and increases ACE2 expression, raising concern for altered response and susceptibility to SARS-CoV-2. *Front Physiol* 12:649604
35. Tomchaney M, Contoli M, Mayo J et al (2021) Paradoxical effects of cigarette smoke and COPD on SARS-CoV-2 infection and disease. *BMC Pulm Med* 21:275
36. Hopkinson NS, Rossi N, El-Sayed Moustafa J et al (2021) Current smoking and COVID-19 risk: results from a population symptom app in over 2.4 million people. *Thorax* 76:714–722
37. Ioannou GN, Locke E, Green P et al (2020) Risk factors for hospitalization, mechanical ventilation, or death among 10 131 US veterans with SARS-CoV-2 infection. *JAMA Netw Open* 3:e2022310
38. Razjouyan J, Helmer DA, Lynch KE et al (2021) Smoking status and factors associated with COVID-19 in-hospital mortality among US veterans. *Nicotine Tobacco Res* 2:2
39. Mazeraud A, Jamme M, Mancusi RL, et al., (2021) Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*
40. Karagiannidis C, Mostert C, Hentschker C et al (2020) Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med* 8:853–862
41. Patel BV, Haar S, Handslip R et al (2021) Natural history, trajectory, and management of mechanically ventilated COVID-19 patients in the United Kingdom. *Intensive Care Med* 47:549–565
42. Schmidt M, Hajage D, Lebreton G et al (2020) Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 8:1121–1131
43. Yang X, Yu Y, Xu J et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centred, retrospective, observational study. *Lancet Respir Med* 8:475–481
44. de Jong B, Schuppers AS, Kruidijk-Gerritsen A et al (2018) The safety and efficacy of nicotine replacement therapy in the intensive care unit: a randomised controlled pilot study. *Ann Intensive Care* 8:70
45. Gottlieb RL, Vaca CE, Paredes R et al (2021) Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med* 2:2
46. Gillies MA, McKenzie CA, Whiteley C et al (2012) Safety of nicotine replacement therapy in critically ill smokers: a retrospective cohort study. *Intensive Care Med* 38:1683–1688
47. Angus DC, Derde L, Al-Beidh F et al (2020) Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 324:1317–1329
48. Horby P, Lim WS, Emberson JR et al (2021) Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 384:693–704