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

in smoking cessation programmes with behavioural support, while low-nicotine-concentration e-cigarettes would be removed from the market as consumer products.

Fourth, smoking-related morbidity and mortality vary by race or ethnicity. For example, in those who smoke ten cigarettes per day, African-American and Native-Hawaiian smokers have higher estimated rates of lung cancer than European-American smokers.[9] Consequently, it is unclear whether smoking reduction would be associated with equal reduction in lung cancer risk across races or ethnicities. Moreover, non-Hispanic Black, American Indian, and Alaskan Native people have been shown to be less likely to use e-cigarettes for smoking cessation than non-Hispanic White people.[10] Therefore, it remains unknown whether high-nicotine-concentration e-cigarettes would reduce lung cancer and other tobacco-related health outcomes equitably across subpopulations.

In conclusion, the role of e-cigarettes in reducing tobacco-related morbidity and mortality and their disparities in the population of the USA and globally remains uncertain. Cobb and colleagues did a carefully designed trial showing that high nicotine concentration might be a potentially important product specification linked to reduced urinary NNAL. To fully evaluate health effects of smoking reduction through e-cigarettes, future research needs to investigate how such behaviour relates to risk of cancer, cardiovascular and other diseases, and mortality in the general and high-risk populations. Future studies are needed to understand how to regulate e-cigarettes (eg, as prescription-based medical devices for use in smoking cessation programmes) to translate the findings of Cobb and colleagues to the naturalistic environment. Findings from future studies, together with those from Cobb and colleagues, could provide the missing pieces of the puzzle to strengthen the evidence for policy making to promote public health. It should always be emphasised that complete smoking cessation provides the most health benefits to smokers and the general population.

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COVID-19 and ECMO: a call for close cooperation and more investigation

COVID-19, which can manifest as severe acute respiratory failure, still holds the world captive. With a third wave rapidly building up in several countries, concern is increasing about mutated variants of the virus, which might be even more contagious or evade available vaccines. When the pandemic reached Europe

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early in 2020, it became clear that the massive surge of severe hypoxaemic lung failure could rapidly overwhelm even well developed health-care systems. In many countries, intensive care physicians quickly recognised the need for supraregional cooperation to fight this serious and unprecedented challenge.

In *The Lancet Respiratory Medicine*, Guillaume Lebreton and colleagues, on behalf of the Paris ECMO-COVID-19 investigators from 17 intensive care units in Île-de-France, a region of France comprising the Greater Paris area with approximately 12 million inhabitants, report on the experience of forming a network for the treatment of critically ill patients with COVID-19 with extracorporeal membrane oxygenation (ECMO).[1] Today, ECMO is largely accepted as an option to support selected patients with refractory respiratory failure.[2–5] Potential shortages of equipment and the need for universally accepted indications and homogenisation of management on ECMO called for a structured approach to ensure fair allocation of treatment to the high number of patients with COVID-19-associated respiratory failure.[6] The different steps in forming the network, consisting of inventory preparation, defining working processes and protocols for rapid feedback on the strategy in place, networking and communication, and dissemination of information, are in themselves worthy of study, serving as an example of much-needed cooperation.

Furthermore, Lebreton and colleagues report on the outcomes of all 302 adult patients treated with ECMO during the first wave in the Greater Paris intensive care units (ICUs). Survival at 90 days after ECMO was 46% (n=138).[1] The European chapter of the Extracorporeal Life Support Organization (ELSO) COVID-19 working group recently observed a survival of about 55% in 1531 patients treated with ECMO registered in 177 centres in Europe and Israel.[3] In an international registry study, the ELSO reported an estimated 90-day survival of 62% in 1035 patients treated with ECMO for COVID-19-associated refractory lung failure.[4] Taking into account the inherent weaknesses of registry reports, including the under-reporting of complications and negative cases as well as incomplete follow-up on patients referred to other facilities, the outcomes recorded by Lebreton and colleagues very likely mirror a more precise picture of reality.

A survival of less than 50% in patients without severe comorbidities and an average age of 52 years, who need ECMO due to an acute viral respiratory infection, is sobering. The results contrast strongly with the findings from the EOLIA trial in 2018, which reported a 60-day survival of 65% in the ECMO group.[7] Notably, ECMO indications and management in the current study were largely derived from EOLIA. Thus, the question arises whether lung failure due to SARS-CoV-2 is worse compared with acute respiratory distress of other origins. It probably is. First, there is no effective treatment against the virus, and therapy is largely supportive, while waiting for the immune response of the body. Second, the number of serious complications during ECMO therapy of this well documented COVID-19 cohort is substantially higher compared with data from EOLIA. The difference in intracranial haemorrhage is striking (27 [12%] of 223 patients with data *vs* 2% in EOLIA), and ventilator-associated pneumonia was very common (257 [85%] of 301 patients *vs* 39% in EOLIA). The incidence of pulmonary embolism is not reported in EOLIA, but was diagnosed in 53 (18%) of 294 patients in the current study, which possibly missed a relevant number because of unavailable CT scans. Due to the hypercoagulability previously observed in COVID-19,[8] the authors decided a priori to follow a more enhanced anticoagulation protocol with a goal of activated partial thromboplastin time of 60–75 s (compared with 40–55 s in EOLIA). It remains unknown whether this or a virus-induced endothelial injury could have caused the high frequency of intracranial haemorrhage, as confirmed in other series.[9] The unparalleled high incidence of ventilator-associated pneumonia might be due to a prolonged time on ECMO (a median of 17 days for survivors) or to an acquired immune paralysis by SARS-CoV-2. Furthermore, the cardiocirculatory involvement in patients with COVID-19 and its impact on the final outcome is still far from being clearly understood,[10] and not reported by Lebreton and colleagues.

Is progress possible in this cohort of critically ill patients in the future? Again, it probably is. First, Lebreton and colleagues' study suggests several important considerations. Selection of appropriate patients remains highly important, especially in times of crisis when equipment might become scarce. Younger age, shorter time from intubation to ECMO, and absence of renal failure can improve outcomes. Also noteworthy is the observation that previous

substantial experience of ICUs with venovenous ECMO (defined by the authors as at least 30 cases annually) was found to increase survival to 60%. Thus, centralisation of venovenous ECMO to dedicated high-volume expert units should be pursued, making mobile ECMO teams essential for realising this objective. Second, ventilatory management in the current study was derived from EOLIA. Although EOLIA is the best available randomised controlled trial on the use of ECMO versus protective conventional ventilation, it did not study the best mode of ventilation on ECMO. A driving pressure of 13 cm H_2O and a respiratory frequency of 20 breaths per min, as observed in the current study, will still place substantial mechanical power on a severely injured lung. Further investigation into different modes of mechanical ventilation during ECMO is needed to analyse whether the often observed pronounced reduction of pulmonary compliance with diffuse alveolar damage and risk of fibrotic change can be lessened. Anticoagulation will need to be individualised and adapted to different stages of COVID-19. In addition, a positive preliminary experience of combined cardiorespiratory support, applied from the start of ECMO in these patients, is interesting and promising.[11]

Finally, we do not know whether experience from the first wave can be transferred to the cases that follow. Almost all patients who now develop refractory respiratory failure have been pretreated with remdesivir and steroids, and have often remained on high-flow nasal oxygen or non-invasive ventilation for extended periods of time. Not uncommonly, severe hypercapnia with stiff lungs has become a leading problem necessitating ECMO.

In conclusion, to be able to combat COVID-19 lung failure successfully in the future, continuing supraregional interdisciplinary cooperation will be needed, as shown convincingly in the Greater Paris area. Still, thorough ongoing investigations are required and all the aforementioned aspects underline the clear need for more in-depth analysis of patient profiles, response to ECMO support, and, particularly, the careful assessment of treatment failures. Is the appalling death rate in this pandemic unavoidably due to overwhelming and unpreventable disease-related complications, or will optimised management and growing experience eventually overcome SARS-CoV-2? These questions remain to be answered.

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RAS inhibition and COVID-19: more questions than answers?

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Since the beginning of the COVID-19 pandemic and the first reports of an increased mortality among patients with COVID-19 treated for hypertension, the potential role of renin–angiotensin system (RAS) blockers on the severity of the disease has been questioned.[1,2] Although RAS blockers have been associated with better outcomes in pneumonia models, they might also upregulate the expression of angiotensin-converting