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

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Letter to the Editor: "The impact of COVID-19 pandemic on the initiation of interventional clinical trials conducted in intensive care units"

To the Editor,

The coronavirus disease 2019 (COVID-19) pandemic has had a devastating impact on virtually all aspects of the healthcare system, including interruption of non-COVID-19-related clinical trials across all fields [1]. Some studies analyzed the characteristics of registered COVID-19-related trials [2-4]. What is missing from the current literature, however, is a specific synthesis of how trials conducted in the intensive care unit (ICU) were influenced by the epidemic. During the early outbreaks, our team assessed clinical features of critically ill patients with COVID-19 and identified similarities and differences in regions by analyzing various high-quality publications [5]. In this study, we aimed to assess how the pandemic impacted the initiation of interventional trials in the ICU worldwide and the association between regional outbreak severity with trial initiations, by analyzing the ClinicalTrials.gov database.

We searched ClinicalTrial.gov [6] to identify interventional studies conducted in the ICU from 2016 to 2020, using the terms: "ICU" OR "intensive care" OR "critical illness" OR "critical care" OR "critically ill". We reviewed the registry entries for each search result and excluded observational studies, those not enrolling ICU patients, those conducted in the neonatal ICU, and those with a primary intervention administered outside the ICU. We obtained counts of confirmed COVID-19 cases from COVID-19 Data Repository [7]. Data analysis was performed using Python version 3.8.

Our search generated 3960 records, of which 1792 were eligible, including 305 COVID-19 trials and 1487 trials not directed towards COVID-19 management, defined as traditional trials in this study. Characteristics of eligible trials are displayed in Table 1. From 2016 to 2019, approximately 300 ICU trials were activated each year.

Compared with 2019, the total number of ICU trials initiated in 2020 increased by 71.7% (565 vs. 329), but with an 18.8% reduction of traditional trials and the emergence of COVID-19 trials contributing to over half of all trials. Although planned to be initiated in 2020, up to 45% (121/267) of traditional trials did not recruit patients. Among the COVID-19 studies, 71.1% (217/305) were randomized controlled trials. Among those, 51.2% (111/217) used a blinded design and 38.4% (117/305) were multi-center; 85.6% (261/305) were to assess treatment and 73.1% (223/305) involved a particular drug or biologic; 12.1% (37/305) were marked completed versus only 3% (8/267) of traditional trials completed. There were more industry-sponsored trials among the COVID-19 trials than traditional trials (22.0% vs. 12.7%). The geographic distribution of these trials was mainly in Europe, North America and Asia.

On a monthly basis in 2020, as COVID-19 cases increased rapidly, traditional ICU trials were negatively impacted in the first five months but resumed at a stable rate in the following months, while the number of COVID-19 studies in the ICU rapidly increased, peaking in April 2020 and then gradually declined (Fig. 1A). When the analysis was restricted by region (Asia, Europe, and North America; Fig. 1B–D), similar associations between the number of new COVID-19 cases with both traditional trials and COVID-19 trials initiations were found.

The COVID-19 pandemic impacted both COVID-19 and non-COVID-19 trials in critical care worldwide, with similar influences among regions including Asia, Europe and North America.

During the early outbreak, there was a rapid proliferation of COVID-19 trials in critical care in response to the COVID-19 global threat. The correlation we reveal between COVID-19 trials and confirmed cases in this period is consistent with what Jones and colleagues found; that the number of overall COVID-19 trials registered gradually increased in the first three months of 2020 and peaked in April as cases numbers increased [3]. However, our study further explores the relationship between COVID-19 infections and ICU trials in the following months until December 2020 and shows contrasting findings to early 2020. We believe there are several explanations. It is possible that as the pandemic unfolded, more limited healthcare resources and burnt-out critical care clinicians had reduced capacity to conduct research. It is also possible that researchers initially responding to alarming morbidity and mortality outcomes were very motivated to conduct trials to address COVID-19. However, with evidence that robust implementation of already recognized management strategies was improving clinical outcomes, there was less appetite for new therapeutic trials.

Fortunately, more than one-third of COVID-19 studies were multicenter, suggesting an unprecedented level of scientific collaboration in critical care. This bodes well for future pandemic responses, a possible approach to eliminate research waste and duplicated effort on small underpowered trials of COVID-19 treatments.

In contrast, in the early phase of 2020, traditional trials were negatively impacted by COVID-19 globally, likely because COVID-19 was managed as a priority and regular research was suspended or switched to studying COVID-19. As the pandemic continued, however, institutions were able to determine safe practices for conducting research and restrictions were lifted [8], allowing traditional trials to gain momentum once more.

Nevertheless, nearly half of the traditional trials failed to recruit subjects as planned in 2020 and only 3% were completed globally, indicating the enormous impact of the public health crisis on routine clinical research in the ICU. Given that clinical trials themselves may lead to a reduction in mortality of various critical diseases, it is time for the global clinical trial community to consider "emergency planning" to address challenges for trials in a future unforeseen major emerging infectious disease.

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Table 1
Characteristics of clinical trials conducted in the intensive care unit registered on ClinicalTrials.gov.

Characteristics[a]	All ICU trials (2016–2020), $N = 1792$	Traditional trials in 2020, $N = 267$	COVID-19 trials in 2020, $N = 305$
Year of trials initiated			
2016	284 (15.8)	–	2 (0.7)[b]
2017	305 (17.0)	–	0
2018	309 (17.2)	–	1 (0.3)[b]
2019	329 (18.4)	–	4 (1.3)[b]
2020	565 (31.5)	267 (100)	298 (97.7)
Region			
Europe	–	108 (40.4)	113 (37.0)
North America	–	66 (24.7)	96 (31.5)
Asia	–	63 (23.6)	57 (18.7)
South America	–	7 (2.6)	27 (8.9)
Africa	–	18 (6.7)	11 (3.6)
Oceania	–	5 (1.9)	1 (0.3)
Number of participants			
0–100	1012 (56.5)	128 (47.9)	187 (61.3)
101–1000	684 (38.2)	123 (46.1)	109 (35.7)
>1000	96 (5.3)	16 (6.0)	9 (3.0)
Recruitment status			
Not yet recruiting	218 (12.2)	121 (45.3)	52 (17.0)
Active, not recruiting	90 (5.0)	5 (1.9)	21 (6.9)
Recruiting or enrolling	737 (41.1)	128 (47.9)	178 (58.4)
Completed	409 (22.8)	8 (3.0)	37 (12.1)
Suspended	15 (0.8)	0	1 (0.3)
Terminated	67 (3.7)	0	7 (2.3)
Withdraw	51 (2.9)	5 (1.9)	9 (3.0)
Unknown status	205 (11.4)	0	0
Study design			
Randomized control trials	1357 (75.7)	210 (78.7)	217 (71.1)
Others	435 (24.3)	57 (21.3)	88 (28.9)
Study primary purpose			
Treatment	1046 (58.4)	142 (53.2)	261 (85.6)[c]
Others	746 (41.6)	125 (46.8)	44 (14.4)
Intervention			
Drug/biological	–	96 (36.0)	223 (73.1)
Device	–	56 (21.0)	21 (6.9)
Behavioral/procedure	–	41 (15.4)	21 (6.9)
Other	–	74 (27.7)	40 (13.1)
Funding source[d]			
Industry	–	34 (12.7)	67 (22.0)
Government	–	5 (1.9)	1 (0.3)
Other	–	254 (95.1)	278 (91.2)

Variables were reported as counts with percentages.
Abbreviations: COVID-19 = coronavirus disease 2019; ICU = intensive care unit.
[a] Percentages may not be total 100 because of rounding.
[b] These registered trials with the start date before the emerge of COVID-19 updated the inclusion criteria to enrol critically ill patients with COVID-19 in 2020 on the website.
[c] Among the COVID-19 trials testing treatment strategies, 15.3% (40/261) involved convalescent plasma treatment.
[d] Trials may be listed in more than one category; totals therefore add to more than 100%.

Our study has limitations as approximately half of the studies conducted outside the United States are estimated to be registered on non-ClinicalTrials.gov [9]. We selected ClinicalTrials.gov because it is the most comprehensive trial registry worldwide and widely used for secondary analysis [1,3,4,10]. Furthermore, we could not rate the quality of the trials in this current work.

In conclusion, our study suggests the COVID-19 pandemic may impact strongly on the design and execution of clinical trials in the ICU worldwide, with non-COVID-19 studies severely hindered and COVID-19 studies boosted. It would be interesting to better understand other factors influencing research, such as funding opportunities, mechanisms to protect the continuation of clinical trials and support adaptations of protocols to rapidly changing clinical practice, and institutional/country capacity to cope with surge conditions.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author's contributions

CH and SG contributed equally to this work.

ZW and YX designed the study. CH and SG contributed to study conception, data acquisition, data analysis, and the writing of the manuscript. AB interpreted the results, provided further inputs, and edited extensively before finalization. XL and WH contributed to data interpretation. All authors revised and approved the final submitted version of the manuscript.

Declaration of Competing Interest

The authors declare to have no competing interests.

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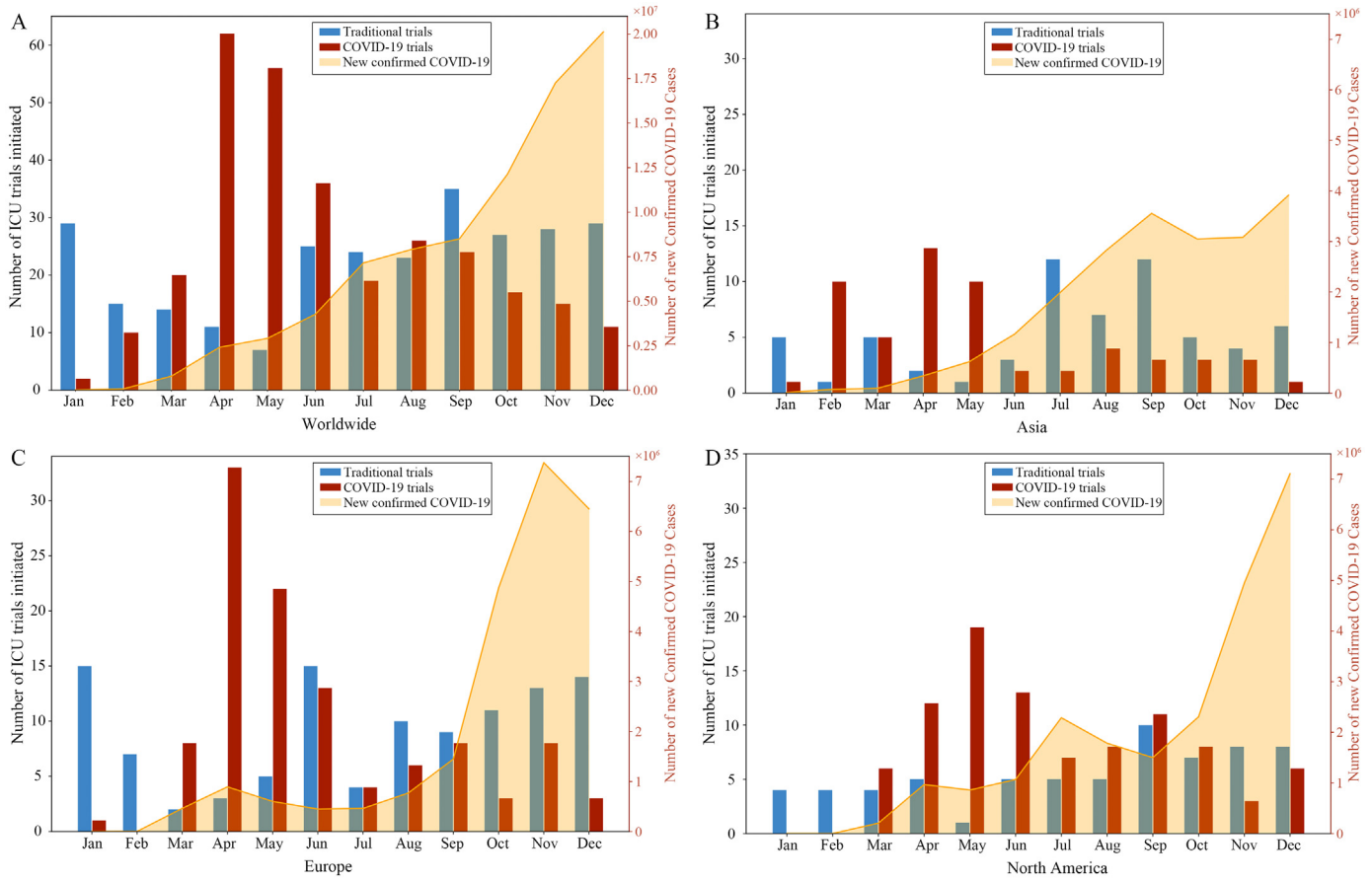

Fig. 1. Number of registered clinical trials conducted in the intensive care unit (ICU) vs. newly confirmed coronavirus disease 2019 (COVID-19) cases in 2020.
Panel (A) illustrates the relationship between counts of interventional clinical trials conducted in the ICU and newly confirmed COVID-19 cases worldwide.
Panel (B, C and D) demonstrate the relationship between counts of interventional clinical trials conducted in the ICU and newly confirmed COVID-19 cases in Asia, Europe and North America, respectively.

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