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RECENT ADVANCES IN ICU

Coronavirus disease 2019

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In less than 4 years, coronavirus disease 2019 (COVID-19) has been diagnosed in 768 million people worldwide, leading to close to 7 million deaths (https://covid19.who.int). In response to this global pandemic, accelerated efforts have been made to evaluate the management of critically ill patients with COVID-19, leading to major advances in the field. We focus this article on patient-level advances during the pandemic, recognizing that the wide introduction of vaccines and improvements in healthcare system response over the course of the pandemic have greatly reduced the severity of the infection and the likelihood of its progression to critical illness [1]. We also address areas with little advances that represent lessons and opportunities for improvement (Fig. 1).

Rapid generation of evidence for therapeutics

One of the hallmarks of the COVID-19 pandemic was the unprecedented pace of evaluation of candidate therapies for COVID-19 across different disease severity levels. Randomized clinical trials (RCTs) conducted across research networks, including adaptive platform trials, demonstrated the global community's ability to be mobilized to evaluate multiple interventions efficiently. Within only a few months after the World Health Organization (WHO) officially declared that the outbreak constituted a Public Health Emergency of International Concern, the Adaptive COVID-19 Treatment Trial (ACTT) RCT reported the results of treatment with remdesivir [2] and the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial reported the results of treatment with dexamethasone [3]. The benefit of corticosteroid therapy in reducing mortality in patients receiving supplementation or invasive mechanical ventilation was quickly confirmed in other trials, many of which willingly shared unpublished data in a collective effort to accelerate learning [4]. The REMAP-CAP (The Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia) trial was the first to report the survival benefits associated with interleukin-6 (IL-6) receptor blockers (tocilizumab or sarilumab), and the collective results of all available RCTs, including unpublished data and some RCTs showing no benefit with IL-6 receptor blockers, were quickly synthesized in a prospective meta-analysis [5, 6]. A third immunomodulator, the Janus kinase (JAK) inhibitor baricitinib, was found to reduce mortality in critically ill patients [7]. The added value of platform adaptive designs was further manifested when, following the publication of the initial results, RECOVERY results evaluated the effect of the combination of different immunomodulators, corticosteroids, baricitinib, and IL-6 receptor blockers [8]. The critical role of thrombosis in the pathogenesis of COVID-19 was recognized early in the pandemic, and RCTs, including a multiplatform trial, evaluated the role of different doses of anticoagulation [9]. There are many other examples, such as studies of secondary infections, of how the global community collaborated to address essential questions efficiently [10].

RCTs were also instrumental in ruling out benefits associated with interventions used at the pandemic's beginning, driving unnecessary costs and potential adverse effects. For example, research efficiency, including the WHO SOLIDARITY trial, largely settled uncertainties regarding hydroxychloroquine, lopinavir–ritonavir, ivermectin, and convalescent plasma [11]. RCTs were essential for defining the indications for antiviral therapies (nirmatrelvir–ritonavir, molnupiravir and remdesivir) in high-risk non-severe cases. RCT data also demonstrated that remdesivir reduced mortality in patients hospitalized with COVID-19 who required no or

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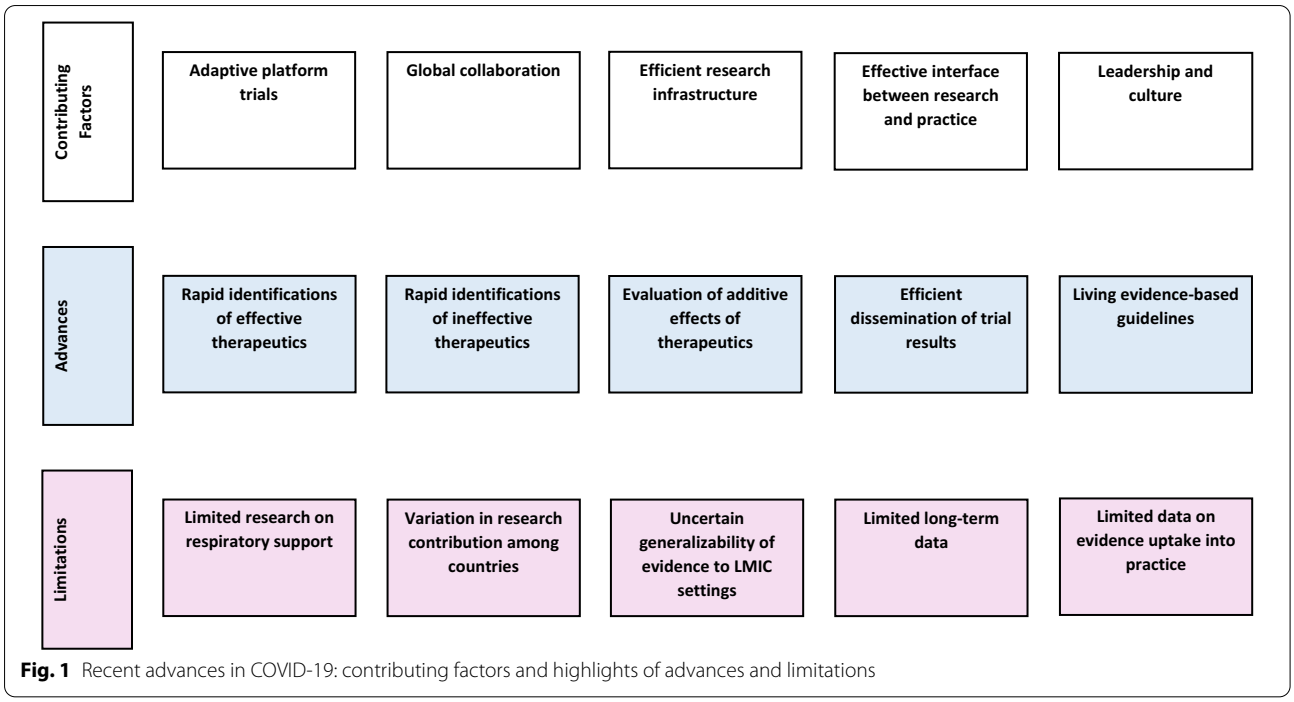

Fig. 1 Recent advances in COVID-19: contributing factors and highlights of advances and limitations

conventional oxygen support but were not yet critically ill [12, 13].

The pandemic also taught us to recognize emerging variants' impact on therapeutics' efficacy, especially monoclonal antibodies. Although early clinical trial data demonstrated the benefit of monoclonal antibodies sotrovimab and casirivimab–imdevimab in high-risk patients with COVID-19, subsequent in vitro neutralization experiments showed that these monoclonal antibodies lost part of their ability to neutralize emerging variants, to the point where clinical benefits are now implausible [12].

Changing landscape in respiratory support

The approach to respiratory support for acute hypoxemic respiratory failure due to COVID-19 evolved during the pandemic, with a decline in endotracheal intubation and an increase in noninvasive respiratory support [14]. Unfortunately, only a few RCTs have compared different respiratory support strategies. The available evidence to date suggests that high-flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP), and noninvasive ventilation (NIV) reduce the risk of endotracheal intubation compared with standard oxygen therapy. However, more work is needed to address several important questions, such as the comparative effectiveness of different modalities (HFNO versus CPAP versus NIV) and different NIV interfaces (for example, helmet versus face mask NIV).

Awake proning has increasingly been utilized in patients with acute hypoxemic respiratory failure due to COVID-19. A systematic review of RCT data demonstrated that awake proning reduces the risk of endotracheal intubation in adults with hypoxemic respiratory failure due to COVID-19 but does not affect mortality [15].

Translating evidence into practice

The pandemic has led to a more efficient research-syntheses-guidelines process. Translating emerging trial evidence into clinical practice guidelines rapidly and transparently was necessary to support busy clinicians, especially with the large flow of misinformation and contradicting reports [16]. However, it was soon recognized that clinical practice guidelines should be kept abreast of the rapidly evolving evidence base. The WHO Living guideline on COVID-19 Therapeutics and Clinical management has been a leading innovation in reviewing and synthesizing emerging evidence into timely and updated recommendations for treating patients with COVID-19 of all disease spectrum [12].

Lessons and opportunities

There has been unprecedented enrollment in clinical trials across several networks, which speaks to their leadership, policy, and integration of research, and highlights the importance of efficient research infrastructure and the adequate interface between research and clinical care

for productive clinical research [17–19]. Yet, there has been considerable variation in the contribution of countries to COVID-19 research. The inequity of research meant that evidence generated in high-resource settings might not be generalizable in low-resource settings. A systematic review of studies before November 2020 identified only 36 studies addressing COVID-19 in low- and middle-income countries [20]. Notwithstanding, the Brazil Coalition COVID-19, in collaboration with the Bricnet (the Brazilian Research in Intensive Care Network), has published the results of 9 major RCTs and one long-term follow-up study, and the work by Crit Care Asia (CCA) network and REMAP-CAP trial have included several low–middle-income countries [18, 19].

With the increasing use of novel adaptive platform trials, there are ongoing learning opportunities regarding their strengths and limitations. Much more is to be learned about the heterogeneity of treatment effect and the presence of subgroup effects, for example, of anticoagulation, so a more individualized patient evidence-based approach according can be applied.

Most clinical trials evaluated treatment effectiveness based on short-term mortality but long-term outcomes remained largely unknown. Only a few clinical trials collected and disseminated long-term data; reassuringly, the results were consistent with short-term outcomes [21, 22].

There is so much to learn from the unparalleled advances made during the COVID-19 pandemic (Fig. 1), but there are also so many lessons from the limitations, opening exciting opportunities for improvement.

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Declarations

Conflicts of interest
YMA is an investigator on the REMAP-CAP trial, investigator on the COVI-PRONE trial, and principal investigator on the Helmet-COVID trial.

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