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Outcomes comparison between the first and the subsequent SARS-CoV-2 waves – a systematic review and meta-analysis

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ABSTRACT

Background: In the beginning of the SARS-CoV-2 pandemic, health care professionals dealing with COVID-19 had to rely exclusively on general supportive measures since specific treatments were unknown. The subsequent waves could be faced with new diagnostic and therapeutic tools (*e.g.*, anti-viral medications and vaccines). We performed a meta-analysis and systematic review to compare clinical endpoints between the first and subsequent waves.

Methods: Three databases were assessed. The primary outcome was in-hospital mortality. The secondary outcomes were intensive care unit (ICU) mortality, ICU length of stay (LOS), acute renal failure, extracorporeal membrane oxygenation (ECMO) implantation, mechanical ventilation time, hospital LOS, systemic thromboembolism, myocarditis and ventilator associated pneumonia.

Results: A total of 25 studies with 126,153 patients were included. There was no significant difference for the primary endpoint (OR=0.94, 95% CI 0.83-1.07, p=0.35). The first wave group presented higher rates of ICU LOS (SMD= 0.23, 95% CI 0.11-0.35, p<0.01), acute renal failure (OR=1.71, 95% CI 1.36-2.15, p<0.01) and ECMO implantation (OR=1.64, 95% CI 1.06-2.52, p=0.03). The other endpoints did not show significant differences.

Conclusions: The analysis suggests that the first wave group, when compared with the subsequent waves group, presented higher rates of ICU LOS, acute renal failure and ECMO implantation, without significant difference in in-hospital or ICU mortality, mechanical ventilation time, hospital LOS, systemic thromboembolism, myocarditis or ventilator-associated pneumonia.

Key words: COVID-19; SARS-CoV-2; critical care; extracorporeal membrane oxygenation.

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Contributions: TC, RET, JMS, study design; TC, literature review in the three different libraries; TC, RET, studies selection and qualification according to the risk of bias, data abstraction, tables building, results organization; PT, statistical analyses; TD, MM, HK, JMS, data analysis; TC, FSLV, RET, TD, JMS, TD, manuscript drafting. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethical approval: Ethical approval of this analysis was not required as no human or animal subjects were involved.

Availability of data and materials: The data underlying this article are available in the article and in its online supplementary material.

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Introduction

In the beginning of the SARS-CoV-2 pandemic, health care professionals dealing with COVID-19 had to rely exclusively in general supportive measures since specific treatments were unknown [1]. National and societies guidelines released initially advised against the administration of systemic corticosteroids and limited the use of non-invasive ventilation to specific populations or clinical scenarios [1,2]. Subsequently, the knowledge about the care of these patients has increased progressively as results of clinical studies became available. While initial observational studies have pointed out high proportions of intensive care unit [3] (ICU) admissions, frequent need of mechanical ventilation (MV) and high mortality in the critically ill patients [1,4], several subsequent randomized controlled trials (RCT) have shown clinical benefit of pharmacological and non-invasive respiratory interventions [3,5-10]. These studies found reduced mortality with administration of systemic corticosteroids and interleukin-6 receptor antagonists [5,6,10]. Although remdesivir was not found to reduce mortality in hospitalized patients its administration led to faster recovery time and reduced intubation rates [7]. Non-invasive respiratory interventions (high flow nasal oxygen - HFNO and non-invasive ventilation - NIV) were shown to reduce the need of intubation and invasive MV [8,9]. As clinical experience increased and evidence from clinical studies became available, it is expected that the clinical profile, employed treatments and outcomes of COVID-19 critically ill patients have also changed. The objective of this systematic review and meta-analysis was to assess and describe differences in the clinical and demographic features, treatments and outcomes of COVID-19 adult patients admitted in subsequent waves of the pandemic.

Methods

Ethical approval of this analysis was not required as no human or animal subjects were involved. This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO, CRD42023405088).

Search strategy

We performed a comprehensive literature search to identify contemporary studies reporting short- and long-term outcomes between patients who had SARS-CoV-2 in the first and subsequent waves. Searches were run on July, 2022, in the following databases: Ovid MEDLINE; Web of Science; and The Cochrane Library (Wiley). The search strategy for Ovid MEDLINE is available in Supplementary Table 1.

Study selection and data extraction

The study selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy. After de-duplication, records were screened by two independent reviewers (TC and FV). Any discrepancies and disagreements were resolved by a third author (JJ). Titles and abstracts were reviewed against pre-defined inclusion and exclusion criteria. Studies were considered for inclusion if they were written in English and reported direct comparison between patients who had SARS-CoV-2 in the first *versus* in the subsequent waves. Animal studies, abstracts, case reports, commentaries, editorials, expert opinions, conference presentations, and studies not reporting the outcomes of interest were excluded. The full text was pulled for the selected studies for a second round of eligibility screening. References for articles selected were also reviewed for relevant studies not captured by the original search. The quality of the included studies was assessed using the "Tool to Assess Risk of Bias in Cohort Studies" developed by the CLARITY Group at McMaster University (Supplementary Table 2).

Two reviewers (TC and FV) independently performed data extraction. Accuracy was verified by a third author (JJ). The extracted variables included study characteristics (publication year, country, sample size, study design, mean follow up, presence or absence from population adjustment and outcome definitions) as well as patient demographics (age, sex, hypertension, diabetes, smoking status, prior cerebrovascular accident – CVA, prior myocardial infarction MI, prior PCI, renal failure, chronic obstructive pulmonary disease – COPD, Charlson Comorbidities Index, vaccination status, Simplified Acute Physiology Score – SAPS, Acute Physiology and Chronic Health Evaluation – APACHE, Sequential Organ Failure Assessment – SOFA, oxygenation index, corticosteroids, remdesivir and IL-6 use).

Outcomes

Primary outcome was in-hospital mortality. Secondary outcomes were ICU mortality, mechanical ventilation time, hospital length of stay (LOS), ICU LOS, systemic thromboembolism, myocarditis, acute renal failure, ventilator associated pneumonia and necessity of extracorporeal membrane oxygenation (ECMO) implantation.

Statistical analysis

We conducted meta-analyses to compare the outcomes during the first wave of SARS-CoV-2 versus the subsequent waves of SARS-CoV-2. Continuous variables were analyzed using standardized mean difference (SMD) and 95% confidence intervals (95% CI). A SMD greater than zero corresponded to larger values in the first wave of COVID-19. Categorical values were analyzed using odds ratio (OR) and 95% CI. An OR greater than 1 indicated that the outcome was more frequently present in the first wave of SARS-CoV-2. Inherent clinical heterogeneity between the studies was balanced via the implementation of random effects models (DerSimonian-Laird). Results were displayed in forest plots.

Between-study statistical heterogeneity was assessed with the Cochran Q statistic and by estimating I^2. High heterogeneity was confirmed with a significance level of $p<0.10$ and I2 of at least 50% or more. Publication bias was assessed *via* funnel plots and Eggers' test for each outcome of interest and $p<0.10$ was considered statistically significant. All analyses were performed using STATA IC17.0 (StataCorp LLC, College Station, TX, USA).

Results

Study characteristics

A total of 1,179 studies were retrieved from the systematic search, out of which 25 met the criteria for inclusion in the final analysis. Figure 1 shows the PRISMA flowchart for study selection. Included studies were published between 2021 and 2022, all studies were observational cohorts, and 13 were multicentric. 1 study was multinational, 1 study originated from Australia, 1 from Austria, 1 from Belgium, 1 from Brazil, 1 from Denmark, 4 from France, 1 from Germany, 1 from Greece, 1 from India, 1 from Japan, 1 from Mexico, 1 from Netherlands, 1 from Pakistan, 1 from South Africa, 1 from Spain, 1 from Sweden, 1 from Switzerland and 3 from the United Kingdom. Table 1 shows the details of the included studies. Thirteen studies were based on risk-

adjusted populations. A total of 126,153 patients were included in the final analysis. The number of patients in each study ranged from 72 to 67,242.

Patient characteristics

Supplementary Table 3 summarizes the demographic data of the patient population in each study. The median age ranged from 49 to 72 years. Percentage of female patients ranged from 11% to 67%; percentage of hypertension ranged from 28% to 65%; percentage of diabetes ranged from 18% to 54%; percentage of positive smoking status ranged from 2.4% to 30%; percentage of prior CVA ranged from 6% to 14%; percentage of prior MI ranged from 5% to 29%; percentage of renal failure ranged from 3% to 63% and the percentage of COPD ranged from 1.5% to 28%.

Meta-analysis

Figure 2 and Table 2 outline the detailed results of the meta-analysis.

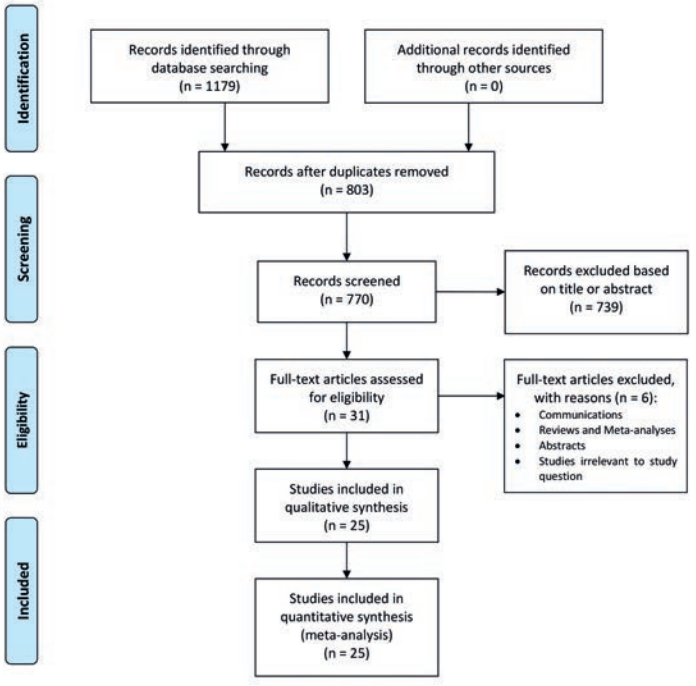

Figure 1. **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.**

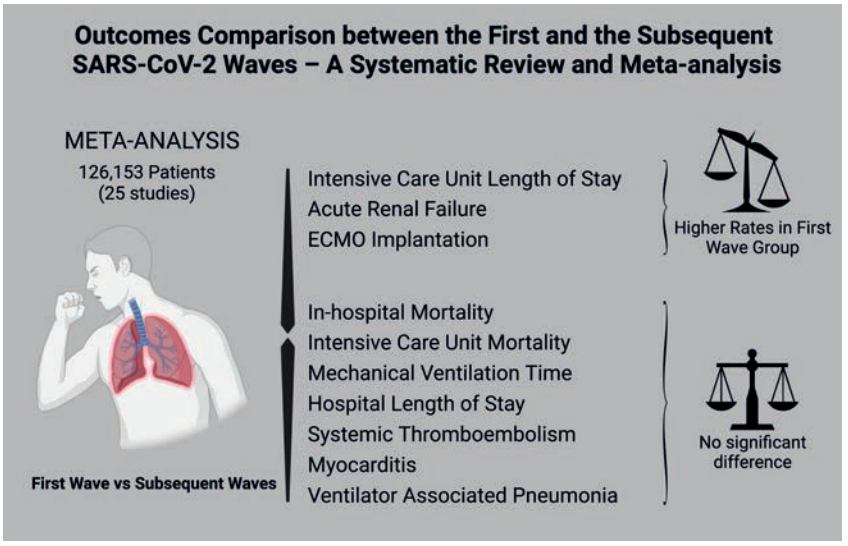

Figure 2. **Graphical abstract showing the main findings of the analysis.**

Table 1. Summary of included studies. References are reported in the Supplementary Material.

Author	Year of publication	Country	N of patients	Study design	Selected outcomes
Aries	2022	France (Mayotte Island)	156	Single center, retrospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis, VAP and ECMO implantation
Asghar	2021	Pakistan	160	Single center, retrospective	Mortality, ST, myocarditis and ARF
Begum	2022	Australia	2493	Multicenter, prospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis, ARF and ECMO implantation
Carbonell	2021	Spain, Andorra and Ireland	3795	Multicenter, retrospective	Mortality, MVT, hospital LOS, ICU LOS, myocarditis, ARF, VAP and ECMO implantation
Countou	2021	France	132	Single center, retrospective	Mortality, MVT, ICU LOS, ST, ARF and VAP
Demoule	2022	France	1166	Multicenter, retrospective	Mortality, MVT, hospital LOS, ICU LOS, ARF, VAP and ECMO implantation
Dongelmans	2022	Netherlands	12,218	Multicenter, prospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis, VAP and ECMO implantation
Haase	2022	Denmark	1374	Multicenter, retrospective	Mortality, MVT, hospital LOS, ICU LOS, ARF and ECMO implantation
Hosoda	2022	Japan	128	Multicenter, retrospective	Mortality, MVT, ICU LOS, ARF and ECMO implantation
Kerai	2021	India	220	Multicenter, retrospective	Mortality, MVT, ICU LOS and ARF
Kieninger	2022	Germany	157	Single center, retrospective	Mortality, ICU LOS, ARF and ECMO implantation
Lalla	2021	South Africa	490	Single center, prospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis, VAP and ECMO implantation
Lazaro	2022	Brazil	767	Single center, prospective	Mortality, ICU LOS and ARF
Le Terrier	2022	Switzerland	223	Single center, prospective	Mortality, MVT, hospital LOS, ICU LOS, ST, ARF, VAP and ECMO implantation
Lopez	2021	France	111	Single center, retrospective	Mortality, hospital LOS, ICU LOS, ST, ARF, VAP and ECMO implantation
Mayerhofer	2021	Austria	508	Multicenter, prospective	Mortality, MVT, hospital LOS, ICU LOS, ARF and ECMO implantation
Namendis-Silva	2021	Mexico	67,242	Multicenter, retrospective	Mortality
Perez-Acosta	2022	Spain (Canary Islands)	72	Single center, prospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis and ARF
Piagnerelli	2021	Belgium	174	Single center, retrospective	Mortality, MVT, hospital LOS, ICU LOS, ST and ARF
Ritchie	2022	United Kingdom	330	Multicenter, retrospective	Mortality and ICU LOS
Routsie	2021	Greece	262	Single center, retrospective	Mortality, MVT, Hospital LOS, ICU LOS and ARF
Szakmany	2021	United Kingdom	178	Single center, retrospective	Mortality and ICU LOS
Taxbro	2021	Sweden	264	Multicenter, retrospective	Mortality, MVT, hospital LOS, ICU LOS, ST, myocarditis, ARF and ECMO implantation
Wilcox	2022	United Kingdom	30,035	Multicenter, retrospective	Mortality and ICU LOS
Zirpe	2021	India	3498	Multicenter, prospective	Mortality

ARF, acute renal failure; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; MVT, mechanical ventilation time; ST, systemic thromboembolism; VAP, ventilator associated pneumonia.

Table 2. Summary of included studies. References are reported in the Supplementary Material.

Outcome	Number of studies	Number of patients	Effect estimate (95%CI, p)
In-hospital mortality	18	123,923	OR= 0.94 (0.83-1.07, p=0.35)
ICU mortality	16	56,408	OR= 0.94 (0.79-1.13, p=0.51)
ICU LOS	22	48,222	SMD= 0.23 (0.11-0.35, p<0.01)
Acute renal failure	17	11,452	OR= 1.71 (1.36-2.15, p<0.01)
ECMO implantation	11	10,019	OR= 1.64 (1.06-2.52, p=0.03)
Mechanical ventilation time	14	8,870	SMD= 0.10 (-0.01-0.21, p=0.09)
Hospital LOS	14	16,343	SMD= 0.10 (-0.04-0.24, p=0.17)
Systemic thromboembolism	9	3,135	OR= 1.25 (0.82-1.91, p=0.29)
Myocarditis	6	6,330	OR= 1.49 (0.72-3.07, p=0.28)
Ventilator associated pneumonia	6	5,583	OR= 0.78 (0.51-1.18, p=0.24)

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; SMD, standard mean difference; OR, odds ratio.

Primary outcome

Figure 3 shows the forest plot for in-hospital mortality. There was no significant difference between the two groups (OR= 0.94, 95% CI 0.83-1.07, p=0.35). Supplementary Figure 1 shows the leave-one-out analysis showing that most of the studies confirm the robustness of the analysis, with minimal variations of the confidence interval. Supplementary Figure 2 provides the funnel plot for the publication bias assessment.

Secondary outcomes

Figure 4 shows the forest plot for ICU mortality. There was no significant difference between the two groups (OR=0.94, 95% CI 0.79-1.13, p=0.51). Figure 5 shows the forest plot for ICU length of stay. The first wave group presented higher ICU length of stay in comparison with the subsequent waves (SMD=0.23, 95% CI 0.11-0.35, p<0.01). Figure 6 shows the forest plot for acute renal failure. The first wave group presented higher acute renal failure rates in comparison with the subsequent waves (OR=1.71, 95% CI 1.36-2.15, p<0.01). Figure 7 shows the forest plot for ECMO implantation. The first wave group presented higher ECMO implantation rates in comparison with the subsequent waves (OR=1.64, 95% CI 1.06-2.52, p=0.03).

Supplementary Figure 3 shows the forest plot for mechanical ventilation time. There was no significant difference between the two groups (SMD=0.10, 95% CI -0.01-0.21, p=0.09). Supplementary Figure 4 shows the forest plot for hospital length of stay. There was no significant difference between the two groups (SMD=0.10, 95% CI -0.04-0.24, p=0.17). Supplementary Figure 5 shows the forest plot for systemic thromboembolism. There was no significant difference between the two groups (OR=1.25, 95% CI 0.82-1.91, p=0.29). Supplementary Figure 6 shows the forest plot for myocarditis. There was no significant difference between the two groups (OR=1.49, 95% CI 0.72-3.07, p=0.28). Supplementary Figure 7 shows the forest plot for ventilator associated pneumonia. There was no significant difference between the two groups (OR=0.78, 95% CI 0.51-1.18, p=0.24).

Discussion

The analysis suggests that the first wave group when compared with the subsequent waves group presented higher rates of ICU LOS, acute renal failure and ECMO implantation, without significant difference in in-hospital or ICU mortality, mechanical ventilation time, hospital LOS, systemic thromboembolism, myocarditis or ventilator associated pneumonia.

Although appointing the reasons of the differences found is beyond the scope of the current study, some aspects are worth considering. First, to study subsequent waves of patients requires comparing data from patients presenting over a different time frame.

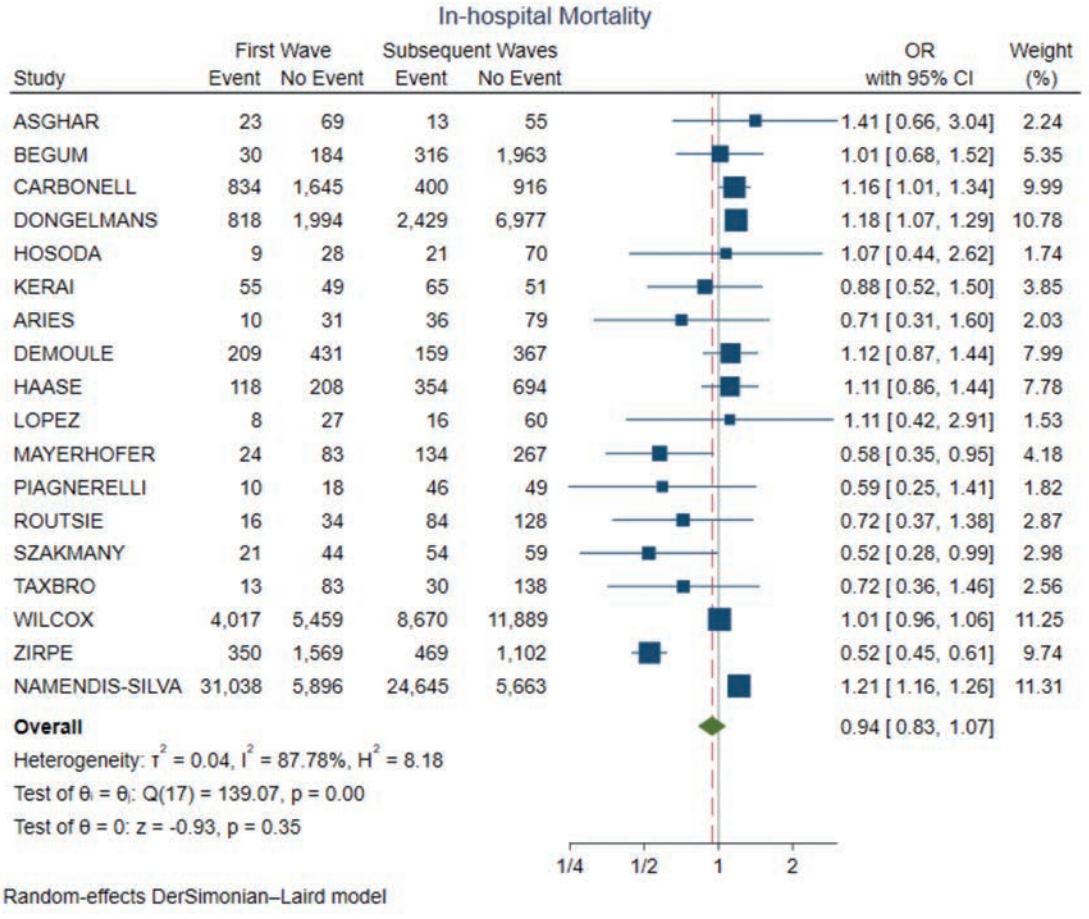

Figure 3. Forest plot for in-hospital mortality. CI, confidence interval; OR, odds ratio.

Second, the fluctuations in ICU bed strain during the pandemic might have changed the ICU admission criteria in each wave. These two factors inherently lead to significant differences of the populations analyzed, which might have driven outcome. For example, in four of the studies included the subsequent waves had less severe patients as shown by the scores of SAPS, APACHE or SOFA, while in two studies the subsequent waves had more severe patients.

It is worth mentioning the organizational aspect of the pandemic in relation to its waves. The reaction to the second and subsequent waves was shaped by the initial reaction to the onset of the disease, so that the disease in this second moment had a relatively more predictable character. In other words, the medical community had no specific weapon for facing the pandemic at that time.

During the first wave of the COVID-19 pandemic, mechanical ventilation played a critical role in the management of severely ill patients [11-14]. As the virus primarily affected the respiratory system, many patients experienced severe respiratory distress and required immediate respiratory support. Invasive ventilation was the primary method used to deliver oxygen to these patients. Ventilation strategies like low tidal volume and higher positive end-expiratory pressure (PEEP) were frequently employed to manage the compromised lung function in these patients [11-14]. Additionally, healthcare professionals faced the daunting task of managing the increased risk of ventilator-associated complications, such as ventilator-associated pneumonia and lack of equipment [15,16].

With the arrival of the second wave of COVID-19, lessons learned from the initial surge guided improvements in the management of mechanically ventilated patients [11-14]. Healthcare systems were better prepared with increased ventilator capacity and improved allocation strategies. Furthermore, advancements in knowledge and experience allowed for refinements in ventilation protocols. Ventilatory management strategies, such as prone positioning and lung-protective ventilation, became more widely utilized during the second wave to optimize patient outcomes [17,18].

The second wave also emphasized the importance of a multidisciplinary approach in mechanical ventilation. Collaborative efforts among pulmonologists, intensivists, respiratory therapists, and nurses played a crucial role in providing comprehensive care [19,20]. Knowledge exchange and shared experiences among healthcare professionals helped develop effective ventilation strategies and mitigate complications. Additionally, advancements in technology and remote monitoring allowed for more efficient and accurate ventilator management, reducing the burden on healthcare providers and improving patient care.

We have found a reduced incidence of acute renal failure (ARF) during the second and subsequent pandemic waves. Acute renal failure is an important risk factor for mortality in these patients [21] and a meta-analysis of the first wave including 142 studies and 49,048 hospitalized patients reported an incidence of ARF of 5.5% in China and of 28.6% in USA and Europe [22]. In patients admitted to the ICU the incidence of ARF and renal replacement therapy was respectively 29.2% and 20.6% [22]. A study evaluating kidney biopsies taken from 47 patients with COVID-19 related ARF showed acute tubular injury in 42.6% of the patients, while glomerular injury was reported in 36.2% of the patients [23].

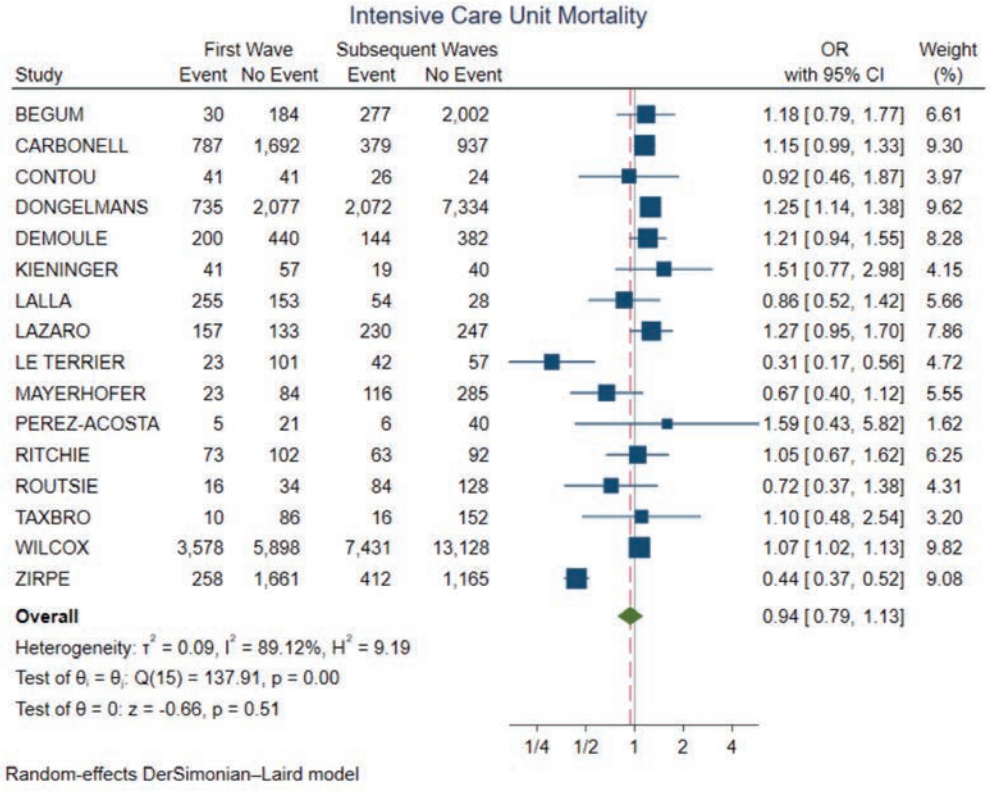

Figure 4. Forest plot for ICU mortality. CI, confidence interval; OR, odds ratio.

Mechanical ventilation and acute renal failure may be just surrogates of the overall clinical severity of critically ill patients, however in COVID-19 there is a temporal relation between the two, as acute renal failure develops 1 to 2 days after the beginning of mechanical ventilation [24,25]. Mechanical ventilation and acute renal failure in these cases may potentially be explained through lung-kidney cross talking or aggressive fluid restrictive therapy leading to hypovolemia [26]. In the initial COVID-19 cases, ECMO implantation was not so common, mainly because of the limited availability of ECMO machines and the lack of experience in managing COVID-19 patients with ECMO. However, after approaching more inside the pathophysiological mechanisms of the disease, ECMO implantation has become more common due to a number of factors. Firstly, as the pandemic has progressed, hospitals have gained more experience in managing critically ill COVID-19 patients with ECMO. Secondly, the availability of ECMO machines has increased, as more hospitals have invested in them. Thirdly, the emergence of new COVID-19 variants, which are more virulent and transmissible, has led to an increase in the number of patients requiring intensive care, including ECMO. The reduction of the ECMO implantation may be associated with the vaccination campaigns, which may have reduced the number of severe cases.

Concerning pharmacological treatment, 12 out of 15 studies that reported data on corticosteroid use have shown significant increase. As has been shown previously in the RECOVERY Trial that dexamethasone use leads not only to reduced mortality but also to reduced ICU length of stay and lower use of renal replacement therapy [6], it is possible that the increase in the administration of corticosteroids may have influenced the outcomes. By December 2020 several countries started vaccination against SARS-CoV-2. In 15 out of 25 of the studies analyzed there was an overlap between the time frames of the vaccination and the second and subsequent waves (Supplementary Table 4). In these studies, the subsequent waves have probably included vaccinated patients. As only one study reported data on vaccination status its influence on outcomes is unknown, although it is expected that vaccination might reduce morbidity even when considering only severe cases [27]. One interesting possibility is that the increase in expertise acquired during the pandemic lead progressively to better indication of supportive and pharmacological measures, which ultimately reduced morbidity, but was not enough to reduce mortality. The reduced morbidity observed may have allowed more patients to be cared in ICUs during a time of unprecedented strain over hospital beds.

Study strength and limitations

This is the first meta-analysis data to address this important topic with a wide systematic approach. We analyzed 9 different outcomes besides in-hospital mortality. However, this work has the intrinsic limitations of observational series, including the risk of methodological heterogeneity of the included studies and residual confounders. Additionally, it was not known the fraction of infected patients being admitted to the hospital in each wave, so a possible selection bias of the sickest patients is possible, and the possi-

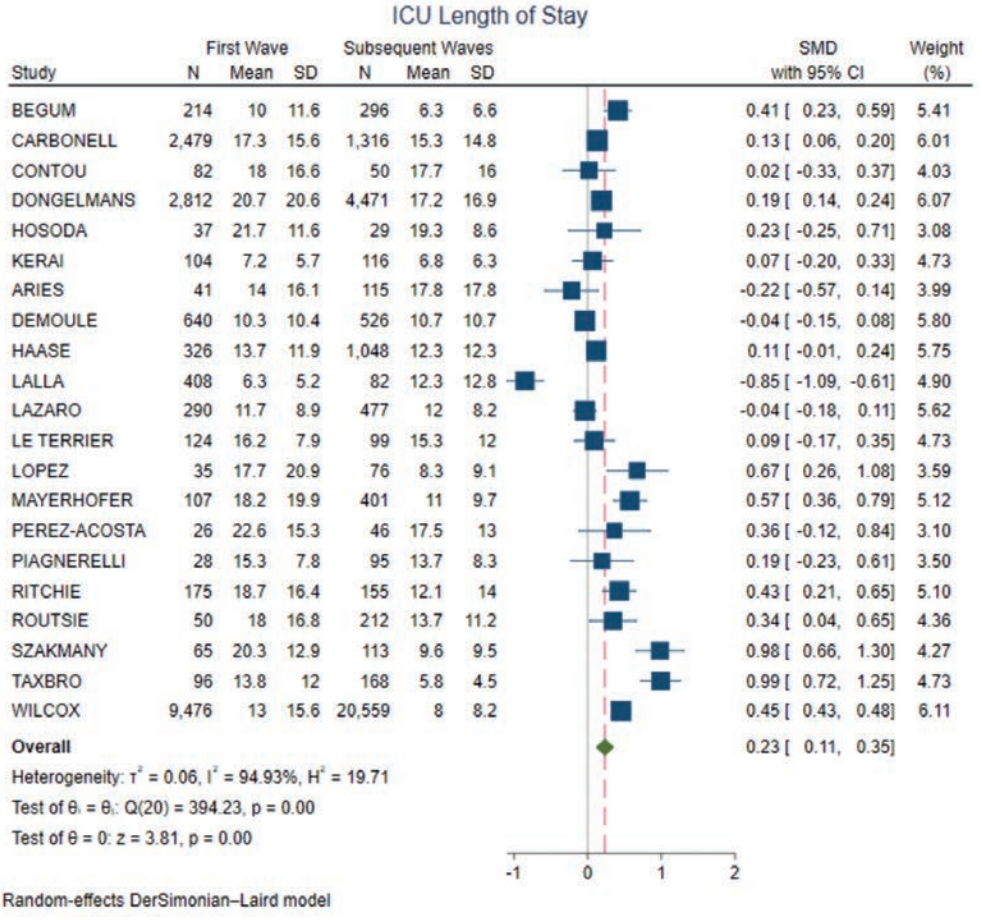

Figure 5. Forest plot for ICU length of stay. CI, confidence interval; SMD, standard mean difference.

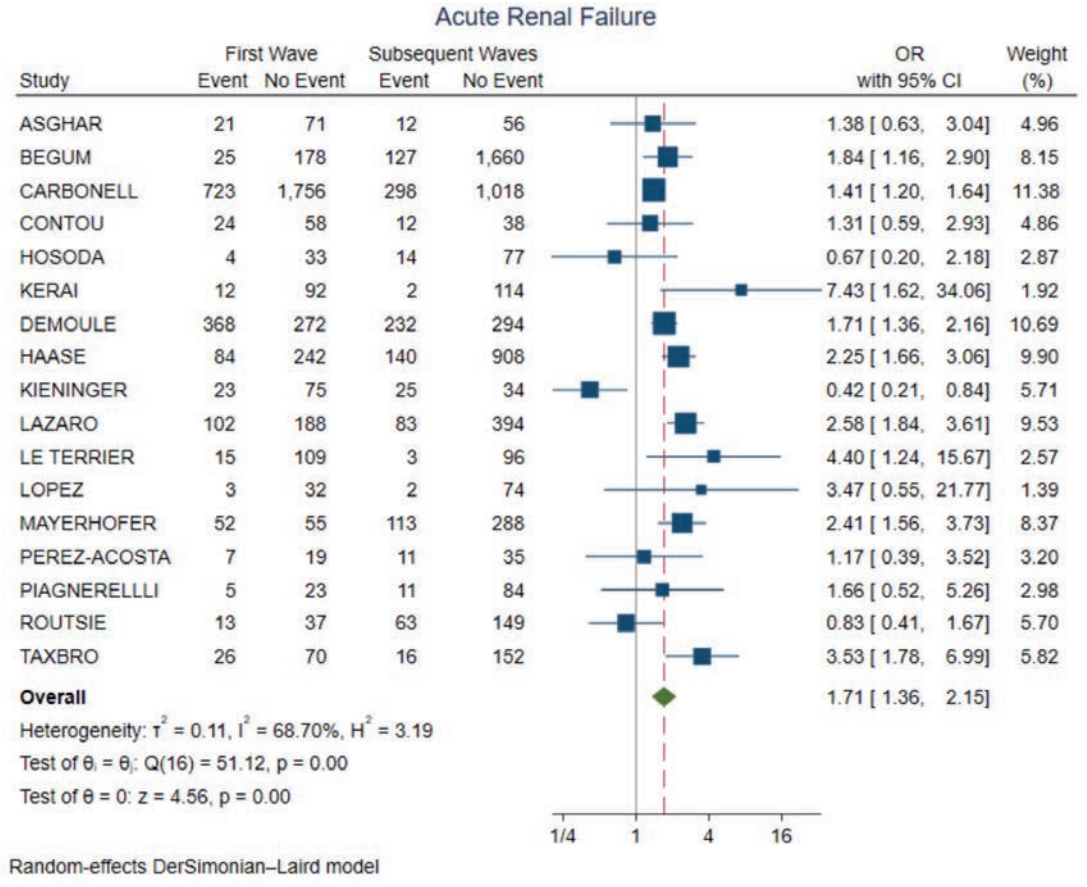

Figure 6. **Forest plot for acute renal failure. CI, confidence interval; OR, odds ratio.**

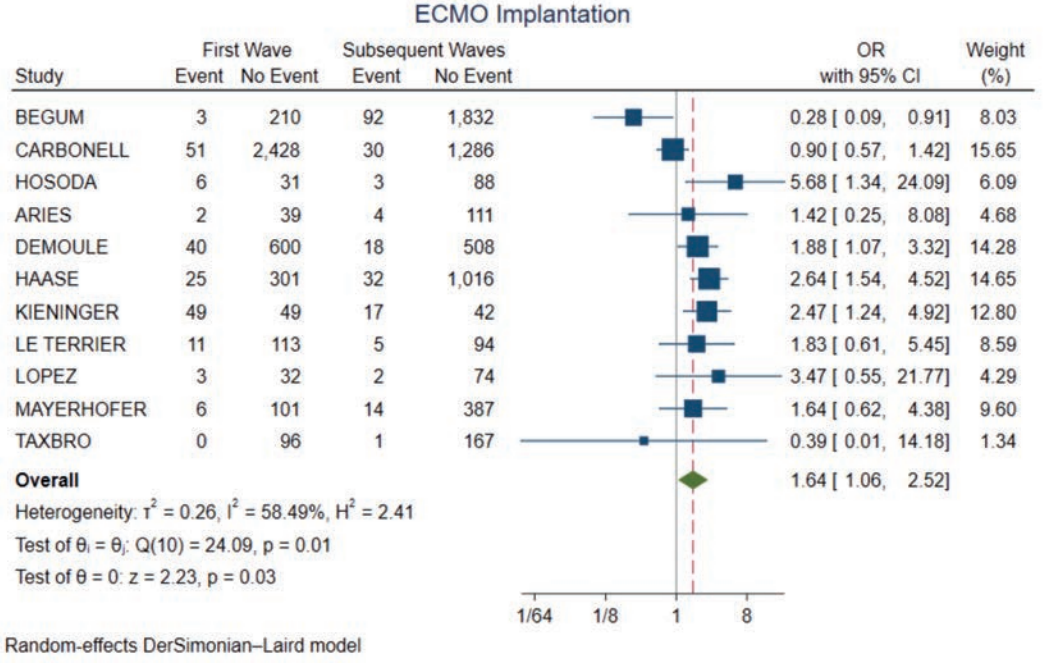

Figure 7. **Forest plot for ECMO implantation. CI, confidence interval; OR, odds ratio.**

ble improvements in therapy and through vaccination may not be as evident.

Moreover, most of the studies involved patients who were diagnosed with SARS-CoV-2 infection based on PCR analysis. However, it is not possible to exclude cases of patients with viral or bacterial co-infections in the initial phase.

Conclusions

The analysis suggests that the first wave group when compared with the subsequent waves group presented higher rates of ICU LOS, acute renal failure and ECMO implantation, without significant difference in in-hospital or ICU mortality, mechanical ventilation time, hospital LOS, systemic thromboembolism, myocarditis or ventilator associated pneumonia.

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Online supplementary material
Supplementary Table 1. Search strategy for Ovid MEDLINE.
Supplementary Table 2. Assessment of risk of bias using the "Tool to Assess Risk of Bias in Cohort Studies" developed by the CLARITY Group at McMaster University.
Supplementary Table 3. Demographics of included patients from the selected studies.
Supplementary Table 4. Waves period, vaccination start date, use of respiratory support.
Supplementary Figure 1. Leave-one-out analysis for in-hospital mortality.
Supplementary Figure 2. Funnel plot for in-hospital mortality.
Supplementary Figure 3. Forest plot for mechanical ventilation time.
Supplementary Figure 4. Forest plot for hospital length of stay.
Supplementary Figure 5. Forest plot for systemic thromboembolism.
Supplementary Figure 6. Forest plot for myocarditis.
Supplementary Figure 7. Forest plot for ventilator associated pneumonia.

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