Coronavirus Disease 2019 as Cause of Viral Sepsis: A Systematic Review and Meta-Analysis*

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OBJECTIVE: Coronavirus disease 2019 is a heterogeneous disease most frequently causing respiratory tract infection, which can induce respiratory failure and multiple organ dysfunction syndrome in its severe forms. The prevalence of coronavirus disease 2019–related sepsis is still unclear; we aimed to describe this in a systematic review.

DATA SOURCES: MEDLINE (PubMed), Cochrane, and Google Scholar databases were searched based on a prespecified protocol (International Prospective Register for Systematic Reviews: CRD42020202018).

STUDY SELECTION: Studies reporting on patients with confirmed coronavirus disease 2019 diagnosed with sepsis according to sepsis-3 or according to the presence of infection-related organ dysfunctions necessitating organ support/replacement were included in the analysis. The primary end point was prevalence of coronavirus disease 2019–related sepsis among adults hospitalized in the ICU and the general ward. Among secondary end points were the need for ICU admission among patients initially hospitalized in the general ward and the prevalence of new onset of organ dysfunction in the ICU. Outcomes were expressed as proportions with respective 95% CI.

DATA EXTRACTION: Two reviewers independently screened and reviewed existing literature and assessed study quality with the Newcastle-Ottawa Scale and the Methodological index for nonrandomized studies.

DATA SYNTHESIS: Of 3,825 articles, 151 were analyzed, only five of which directly reported sepsis prevalence. Noting the high heterogeneity observed, coronavirus disease 2019–related sepsis prevalence was 77.9% (95% CI, 75.9–79.8; $I^2 = 91\%$; 57 studies) in the ICU, and 33.3% (95% CI, 30.3–36.4; $I^2 = 99\%$; 86 studies) in the general ward. ICU admission was required for 17.7% (95% CI, 12.9–23.6; $I^2 = 100\%$) of ward patients. Acute respiratory distress syndrome was the most common organ dysfunction in the ICU (87.5%; 95% CI, 83.3–90.7; $I^2 = 98\%$).

CONCLUSIONS: The majority of coronavirus disease 2019 patients hospitalized in the ICU meet Sepsis-3 criteria and present infection-associated organ dysfunction. The medical and scientific community should be aware and systematically report viral sepsis for prognostic and treatment implications.

KEY WORDS: coronavirus disease 2019; organ dysfunction; organ replacement; Sequential Organ Failure Assessment; viral sepsis

Coronavirus disease 2019 (COVID-19) is a recognized pandemic that spread rapidly around the globe and led to millions of confirmed cases and deaths worldwide (1). Severe forms are complicated by respiratory insufficiency and need for invasive mechanical ventilation (IMV) (2). Reported cases often present with other organ failures; such involvement resembles the systemic counterparts of bacterial and viral sepsis (3–5). The current Sepsis-3 definitions define sepsis as a life-threatening organ dysfunction due to the dysregulated host response to an infection. The same definitions introduce the

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Sequential Organ Failure Assessment (SOFA) score as measure of organ dysfunction (6). According to World Health Organization, manifestations of sepsis and septic shock can be the final pathway of infections by highly transmissible pathogens of public health concern, like avian and swine influenza viruses, or corona viruses (7). Respiratory failure of COVID-19 is accompanied by complex host immune dysregulation (8). As a consequence, all elements of the Sepsis-3 definition may apply for COVID-19 (9).

With this in mind, we systematically investigated peer-reviewed published literature to describe the prevalence of COVID-19-related sepsis. In parallel, the prevalence of new-onset organ dysfunctions, organ replacements, and need for ICU admission were assessed as surrogates for viral sepsis.

MATERIALS AND METHODS

Protocol and Registration

This review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (10), based on a prespecified protocol (International Prospective Register for Systematic Reviews: CRD42020202018).

Eligibility Criteria

Eligibility criteria were defined using the Population, Intervention, Comparison, Outcome (PICO) statement; *P*: hospitalized patients with confirmed COVID-19. Duration of follow-up was defined by the length of hospital stay. *I*: diagnosis of sepsis and any infection-related organ dysfunction or need for organ replacement (dialysis, mechanical ventilation [MV], extracorporeal membrane oxygenation [ECMO], and liver replacement). Sepsis was primarily defined according to Sepsis-3, as any SOFA score greater than or equal to 2 at admission; quick SOFA (qSOFA) score greater than or equal to 2, severe sepsis according to Sepsis 1/2 criteria, or relevant *International Classification of Diseases* (ICD) codes were acceptable alternative definitions (6, 7, 11). Organ dysfunction was also reported based on admission values, whereas organ replacement was assessed throughout the follow-up period. *C*: no control group was included, whereas *O* was the prevalence of sepsis, infection-related organ dysfunction, need for organ support/ replacement, and sepsis-related mortality. All randomized and nonrandomized trials and observational studies, published as full text in English, were included, whereas editorials, conference abstracts, animal studies, case reports, articles not in English or not providing full text, and studies with fewer than 30 participants were excluded. Systematic reviews were consulted for additional information but were excluded to avoid duplication.

Information Sources and Search Strategy

Search was conducted on August 27, 2020, and repeated on October 3, 2020, and on March 29, 2021, by two independent authors (E.Ka., E.Ky.) across MEDLINE (PubMed), Cochrane, and Google Scholar databases using the following terms: "COVID-19" or "SARS-CoV-2" and "sepsis," "organ failure," "organ dysfunction." Detailed strategy is provided in **Supplement** (http://links.lww.com/CCM/G588).

Study Selection, Data Collection, and Data Items

Both reviewers assessed all articles by title and, then, by abstract and full text to find those eligible. The following data were extracted: first author name, country of origin, publication time, study design, total number of patients, criteria for enrollment, number of patients presenting sepsis, criteria used to assess sepsis, new onset organ dysfunction, organ support/replacement therapy, number of patients requiring ICU, ICU/hospital discharge, and mortality. Any controversies were resolved by a third reviewer (E.J.G.B). The corresponding authors were contacted to provide relevant data.

For studies allowing extraction of SOFA score greater than or equal to 2 for different organ dysfunctions, a conservative approach was followed, and only the organ with the maximum number of affected patients within the cohort was considered, for example, in a cohort with x patients presenting respiratory SOFA greater than or equal to 2, y patients presenting cardiovascular SOFA greater than or equal to 2, and $x > y$, the number of patients considered to have sepsis would be defined as x. Among studies reporting medians (interquartile range [IQR]), outcomes were calculated as the minimum n observed, for example, if SOFA score at baseline was reported as 4 (2–6), then at least 75% of the study population was expected to have a SOFA score greater than or equal to 2. For studies reporting on both ICU and general ward patients, these

were included in the analysis with the total number of ICU or general ward patients as denominator.

Quality Assessment and Individual Risk of Bias

Each study was evaluated by both reviewers with the Newcastle-Ottawa scale for observational studies (12). Since not all parameters of this scale were applicable in case of single cohorts, their quality was also evaluated with the methodological index for nonrandomized studies (MINORS) (13). Furthermore, the level of certainty in extraction of the primary endpoint was assessed using a three-star scale, from zero (one star) to intermediate/high uncertainty (three stars). Studies providing the exact number of patients fulfilling Sepsis-3 criteria (in the original publication or after contacting corresponding authors) were qualified as zero uncertainty; studies reporting baseline median SOFA score (IQR) were qualified as low; studies allowing extraction of SOFA score greater than or equal to 2, based at least on one reported specific organ dysfunction at baseline, were characterized as intermediate/high. The highest level of certainty achievable within the study was used to assess sepsis prevalence, for example, if x patients were considered to have sepsis according to our criteria for low certainty and y according to criteria for intermediate, we would report sepsis prevalence as x, even when $x < y$.

End Points and Outcome Measures

The primary end point was the prevalence of COVID-19-related sepsis among adults hospitalized in the ICU and general ward, expressed as proportion (95% CIs). Secondary endpoints were: 1) the prevalence of new onset infection-related organ dysfunction in the ICU, 2) the prevalence of organ support and/or replacement (IMV and noninvasive MV, vasopressors, ECMO, liver, and renal replacement therapy) in the ICU, 3) the prevalence of ICU admission, 4) mortality of COVID-19 patients with sepsis, and 5) the prevalence of pediatric COVID-19-related sepsis. The outcome measure for each secondary outcome was the proportion (95% CI) of patients presenting the respective outcome.

Result Synthesis and Risk of Bias Across Studies

The meta-analyses were performed using the R software Version 4.0.2 (R Core Team, The University of Auckland, Auckland, New Zealand) after installing the packages "meta," "metaphor," and "dmetar" (14, 15). In all cases, the random effects (DerSimonian and Laird) model was employed (16). For each analysis, the corresponding forest plot was produced, whereas publication bias was assessed with the Egger test via funnel plot asymmetry (17). Subgroup differences were reported by the Q-statistic (18).

Additional Analyses

The following analyses were planned regarding the primary endpoint: 1) per level of uncertainty regarding the extraction of the primary end point, as previously described, 2) per geographical location of studies, 3) per period of study enrollment, and 4) per nonpulmonary versus pulmonary acute organ dysfunction assessment, since COVID-19 is often associated with hypoxemic respiratory failure.

RESULTS

Study Selection

The literature search yielded 3,825 records; after removal of duplicates and records with irrelevant title, 834 were screened full text by the reviewers. After applying exclusion criteria, 151 studies including a total of 218,184 patients were finally analyzed (**Fig. 1**).

Study Characteristics

Of the 151 included studies, mainly observational retrospective, 104 were published in 2020 (19–122) and 47 in 2021 (123–169). Forty-seven studies reported results from Asia, mainly China (19–22, 25, 27, 29–37, 40–42, 44–47, 52–54, 59, 60, 66–68, 77, 92, 104, 106–108, 122, 124, 129, 133, 143, 147, 149, 150, 156, 158, 164), 21 from North America (24, 39, 43, 48, 56, 58, 74, 75, 78–80, 82, 95, 103, 114, 118, 131, 135, 162, 166, 169), seven from Central and South America (96, 123, 142, 145, 154, 160, 167), 73 across Europe (23, 26, 28, 38, 50, 51, 55, 57, 61–65, 69–73, 76, 81, 83–91, 93, 94, 97–102, 105, 109, 110, 112, 113, 115–117, 119–121, 125–128, 130, 132, 134, 136–139, 141, 144, 146, 148, 151–153, 155, 157, 159, 161, 163, 165, 168), one from Australia (111), and two were international (49, 140). All studies reported data on hospitalized patients due to confirmed COVID-19, and follow-up was mainly

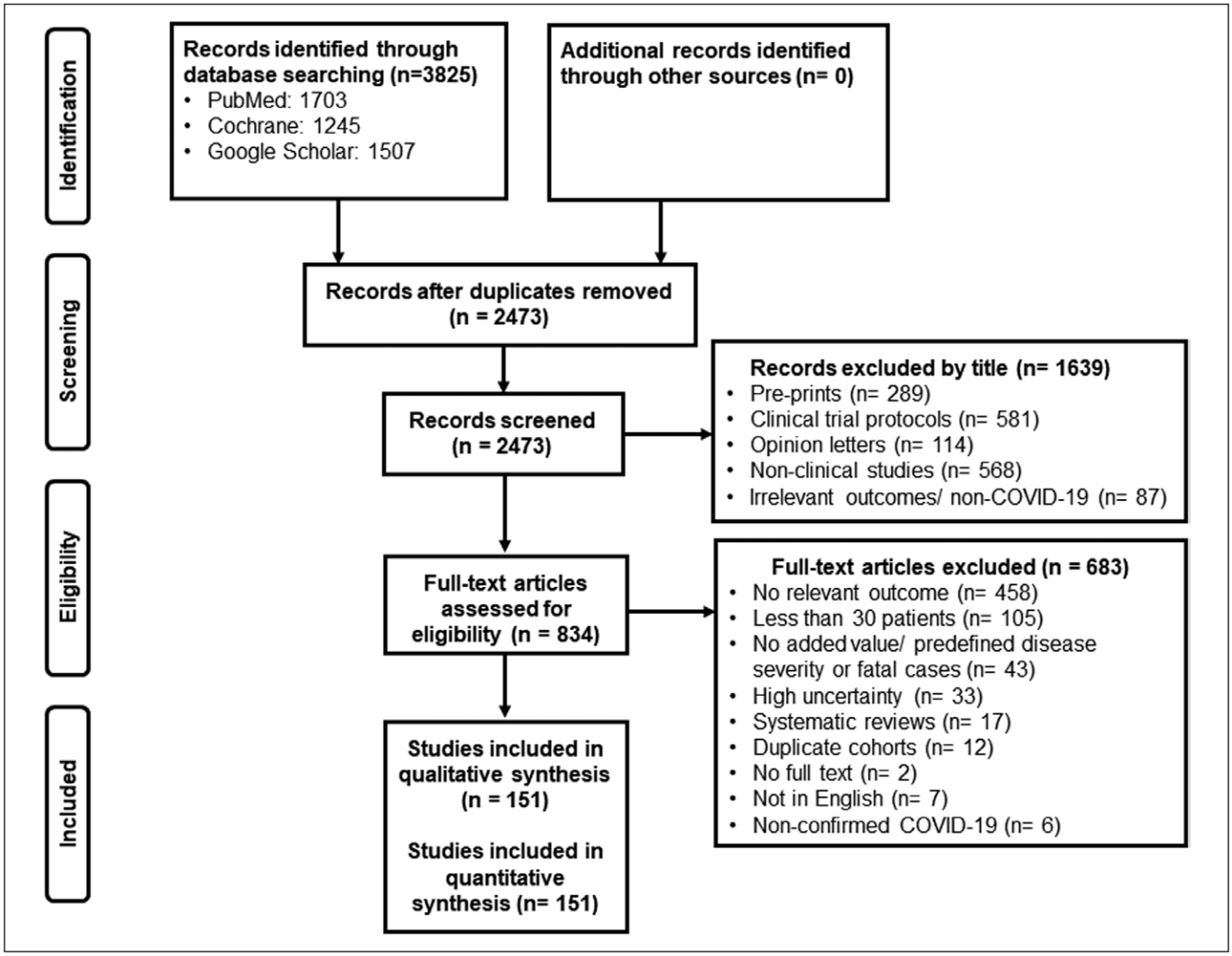

Figure 1. Study selection. COVID = coronavirus disease.

defined by the length of hospital stay, which varied per study; 56 concerned the ICU (22, 24, 27, 38, 39, 42, 44, 50–53, 57, 59, 60, 65, 68, 71, 73, 75–78, 86–89, 93, 95, 104, 107, 109–111, 115, 117, 123, 126, 128–130, 132–135, 140, 141, 143, 145, 147, 153, 155–158, 164, 165, 168). Nine studies were pediatric (35, 80, 83, 98, 116, 136, 142, 146, 166). Characteristics are presented in **Supplementary Table 1** (http://links.lww.com/CCM/G588).

Individual Risk of Bias

Quality assessment according to Newcastle-Ottawa Scale and MINORS is provided in **Supplementary Tables 2** and **3** (http://links.lww.com/CCM/G588), respectively. The overall quality was low to intermediate. None of the studies reported severe sepsis based on Sepsis-1/2 criteria or by other relevant ICD codes; thus, assessment of presence of COVID-19-related sepsis was mainly performed by Sepsis-3 criteria: reported median SOFA score (19, 22, 27, 35–37, 39, 44, 50, 52, 56, 60, 65, 68, 73, 75, 77, 78, 83, 87, 88, 89, 92, 93, 94, 95, 96, 98, 104, 107, 110, 111, 115, 119, 121–123, 128, 132, 137, 141, 143, 147, 153–156, 158, 160, 162, 169), SOFA score extraction by reported organ failures (20, 21, 25, 28–34, 40–43, 45–49, 51, 53–55, 57–59, 61–64, 66, 67, 69, 72, 74, 76, 79, 80, 82, 84–86, 90, 91, 97, 99, 100, 102, 103, 105, 108, 109, 112–114, 116, 117, 120, 124–127, 130, 131, 134–136, 138–140, 142, 145, 146, 148–152, 157, 159, 161, 163, 168), or exact number of patients with Sepsis-3 (reported, or provided by corresponding authors). Only five studies reported the exact number of patients meeting Sepsis-3 criteria (106, 118, 129, 133, 144), and for another eight studies, this was later provided by the authors (23, 24, 26, 35, 38, 71, 72, 101). The term "sepsis" was found in nine studies (70, 103,

121, 122, 129, 133, 144, 149, 152), in eight of which describing bacterial complications during hospitalization for COVID-19; only one described sepsis as a presenting feature of COVID-19 (133).

Primary End Point

COVID-19-Related Sepsis in the ICU. Data regarding the prevalence of COVID-19-related sepsis were available from 56 studies in the ICU (38,058 adult patients). The pooled estimate was 77.9% (95% CI, 75.9–79.8; I^2 = 91%), as shown in **Figure 2**, with evidence of publication bias (p = 0.012; **Supplementary Fig. 1**, http://links.lww.com/CCM/G588). The lowest level of heterogeneity was achieved among studies with zero (I^2 = 67%) and low (I^2 = 60%) uncertainty. Conversely, heterogeneity remained substantial (I^2 = 97%) among studies with intermediate/high uncertainty (Fig. 2).

Subgroup analysis per geographical location reduced without eliminating heterogeneity ($I^2 \geq 76\%$), and the meta-analytical outcome remained constant among subgroups (test for subgroup differences: p = 0.543; **Supplementary Fig. 2**, http://links.lww.com/CCM/G588). Analysis per chronological period also failed to eliminate heterogeneity ($I^2 \geq 76\%$). A slight increase in sepsis prevalence of 79.5% (95% CI, 76.8–82.0; I^2 = 94%) was observed during the second period of the pandemic (test for subgroup differences: p = 0.047; **Supplementary Fig. 3**, http://links.lww.com/CCM/G588). None of the included studies reported data as of 2021. Subgroup analysis of pulmonary versus nonpulmonary acute organ dysfunction could not be performed in the ICU; due to IMV, the presence of a pulmonary component for SOFA could not be excluded.

COVID-19-Related Sepsis in General Ward. Eighty-six studies, including 179,119 adult patients, reported on COVID-19-related sepsis among patients in the general ward. The pooled estimate was 33.3% (95% CI, 30.3–36.4; I^2 = 99%) (**Supplementary Fig. 4**, http://links.lww.com/CCM/G588), without evidence of reporting bias (p = 0.372; Supplementary Fig. 1, http://links.lww.com/CCM/G588). Subgroup analysis did not eliminate heterogeneity in none of the categories of uncertainty; pooled estimates of COVID-19-related sepsis prevalence and heterogeneity for studies with zero, low, and intermediate/high uncertainty were 43.4% (95% CI, 29.4–58.6; I^2 = 99%), 44.4% (95% CI, 36.8–52.4; I^2 = 98%), and 29.9% (95% CI, 26.6–33.3; I^2 = 99%), respectively (Supplementary Fig. 4, http://links.lww.com/CCM/G588). Studies with zero and low uncertainty had increased viral sepsis prevalence (test for subgroup differences: p = 0.0009; Supplementary Fig. 4, http://links.lww.com/CCM/G588).

Subgroup analysis according to nonpulmonary (n = 22) versus pulmonary (n = 64) acute organ dysfunction provided a pooled estimate of sepsis of 21.7% (95% CI, 18.7–25.1; I^2 = 95%) and 37.8% (95% CI, 34.1–41.7; I^2 = 99%), respectively (test of subgroup differences: $p < 0.001$, **Supplementary Fig. 5**, http://links.lww.com/CCM/G588).

Based on the above, the overall pooled sepsis prevalence estimate among 218,184 COVID-19 patients, irrespectively of ICU or non-ICU admission, was 51.6 (95% CI, 47.6–55.5; I^2 = 100%), as shown in **Supplementary Figure 6** (http://links.lww.com/CCM/G588).

Secondary End Points

Organ Dysfunctions in the ICU. Organ dysfunctions were assessed as defined in the original publications. Septic shock was defined by Sepsis-3 criteria (6) and acute respiratory distress syndrome (ARDS) by the Berlin definition (170) in all studies but one (129), which used the Kigali modification (171). A synthesis of prevalence estimates of organ dysfunctions in adults in the ICU is presented in **Table 1** and **Supplementary Table 4** (http://links.lww.com/CCM/G588). ARDS was the most common dysfunction reaching 87.5% (95% CI, 83.3–90.7; I^2 = 98%). Septic shock was the second most common dysfunction (Table 1; and **Supplementary Fig. 7**, http://links.lww.com/CCM/G588).

Organ Support in the ICU. Need for organ support/replacement was likely among ICU patients (**Table 2**). Pooled estimates of patients requiring IMV, renal replacement, vasopressors, and ECMO were 62.4 (95% CI, 57.8–66.7; I^2 = 98%), 19.9% (95% CI, 17.6–22.4; I^2 = 90%), 49.5% (95% CI, 41.1–57.8; I^2 = 98%), and 6.2% (95% CI, 4.7–8.1; I^2 = 85%), respectively (**Supplementary Fig. 8**, http://links.lww.com/CCM/G588).

Need for ICU Admission. ICU admission was evaluated, among 57 studies (165,008 patients initially hospitalized in the general ward), as surrogate for the presence of COVID-19-related organ dysfunction or support. A pooled estimate of 17.7% (95% CI, 12.9–23.6; I^2 = 100%) of those patients required ICU admission (**Supplementary Fig. 9**, http://links.lww.com/CCM/G588).

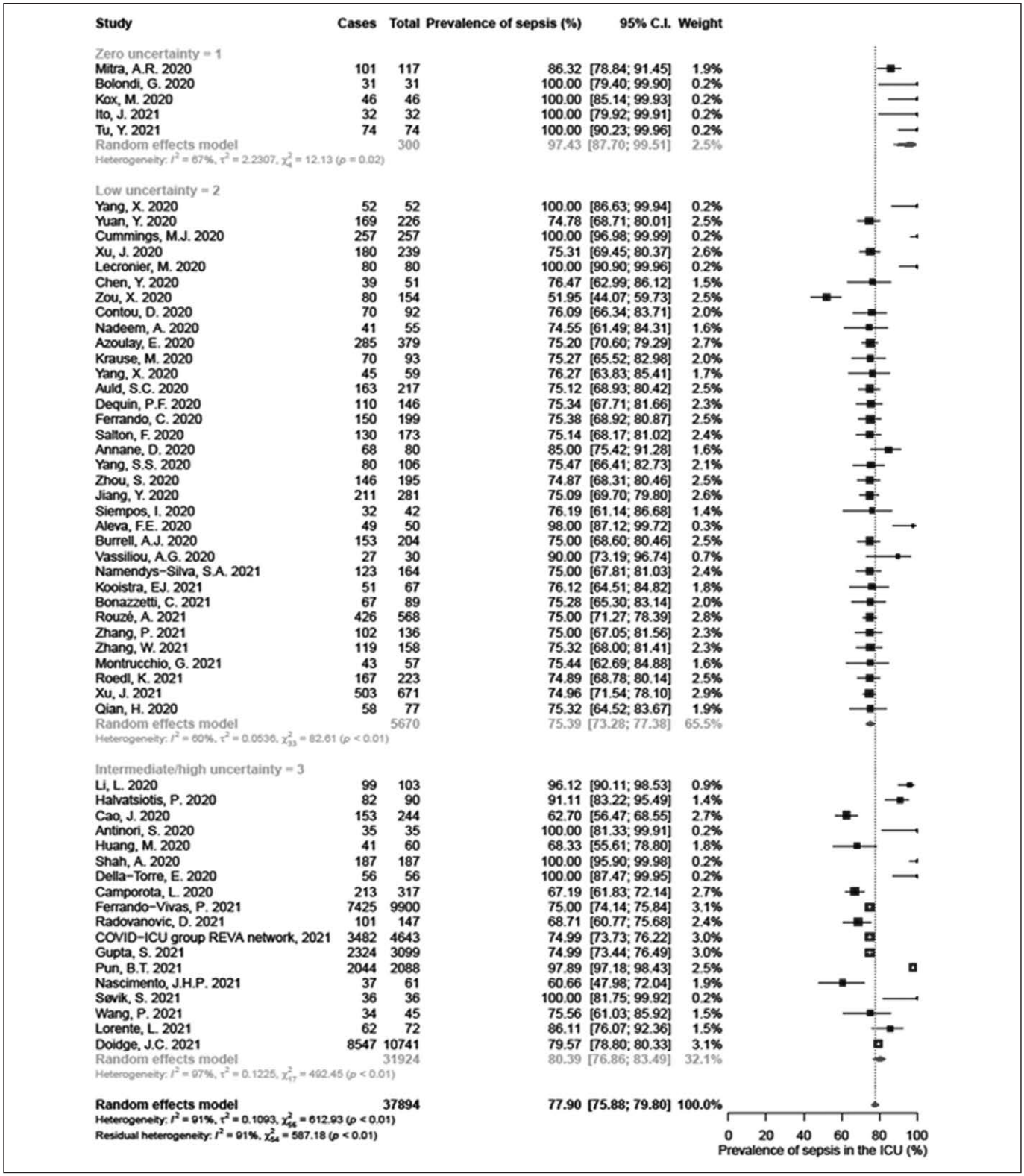

Figure 2. Forest plot of sepsis prevalence among adult patients hospitalized in the ICU.

Mortality. Mortality could not be assessed separately for patients with and without sepsis, since none of the studies reported such outcomes. To overcome this, ICU mortality and mortality among patients under IMV were investigated as surrogates of sepsis-related mortality. ICU mortality was 33.0% (95% CI, 29.1–37.2; I^2 = 97%) (**Fig. 3*A***), whereas IMV-related mortality was 42.0% (95% CI, 36.8–47.4; I^2 = 94%)

TABLE 1.
Summary of the Pooled Estimates of Prevalence of Organ Dysfunctions Among Adult Patients Hospitalized in the ICU

Dysfunction	No. of Studies	No. of Patients	No. With Dysfunction	Prevalence (%)	95% CI	I^2 (%)
Acute respiratory distress syndrome	41	21,678	15,809	87.5	83.3–90.7	98
Mild ($200 < Pao_2:Fio_2 < 300$)	21	9,688	1,796	21.5	13.9–31.8	98
Moderate ($100 < Pao_2:Fio_2 < 200$)	26	33,210	16,505	43.7	32.4–55.8	100
Severe ($Pao_2:Fio_2 < 100$)	28	20,034	7,377	32.1	26.3–39.8	99
Septic shock	22	3,262	1,189	36.4	27.2–46.8	96
Lactate elevated (> 2 mmol/L)	9	978	390	47.2	33.5–61.3	93
Renal dysfunction	32	32,785	11,215	28.6	23.1–33.6	98
Coagulopathy	25	3,346	724	17.7	13.1–23.3	92
Liver dysfunction	19	2,045	495	20.3	12.3–31.6	95
CNS dysfunction	6	4,151	755	8.8	4.0–18.1	95

Prevalence (%) is considered the pooled estimate of each organ dysfunction as calculated in the respective meta-analysis of the respective studies providing such data, taking into consideration different weights of each study in the meta-analysis (resulting from number of patients in each meta-analyzed trial).

(**Fig. 3*B***) both without reporting bias (**Supplementary Fig. 10**, http://links.lww.com/CCM/G588).

Pediatric Population. Four studies (521 patients) reported on sepsis prevalence among hospitalized children in ICU and five studies (692 patients) in non-ICU cohorts. Since Sepsis-3 definitions are not yet universally accepted for children, we used the presence of organ dysfunction as proxy for sepsis. Prevalence of viral sepsis was 67.0% (95% CI, 56.0–82.9; I^2 = 94%) in ICU and 21.3% (95% CI, 7.6–47.3; I^2 = 97%) in non-ICU, respectively, without reporting bias (**Supplementary Fig. 11**, http://links.lww.com/CCM/G588). A synthesis of pediatric organ dysfunctions is presented in **Supplementary Table 5** (http://links.lww.com/CCM/G588). ICU mortality, evaluable for four studies, remained low (2.2%; 95% CI, 0.8–5.7; I^2 = 47%) (**Supplementary Fig. 12**, http://links.lww.com/CCM/G588).

DISCUSSION

In this systematic review and meta-analysis, we showed that COVID-19-related sepsis, based on Sepsis-3, is present in a considerable proportion of hospitalized patients; 77.9% of adult patients in the ICU have viral sepsis. This is also the case for 33.3%

TABLE 2.
Summary of the Pooled Estimates of Prevalence of Organ Replacement Among Adult Patients Hospitalized in the ICU

Type of Replacement	No. of Studies	No. of Patients	No. With Replacement	Prevalence (%)	95% CI	I^2 (%)
Vasopressor use	24	11,278	2,843	49.5	41.1–57.8	98
Noninvasive mechanical ventilation	29	7,784	1,531	20.9	13.8–30.5	98
Mechanical ventilation	53	25,243	17,662	62.4	57.8–66.7	98
Extracorporeal membrane oxygenation	27	9,159	568	6.2	4.7–8.1	85
Continuous renal replacement therapy/dialysis	28	21,629	5,057	19.9	17.6–22.4	90

Prevalence (%) is considered the pooled estimate of each organ replacement as calculated in the respective meta-analysis of the respective studies providing such data, taking into consideration different weights of each study in the meta-analysis (resulting from number of patients in each meta-analyzed trial).

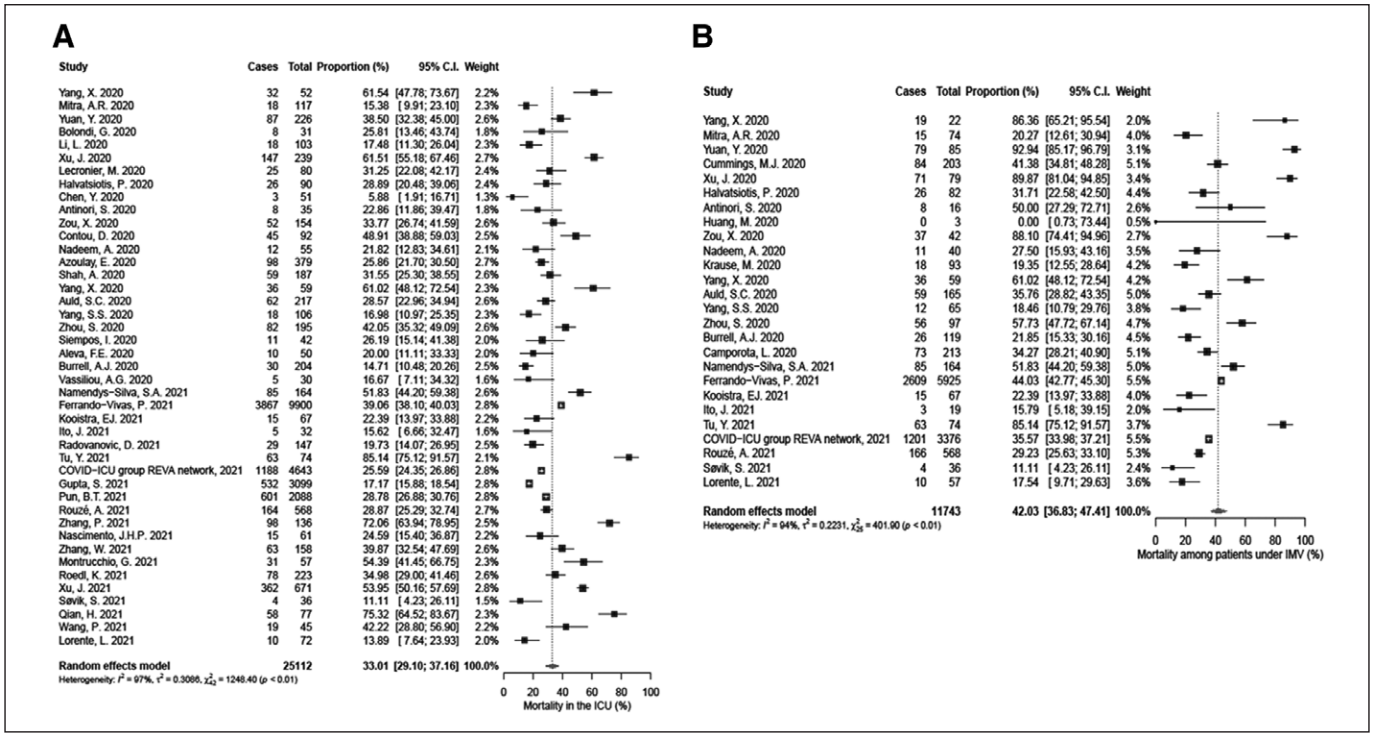

Figure 3. Forest plot of mortality among patients with coronavirus disease 2019 (COVID-19). **A**, Hospitalized in the ICU. **B**, Under invasive mechanical ventilation (IMV). REVA = Réseau Européen de Recherche en Ventilation Artificielle.

of patients originally admitted in the general ward, 17.7% of which are transferred to the ICU. ARDS is the most common organ dysfunction, followed by septic shock.

Despite separate analysis for ICU and general ward populations, adult and pediatric, and conservative reporting with the highest level of certainty, heterogeneity remained high. The most probable explanation was the absence of reporting of specific numbers of patients with greater than or equal to 2 SOFA values in most studies. This was limited when raw data were used after contacting the authors.

Interestingly, COVID-19-related sepsis was rarely reported as "sepsis" syndrome within the studies searched. On the contrary, of the nine articles where the term was used, (70, 103, 121, 122, 129, 133, 144, 149, 152), eight reported it as complication of secondary bacterial infections. This raises a question of awareness regarding viral sepsis in the medical and scientific community. Sepsis is traditionally seen as a consequence of bacterial infection but may occur regardless of the type of pathogen (172). Although viral sepsis, in the form of ARDS, shock, and other organ-failures, has also been associated with influenza A, authors still focus on secondary bacterial infections (173, 174). In COVID-19, low proportion (7%) of hospitalized patients suffer bacterial coinfection or secondary infection; this is slightly higher for ICU patients (175, 176), whereas the frequency of opportunistic infections is likely to rise after the widespread introduction of dexamethasone (177). Thus, reporting of septic episodes should be separate for viral and bacterial pathogens throughout hospitalization, but it is unlikely that sepsis estimates within the current study reflect bacterial coinfection. Given that most of the evidence comes from retrospective, observational studies, where a standardized assessment of SOFA components may be complex, the Centers for Disease Control and Prevention Adult Sepsis Event organ dysfunction criteria optimized for electronic health record systems criteria for Adult Sepsis Events (178) may be an interesting, simpler, nonscalar and based on fewer parameters alternative to facilitate sepsis reporting. More interestingly, by highlighting the importance of microbiological documentation, it may help distinguishing inhospital viral from secondary bacterial infection-related sepsis.

The above analysis highlights that COVID-19 is not yet perceived as viral sepsis, which is probably underreported. The trials included were not designed to answer this clinical question. This is considered as a major source of heterogeneity in our results; increased

awareness might prompt future publications to report more precisely and systematically SOFA components.

Nevertheless, this would not eliminate clinical heterogeneity due to differences in cohorts, time periods, hospital or geographical settings, different levels of care, different timing of assessment, and variable immune response of the host; heterogeneity remained substantial even after subgroup analysis by geographical settings and time periods and all of the above are acknowledged as limitations within this study and known features of sepsis studies in general. A recent meta-analysis focusing on a harder end point than ours, that is, IMV-associated mortality, reported as high as 45%, could not eliminate heterogeneity, attributed to different locations and practices concerning intensive care allocation (179).

Children are less affected by the virus, but, if hospitalized, still at risk of organ failure. The use of organ dysfunctions as pediatric sepsis indicator might have been conservative and did not fully capture patients with multiinflammatory syndrome associated to COVID-19, a novel entity described in children with high inflammatory features and multiple organ involvement (180), as potential equivalent of adult sepsis.

Underlying pathophysiological mechanisms of multiorgan injury in COVID-19 may be partly unique to severe acute respiratory syndrome coronavirus 2 (direct viral toxicity) and partly common with bacterial sepsis, such as endothelial cell damage, thromboinflammation, dysregulated immune system activation coupled with tissue damage by neutrophils, monocytes, and lymphocytes, and dysregulation of the rennin-angiotensin-aldosterone system (181–187). Overlap between severe COVID-19 and sepsis, as shown in the current analysis, may be neither surprising nor unexpected, but quantifying the link has important treatment and policy-making implications. Following the paradigm of bacterial sepsis, guidelines for COVID-19 management have been issued highlighting the importance of supportive care in critically ill patients (188). Pathogen-specific treatments, such as remdesivir, may accelerate clinical recovery (189), whereas immune-targeting therapies have been tested through clinical trials, with conflicting results (93, 190–194). Further research is needed to identify which patients would benefit from such interventions. On a public health level, this awareness might lead to prioritizing national sepsis-infection action plans, to deal with current and future pandemics.

To the best of our knowledge, this is the first study to address in a systematic way the presence of COVID-19-related sepsis, according to Sepsis-3 criteria, and the first to provide pooled estimates of specific organ dysfunctions. Results are highly heterogeneous and should be interpreted with caution, given the paucity of data on SOFA components and the conservative approach used for SOFA score extraction. Higher precision resulted in increased detection of sepsis, and every effort should be made to identify patients at high risk for those complications.

CONCLUSION

A considerable proportion of patients with COVID-19 meet Sepsis-3. True prevalence is probably underestimated, and estimates increase with improved data reporting quality and limiting uncertainty. Lessons learned from bacterial sepsis may apply, in terms of early recognition by means of SOFA score, importance of supportive care, as well as potential benefit from immune regulating strategies.

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Drs. Reinhart and Kyriazopoulou contributed equally.

Dr. Kyriazopoulou performed literature search and study selection, participated in data analysis, and drafted the article. Dr. Karakike performed literature search and study selection and participated in data analysis and drafting of the article. Dr. Kyprianou performed data analysis. Drs. Fleischmann-Struzek, Netea, and Reinhart conceptualized the study and revised the article for important intellectual content. Dr. Pletz revised the article for important intellectual content. Dr. Giamarellos-Bourboulis conceptualized the study and participated in literature search, study selection, and drafting the article. All authors gave approval for the version to be published.

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