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Characteristics, outcomes and global trends of respiratory support in patients hospitalized with COVID-19 pneumonia: a scoping review.

Respiratory support in patients with COVID-19 pneumonia: a scoping review.

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ABSTRACT

INTRODUCTION: To date, a shared international consensus on treatment of Coronavirus Disease 2019 (COVID-19) with invasive or non-invasive respiratory support is lacking. Patients' management and outcomes, especially in severe and critical cases, can vary depending on regional standard operating procedures and local guidance.

EVIDENCE ACQUISITION: Rapid review methodology was applied to include all the studies published on PubMed and Embase between December 15th 2019 and February 28th 2021, reporting in-hospital and respiratory support-related mortality in adult patients hospitalized with COVID-19 that underwent either continuous positive airway pressure (CPAP), non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV). Only English language studies with ≥100 patients and reporting data on respiratory failure were included. Data on comorbidities, ventilatory parameters and hospital-related complications were registered.

EVIDENCE SYNTHESIS: Fifty-two studies (287359 patients – 57.5% males, mean age 64 years (range 24-98)) from 17 different countries were included in the final analysis. 33.3% of patients were hospitalized in intensive care units. 44.2% had hypertension, 26.1% had diabetes, and 7.1% a chronic respiratory disease. 55% of patients underwent respiratory support (36% IMV, 62% NIV and 2% CPAP). Without considering a study with the highest number of patients treated with NIV (n=96729), prevalence of NIV and CPAP use was 12.5% and 13.5% respectively. Globally, invasive and non-invasive approaches were heterogeneously applied. In-hospital mortality was 33.7%, and IMV-related mortality was 72.6% (range: 4.3%-99%). Specific mortality in patients treated with CPAP or NIV was available for 53% of studies, and was 29% (range: 7.2%-100%). The median length of hospital stay was 13 days (range: 6-63). The most frequent hospital-related complication was acute kidney injury being reported in up to 55.7% of enrolled patients.

CONCLUSIONS: Global employment of respiratory supports and related outcomes are very heterogeneous. The most frequent respiratory support in patients with COVID-19 pneumonia is IMV, while NIV and CPAP are less frequently and equally applied, the latter especially in Europe, while data on NIV/CPAP-related mortality is often under-reported. Integrated and comprehensive reporting is desirable and needed to construct evidence-based recommendations.

Key words: COVID-19, respiratory failure, invasive mechanical ventilation, continuous positive expiratory pressure, mortality.

TEXT

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has currently involved more than 150 countries, causing more than 40,000 deaths per week worldwide since July 2020[1]. COVID-19 pneumonia can cause an acute respiratory failure through alveolar and endothelial damage, that in severe cases can be associated with a pro-thrombotic diathesis[2,3] and a rapidly evolving cytokine storm[4].

The mortality rate observed in COVID-19 is strongly dependent upon the severity of respiratory failure[5,6], reaching 48% in patients with acute respiratory distress syndrome (ARDS) requiring invasive mechanical ventilation (IMV)[7].

The best clinical management of COVID-19 patients that present with acute respiratory failure is still debated,[8-15] especially regarding the role of non-invasive approaches and on the best ventilation strategies. While European consensus documents[16-18] suggested that continuous positive airway pressure (CPAP) should be the initial treatment of choice, other recent observational studies demonstrated that CPAP failed in 44% of patients with moderate-to-severe acute respiratory failure secondary to COVID-19[19]. The Surviving Sepsis Campaign does recommend an initial trial with high flow nasal cannula (HFNC) or non-invasive ventilation (NIV), but not CPAP, as the first approach for patients with severe COVID-19[9]. Close monitoring and early intubation in patients with rapidly worsening respiratory distress associated with higher PEEP strategies during IMV were initially recommended[9,10], although this approach has been lately put into discussion[8].

To date, a shared international consensus is lacking, and patients' management, especially in severe COVID-19 cases, can vary depending on regional standard operating procedures and local guidance.

Due to the rapid evolving of scientific literature on the topic, we designed a scoping review with the aim of describing the worldwide distribution and prevalence of respiratory support approaches and to explore the difference in characteristics, mortality and hospital-related complications in studies involving COVID-19 patients treated with invasive and non-invasive respiratory supports.

MATERIALS AND METHODS

Scoping review methodology was applied according to the latest recommendations,[20-22] and PubMed, Embase, and web-based articles were systematically searched for studies reporting data about adult patients hospitalized with COVID-19 treated with IMV, NIV or CPAP, including all results published since December 15th 2019 until February 28th 2021. To be as inclusive as possible, the keywords used for the research were "COVID", "SARS-CoV-2", "2019-nCOV" or "novel coronavirus" associated with: "helmet", "noninvasive", "non-invasive", "positive pressure", "NIV", "HFNC", "CPAP", "NIPPV", "nasal intermittent positive pressure ventilation", "high flow nasal cannula", "non-invasive ventilation", "noninvasive ventilation", "non-invasive support", "noninvasive support", "continuous positive airway pressure", "positive airway", "invasive mechanical ventilation", "intubation", "IMV", "respiratory support". Reference lists were also examined for any additional relevant studies not identified through the former search.

Studies were included if satisfied the following inclusion criteria: enrolling patients with a confirmed COVID-19 diagnosis and hospitalized with interstitial pneumonia; patients >18 years old; ≥100 patients

enrolled; English language; reporting overall in-hospital mortality; reporting specific mortality rate at least for patients treated with IMV; reporting the prevalence of patients treated with non-invasive (CPAP and NIV) or IMV; reporting the severity of respiratory failure through at least one parameter such as PaO2, SpO2, PaO2/FiO2 ratio or SpO2/FiO2 ratio or the proportion of patients with respiratory failure. Studies were excluded if: >10% of the study sample was still hospitalized at the moment of writing; characteristics and outcomes in patients treated with HFNC and NIV/CPAP were pooled; studies were randomized controlled trials (RCTs) if the intervention was a non-invasive or invasive respiratory support; methods, and results were unclearly stated or impossible to extract. Patients treated with HFNC were not considered in the present review.

The abstracts obtained from the initial systematic research were independently reviewed and for studies fitting the inclusion criteria full-text was retrieved. Main manuscripts and supplementary materials, when available, were individually and manually examined by three Authors (D.R., M.S. and D.A.C.) and the following data were extracted from text, tables, charts and figures: study design and primary outcome, setting, total number of patients and gender for general wards and ICUs, age, comorbidities (hypertension, diabetes, obesity, chronic respiratory diseases), number of patients treated with invasive and non invasive mechanical ventilation (IMV and NIV), continuous positive expiratory pressure (CPAP). Respiratory failure parameters, mean PEEP, prevalence of pronated patients and number of patients with do-not intubate order were also included.

Outcomes were overall, IMV and CPAP/NIV specific mortality, acute kidney injury/renal replacement therapy (AKI/RRT), acute cardiac injury (including myocardial infarction and arrhythmias), ventilator associated (VAP) and hospital acquired pneumonia (HAP), sepsis/bacteremia and pneumothorax (PNX) and duration of hospital stay.

Percentages and absolute numbers, if not directly available, were calculated separately.

RESULTS

After excluding duplicates, the research yielded 2851 manuscripts, which were individually considered for exclusion criteria. 296 articles were considered for eligibility and 52 were included in the final analysis (Figure 1).

Studies' characteristics

Setting, design and main outcomes of the studies included in the final analysis are reported in the Supplementary Digital Material 1: Supplementary Table 1[7,19,23-72]. Ninety-six percent of studies had an observational design, while only 2 were RCTs. Forty (77%) were retrospective and 10 (19%) were prospective (Figure 1). 32.7% of studies were conducted exclusively in ICU, 46.2% mainly in general wards and 21.2% in high dependency respiratory units (HDRU) (Supplementary Digital Material 1: Supplementary Figure 1). The country distribution of the included studies is reported in Table 1. The number of patients enrolled ranged from 100[59] to 254288[54]. Nine studies had a population that was equivalent or exceeded 1000 patients[7,24,28,42,45,46,54-56].

Patients' characteristics

A total of 287359 COVID-19 patients (165091 males, 57.5%) were included in the analysis. 95660 patients (33.3%) were hospitalized in ICUs (Supplementary Digital Material 1: Supplementary Table 1). The median age of the study population was 64 years (widest range 23-98[73]), with the lowest mean age of 54 years reported by Khan Chachar and coworkers[36] and the highest (median 72 - IQR, 60-82) reported by Amit et al[57]. Distribution of comorbidities is reported in Supplementary Digital Material 1: Supplementary Figure 1. The most prevalent comorbidity was hypertension (44.2%), followed by diabetes (26.1%), chronic respiratory diseases (7.1%) and obesity (6.6%).

Gas exchange at admission

Thirty studies[7,19,24,25,27,29-33,35,37,41,43,45,48-51,53,59,60,62,63,65-69,71,72] (58%) reported data on PaO_2/FiO_2. The median PaO_2/FiO_2 at admission ranged from 60 mmHg[44] to 442 mmHg[32]. Data on SpO2 and PaO2 were reported respectively in 14[19,23,27,28,34-36,40,45,47,56-58,61,70] (27%) and seven studies[7,19,27,29,30,35,42] (13%). $PaCO_2$ at admission was available in nine studies[19,24,27,29-31,33,35,42] (17%), and median $PaCO_2$ values ranged from 33 mmHg[19,33] to 42 mmHg[30] (Supplementary Digital Material 1: Supplementary Table 2). Respiratory rate at admission was reported in 21 studies[19,23,25,27,28,30,32,33,35,36,39,40,45,47,56-58,60,62,70] (40.4%), and generally ranged from 18-20 breaths/min[28,45,56,60] to 27-28 breaths/min[25,35].

Characteristics of respiratory support

Fifty-five percent (n = 159282) of all patients were treated with either an invasive or a non-invasive respiratory support; of them, 36% were exposed to IMV, 62% to NIV and 2% to CPAP (Figure 2 and Supplementary Digital Material 1: Supplementary Figure 2). A sensitivity analysis was conducted excluding the study by Ranzani et al[54], due to the very large sample and the unusually high utilization of NIV in that study (38% of the patients enrolled). Excluding patients from the study by Ranzani et al, the proportion of patients treated with any support was 52%, and, of those, NIV and CPAP were comparably applied in 13.5% and 14.5% of patients, respectively.

CPAP was administered in 11 studies (21.1%), and delivered generally by helmet[19,25,27,30,31,33,35,53] (8 studies, 72.7%), while in the remaining three studies the interface used was not reported[32,67,68]. In the study by Bellani et al[27], the Authors report using the helmet CPAP in 68% of patients, while Vaschetto and colleagues[35] applied CPAP by helmet in 74%, by oro-nasal masks in 23% and by helmet/mask alternation in 3% of patients. The PEEP used for CPAP, NIV or IMV was reported only in 11 studies[19,24,25,27,33,37,39,67-69,71] (Supplementary Digital Material 1: Supplementary Table 2), and the median value during CPAP/NIV application ranged from 5 cmH_2O in the study by Coppadoro et al[33] to 16 (15-18) cmH_2O in the study by Balbi et al[68].

The regional distribution of IMV and non invasive respiratory support approaches in Europe and the rest of the world is reported in Figure 3. The most common non-invasive respiratory support applied in Europe was CPAP, while in the rest of the world NIV was more frequently used.

Prone position

Data on pronation was available in 11 studies[24,28,44,52,55,57,64,67-69,71] (21.1%) (Supplementary Digital Material 1: Supplementary Figure 3). In total, 54% of patients (n = 2843) with available data were pronated during

the hospital stay. Among studies performed exclusively in ICUs, COVID-ICU group[25], Rouzè et al[44] and Grimaldi et al[69] performed pronation in 59%, 67% and 80% of patients exposed to IMV, respectively. Specific data on pronation during non-invasive respiratory support was lacking.

Length of stay

Length of stay was available for 30 studies[19,25,26,28,38-40,43-47,49,50,52-55,57,59,61-65,67,68,70-72] (57.7%). The mean duration of the hospital stay was of 13 days, ranging from a minimum of 6 days (IQR 3-14)[55] to a maximum of 63 days (IQR, 8-67)[68] (Supplementary Digital Material 1: Supplementary Figure 4).

Overall mortality

Overall in-hospital mortality ranged from 3-8%[28,33,36,60] to 70-76%[34,48]. Four studies had an overall mortality of less than 10% (Supplementary Digital Material 1: Supplementary Table 3), while 25 studies (48%) reported a mortality of ≥30% (Supplementary Digital Material 1: Supplementary Table 3).

Mortality during invasive mechanical ventilation

IMV-related death rate was reported in all studies but one, that was focused only on patients exposed to non-invasive respiratory support[27]. The overall trend of IMV-related mortality is shown in Figure 4, and ranged from 4% in two cases[31,62] to ≥50% in 25/51 studies.[7,23,29,30,34,36,38,40,42,46-48,50,52-54,56-59,61,65-67,70]

Mortality during non invasive respiratory support

Mortality in patients treated with CPAP was reported in 8/11 studies (73%), while mortality on NIV was available in 13/38 (34%) of studies. Cumulative mortality on CPAP was 24.8%, while on NIV was 29.1%. However, due to the under-reporting of mortality rates in patients treated with NIV, data for CPAP and NIV were pooled. Specific mortality in patients treated to CPAP/NIV was reported in 19/37 studies[7,19,23-27,31-35,41,42,46,48,54,62,67] (51%), and globally was 29%, ranging from 7.2%[33] to 100%[46]. In 13 studies (68.4%) mortality on CPAP/NIV exceeded 25%[7,24-27,31,32,34,35,42,46,54,67] (Figure 5). Without considering the study by Ranzani et al[54], allover mortality on non-invasive respiratory supports (CPAP/NIV) was reduced to 24.8%.

Complications

Hospital-related complications were reported in 33 studies[19,23,24,26,28,32,36,39,40,42-48,51,52,55-58,60,61,63-67,69-72] (63.4%) (Supplementary Digital Material 1: Supplementary Figure 5 and Supplementary Table 3). The most frequent complication was AKI/RRT (25 studies[23,24,26,28,32,36,39,42-45,47,48,52,55-58, 61,63,64,67,69,71,72]), that ranged from 0.9%[26] to 55.7%[69]. Cardiac injury and arrhythmia (11 studies[23,24,32,44,55,56-58,66,70,71]) ranged from 0.5%[44] to 36.3%[58]. Sepsis/bacteremia were reported in 14 studies[23,26,28,39,40,42,43,45,51,56-58,60,65] and ranged from 0.6%[28] to 40.4%.[39] Incidence of VAP/HAP and PNX were less frequently reported (seven[24,28,32,44,55,58,65] and five[19,23,46,56,58] studies, respectively) (Supplementary Digital Material 1: Supplementary Figure 5 and Supplementary Table 3).

DISCUSSION

The main results of the present systematic review con be summarized as follows: 1) the most frequently applied non invasive respiratory support is represented by NIV (62%), while only 2% of patients were treated with CPAP; 2) when the study by Ranzani and colleagues[54] was not considered, NIV and CPAP were similarly applied in 12.5% and 13.5% of cases, respectively; 3) CPAP is most commonly used in Italy (81.8% of studies) and the most common interface to deliver CPAP was helmet (72.7% of cases); 4) mortality on IMV is very high, being ≥50% in 49% of the included studies; 5) specific CPAP/NIV mortality is unfrequently reported, and ranges from low to very high rates, depending on the severity of patients enrolled and the proportion of patients deemed not suitable for IMV; 6) the most frequently reported complication in patients with COVID-19 is AKI.

Overall, patients' baseline characteristics appeared to be inhomogeneous across the analyzed studies. Age at admission, severity of the acute respiratory failure and comorbidities showed a large variability and may have influenced clinical outcomes such as mortality and complication rates. According to current knowledge, beside aging, cardiovascular and metabolic disorders represent major risk factors for unfavorable outcomes in patients hospitalized with COVID-19 pneumonia[7,73,74]. In the present review, the most prevalent comorbidity was hypertension (44.2%), while diabetes, chronic respiratory diseases and obesity were reported in 26.1%, 7.1% and 6.6% of patients. However, data on comorbidities such as hypertension and obesity were often under-reported.

Confirming current knowledge[5,75,76], the current analysis showed that patients hospitalized for COVID-19 pneumonia present with acute respiratory failure, with PaO2/FiO2 ratio usually < 150 mmHg in patients with worse outcomes. Hypercapnia, although data on PaCO2 were often lacking, it is usually rare also in patients needing ventilatory support (cfr. Supplementary Digital Material 1. Supplementray Table 2).

The most frequent critical finding in patients affected by COVID-19 related pneumonia is represented by acute hypoxemic respiratory failure[8,75,77], caused by progressive pulmonary infiltrates that can lead to respiratory distress and determine the need for hospitalization, careful monitoring or ICU admittance[8,16,75]. According to our results, the most frequently adopted non-invasive respiratory support for patients with severe disease was NIV (62%) rather than CPAP (2%), while endotracheal intubation and IMV were adopted in the 36% of the included patients. These data were strongly biased by the number of patients treated with NIV in the study by Ranzani and colleagues[54], that report a very high utilization of NIV in Brazil during the pandemic (96729 out of 254288 patients enrolled). If the study by Ranzani et al is not considered in the analysis, the prevalence of NIV and CPAP application becomes comparable (12.5% vs. 13.5% of the treated patients). These data are is accordance with the guidelines on the Management of Critically Ill Adults With COVID-19 promoted by the Surviving Sepsis Campaign and released in March 2020[9], which suggested to adopt HFNC and non-invasive ventilatory supports such as NIV with precaution (weak recommendations and low quality of evidence). Indeed, CPAP (and helmets) were not recommended in view of the lack of safety data[9]. On the other hand, the latest European Respiratory Society guidelines released in February 2021 suggest the use of helmet CPAP as a non invasive respiratory approach in patients that are still hypoxic despite the application of standard oxygen masks[15] (conditional recommendation, very low quality of evidence). According to our analysis, CPAP has been confirmed to represent the preferred

non-invasive respiratory approach in Europe, and especially in Italy, while NIV appeared to be preferred outside European countries.

We also observed that during NIV/CPAP, a low PEEP strategy was generally adopted, while higher PEEP values (sometimes up to 18 cmH_2O[68]) were used in patients with ARDS treated with IMV. Due to the micro-vascular bed damage and the possible presence of poorly recruitable lung areas, it is currently generally accepted that unnecessary high PEEP may be detrimental in patients with severe pneumonia secondary to SARS-CoV-2 infection[8].

Pronation appeared to be prevalently adopted in ICU patients. Implementation of the pronation technique seemed to be variable, with figures ranging from 21% to 85% of the ICU patients involved. However, the data retrieved did not allow to assess the impact of such procedure on patients' outcomes.

Despite mortality on CPAP appeared slightly less than in patients treated with NIV (24.8% vs. 29.1%), mortality was available only in 34% of the studies that treated patients with NIV, therefore the assessment of any difference in survival between non invasive and invasive ventilatory strategies was not possible. Nevertheless, mortality rate on non invasive ventilatory supports was 29%, reduced to 24% when the study by Ranzani et al[54] was not considered. Unfortunately, the proportion of patients with a "do not intubate" order and thus not deemed suitable for an escalation to IMV and having CPAP/NIV as ceiling treatment, was scarcely reported. In the absence of comparative studies, this limits further speculations on the possible role of CPAP or NIV in the prevention of IMV or any possible "best practice" between the two non invasive approaches.

Mortality rates for patients exposed to IMV ranged from <10%[31,62] to ≥50% in 49% of cases[7,23,29,30,34,36,38,40,42,46-48,50,52-54,56-59,61,65-67,70], while overall mortality generally varied from 3-8%[28,33,36,60] to >70%[34,48]. We hypothesize that wide regional differences in IMV-related and overall mortality may derive from different local standard operating procedures and criteria for hospitalization, decision to start a trial of non invasive ventilation or CPAP, or criteria for intubation. Moreover, the portion of patients having received a "do not intubate" order was rarely reported.

The most frequently reported hospital-related complications were AKI/RRT, 0.9%[26] to 55.7%[69]. This wide variability was also observed in cardiac injury and arrhythmia, that ranged from 0.5%[44] to 36.3%[58].

Specific infectious ICU-related complications such as sepsis/bacteremia and VAP/HAP, although unfrequently reported, appeared to have a high incidence during the ICU stay, with a prevalence frequently >15% of enrolled patients.

The present scoping review has limitations. First, due to the large amount of literature published especially in the second half of 2020-beginning of 2021, we decided to apply strict inclusion and exclusion criteria (e.g. data on respiratory failure) to account as much as possible for study heterogeneity and quality of reporting. As a consequence, numerous studies were excluded, which may constitute a bias in the representation of global trends in respiratory support use and mortality. Second, CPAP and NIV-related mortality was not always reported, conditioning the synthesis of the results regarding non-invasive respiratory support.

CONCLUSIONS

From a global perspective, invasive mechanical ventilation appears to be the most commonly applied respiratory support in patients suffering from severe COVID-19 pneumonia. Although heterogeneously

applied, NIV and CPAP appear to be equally used worldwide, although helmet CPAP is most commonly used in Europe especially in Italy. Mortality in patients exposed to IMV and CPAP/NIV is consistently high, but with a very large geographical and inter-study variability. The heterogeneity of the clinical approach found in many studies involving patients affected by COVID-19 pneumonia indicates the need for shared decision making recommendations, which must rely on well designed observational studies, and integrated and comprehensive reporting.

KEY MESSAGES

- A shared international consensus on treatment of COVID-19 related respiratory failure is lacking.
- We conducted a scoping review to describe the worldwide distribution and prevalence of ventilatory approaches, including a total of 52 studies (287359 patients).
- 55% of patients underwent ventilatory support (36% IMV, 62% NIV and 2% CPAP); invasive and non-invasive approaches were heterogeneously applied.
- Our results emphasized the lack of consistent data about operational procedures and decisional criteria for ventilatory management.

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TABLES

Table 1. Study design and countries for studies included in the final analysis.

Study design	**Proportion**
Observational	50/52
RCT	2/52
Retrospective	40/52
Prospective	10/52
Multicenter	27/52
Single center	25/52
Country	
Europe	
Italy	16 (31%)
France	2 (4%)
France/Belgium*	2 (4%)
Spain	2 (4%)
UK	1 (2%)
Norway	1 (2%)
Germany	1 (2%)
EU**	1 (2%)
Rest of the World	
USA	13 (25%)
China	4 (8%)
Brazil	3 (6%)
Canada	1 (2%)
India	1 (2%)
Israel	1 (2%)
Japan	1 (2%)
Mexico	1 (2%)
Pakistan	1 (2%)

* the study by the COVID-ICU[24] group was a multicenter study conducted in France, Belgium and Switzerland. ** the study by Rouzé et al[44] included 28 centers in France, three in Spain, three in Greece, one in Portugal and one in Ireland.

TITLES OF FIGURES

Figure 1. Screening and selection of the studies included in the systematic review. The flow diagram has been designed according to PRISMA guidelines.

Figure 2. Distribution of invasive and non-invasive ventilator support.

Distribution of invasive and non-invasive respiratory support in the 52 studies included in the final analysis (panel A), and after the sensitivity analysis performed removing the study by Ranzani et al[54] (panel B). CPAP: continuous positive airway pressure; IMV: invasive mechanical ventilation; NIV: non invasive ventilation.

Figure 3. Regional distribution of ventilator support approaches

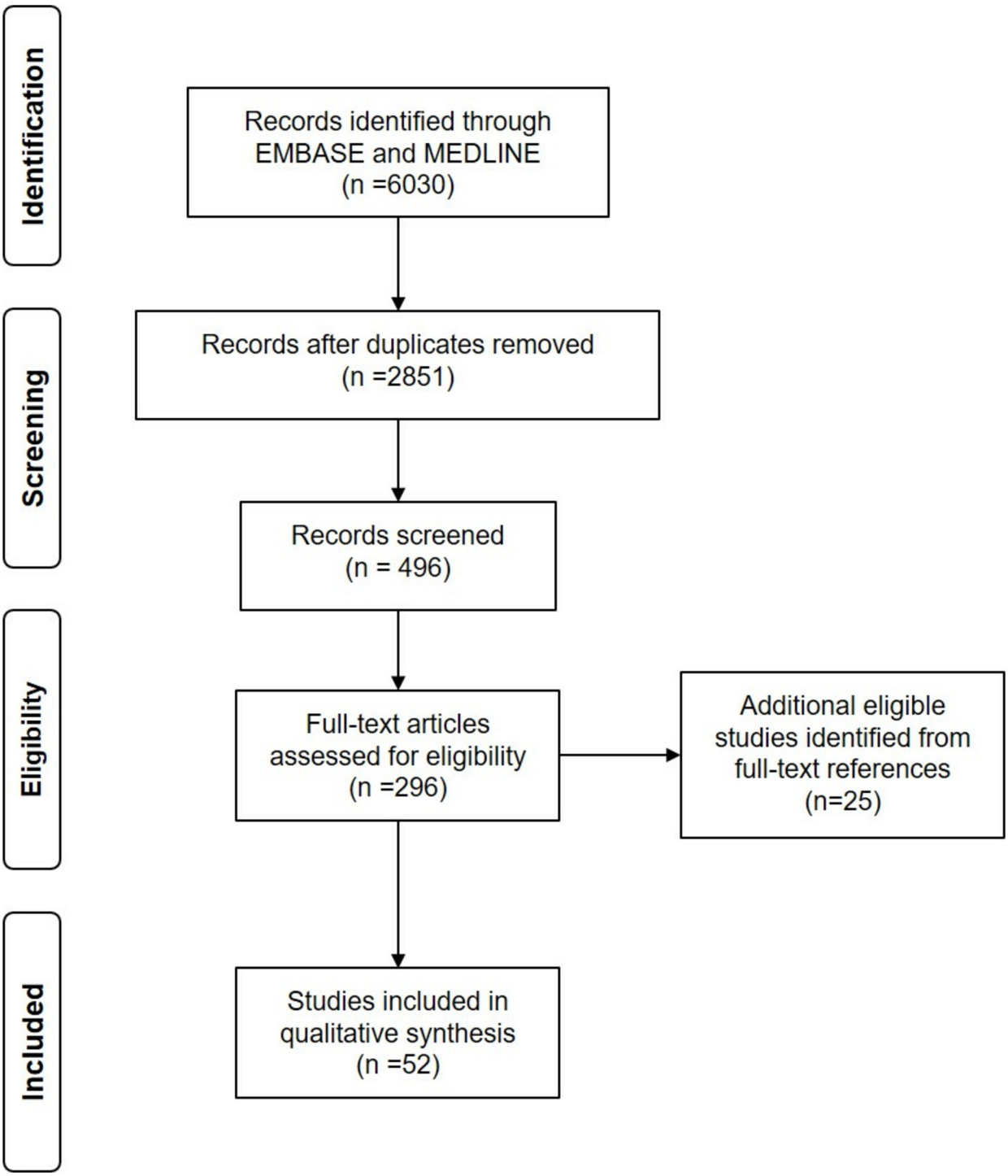
Percentage of patients treated with invasive or non invasive respiratory supports in studies published in Europe (Panel A) and in the rest of the world (Panel B). Data for studies performed in the same country were pooled. Different shades of blue indicate the prevalence of in-hospital mortality. CPAP: continuous positive expiratory pressure; IMV: invasive mechanical ventilation; NIV: non invasive ventilation.

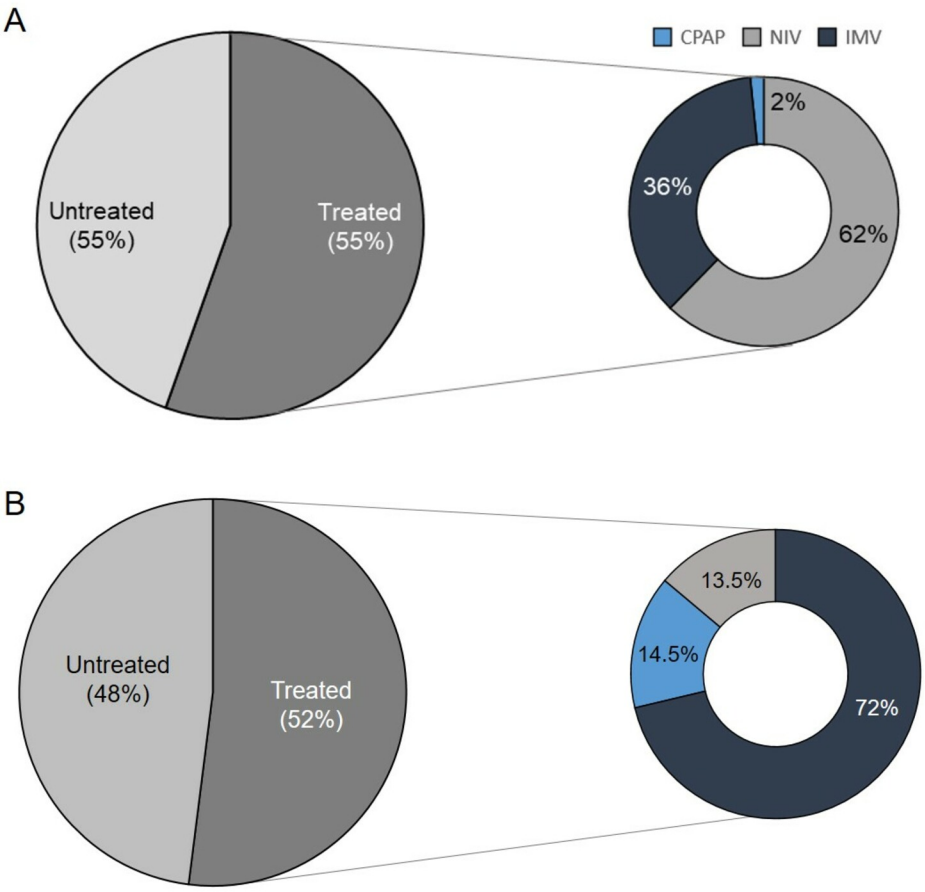
Figure 4. IMV-related mortality.

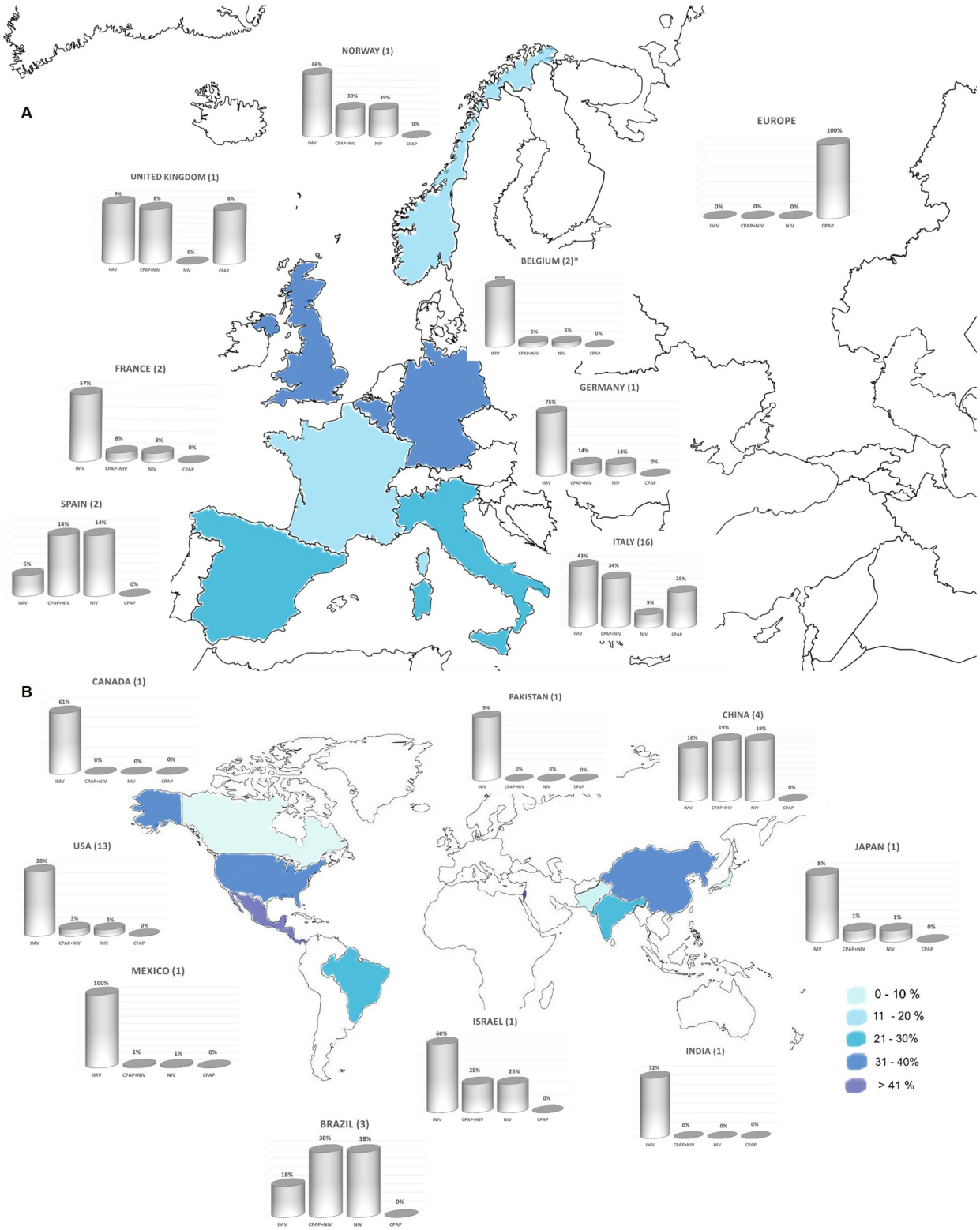
Proportion of dead patients among those exposed to IMV (striped areas). Numbers in each histogram represent the actual number of patients dead during IMV in each study. IMV: invasive mechanical ventilation.

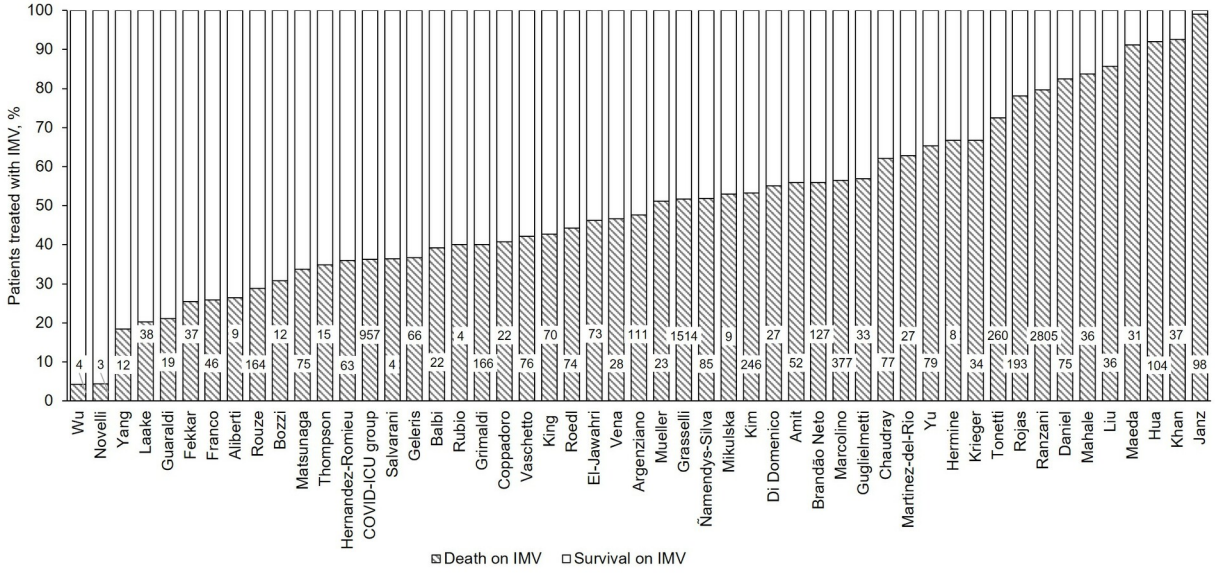
Figure 5. CPAP/NIV-related mortality.

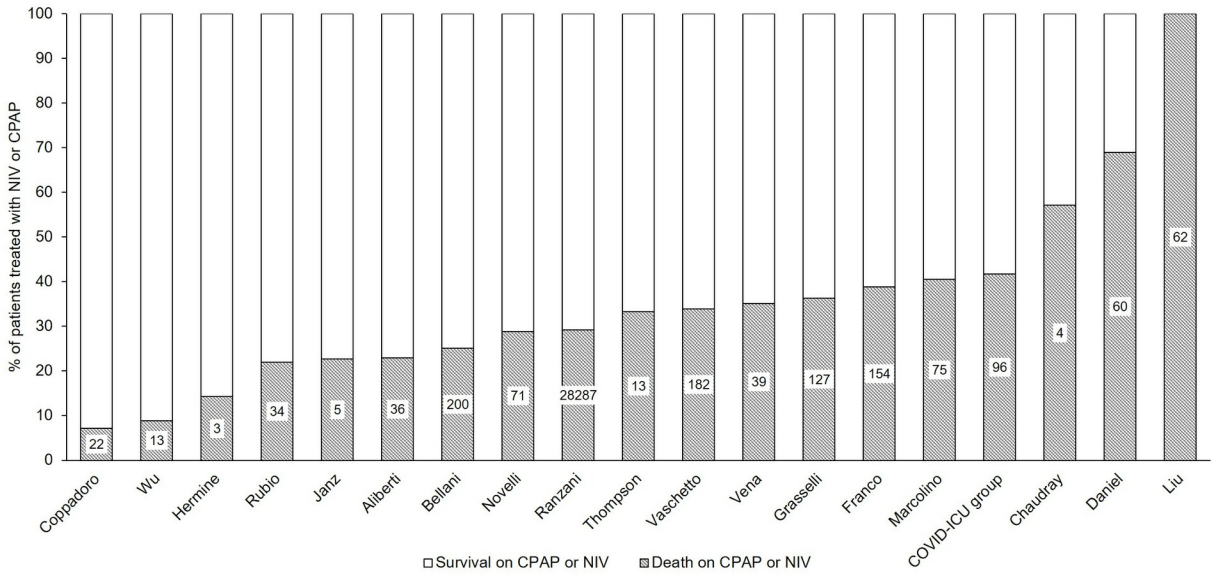
Proportion of dead patients among those exposed to CPAP or NIV (striped areas). Numbers in each histogram represent the actual number of patients dead during CPAP/NIV in each study. NIV: non-invasive ventilation; CPAP: continuous positive airway pressure.











Supplementary Digital Material

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