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

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Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: A rapid review

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ABSTRACT

Introduction and aim: Non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) have been widely employed to treat acute respiratory failure secondary to COVID-19 pneumonia, but their role in terms of efficacy and safety are still debated. The aim of this review was to analyse mortality and intubation rates in COVID-19 patients treated with NIV/CPAP.
Methods: Rapid review methodology was applied to include all the studies published since December-2019 until November-2020 with available data on in-hospital mortality in COVID-19 patients treated with NIV or CPAP.
Results: 23 manuscripts were included (4776 patients, 66% males, 46% with hypertension). 46% of patients received non-invasive respiratory support, of which 48.4% with CPAP, 46% with NIV, and 4% with either CPAP or NIV. Non-invasive respiratory support failed in 47.7% of patients, of which 26.5% were intubated and 40.9% died. In-hospital mortality was higher in patients treated with NIV compared with CPAP (35.1% vs. 22.2%). Complications were under-reported, but mostly not related to CPAP/NIV treatment.
Conclusion: CPAP and NIV appear equally and frequently applied in patients with COVID-19 pneumonia, but associated with high mortality. Robust evidence is urgently needed to confirm the clinical efficacy of non-invasive respiratory support in COVID-19-related ARDS.

1. Introduction

In March 2020, the World Health Organization declared the novel Coronavirus disease (COVID-19) outbreak a pandemic and a threat for the global public health [1].

One of the most common complications of COVID-19 is represented by interstitial pneumonia, that can lead to acute hypoxic respiratory failure, eventually causing multiorgan failure and death [2,3]. COVID-19 with respiratory failure often experience increased respiratory rate and respiratory distress, due to profound oxygen desaturation secondary to diffuse alveolar damage and micro and macro-thrombi in pulmonary arterial vessels [4,5]. The application of a continuous positive airway pressure (CPAP) in case of acute hypoxic respiratory failure was previously shown to improve arterial oxygenation, reduce work of breathing and recruit non-aerated alveoli in dependent pulmonary regions, thus reducing the need for endotracheal intubation (ETI) [6-8]. Non-invasive ventilation (NIV) has also demonstrated to reduce intubation rates, being superior to CPAP in reducing the inspiratory effort and assisting patients with hypercapnia and respiratory acidosis [9]. However, CPAP and NIV can pose patients at higher risk of unfavourable outcomes by delaying the institution of invasive mechanical ventilation [10]. On March 2020, the Surviving Sepsis Campaign guidelines for the management of critically ill adults with COVID-19 recommended the use of High Flow Nasal Cannula (HFNC) or non-invasive ventilation (NIV) as the initial approach to treat COVID-related ARDS [11]. The application of continuous positive airway pressure (CPAP) was not suggested due to safety and efficacy concerns [11]. At the same time, however, European consensus documents recommended CPAP for the treatment of acute hypoxic respiratory failure in patients with COVID-19 pneumonia and persistent hypoxemia despite oxygen

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; CPAP, Continuous Positive Airway Pressure; DNI, Do Not Intubate; ETI, EndoTracheal Intubation; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation; NIV, Non Invasive Ventilation; WHO, World Health Organization.

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application [12,13]. During the pandemic, in fact, considering also its safety in limiting the risk of exposure to viral droplets of the healthcare personnel [14], helmet CPAP has been widely used also outside ICU especially in Europe. Despite the diffusion of NIV and CPAP in COVID-19 treatment algorithms, the indications for initiating a non-invasive respiratory support are still heterogeneous, and the efficacy in terms of avoidance of endotracheal intubation (ETI) poorly understood [15-19]. Furthermore, despite known predictors of disease severity and mortality [20-22], strong clinical predictors of CPAP/NIV success or failure are still missing.

The aim of the present review was to analyse the outcomes such as failure of non-invasive respiratory support in terms of need for ETI and mortality in patients treated with CPAP or NIV in.

and outside the ICU.

2. Material and methods

We performed a revision of the literature according to scoping review methodology [23,24]. Only studies including patients treated with non invasive respiratory supports such as CPAP, NIV or invasive mechanical ventilation (IMV) in presence of NIV or CPAP failure were included in the analysis. Patients treated with low or high flow nasal cannulas, Venturi Masks, non-rebreather oxygen masks were excluded from the analysis. Studies focused exclusively on patients treated with IMV or with home ventilation (e.g. nocturnal CPAP in patients with obstructive sleep apnoea) were also excluded.

We considered separately patients for which CPAP/NIV was the ceiling treatment (i.e. patients with a "do not intubate order") from those that were eligible for escalation to IMV.

Medline and Embase databases were searched considering manuscripts published between December 2019 and 15th November 2020 according to the following research strings (abstract or title): "COVID AND CPAP", "COVID AND ventilation", "coronavirus AND CPAP", "coronavirus AND NIV", "COVID AND NIV", "coronavirus AND ventilation".

We selected all the studies that investigated the mortality rate in hospitalized patients with COVID-19 pneumonia and respiratory failure that underwent either CPAP or NIV. All-cause in-hospital mortality was also reported, but was outside the scope of the review.

The studies included in the analyses satisfied the following inclusion criteria: 1) available full text in English language; 2) patients >18 years old; 3) >20 patients treated a non-invasive respiratory support. Case reports, case series, studies that considered only short term outcomes (e.g. 7-day mortality rate), with >20% of patients missing mortality outcomes, or with >20% patients still hospitalized at the moment of the writing were excluded from the analysis. We excluded also manuscripts with unclear outcomes or that did not consider outcomes in patients treated specifically with CPAP or NIV.

Risk of bias and study quality were assessed by means of the Newcastle-Ottawa Quality Assessment Scale (NOS) [25]. The latter is currently used for assessing quality and bias for cohort and non-randomized studies to be included in systematic reviews and meta-analyses. The NOS includes a 3 star ranking system (3 stars being the highest grade) on three different domains: "selection", "comparability" and "outcome". The grading of the category "comparability" is limited to a maximum of 2 stars.

The literature research was independently conducted by two Authors (S.P. and E.F.) and then revised by D.R., P.S. and D.C. that reached a shared decision by consensus in case of discordance.

3. Results

3.1. Studies overview

The Medline and Embase research yielded a total of 5794 manuscripts, of which only 63 were assessed for eligibility and 23 satisfied the inclusion and exclusion criteria and were therefore included in the final analysis (Fig. 1; Table 1). The list of excluded papers and the reason for their exclusion are reported in the Supplementary File. The NOS grading for each study is reported in the Supplementary Material Table 1.

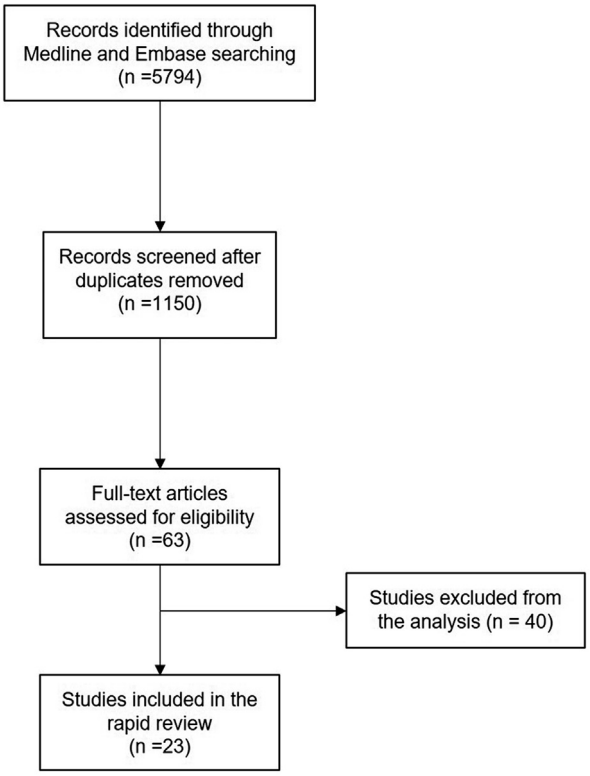

Fig. 1. Flow diagram according to PRISMA guidelines showing the phases of the research process for study selection.

Eighteen (78%) studies were conducted in Europe (8 in Italy and 7 in the UK) and 3 (12.5%) in China. Most of them were retrospective and single centre studies, while only 2 (9%) had a prospective observational design. None was a randomized controlled trial (RCT).

Eight (35%) studies included patients hospitalized in ICU and 2 (8%) were conducted in the Emergency Department.

The pooled study population was composed by 4776 patients (3145 males, 66%), with a median age ranging between the 5th and 6th decade. Considering the available data, arterial hypertension was the most frequent comorbidity ($n = 2194$, 46%), followed by diabetes mellitus ($n = 1225$, 25.5%) and chronic heart disease ($n = 909$, 19%).

3.2. Respiratory supports

The mean partial arterial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio before starting the non-invasive respiratory support was reported in 13 studies, and, on average, was <200 mmHg, indicating a moderate-to-severe respiratory failure according to the Berlin's criteria [43].

Non-invasive respiratory support was applied to 2192 (46%) patients: 1061 (48.4%) were treated with CPAP, 1011 (46%) with NIV, and 90 (4%) with either CPAP and/or NIV (Fig. 2).

The median positive end expiratory pressure (PEEP) used was on average 10 cmH_2O. The pressure support during NIV, when reported, ranged from 10 [17] to 17 cmH_2O [14] (Table 1).

3.3. Failure of the non-invasive support

Patients that failed the non-invasive respiratory support (a combination of intubation + death on CPAP/NIV + discontinuation due to

Table 1
Study design, setting, patients' characteristics and type of respiratory support in studies included in the analysis.

Study	Country	Setting	Study design	Primary outcome	Patients, n	Males, n (%)	Age, y	Comorbidities, n (%)					PaO_2/FiO_2 at admission	Ventilatory approach, n (%)		Ventilation settings		DNI
								Hypertens	DM	CHD	CKD	Obes.		CPAP	NIV	$PEEP/FiO_2$	$PEEP/PS/FiO_2$	
Aliberti et al. [15]	Italy	H/HDRU	Retrospective, observational	Describe characteristics and outcomes of CPAP treatment	157	117 (74.5%)	64 (55–75)	69 (43.9%)	36 (22.9%)	13 (8.3%)	9 (5.7%)	29 (18.5%)	143 (97–203)	157 (100%)	0	10.8 (2.3)/0.6	N/A	65 (41.4%)
Alviset S et al. [26]	France	H/ED/ICU	Retrospective, observational	Reason for CPAP discontinuation	49	36 (73.5%)	65 (54–71)	31 (63.3%)	16 (32.7%)	2 (4.1%)	5 (10.2%)	13 (26.5%)	N/A	49 (100%)	0	N/A	N/A	8
Arina P et al. [27]	UK	ICU	Retrospective, observational	Predictors of CPAP success	93	68 (73.1%)	N/A	32 (34.4%)	16 (28%)	12 (12.9%)	N/A	N/A	97.5 (75–135)	93 (100%)	0	N/A	N/A	16
Avdeev et al. [16]	Russia	H	Retrospective, observational	Outcomes of NIV in COVID-19 patients with AHRF	61	37 (60.7%)	62 (53–70)	29 (47.5%)	8 (13.1%)	3 (4.9%)	2 (3.3%)	N/A	164 (131−200)	45 (74%)	16 (26%)	10.0 (9.7–12.2)	9.9/20	N/A
Brusasco et al. [28]	Italy	H/HDRU	Retrospective, observational	4-week survival without invasive mechanical ventilation	64	N/A	Range 25–83	N/A	N/A	N/A	N/A	N/A	119 (99–153)	64 (100%)	0	N/A	N/A	15
Burns et al. [17]	UK	H	Retrospective, observational	Mortality in DNI patients eligible for CPAP/NIV	28	15 (53.6%)	81.5 (54–91)	22 (78.6%)	15 (53.6%)	7 (25%)	15 (53.6%)	N/A	N/A	23 (82)	5 (18%)	PEEP max 12.7	EPAP max 10.2/IPAP max 22.4	28
Corradi et al. [29]	Italy	ICU	Retrospective, observational	Diaphragmatic thickening fraction as predictor or response of positive pressure ventilation	27	23 (85.2%)	66 (57–73)	14 (51.9%)	3 (11.1%)	8 (29.6%)	2 (7.4%)	N/A	195 (168–246)	27 (100%)	0	10/0.4–0.7	N/A	N/A
Di Domenico et al. [30]	Italy	ED	Retrospective, case series	Characteristics and outcomes of COVID-19 pneumonia	310	200 (64.5%)	64 (52–76)	134 (43.2%)	53 (17.1%)	50 (16.1%)	N/A	34 (10.1%)	248 (17) (NIV)	90 (29%, CPAP or NIV)		N/A	N/A	27
Duca et al. [19]	Italy	ED	Retrospective, observational	Describe the severity of respiratory failure	85	72 (84.7%)	70 (62–79)	46 (54.1%)	19 (22.4%)	21 (24.7%)	1 (1.2%)	N/A	28 (85–168)	71 (83%)	7 (8%)	15 (12–18)/0.6 (0.6–0.8)	16 (12−20)/N/A/0.6 (0.5–1.0)	0
Faraone et al. [31]	Italy	H	Retrospective, observational	Efficacy of NIV in COVID-19 patients	50	33 (66.0%)	74.6 (11)	28 (56%)	12 (24%)	22 (44%)	10 (20%)	N/A	130 (63.5)	25 (50%)	25 (50%)	N/A	N/A	25
Franco et al. [14]	Italy	H	Retrospective, observational, multicenter	Safety of hospital staff, and feasibility and outcomes of NIV/CPAP outside ICU	670	464 (69.3%)	68.3 (13.3)	311 (51.2%)	125 (20.6%)	105 (17.3%)	34 (6.4%)	108 (17.8%)	152 (79)	330 (49.3%)	177 (26.4%)	10.2 (1.6)	9.5 (2.2)/17.3 (3)/N/A	28 (4.2%)
Giacomelli et al. [32]	Italy	H	Prospective, observational	Mortality	233	161 (69.1%)	61 (50–72)	N/A	N/A	N/A	N/A	38 (16.3%)	N/A	29 (12%)	0	N/A	N/A	N/A

(continued on next page)

Table 1 (*continued*)

Study	Country	Setting	Study design	Primary outcome	Patients, n	Males, n (%)	Age, y	Comorbidities, n (%)					PaO_2/FiO_2 at admission	Ventilatory approach, n (%)		Ventilation settings		DNI
								Hypertens	DM	CHD	CKD	Obes.		CPAP	NIV	$PEEP/FiO_2$	$PEEP/PS/FiO_2$	
Hallifax et al. [18]	UK	HDRU	Retrospective, observational	Outcome of awake prone positioning	48	32 (66.7%)	69 (54–80)	23 (47.9%)	17 (35.4%)	8 (16.7%)	9 (18.8%)	N/A	N/A	48 (100%)	0	N/A	N/A	26
Hua J et al. [33]	China	ICU	Retrospective, observational	Outcomes of IMV vs. NIV and vs. non ventilated	469	266 (56.7%)	68 (13)	240 (51.4%)	110 (23.6%)	84 (18%)	42 (9%)	N/A	N/A	0	152 (32%)	N/A	N/A	N/A
Karagiannidis et al. [34]	Germany	H	Retrospective, observational	Characteristics and outcomes of COVID-19 patients requiring mechanical ventilation	1727	1147 (66.4%)	71 (60–79)	1077 (62.4%)	671 (38.9%)	527 (30.5%)	417 (24.1%)	229 (13.3%)	N/A	0	351 (20%)	N/A	N/A	N/A
Mukhtar et al. [35]	Egypt	ICU	Retrospective, observational	NIV success in ICU	55	36 (65.5%)	59 (14)	31 (56.4%)	28 (50.9%)	9 (16.4%)	N/A	15 (27.3%)	190 (123–247)	0	39 (53%)	N/A	N/A	N/A
Nightingale et al. [36]	UK	H	Retrospective, observational	CPAP to treat type 1 respiratory failure	24	21 (87.5%)	52 (46.5–60)	8 (33.3%)	6 (25%)	3 (12.5%)	N/A	N/A	122 (97–175)	24 (100%)	0	8.75 (7.5–10)	N/A	0
Noeman-Ahmed et al. [37]	UK	HDRU	Retrospective, observational	Outcomes in patients treated with CPAP	52	34 (65.4%)	N/A	22 (42.3%)	13 (25%)	8 (15.4%)	2 (3.8%)	15 (28.8%)	123 (59)	52 (100%)	0	N/A	N/A	11
Rahim et al. [38]	Pakistan	ICU	Retrospective, observational	Mortality in COVID-19 patients in ICU	204	151 (74.0%)	55.7 (11.6)	6 (2.9%)	25 (12.3%)	4 (2%)	N/A	N/A	N/A	0	126 (62%)	N/A	N/A	N/A
Sivaloganathan et al. [39]	UK	H	Retrospective, observational	Role of NIV in patients with COVID-19 respiratory failure	103	63 (61.1%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0	58 (56%)	N/A	N/A	24
Winearls et al. [40]	UK	H	Retrospective, observational	Effect of prone positioning	24	15 (63%)	62 (13)	13 (54%)	7 (29%)	1 (4%)	2 (8%)	N/A	112 (106–194)	24 (100%)	0	12 (12–15)/0.6 (0.5–0.7)	N/A	10
Yang et al. [41]	China	ICU	Retrospective, observational	28-day mortality after ICU admission	52	35 (67%)	59.7 (13.3)	N/A	9 (17%)	5 (10%)	N/A	N/A	N/A	0	29 (56%)	N/A	N/A	N/A
Zhou et al. [42]	China	H/ICU	Retrospective, observational, multicenter	Risk factors for death and characteristic of clinical course	191	119 (62%)	56 (46–67)	58 (30%)	36 (19%)	15 (8%)	2 (1%)	N/A	N/A	0	26 (14%)	N/A	N/A	N/A

Data are presented as frequencies and percentage. Age, PaO_2/FiO_2 values and ventilatory settings are reported as medians (inter quartile range), means (standard deviation), or ranges, as appropriate. AHRF: acute hypoxic respiratory failure; CHD: chronic heart disease; CKD: chronic kidney disease; DM: diabetes mellitus; Hypert.: arterial hypertension; Obes.: obesity; PEEP: positive end expiratory pressure; EPAP: expiratory positive airway pressure; IPAP; inspiratory positive airway pressure; N/A: not applicable/not available; ICU: intensive care unit; HDRU: high dependency respiratory unit; H: hospital/general ward.

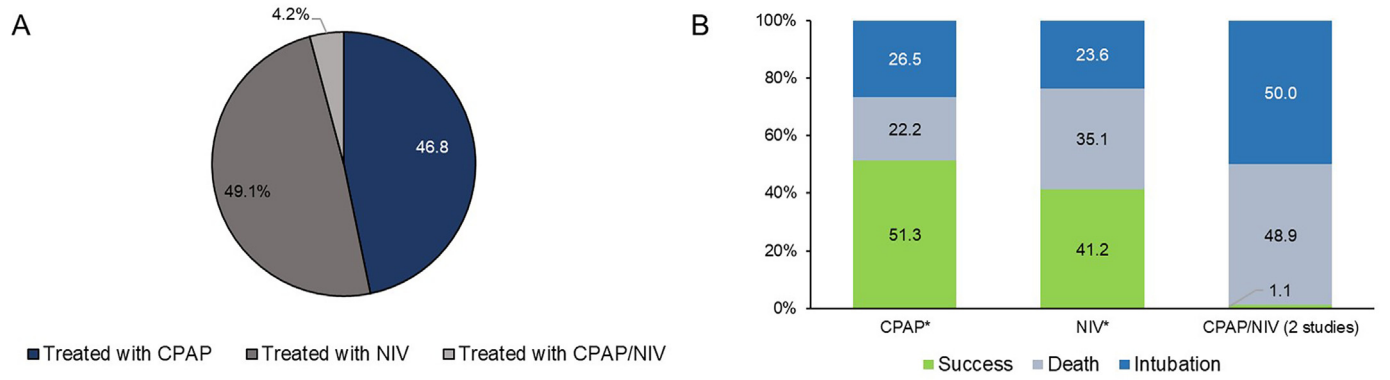

Fig. 2. Distribution of CPAP and NIV use in the 23 studies included in the final analysis (Panel A) and mortality and intubation rate according to the non invasive respiratory support (Panel B). CPAP: continuous positive airway pressure; NIV: non invasive ventilation. * mortality from the study by Avdeev SN et al. [CITAZIONE] is not reported (17 patients) because data on mortality in patients treated with CPAP and NIV were pooled.

intolerance) were 1217 (55.5%). In total, 582 patients (26.5% of those exposed to CPAP or NIV) were intubated after failing CPAP ($n = 281$), NIV ($n = 239$) or, as reported in three studies that pooled intubation rates after both CPAP and NIV failure, CPAP/NIV ($n = 62$) (Fig. 2). The reasons that lead to intubation consisted in decreased level of consciousness, exhaustion, refractory hypoxemia, sepsis and hemodynamic instability.

3.4. Mortality

Overall in-hospital mortality was 40.9% ($n = 1956$). Mortality in patients on CPAP or NIV was available for 17 and 13 studies, respectively. In total, 635 (29%) of patients treated with CPAP or NIV died while on non –invasive respiratory support (236 patients on CPAP (22.2%), 355 on NIV (35.1%), and 44 (49%) on CPAP/NIV, Fig. 2).

Of the 582 patients that were intubated after CAP/NIV failure, 348 (59.8%) died on IMV (Table 2).

3.5. Length of hospitalization

The length of hospital stay ranged, on average, from a minimum of 6.2 [38] to a maximum of 21 days [34]. Aliberti and colleagues found that patients that were successfully weaned from CPAP had a longer hospital stay (median [IQR] 18 [14–25.5] days) compared with patients that failed CPAP (median [IQR] 8 [4-22] days) [15].

3.6. Complications

Complications during application of CPAP/NIV were available in 5 studies. The most common complications described were pulmonary embolisms, renal failure, cerebrovascular accident, heart failure, septic shock, arrhythmia, ventilator-associated pneumonia, myocardial infarction. One case of pneumothorax was reported by Aliberti et al. [15], and one case in the study by Yang et al. [41].

4. Discussion

The main findings of this rapid review can be summarized as follows: 1) CPAP and NIV were equally employed (48.4 VS. 46%), maintaining PEEP levels not to exceed 10 cmH2O; 2) almost half of patients exposed to CPAP/NIV failed the non-invasive support trial and only half of cases were eligible for intubation; 3) mortality was higher for patients treated with NIV (35.1%) than in patients treated with CPAP (22.2%); 4) CPAP/NIV-related complications such as pneumothorax were uncommon.

One of the most feared complications of COVID-19 pneumonia is progressive hypoxic respiratory failure, associated with dyspnea, tachypnea and, sometimes, respiratory alkalosis [44,45]. Both CPAP and NIV have been demonstrated to reduce work of breathing, increase oxygenation and reduce intubation rates in patients with acute hypoxic respiratory failure [46-48]. However, the indication for starting a non-invasive respiratory support in COVID-related ARDS is still debated. To date, oxygen supplementation to maintain SpO2 > 90% is strongly recommended [11] but the utilization of NIV or CPAP is suggested with weak recommendation and very low quality of evidence [11,49]. The main concerns being represented by the risk of aerosol generation and virus spread that could be harmful for the healthcare workers, and the ventilation-related lung injury secondary to late initiation of invasive mechanical ventilation. Indeed, guidelines suggest a careful titration of PEEP and low tidal volume ventilation due to the risk of barotrauma and volotrauma [8,11,13,49].

Despite the aforementioned uncertainties, it appears that since the beginning of the pandemic, CPAP (delivered by means of the Helmet or with face mask) and NIV have been widely employed worldwide to treat patients with COVID-19 pneumonia, with an acceptable tolerance and safety profile, both in ICU and non-ICU settings [14,15,19,47,50]. This is reflected by the equal application of CPAP and NIV reported in the present review.

The studies included in the analysis showed that the application of CPAP/NIV is a safe and feasible strategy for critically ill COVID-19 patients, also outside the ICU. COVID-19 patients eligible for CPAP/NIV generally had a moderate to severe respiratory failure, with a high prevalence of cardiovascular and metabolic comorbidities. Criteria for NIV or CPAP initiation were heterogeneous, thus it appeared unfeasible to compare patients' characteristics separately for patients treated with either CPAP or NIV. However, heterogeneity appeared unrelated to the setting. Moreover, only two studies [32,34] with missing criteria for CPAP/NIV were conducted in general wards. Shared and evidenced-based criteria for initiating CPAP and NIV in COVID-19 patients are urgently needed, especially to avoid over-treatment in patients with a low risk of disease progression and under-treatment in patients in which prompt intubation would be beneficial [51]. Unfortunately, to date, solid indicators for CPAP/NIV failure are missing.

Rate of failure of CPAP/NIV was high (almost 50%), and in almost half of cases, the non-invasive respiratory support represented the ceiling treatment in patients that received a DNI order. In fact, only 55% of patients that failed CPAP/NIV were intubated. To date, it is still poorly understood if an initial trial with CPAP or NIV may delay ETI, and thus cause a deterioration of patients' respiratory conditions. Indeed, on average, mortality in patients treated with CPAP/NIV was lower than that generally reported in patients exposed to IMV [46]. According to our results, mortality in patients treated with NIV was higher compared with patients treated with CPAP. However, due to the heterogeneity of data reporting and patients' baseline characteristics, it was difficult to assess if treatment with NIV was dedicated to patients with more severe

Table 2
Clinical outcomes in studies included in the analysis.

Study	Death				Intubation			CPAP/NIV failure[b]	Patients still hospitalized		Lenght of hospitalization, days				CPAP/NIV discontinuation		
	In-hospital mortality	Death in CPAP	Death in NIV	Death in IMV[a]	ETI at admission	ETI at CPAP failure	ETI at NIV failure		Hospital	ICU	Overall	CPAP	NIV	ICU/IMV	Intolerance	Other complications	PNX
Aliberti et al. [15]	45 (29%)	36 (23%)	N/A	9	N/A	34 (22%)	N/A	70 (44%)	0	0	18 (14–25.5) CPAP success 8 (4–22) CPAP failure				4	2	1
Alviset et al. [26]	18 (37%)	6 (12%)	N/A	12	0	26 (53%)	N/A	32 (65%)	0	0	N/A	N/A	N/A	N/A	2	N/A	N/A
Arina et al. [27]	40 (43%)	14 (15%)	N/A	26	N/A	47 (50%)	N/A	61 (66%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Avdeev et al. [16]	15 (25%)	0	0	15	9	17 (28%) CPAP/NIV		17 (28%)	0	0	N/A	N/A	N/A	N/A	N/A	17	N/A
Brusasco et al. [28]	9 (14%)	4 (6%)	N/A	5	N/A	7 (11%)	N/A	7 (11%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Burns et al. [17]	14 (50%)	12 (52%)	2 (40%)	0	0	0/28 CPAP/NIV		14 (50%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Corradi et al. [29]	3 (11.1%)	0	N/A	3	N/A	9 (33%)	N/A	9 (33%)	0	0	9 (3−12)	N/A	N/A	N/A	N/A	N/A	N/A
Di Domenico et al. [30]	84 (30.4%)	25 (28%) (CPAP/NIV)		0	13	36 (40%) CPAP/NIV		61 (68%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duca et al. [19]	65 (76.5%)	39 (55%)	4 (57%)	15	7	26 (37%)	0	69 (88%)	0	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Faraone et al. [31]	25 (50%)	19 (38%) (CPAP/NIV)		3	N/A	9 (18%) CPAP/NIV		28 (56%)	0	0	19.6 (14.5)	N/A	N/A	N/A	N/A	N/A	N/A
Franco et al. [14]	180 (26.9%)	74 (22%)	45 (25%)	35	0	82 (25%)	49 (28%)	250 (49%)	0	0	20.3 (13.2)	9.8 (12.1)	1.5 (15.1)	N/A	N/A	N/A	N/A
Giacomelli et al. [32]	48 (20.6%)	10 (34%)	N/A	7	N/A	8 (27%)	N/A	18 (62%)	0	0	12 (8–21)	N/A	N/A	N/A	N/A	N/A	N/A
Hallifax et al. [18]	26 (51.2%)	26 (54%)	N/A	N/A	11	11 (23%)	N/A	41 (85%)	0	2	N/A	N/A	N/A	N/A	21	N/A	N/A
Hua et al. [33]	179 (38.2%)	N/A	62 (41%)	104	113	N/A	N/A	62 (41%)[c]	0	0	20.4 (13.2)	N/A	16.1 (9.6)	17.9 (12.3)	N/A	44 (9.4%)	N/A
Karagiannidis et al. [34]	906 (52.5%)	N/A	107 (30%)	70	1318	N/A	141 (40%)	248 (71%)	0	0	21 (10–37)	N/A	15 (8–25)	23 (11–39)	N/A	N/A	N/A
Mukhtar et al. [35]	10 (18.2%)	N/A	3 (8%)	7	N/A	N/A	9 (23%)	12 (31%)	0	0	5 (3–7)	N/A	7 (4–8)	7 (3–18)	0	9	0
Nightingale et al. [36]	5 (20.8%)	1 (4%)	N/A	4	N/A	9 (37%)	N/A	10 (42%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Noeman-Ahmed et al. [37]	18 (34.6%)	10 (19%)	N/A	8	N/A	21 (40%)	N/A	31 (60%)	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rahim et al. [38]	157 (76.2%)	N/A	84 (67%)	N/A	78	N/A	N/A	84 (67%)[c]	N/A	N/A	6.2 (6.5)	N/A	N/A	N/A	N/A	N/A	N/A
Sivaloganathan et al. [39]	23 (28.0%)	N/A	20 (34%)	3	21	N/A	27 (46%)	47 (81%)	11	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Winearls et al. [40]	4 (16.7%)	4 (17%)	N/A	0	N/A	1 (4%)	N/A	5 (21%)	1	0	N/A	N/A	N/A	N/A	N/A	2	N/A
Yang et al. [41]	32 (61.5%)	N/A	4 (14%)	22	N/A	N/A	13 (25%)	17 (59%)	0	12	N/A	N/A	N/A	N/A	N/A	7	1
Zhou et al. [42]	54 (28.3%)	N/A	24 (92%)	N/A	N/A	N/A	N/A	24 (92%)[c]	0	0	11 (7–14)	N/A	N/A	8 (4–12)	N/A	112 (sepsis)	N/A

Variables within brackets are standard deviations or inter-quartile ranges. N/A = not applicable/not available.

[a] After CPAP/NIV failure.

[b] Includes intubation, discontinuation for intolerance or death in patients with a "do –not-intubate" order (CPAP/NIV death + IMV after NIV failure + intolerance).

[c] Incomplete data, only proportion of patients that died on CPAP or NIV.

disease. We hypothesize that, in the majority of cases, the choice depended upon local/regional resources, availability and clinicians' confidence with the support employed.

Complications during CPAP or NIV were usually under-reported, but in the majority of cases appeared not related with the non-invasive respiratory support. Indeed, according to our results, pneumothorax was a rare event in patients with COVID-19 undergoing CPAP/NIV.

A recent RCT has demonstrated the superiority of NIV delivered by helmet compared with HFNC in preventing intubation in 109 COVID-19 patients suffering from acute hypoxic respiratory failure and a $PaO_2/FiO_2 < 200$ mmHg [52]. To date, however, there are no available studies that compared the efficacy of CPAP with NIV, or different interfaces such as oro-nasal masks and the helmet. To date, in fact, NIV was often dedicated to COVID-19 patients with hypercapnia, respiratory acidosis, significant respiratory distress or with a history of chronic obstructive disease [16,19,31].

5. Study limitations

The present review has limitations. First, the lack of differentiation between CPAP and NIV. In fact, in many manuscripts, both CPAP and NIV were included under the definition of "non-invasive ventilation", and the clinical outcomes (such as mortality) was often intended both for CPAP and NIV. Second, many essential parameters were missing, especially in regard to the ventilator settings and interfaces used, criteria for the initiation and failure of the non-invasive support. Third, it is possible that the clinical outcomes in patients exposed to CPAP or NIV may have been influenced by the pandemic period during which patients were enrolled. In fact, the majority of studies were conducted in the first months of the pandemic for each Country (e.g. March–May for Europe, January–March for China), during an unprecedented burden on the regional healthcare systems [50]. Indeed, it has been reported that mortality in patients requiring IMV was higher in early pandemic centres [53], while to date, data for patients treated with non invasive respiratory supports are limited.

5.1. Limitations and advantages of the rapid review methodology

The rapid review methodology has intrinsically some pitfalls: 1) no PICO questions were applied, the review was based on a single primary outcome; 2) the literature research was conducted only on PUBMED and EMBASE databases; 4) only full articles written in English were considered; 5) the timeframe of literature research ended on November 15th 2020 (publication bias) [54].

Although systematic reviews provide more definite recommendations with a greater quality of evidence, rapid reviews require less time and resources, and are useful to answer to few, focused clinically important questions. The rapid evolving COVID-19 pandemic and the fast growing amount of literature on patients' respiratory management necessitates a timely response in terms of evidence assessment. The scoping review methodology has been recently introduced as a useful evidence condensation tool [24,54], allowing for rapid data processing, and providing a timely answer to a specific question such as the evaluation of outcomes in patients treated with non invasive respiratory supports, which can be helpful for clinicians assisting patients with COVID-19 pneumonia.

6. Conclusion

The application of non-invasive respiratory support with CPAP or NIV in patients with COVID-19 pneumonia and acute hypoxic respiratory failure appears feasible and safe also outside the ICU setting. Properly designed prospective comparative studies are urgently needed to assess any possible difference in terms of clinical outcomes of the application of CPAP and NIV, both as a ceiling treatment in DNI patients and in patients eligible for ETI.

Data availability statement

DR, DAC and PS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and had final responsibility for the decision to submit for publication. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

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Declaration of interest

The authors declare no conflicts of interest in regard to the present manuscript.

CRediT authorship contribution statement

Dejan Radovanovic: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft. **Silvia Coppola**: Formal analysis, Writing - review & editing. **Elisa Franceschi**: Data curation, Formal analysis, Writing - original draft. **Fabrizio Gervasoni**: Formal analysis, Writing - review & editing. **Eleonora Duscio**: Formal analysis, Writing - review & editing. **Davide Alberto Chiumello**: Conceptualization, Methodology, Writing - original draft, Supervision. **Pierachille Santus**: Conceptualization, Methodology, Writing - original draft, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.05.007.

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