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Original Contribution

Effect of prone versus supine position in COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

Study objective: To review the effects of prone position and supine position on oxygenation parameters in patients with Coronavirus Disease 2019 (COVID-19).
Design: Systematic review and meta-analysis of non-randomized trials.
Patients: Databases of EMBASE, MEDLINE and CENTRAL were systematically searched from its inception until March 2021.
Interventions: COVID-19 patients being positioned in the prone position either whilst awake or mechanically ventilated.
Measurements: Primary outcomes were oxygenation parameters (PaO_2/FiO_2 ratio, $PaCO_2$, SpO_2). Secondary outcomes included the rate of intubation and mortality rate.
Results: Thirty-five studies ($n = 1712$ patients) were included in this review. In comparison to the supine group, prone position significantly improved the PaO_2/FiO_2 ratio (study = 13, patients = 1002, Mean difference, MD 52.15, 95% CI 37.08 to 67.22; $p < 0.00001$) and SpO_2 (study = 11, patients = 998, MD 4.17, 95% CI 2.53 to 5.81; $p \leq 0.00001$). Patients received prone position were associated with lower incidence of mortality (study = 5, patients = 688, Odd ratio, OR 0.44, 95% CI 0.24 to 0.80; $p = 0.007$). No significant difference was noted in the incidence of intubation rate (study = 5, patients = 626, OR 1.20, 95% CI 0.77 to 1.86; $p = 0.42$) between the supine and prone groups.
Conclusion: Our meta-analysis demonstrated that prone position improved PaO_2/FiO_2 ratio with better SpO_2 than supine position in COVID-19 patients. Given the limited number of studies with small sample size and substantial heterogeneity of measured outcomes, further studies are warranted to standardize the regime of prone position to improve the certainty of evidence.
PROSPERO Registration: CRD42021234050

1. Introduction

The surge of Coronavirus Disease 2019 (COVID-19) cases has overwhelmed the healthcare services in some countries [1]. Persistent hypoxemia is a common presentation in patients with severe COVID-19. Large numbers of hospitalized COVID-19 patients fulfilled the criteria of acute respiratory distress syndrome (ARDS), which require invasive mechanical ventilation and high level of patient care [2]. The need for invasive mechanical ventilation has exceeded the capacity of healthcare systems, especially for those heavily affected countries.

Prior to this pandemic of COVID-19, the application of prone position has been studied in awake patients with acute respiratory failure to avoid endotracheal intubation and reduce the need for intensive care units (ICU) admissions [3–5] In view of a huge demand for mechanical ventilation among COVID-19 patients, the method of prone position has been extensively utilized to improve oxygenation, minimizese incidence of intubation rate and ICU admission. The method of awake self-pronation can be applied in spontaneously breathing patients

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receiving non-invasive ventilation or high-flow nasal cannula (HFNC) in the setting of outside ICU. Some studies have reported an improved oxygenation with a decrease in respiratory effort when applied early in COVID-19 patients with acute respiratory failure [6]. Prone position improves the ventilation/perfusion ratio and recruitment of the dorsal lung segments, resulting in the opening of collapsed dorsal alveoli with better gas exchange and oxygenation [7,8]. In mechanically ventilated non COVID-19 patients with severe ARDS, those who received prone ventilation had a lower mortality rate [9]. However, the clinical outcomes of prone position in COVID-19 (intubated/non-intubated) patients remain unclear from the literature. Therefore, a systematic review and meta-analysis is warranted to examine the effectiveness and safety of prone position in COVID-19 patients before any recommendation can be made.

We hypothesized that prone position improved oxygenation parameters in COVID-19 patients. Our primary aim was to investigate the effect of prone position on partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio. Secondary aims were to examine the effect of prone position on peripheral oxygen saturation (SpO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), incidence of intubation, mortality rate and number of patients discharged alive.

2. Method

2.1. Data sources and searches

The review was conducted and reported in accordance to the Cochrane Handbook Systematic Reviews of Interventions [10] and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA statement) 2015 [11], respectively. Our review protocol was published in a public database (PROSPERO CRD42021234050) prior to the literature search. The Population (COVID-19 patients), Intervention (prone position), Comparison (supine position) and Outcomes approach was used to formulate our review questions (Online Supplement eTable 1). Databases of EMBASE (OvidSP), MEDLINE (OvidSP) and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from their inception until March 2021. The ClinicalTrials.gov and WHO International Clinical Trials Registry Platform Search Portal were searched for any ongoing or unpublished trials. The search terms and strategy used are showed in Online Supplement eTable 2. Inclusion criteria were:

1. Cohort or case-control observational studies (prospective or retrospective)
2. Randomized controlled trials
3. Examining prone position versus supine position
4. Adults ($\geq$ 18 years old) diagnosed with COVID-19 infection

Case series, case reports and editorials were excluded. There was no restriction applied to the publication language and publication date. The reference lists of all the included studies were manually searched for any new or additional papers. The authors of relevant studies were contacted at least twice for any missing or unclear data.

2.2. Study selection, data items, data collection, and assessment of validity

Titles and abstracts were independently screened by two authors (EC and SMI) based on the pre-defined inclusion and exclusion criteria. Studies coded with “no” were excluded. Any studies coded with “yes” were retrieved for full text screening and screened independently by two authors (EC and SMI). Studies coded with “maybe” at any stage of study selection were resolved by third author (KN) via a discussion to achieve consensus. The selection of final included studies was discussed and agreed by all the authors.

Data of all included studies were extracted independently by two authors (EC and SMI) using a standardized online data extraction form, which was piloted prior to the data extraction. Any disagreements were resolved by a third author (KN). In addition to the measured outcome, the following data, namely author, year of publication, country, study design, total sample size, mean age, gender, body mass index, citation, severity of APACHE II, duration of prone position and types of oxygen delivered were extracted.

2.3. Outcomes

Primary outcome of this review was PaO_2/FiO_2 ratio after prone and supine position. Secondary outcomes included SpO_2, $PaCO_2$, mortality rate, incidence of intubation rate and number of patients discharged alive.

2.4. Risk of bias in individual studies, summary of findings and GRADE assessment

The risk of bias for all included observational studies was independently assessed by two authors (EC and SMI) using the Newcastle-Ottawa Scale [12]. Study which scored $\geq$7 was considered as low risk of bias. Any disagreements were discussed and resolved by a third author (KN). The certainty of evidence (GRADE) was conducted by two authors (EC and SMI) independently. Several domains, namely the risk of bias, inconsistency, imprecision, indirectness and publication bias were assessed for all the measured outcomes. Any conflicts were discussed with a third author (KN).

2.5. Summary measures and synthesis of results

Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) was used for all statistical analyses. A two-sided *p*-value of $<$0.05 was denoted as statistically significant. Findings were reported as odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes, along with 95% confidence interval (CI). When the data were presented as median and range/interquartile range, these data were converted to mean and standard deviation [13]. I-square (I^2) test was used to assess heterogeneity of studies. I^2 of less than 40%, 40–60% and more than 60% were categorized as low, moderate and substantial heterogeneity, respectively [10]. In view of the limited number of studies with high heterogeneity, the random-effect model (DerSimonian-Laird method) was used to pool data for all the measured outcomes. Subgroup analysis based on intubated and non-intubated COVID-19 studies was performed on the measured outcomes to explore the substantial degree of heterogeneity. Funnel plots were used to assess for publication bias.

3. Results

3.1. Study selection

The study selection process is summarized in the PRISMA flow diagram (Fig. 1). The search strategy yielded 1012 articles for titles and abstracts screening, of which 47 articles were retrieved for full text screening. After applying inclusion and exclusion criteria, thirty-five studies with a total of 1712 patients were included in this review. The list of excluded studies is showed in the Online Supplement eTable 3. Searching of trial registries found 9 ongoing studies (Online Supplement eTable 4).

3.2. Clinical characteristics of eligible studies

The clinical characteristics of included studies are demonstrated in Table 1. All the included studies were cohort studies. There were no randomized clinical studies investigating the effect of supine and prone position in COVID-19 patients. Of all, seven studies [14–20] had two

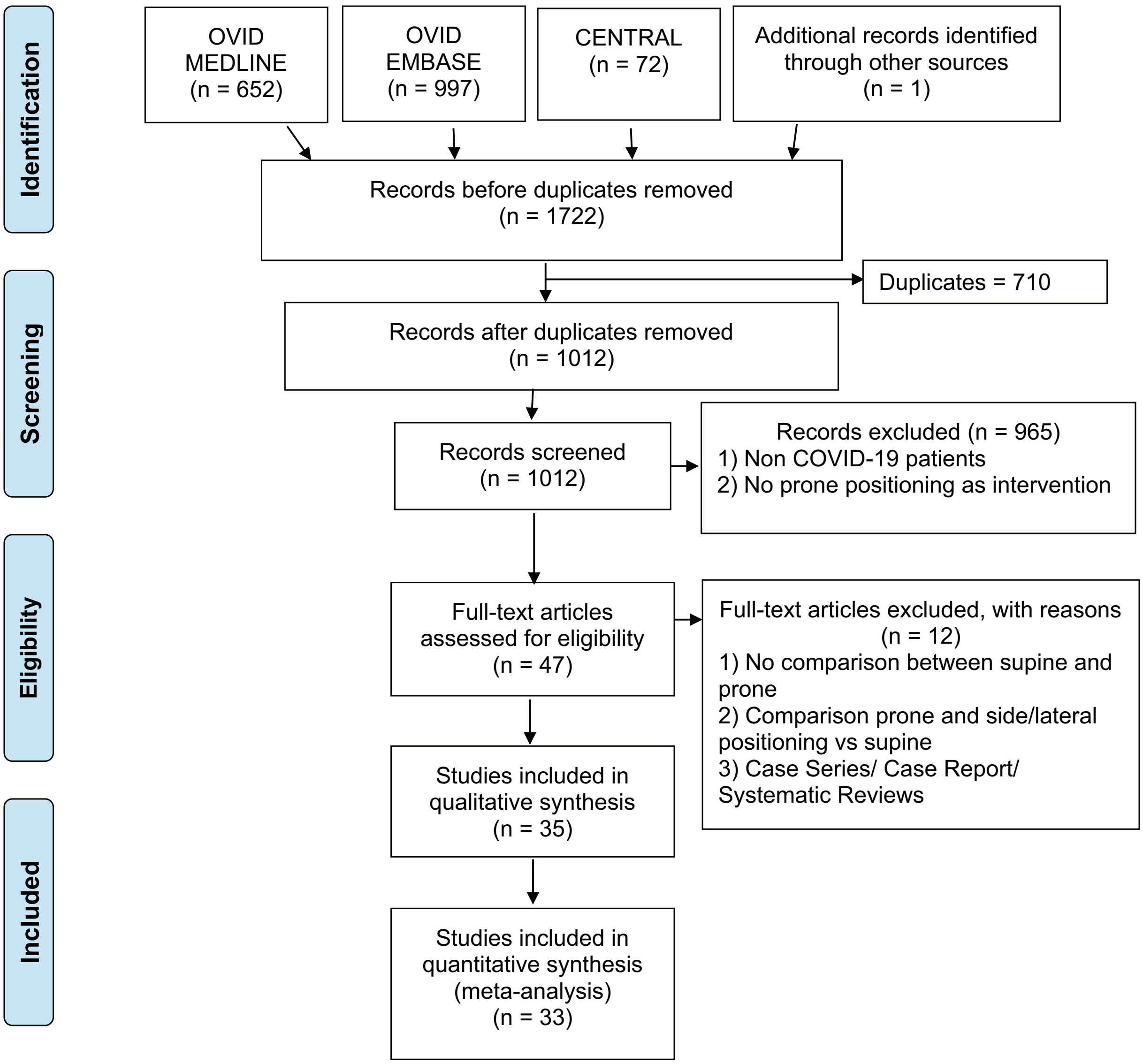

Fig. 1. PRISMA flow diagram.

separate cohorts for intervention and a control group whilst the rest of them [21–48] only had one cohort with pre-intervention (supine position) and post-intervention (prone position). The majority of included studies were of single centered, except two which were multi-centered [14,29]. The total sample size varied across all the included studies, ranging from 9 patients to 261 patients. Most of the recruited COVID-19 patients were from general wards, emergency departments and ICUs. The mean age of all the included studies ranged between 53 and 68 years old. Out of the 35 studies, twenty-one studies [14–16,18–20,23–26,29–36,38–40] utilized non-invasive ventilation (nasal cannula, simple face mask, venturi mask, non-rebreather mask, continuous positive airway pressure, bi-level positive airway pressure or high flow nasal cannula) and 14 studies [17,21,22,27,28,37,41–48] included mechanically ventilated COVID-19 patients. The duration of prone position sessions varied across all the studies from 30 min, 4 h and 16 h. The risk of bias for 27 studies [14–23,27,29–34,38–40,42–48] were assessed as low risk bias (≥7) based on the three domains of study selection, comparability and exposure (eTable 5). Five [24,26,36,37,41] and three [25,28,35] studies were rated as 6 and 5, respectively due to high risk of bias in the domain of comparability. The PRISMA checklist is outlined in the Online Supplementary eTable 6. The summary of findings and certainty of evidence assessment are showed in the Tables 2 and 3, respectively.

3.3. *Primary outcome: PaO_2/FiO_2 ratio*

In the combined data of thirteen studies [14,21,22,30,32,34,37,40,41,43,45–47] involving 1002 patients, our review demonstrated that COVID-19 patients with prone position were associated with higher PaO_2/FiO_2 ratio as compared to the supine group (MD 52.15, 95% CI 37.08 to 67.22; $p < 0.00001$, Fig. 2). However, statistical heterogeneity was observed as substantial ($I^2 = 87\%$). The magnitude and effect size of subgroup analysis for both intubated (studies = 8, $n = 579$ patients, MD 46.74, 95% CI 33.34 to 60.15; $p < 0.00001$) and non-intubated (studies = 5, $n = 423$ patients, MD 68.81, 95% CI 15.94 to 121.69; $p = 0.01$) studies remained significant, which was consistent with the overall finding of PaO_2/FiO_2 ratio. Funnel plot was asymmetry, suggestive of publication bias.

3.4. *Secondary outcomes: SpO_2, $PaCO_2$, incidence of mortality, incidence of intubation, number of patients discharged alive*

Eleven studies [16,18,21,24,25,28,32,34,38,39,43] ($n = 998$ patients) examined the SpO_2 in COVID-19 patients who received prone and

Table 1
Baseline characteristics of all the included studies.

Author	Year	Design	N	Country	Setting	Age (mean + -SD)	BMI (mean + -SD)	Severity		Types of Oxygen Delivery Interface	Intervention	Successful duration of proning (standard)	Average/ Total duration of proning
								APACHE II	SOFA				
Ferrando et al	2020	Multicenter Cohort study (Non-intubated)	199	Spain & Andorra	NR	62.2 (12.1)	**Int:** 27.6 (4.9) **Con:** 27.2 (3.2)	**Int:** 11 (4.5) **Con:** 9.2 (5.4)	**Int:** 4.3 (0.8) **Con:** 4.0 (0)	**Int & Con:** High flow nasal oxygen therapy	Awake PP	>16 h/ day	NR
Jagan et al	2020	Single Center Cohort study (Non-intubated)	105	USA	NR	60.9 (15.4)	**Int:** 60.0% obese **Con:** 40.0% obese	**Int:** 6.7 (3.8) **Con:** 11 (6.8)	**Int:** 2.3 (0.8) **Con:** 3.7 (2.3)	**Int & Con:** Non-invasive ventilation	Awake PP	≥ 1 continuous hr on ≥ 5 occasions per day & for ≥ 1 continuous hr overnight	NR
Padrao et al	2020	Single Center Cohort study (Non-intubated)	166	Brazil	ED	58.1 (14.1)	**Int:** 58% BMI > 30 **Con:** 51% BMI > 30	NR	NR	**Int:** 34% nasal cannula 5% venturi mask 61% non-rebreathable mask **Con:** 49% nasal cannula 13% venturi mask 39% non-rebreathable mask	Awake PP	at least 4 h twice daily up to 15 days	NR
Shelhamer et al	2020	Single Center Cohort study (Intubated)	261	USA	Across all hospital services (medicine, surgery, ICU)	64 (13.4)	**Int:** 31.7 (5.8) **Con:** 31.6 (7.8)	**Int:** 17.9 (8.9) **Con:** 19 (11.9)	**Int:** QuickSOFA 61.3% **Con:** QuickSOFA 61.3%	**Int & Con:** Mechanical ventilation	PP	at least 16 h	NR
Weiss et al	2020	Single Center Cohort study (Intubated)	42	USA	ICU	59.9 (13.4)	34.2 (7.5)	NR	6.8 (2.5)	Mechanical ventilation	PP	at least 16 h	NR
Berrill et al	2020	Single Center Cohort study (Intubated)	34	UK	ICU	58.5 (11.1)	31 (5.1)	14 (4.7)	NR	Mechanical ventilation	PP	NR	**Average**: 16.5 (2.7) hrs **Total duration**: 63.5 (38.2), 2 days
Burton et al	2020	Single Center Cohort study (Non-intubated)	20	UK	ICU	53.4 (8.3)	55% BMI >30	11.5 (IQR 5)	3 (IQR 0)	NIV: 20% CPAP, 8.% CPAP+ BiPAP	Self-prone	NR	**Median duration:** 3 h (IQR 2)/CYCLE **Cycles per patient:** 5(6.25)
Caputo et al	2020	Single Center Cohort study (Non-intubated)	50	USA	ED	59 (13.7)	NR	NR	NR	76% non-rebreathable mask 24% nasal cannula at 5 L/min	PP	NR	NR
Ishak et al	2020	Single Center Cohort study (Non-intubated)	21	Turkey	Ambulance	69.2 (13.1)	NR	NR	NR	2 L/min nasal cannula	PP	NR	<15mins: 7 >15 mins: 14
Kelly et al	2020	Single Center Cohort study (Non-intubated)	17	UK	Ward & critical care	62.3 (11.3)	26.2 (3)	NR	NR	Non-invasive ventilation	Awake PP	4 h twice a day	**Total:** 10.7 (10.0) hrs/ cycle 2.3 (1.6) days
Mitter-maier et al	2020	Single Center Cohort study (Intubated)	9	Germany	ICU	62 (14.2)	30.4 (6.5)	26.2 (6.5)	7.4 (4.9)	Mechanical ventilation	PP	NR	15.4 ± 2.5 h/ session **Total:** 6.2 (3.4) days
Perrier et al	2020	Single Center Cohort study (Intubated)	9	France	NR	54 0.3 (8.7)	32.8 (5.1)	NR	NR	Mechanical ventilation	PP	NR	NR
Solverson et al	2020	Multicenter Cohort study (Non-intubated)	17	Canada	ICU & ward	56 (38)	18% BMI > 35	NR	NR	Non-invasive ventilation	Awake PP	NR	**Total:** 3 (4.9) days
Winearls et al	2020		24	UK		62 (13)	NR	11 (5)	NR	Non-invasive ventilation including CPAP	PP	NR	**Mean duration in 1st 24 h:** 8 (5)

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Table 1 (*continued*)

Author	Year	Design	N	Country	Setting	Age (mean + -SD)	BMI (mean + -SD)	Severity		Types of Oxygen Delivery Interface	Intervention	Successful duration of proning (standard)	Average/ Total duration of proning
								APACHE II	SOFA				
		Single Center Cohort study (Non-intubated)			COVID-19 Respirato-ry high care unit								hrs **Total:** 10(5) days
Thompson et al	2020	Single Center Cohort study (Non-intubated)	25	USA	Interme-diate care unit	**Intu:** 68.7 (26.7) **Non-intu:** 61 (20.4)	**Intu:** 27.5 (8.6) **Non-intu:**32.3 (20.4)	NR	NR	1) 6 L/min nasal cannula 2)15 L/min non-rebreather face mask	Awake PP	NR	Total duration: **Intubated:** 2.0 (1.7) days **Non-intubated:** 2.7 (3.3) days
Coppo et al	2020	Single Center Cohort study (Non-intubated)	56	Italy	Medical wards, ED & respiratory HDU	57.4 (7.4)	27.5 (3.7)	NR	NR	79% Helmet CPAP 16% Reservoir mask 5% venturi mask	PP	at least 3 h	Total duration: 1 day
Elharrar et al	2020	Single Center Cohort study (Non-intubated)	24	France	Non-ICU	66.1 (10.2)	23% BMI > 30	NR	2.8 (0.9)	67% <4 L/min 33% ≥4 L/min or HFNC	PP	NR	<1 h (n = 4) to <3 h (n = 5) ≥ 3 h (*n* = 15)
Taboada et al	2020	Single Center Cohort study (Non-intubated)	29	Spain	Non-ICU	64 (12)	29.2 (3.6)	NR	NR	Nasal cannula or face mask	PP	At least 30 min 3 times a day	NR
Golestanie-ragh et al	2020	Cohort study (Non-intubated)	10	NR	NR	NR	NR	NR	NR	Non-invasive ventilation	PP	NR	Mean duration: 9 h
Sartini et al	2020	Single Center Cohort study (Non-intubated)	15	Italy	General wards	59 (6.5)	24 (3.4)	NR	NR	Non-invasive ventilation	PP	NR	Per session: 3.3 (4.1) hrs
Astua et al	2020	Single Center Cohort study (Intubated)	31	USA	NR	58.3 (1.7)	27.9 (3.8)	NR	NR	Mechanical ventilation	PP	16 h each day	NR
Zang et al	2020	Single Center Cohort study (Non-intubated)	60	China	ICU	**Int:** 62.65 (10.83) **Con:** 66.14 (9.19)	NR	NR	NR	High Flow Nasal Cannula	PP	10 or 30 min	30 min
Wormser et al	2021	Single Center Cohort study (Non-intubated)	27	France	Wards	70.67 (14.87)	28.8 (5.8)	NR	NR	74% > 6 L/min	PP	61 sessions	NR
Wendt et al	2020	Single Center Cohort study (Non-intubated)	31	USA	ED	62 (12)	31 (5)	NR	NR	2 to 21 L/min by nasal cannula and/or nonrebreather mask	PP	At least 30 min	NR
Prud'hom-me et al	2021	Single Center Bicentric study (Non-intubated)	96	France	Outside ICU	**Int:** 62 (11) **Con:** 61 (18)	**Int:** 27 (5) **Con**: 28 (5)	NR	NR	Conventional Oxygen therapy or High Flow Nasal Cannula	Awake PP	At least 3 h a day	3 consecutive days
Taylor et al	2020	Single Center Pilot study (Non-intubated)	40	USA	NR	**Int:** 55.7 (16.4) **Con:** 59 (7.5)	**Int:** 31.3 (10.2) **Con:** 32.3 (7.8)	NR	NR	Nasal cannula, BiPAP	PP	At least 48 h	Lie prone between 10 and 120 minures per day
Dubosh et al	2020	Single Center Cohort study (Non-intubated)	22	USA	ED	58.7 (11.9)	NR	NR	NR	Nasal cannula or nonrebreather	Awake PP	At least 30 min	**Mean duration:** 111 (74.5)
Khullar et al.	2020	Single Center Cohort Study (Intubated)	23	USA	NR	53.5 (13.0)	32.3 (6.0)	NR	4.78	NR	PP	≥16 consecutive hrs of PP for ≥1 d	
Douglas et al	2020		61	USA	ICU	56.7 (13.5)	33.39 (8.9)	NR	14.2 (3.4)	Mechanical ventilation	PP	NR	**Mean duration:** 5.1 (4.6)

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Table 1 (*continued*)

Author	Year	Design	N	Country	Setting	Age (mean + -SD)	BMI (mean + -SD)	Severity		Types of Oxygen Delivery Interface	Intervention	Successful duration of proning (standard)	Average/ Total duration of proning
								APACHE II	SOFA				
		Single Center Cohort study (Intubated)											
Clarke et al	2020	Single Center Cohort study (Intubated)	20	Ireland	ICU	52.8 (11.6)	36.5 (10.7)	NR	8.2 (3.4)	Mechanical ventilation	PP	At least 16 h	NR
Osama et al	2020	Single Center Cohort study (Intubated)	25	France	ICU	61.0 (5.5)	30.0 (3.1)	NR	NR	Mechanical ventilation	PP	At least 16 h	NR
Doussot et al	2020	Single Center Cohort study (Intubated)	67	France	ICU	67.5 (8.3)	30.0 (6.1)	NR	NR	Mechanical ventilation	PP	NR	Mean duration: 17 min (6.9)
Gleissman et al	2020	Single Center Cohort study (Intubated)	44	Sweden	ICU	61.0 (13.0)	50% BMI > 30	NR	NR	Mechanical ventilation	PP	1 h each session	Median for 5 sessions: 14 (12–17)
Sang et al	2020	Single Center Cohort Study (Intubated)	20	China	ICU	69.5 (9.5)	NR	24.1 (3.4)	NR	Mechanical ventilation	PP	18–20 h	NR
Sharp et al	2020	Retrospective Observational Study (Intubated)	12	UK	ICU	56.5 (14.1)	NR	NR	NR	Mechanical ventilation	PP	NR	Successful 2 or more full proning cycles

USA: United States of America; UK: United Kingdom; ED: Emergency Department; ICU: Intensive Care Unit; HDU: High Dependency Unit;
Intu: Intubated; Non-intu: Non-intubated; SD: Standard Deviation; NR: Not reported; Int; Intervention; Con: Control; BMI: Body Mass Index;
APACHE ll: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment;
CPAP: Continuous positive airway pressure; BiPAP: Bilevel Positive Airway Pressure; PP: Prone Positioning; min: minute; hr: hour.

Table 2
Summary of findings for primary and secondary outcomes.

No	Outcomes	Trials	N	I^2 (%)	MD/OR (95% CI)	p-value
1.	PaO_2/FiO_2	13	1002	87	52.15 (37.08, 67.22)	<0.00001
	- Intubated group	8	579	78	46.74 (33.34, 60.15)	<0.00001
	- Non-intubated group	5	423	91	68.81 (15.94, 121.69)	0.01
	Heterogeneity: $Tau^2 = 541.13$; $Chi^2 = 95.88$, df = 12 ($P < 0.00001$); $I^2 = 87\%$ Test for overall effect: Z = 6.78 (P < 0.00001) Test for subgroup differences: $Chi^2 = 0.63$, df = 1 ($P = 0.43$), $I^2 = 0\%$					
2.	$PaCO_2$ (mmHg)	10	793	92	0.57 (−2.74, 3.88)	0.74
	- Intubated group	6	436	93	1.07 (−4.12, 6.26)	0.69
	- Non-intubated group	4	357	0	−0.08 (−1.41, 1.26)	0.91
	Heterogeneity: $Tau^2 = 24.70$; $Chi^2 = 107.86$, df = 9 ($P < 0.00001$); $I^2 = 92\%$ Test for overall effect: Z = 0.34 (P = 0.74) Test for subgroup differences: $Chi^2 = 0.17$, df = 1 ($P = 0.68$), $I^2 = 0\%$					
3.	SpO_2 (%)	11	998	94	4.17 (2.53, 5.81)	<0.00001
	- Intubated group	3	432	0	1.67 (1.08, 2.26)	<0.00001
	- Non-intubated group	8	566	95	5.51 (3.17, 7.85)	<0.00001
	Heterogeneity: $Tau^2 = 6.57$; $Chi^2 = 158.60$, df = 10 ($P < 0.00001$); $I^2 = 94\%$ Test for overall effect: Z = 4.98 ($P < 0.00001$) Test for subgroup differences: $Chi^2 = 9.72$, df = 1 ($P = 0.002$), $I^2 = 89.7\%$					
4.	Incidence of intubation	5	626	25	1.20 (0.77, 1.86)	0.42
	- Intubated group	–	–	–	–	–
	- Non-intubated group	5	626	25	1.20 (0.77, 1.86)	0.42
	Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.37$, df = 4 ($P = 0.25$); $I^2 = 25\%$ Test for overall effect: Z = 0.81 (P = 0.42) Test for subgroup differences: Not applicable					
5.	Mortality rate	5	688	31	0.44 (0.24, 0.80)	0.007
	- Intubated group	1	261	–	0.66 (0.32,1.33)	0.24
	- Non-intubated group	4	427	28	0.35 (0.16, 0.75)	0.007
	Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 5.78$, df = 4 ($P = 0.22$); $I^2 = 31\%$ Test for overall effect: Z = 2.69 (P = 0.007) Test for subgroup differences: $Chi^2 = 1.43$, df = 1 ($P = 0.23$), $I^2 = 30.2\%$					
6.	Number of patients discharged alive	3	532	63	1.72 (0.85, 3.48)	0.13
	- Intubated group	1	261	–	1.49 (0.72, 3.08)	0.28
	- Non-intubated group	2	271	82	1.90 (0.55, 6.63)	0.31
	Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 5.47$, df = 2 ($P = 0.07$); $I^2 = 63\%$ Test for overall effect: Z = 1.50 (P = 0.13) Test for subgroup differences: $Chi^2 = 0.11$, df = 1 ($P = 0.74$), $I^2 = 0\%$					

PaO_2/ FiO_2: Ratio of partial pressure of arterial oxygen/fractional concentration of inspired oxygen; $PaCO_2$: Partial Pressure of Carbon Dioxide; SpO_2: Peripheral capillary oxygen saturation;
I^2: heterogeneity; MD: Mean difference; OR: Odds ratio; REM: Random effect model; FEM: Fixed effect model.

supine position. In the pooled data, our review showed that the prone group had a higher SpO_2 reading than the supine group (MD 4.17, 95% CI 2.53 to 5.81; $p \leq 0.0001$, $I^2 = 94\%$). In term of $PaCO_2$, the combined data of ten studies [14,21,25,32,33,37,42,43,46,47], ($n = 793$ patients) found no significant difference in both the prone and supine group (MD 0.57, 95% CI -2.74 to 3.88; $p = 0.74$, $I^2 = 92\%$). Of note, both outcomes were noted to have substantial degree of heterogeneity.

Five studies [15–19] ($n = 688$ patients) assessed the mortality rate in COVID-19 patients who received prone and supine position. The pooled data demonstrated that the prone group had a lower mortality rate than the supine group (OR 0.44, 95% CI 0.24 to 0.80; $p = 0.007$, $I^2 = 31\%$), which was statistically significant. In term of incidence of intubation rate (studies = 5 [14–16,18,19], $n = 626$ patients, OR 1.20, 95% CI 0.77 to 1.86; $p = 0.42$) and number of patients discharged alive (studies = 3 [15–17], $n = 532$, OR 1.72, 95% CI 0.85 to 3.48; $p = 0.13$), no significant differences were noted between the prone and supine groups.

In the subgroup analysis of secondary outcomes, the effect size and direction of findings remained unchanged in both intubated and non-intubated groups for the outcomes of SpO_2, $PaCO_2$, incidence of intubation and number of patients discharged alive, except the incidence of mortality. The incidence of mortality became non-significant in the subgroup analysis of intubated group (studies = 1, $n = 215$, OR 0.66, 95% CI 0.32 to 1.33; $p = 0.24$, Fig. 3). Funnel plots were suggestive of publication bias for all the secondary outcomes, except for the number of patients discharged alive.

Table 3
Certainty of evidence assessment.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prone	supine	Relative (95% CI)	Absolute (95% CI)	
PaO_2/FiO_2											
13	observational studies	not serious	very serious [a]	not serious	not serious	publication bias strongly suspected [b]	496	506	–	MD **52.15 higher** (37.08 higher to 67.22 higher)	⨁◯◯◯ VERY LOW
$PaCO_2$ (mmHg)											
10	observational studies	not serious	very serious [a]	not serious	not serious	publication bias strongly suspected [b]	355	438	–	MD **0.57 higher** (2.74 lower to 3.88 higher)	⨁◯◯◯ VERY LOW
SpO_2 (%)											
11	observational studies	not serious	very serious [a]	not serious	not serious	publication bias strongly suspected [b]	489	509	–	MD **4.17 higher** (2.53 higher to 5.81 higher)	⨁◯◯◯ VERY LOW
Incidence of intubation											
5	observational studies	not serious	not serious	serious [c]	serious [d]	publication bias strongly suspected [b]	80/223 (35.9%)	143/403 (35.5%)	OR 1.20 (0.77 to 1.86)	**43 more per 1000** (from 57 fewer to 151 more)	⨁◯◯◯ VERY LOW
Incidence of death											
5	observational studies	not serious	not serious	not serious	not serious	publication bias strongly suspected [b]	68/230 (29.6%)	239/458 (52.2%)	OR 0.44 (0.24 to 0.80)	**197 fewer per 1000** (from 314 fewer to 56 fewer)	⨁◯◯◯ VERY LOW
Number of patients discharged alive											
3	observational studies	not serious	serious [a]	not serious	serious [d]	none	65/159 (40.9%)	100/373 (26.8%)	OR 1.72 (0.85 to 3.48)	**118 more per 1000** (from 31 fewer to 292 more)	⨁◯◯◯ VERY LOW

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio.
Explanations.
[a] Substantial heterogeneity I2 > 60%.
[b] Funnel plot suggested of publication bias.
[c] Different threshold of intubation criteria varied across all included studies.
[d] Total number of events is less than 300.

4. Discussion

Our meta-analysis demonstrated that COVID-19 patients with prone position were associated with higher PaO_2/FiO_2 ratio and SpO_2 than those with supine position. However, no significant differences were observed in the $PaCO_2$ level, incidence of intubation and number of patients discharged alive. The certainty of evidence for our measured outcomes was very low due to observational studies in nature, inconsistency, indirectness and suggestive of publication bias. It is believed that prone position expands the collapsed dorsal lung region, resulting in a better ventilation/perfusion ratio and more homogenous distribution of lung ventilation [49–51]. The changes of regional ventilation in the prone and supine position can be observed in both normal and ARDS lung, indicating an even distribution of distending forces throughout the lung tissues [52]. The distribution of pulmonary blood flow in the normal or diseased lung is mainly directed dorsally whether one is in supine or prone position. With this relatively constant regional perfusion in the prone position along with a significant improvement in lung homogeneity, the effect of shunt fraction is expected to reduce and lead to a marked improvement in oxygenation. This has been demonstrated in animal and human studies that the relative shunt fraction of prone position was reduced by 30% than the supine group with injured lungs [53,54]. However, Gattinoni and colleagues reported that the improvement in oxygenation during prone position did not persist after returning to supine position and the PaO_2/FiO_2 ratio returned to baseline at 6 h following re-supination [55]. This may be explained by the recollapsed of the previously opened dorsal lung units during prone position, resulting in ventilation/perfusion mismatch and rebound hypoxemia.

Our finding did not show an improvement in $PaCO_2$ after the application of prone position in COVID-19 patients. This finding has to be interpreted with caveat as our review included both spontaneously breathing and mechanically ventilated patients. The outcome of $PaCO_2$ may not be accurate in awake spontaneously breathing patients due to the variation in respiratory rate, tidal volume and minute ventilation. However, in the mechanically ventilated patients, controlled ventilation in prone position decreased the shunt fraction and promoted elimination of carbon dioxide [56]. Prone position is believed to reduce areas of over-distension in lung, resulting in a reduction in physiological deadspace and possibly $PaCO_2$. Gattinoni et al. stated that the effect of $PaCO_2$ in the prone and supine position is also affected by the alveolar ventilation and its relationship with the total ventilated lung volume [56].

Study or Subgroup	Prone Mean	Prone SD	Prone Total	Supine Mean	Supine SD	Supine Total	Weight	Mean Difference IV, Random, 95% CI	Year
1.1.1 Intubated									
Sharp 2020	110.2	28.1	12	89	19.3	12	9.3%	21.20 [1.91, 40.49]	2020
Gleissman 2020	144.7	56	44	104	27.6	44	9.4%	40.70 [22.25, 59.15]	2020
Osama 2020	123.3	40.9	25	102	46.4	25	8.5%	21.30 [-2.95, 45.55]	2020
Weiss 2020	211.5	91.5	42	134.3	54	42	7.3%	77.20 [45.07, 109.33]	2020
Artua 2020	152.8	11.2	31	108	5.4	31	10.8%	44.80 [40.42, 49.18]	2020
Berill 2020	151.9	58.9	89	87.8	38.2	20	9.1%	64.10 [43.36, 84.84]	2020
Clarke 2020	276.3	122	20	125.7	43.1	20	4.3%	150.60 [93.89, 207.31]	2020
Douglas 2020	134.7	45	61	100	41.8	61	9.8%	34.70 [19.29, 50.11]	2020
Subtotal (95% CI)			**324**			**255**	**68.5%**	**46.74 [33.34, 60.15]**	
Heterogeneity: Tau² = 244.71; Chi² = 31.67, df = 7 (P < 0.0001); I² = 78%									
Test for overall effect: Z = 6.84 (P < 0.00001)									
1.1.2 Non-intubated									
Coppo 2020	285.5	112.9	46	180.5	76.6	46	6.3%	105.00 [65.57, 144.43]	2020
Taboada 2020	242	107	29	196	68	29	5.4%	46.00 [-0.14, 92.14]	2020
Winearls 2020	201	70	22	143	73	24	6.0%	58.00 [16.67, 99.33]	2020
Ferrando 2020	102.7	34.3	51	98.3	36.4	128	10.3%	4.40 [-6.93, 15.73]	2020
Wormser 2020	339.8	157	24	189.3	42.9	24	3.6%	150.50 [85.39, 215.61]	2020
Subtotal (95% CI)			**172**			**251**	**31.5%**	**68.81 [15.94, 121.69]**	
Heterogeneity: Tau² = 3162.64; Chi² = 45.03, df = 4 (P < 0.00001); I² = 91%									
Test for overall effect: Z = 2.55 (P = 0.01)									
Total (95% CI)			**496**			**506**	**100.0%**	**52.15 [37.08, 67.22]**	
Heterogeneity: Tau² = 541.13; Chi² = 95.88, df = 12 (P < 0.00001); I² = 87%									
Test for overall effect: Z = 6.78 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%									

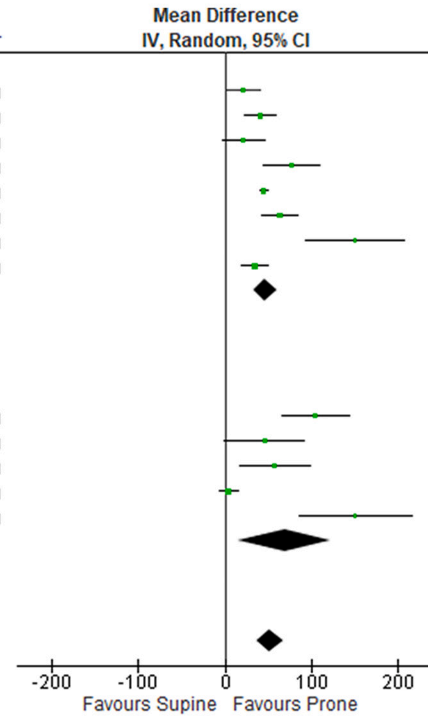

Fig. 2. PaO_2/FiO_2 ratio.

Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.5.1 Intubated							
Selhamer 2020	48	62	167	199	34.9%	0.66 [0.32, 1.33]	2020
Subtotal (95% CI)		**62**		**199**	**34.9%**	**0.66 [0.32, 1.33]**	
Total events	48		167				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.17 (P = 0.24)							
1.5.2 Non-intubated							
Prud'hormme 2020	4	48	6	48	15.7%	0.64 [0.17, 2.42]	2020
Jagan 2020	0	40	16	65	4.2%	0.04 [0.00, 0.64]	2020
Zang 2020	10	23	28	37	20.4%	0.25 [0.08, 0.75]	2020
Padrao 2020	6	57	22	109	24.7%	0.47 [0.18, 1.22]	2020
Subtotal (95% CI)		**168**		**259**	**65.1%**	**0.35 [0.16, 0.75]**	
Total events	20		72				
Heterogeneity: Tau² = 0.17; Chi² = 4.16, df = 3 (P = 0.24); I² = 28%							
Test for overall effect: Z = 2.68 (P = 0.007)							
Total (95% CI)		**230**		**458**	**100.0%**	**0.44 [0.24, 0.80]**	
Total events	68		239				
Heterogeneity: Tau² = 0.14; Chi² = 5.78, df = 4 (P = 0.22); I² = 31%							
Test for overall effect: Z = 2.69 (P = 0.007)							
Test for subgroup differences: Chi² = 1.43, df = 1 (P = 0.23), I² = 30.2%							

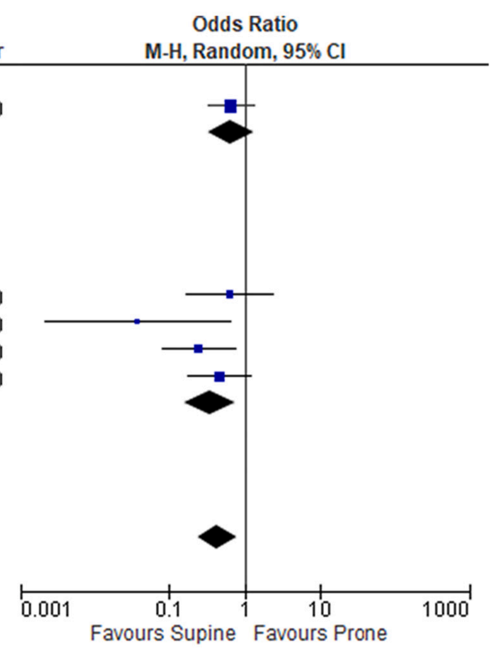

Fig. 3. Incidence of mortality.

In this review, we demonstrated no significant differences in the rate of intubation and number of patients discharged alive between the prone and supine groups. Ferrando et al. emphasized that it may be due to non-standardized or non-protocolized intubation criteria, which may limit the generalizability of the results [14]. Among all the three included studies, there was only one paper reporting their intubation criteria [16]. The duration of prone position varied at the discretion of treating physicians across all the included studies, which introduced significant bias to our findings. Pavlov and colleagues reported that COVID-19 patients with longer duration of awake prone position were associated with lower incidence of intubation [57]. The absence of standardized intubation criteria can limit the interpretation of our findings [58].

Our meta-analysis reported that the mortality rate was lower in those who received prone ventilation. The level of evidence for mortality rate was low due to limited number of studies with small sample size. Among the five included studies, four studies included awake spontaneously breathing patients and only one study examined mechanically ventilated patients. The benefit of prone position was not significant in the subgroup analysis of intubated group. However, a cohort study by Mathews and team showed that prone ventilation reduced mortality rate in mechanically ventilated COVID-19 patients with ARDS [59]. Prone position is a cornerstone treatment for intubated classical ARDS patients. The evidence of prone position on mortality rate in intubated or non-intubated COVID-19 patients remains uncertain as the pathophysiology of classical ARDS and COVID-induced ARDS were different.

In view of the absence of randomized controlled trials in the literature, our review included observational studies only to summarize the evidence of prone and supine position on oxygenation parameters in COVID-19 patients. In this meta-analysis, a set of strict criteria were applied to assess the included observational studies, which utilized complete full prone position as an intervention group with a control group of supine ventilation. Studies with prone position sessions that were not conducted in full prone position, namely lateral position were excluded [60,61]. There are currently two randomized controlled trials (NCT04350723–350 patients; NCT04395144–346 patients) assessing the effect of awake prone position in COVID-19 patients. The safety on prone position remains uncertain, especially in the hospital setting where back-up for invasive ventilation is not readily available. Most of our included studies did not report adverse events of both prone and supine position. In a recently published article evaluating the safety of prolonged prone position in mechanically ventilated COVID-19 patients, there were nearly 72% (38/61) developed ventral pressure wounds and 95% (58/61) had limb weakness with 8% (5/61) suffered from brachial plexus injury [47]. In another case-control study by Ibarra and team, patient's nutritional status and duration of more than 24 h in prone position were found to be the risk factors for the development of pressure sores in mechanically ventilated COVID-19 patients [62]. It is believed that awake prone position may be associated with lesser adverse events as the duration of prone position would be determined by patients as tolerated. Hyman et al. showed that COVID-19 patients who were intubated and mechanically ventilated earlier in the course of hospital admission were associated with an improved survival rate [63]. Hence, one should consider early invasive ventilation in a select group of awake prone position patients, especially when there is an excessive respiratory drive which may lead to further lung damage through patient self-inflicted lung injury [64].

The recommendations on prone position in mechanically ventilated ARDS patients are clear, but it remains uncertain for awake prone position in COVID-19 patients. The updated 'Surviving Sepsis Campaign Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU' stated that there is insufficient evidence to issue a recommendation on the use of awake prone position in non-intubated adults with severe COVID-19 [65]. There were several confounding factors, namely indication, timing, duration, frequency of prone position and type of oxygen supplementation techniques were not standardized across all the included studies. However, the World Health Organisation COVID-19 Clinical Management Living Guidance (25 Jan 2021) suggested a conditional recommendation for awake prone position of severely ill Covid-19 patients requiring supplemental oxygen (including high-flow nasal oxygen) [66]. The recently updated "British Thoracic Society/ Intensive Care Society Guidance: Respiratory care in patients with Acute Hypoxaemic Respiratory Failure associated with COVID-19" also suggested prone position or side repositioning for COVID-19 patients in the respiratory support pathway [67]. A recent expert consensus for the management of COVID-19 related acute respiratory failure (16 Mar 2021) concluded that awake self-prone position may be considered to improve oxygenation and it should be used when supplemental oxygenation is required to maintain $SpO_2 > 90\%$ [68]. At present, awake prone position may be used to delay the respiratory deterioration in selected patients who require oxygen supplementation. This will decrease the demand for invasive mechanical ventilation and further offload the pressure placed on intensive care services worldwide, especially in the resource-limited countries. In the meantime, we await the findings of ongoing high-quality clinical trials to address the uncertainties surrounding this intervention.

Our review had several limitations, which included observational studies in nature, high degree of heterogeneity, high risk of publication bias, low level of evidence, non-standardized regime of prone position and different mode of ventilation across all the included studies. Previous studies have shown that awake prone position may be most effective when started early during the exudative phase, as opposed to the intermediate phase of ARDS [49,69]. An optimum duration of prone ventilation needs to be studied further to ensure no delay in intubation if hypoxemia condition deteriorates. The clinical criteria for endotracheal intubation should be defined to minimize heterogeneity of our measured outcomes. Different adjuvant of respiratory assist devices, namely high flow nasal cannula, continuous positive airway pressure or bi-level positive airway pressure were used across included studies, which may introduce variances to our findings.

5. Conclusion

In this meta-analysis, prone position improved PaO_2/FiO_2 ratio with better SpO_2 than supine position in COVID-19 patients. Given the limited number of studies with small sample size and substantial heterogeneity of measured outcomes, further studies are warranted to standardize the regime of prone position to improve the certainty of evidence.

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Contributions

EC: Data curation; Methodology; Project administration; Writing - original draft; Writing - review & editing. SMI: Data curation; Methodology; Project administration; Writing - original draft. KN: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. WT: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. MS: Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. SR: Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. MA: Validation; Visualization; Writing - original draft; Writing - review & editing.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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