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Closed-loop oxygen control for hypoxemic patients during hospitalization: a living systematic review and meta-analysis protocol

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Abstract

Introduction: The oxygen is the most common drug used in critical care patients to correct episodes of hypoxemia. The adoption of new technologies in clinical practice, as closed-loop systems for an automatic oxygen titration, may improve outcomes and reduce the healthcare professionals' workload at the bedside, however, certainty of the evidence about the safety and benefits are still low. We aim to evaluate the effectiveness, efficacy and safety of the closed-loop oxygen control for hypoxemic patients during the hospitalization period by conducting a systematic review and meta-analysis. **Methods and analysis:** MEDLINE, CENTRAL, EMBASE, LILACS, CINAHL and LOVE evidence databases will be searched. Randomized controlled trials and crossover studies investigating the PICO will be included. The primary outcomes will be the time in the SpO_2 target. Secondary outcomes will include time for oxygen weaning; length of stay; costs; adverse events; mortality; and healthcare professionals workload. Two reviewers will independently screen and extract data and perform quality assessment of included studies. The Cochrane risk of bias tool will be used to assess risk of bias. The RevMan V5.4 software will be used for statistical analysis. Heterogeneity will be analyzed using I^2 statistics. Mean difference or standardized mean difference with 95% CI and *p* value will be used to calculate treatment effect for outcome variables. **Ethics and dissemination:** Ethical approval is not required because this systematic review and meta-analysis is based on previously published data. Final results will be published in peer-reviewed journals and presented at relevant conferences and events. **PROSPERO registration number:** [CRD 42022306033]

Keywords: Oxygen; oxygen inhalation therapy; hypoxia; hyperoxia; artificial intelligence; machine learning.

Introduction

The oxygen is vital for cellular metabolism and it is considered the most common drug used in critical care patients to correct episodes of hypoxemia [1,2]. Low levels of oxygen in the arterial blood is frequently associated with impairment of adequate gas exchange [1,2], and prolonged cellular hypoxia promotes rapid and severe organ injuries triggered by natural adaptive mechanisms [2,3]. Thus, the supplemental oxygen administration can be considered a lifesaving treatment, and may reduce the morbidity and mortality associated with hypoxemia [1,4].

Despite the benefits of oxygen therapy indication, either hypoxemia or hyperoxia, have potential harmful side effects and complications [5–8]. The literature suggests safe and acceptable targets of peripheral oxygen saturation (SpO_2) are between 92-98% for patients without lung diseases, and 88-92% for patients with previous lung diseases [9,10]. However, the patients' need for oxygen varies during hospital stay, and the manual adjustment to promote adequate oxygen delivery titration has been shown to be ineffective [9]. A precise delivery oxygen method for maintaining the SpO_2 inside the target is challenging [10–12]. It is even more challenging when we look at patients requiring invasive mechanical ventilation (IMV) support admitted to the intensive care unit (ICU), who commonly need supplemental oxygen administration during ICU and hospital stay [1,2,4].

The use of artificial intelligence (AI) and machine learning (ML) is increasing in health science to make predictions, improve the interpretation of monitored data and support decision-making [10]. Closed-loop systems are part of these advances, using a feedback principle to maintain a given variable around a desired set point [10–12]. Delivery oxygen devices based on closed-loop

technology have been developed and utilized in patient care in order to provide a real-time adjustment of oxygen titration, based on patients' SpO_2 avoiding episodes of hypoxemia or hyperoxia [11,12]. The adoption of new technologies of AI and ML in clinical practice, may reduce the healthcare professionals' workload at the bedside, however, certainty of the evidence about the safety and benefits are still low [11,12]. It is still unclear whether closed-loop oxygen control devices could improve clinical outcomes, and with the technological advances, new randomized clinical trials (RCTs) have been published since the last two systematics reviews were conducted [11,12]. Thus, the aim of this systematic review is to investigate the effectiveness, efficacy and safety of the closed-loop oxygen control for hypoxemic patients during the hospitalization.

Methods and analysis

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [13] and followed the recommendations of the Cochrane Collaboration Handbook. The protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO) [14], under registration number CRD42022306033.

Search strategy

A search strategy was initially designed for the Medical Literature Analysis and the Retrieval System Online – MEDLINE, via PubMed by an information specialist, responsible for assist the authors, searching potential studies for inclusion in their reviews, and for keeping up to date with Cochrane methodological developments in information retrieval. The search strategy was independently peer-reviewed by the information specialist, and afterwards will be adapted for use into five databases, as follows: 1) Cochrane Central Register of

Controlled Trials (CENTRAL) – via Wiley; 2) EMBASE – via Elsevier; 3) the Latin American the Caribbean Literature in Health Sciences (LILACS) – via Virtual Health Library; 4) CINALH – via EBSCO; and 5) LOVE evidence databases. A handsearching will be performed to check preprints, editorials about the included studies, errata of published articles, and references lists from the included studies and any relevant systematic review identified. We will track the randomized controlled trials in progress on a specific website (https://ClinicalTrials.gov) and on the World Health Organization (WHO) website. There will not be restrictions to any specific language, date or type of publication. The detailed search strategy for MEDLINE – via PubMed is shown in **Table 1**. The study selection process will be conducted by two reviewers independently, and any disagreement between the reviewers will be resolved by consensus or by consulting a third reviewer.

Inclusion criteria

The eligibility criteria were determined using the Population, Intervention, Comparator, and Outcome (PICO) acronym [15]. The studies will be considered eligible based on the following inclusion criteria, as follows: 1) population: hospitalized adult patients requiring supplemental oxygen – either for hypoxemic patients (SpO_2 < 92%) or with acute chronic hypoxemia (SpO_2 < 88%); 2) type of interventions: any devices that allow an automatic oxygen delivery; 3) type of comparison: manual adjustments of oxygen; 4) type of outcome: time in the SpO_2 target, time for oxygen weaning, length of stay, costs, adverse events, mortality, and healthcare professionals workload – process optimization. Two reviewers will independently assess the titles, abstracts, and full-text published RCTs without language restriction.

Study selection

The reviewers will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. For the selection process we will use Rayyan – a web and mobile app for systematic reviews software [16]. The selection process will be recorded in sufficient detail to complete the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (**Figure 1**). Two review authors will independently screen the titles and abstracts of all the potential studies we identify as a result of the search. All the potential full-texts of the articles that fulfilled eligibility criteria will be included. If a consensus will not be reached, a third reviewer will be consulted to solve potential disagreements regarding the included articles.

Outcome measures

The primary outcome of interest will be the time in the peripheral arterial oxygen saturation target. Secondary outcomes of interest will be the time for oxygen weaning, length of stay, costs, adverse events, mortality, and healthcare professional's workload.

Data extraction

Two reviewers will independently extract the data on a standard worksheet. The data will be extracted from each included study utilizing a standardized spreadsheet developed at Microsoft Excel, as follows: authors, year, protocol number, DOI, study type, country of publication; the participants demographics (i.e.: age, gender, inclusion and exclusion criteria, number of participants, diseases, severity scores, severity of condition, comorbidity, phase of hypoxemia), Interventions – type of device and form of delivery (i.e.: mechanical ventilation or conventional oxygen therapy), duration of intervention, follow-up,

Comparators and Outcomes – defined in this review. We will also extract variables, as follows: the time in the target SpO_2 and other relevant variables to answer the review question (i.e.: time for oxygen weaning, length of stay, costs, adverse events, mortality, health professional's workload – process optimization). Additionally, we will extract data from the funding, sponsorship of the included studies and notable conflicts of interest of trial authors. For missing data, we will contact the corresponding authors of the studies through the email provided. In case of crossover studies inclusions, we will consider a paired analysis or if carry-over is thought to be a problem, the first period will be used to perform the analysis. If the data are homogeneous for conducting meta-analyses, one review author will transfer data into the Review Manager (RevMan) version 5.4 software. We will double-check if the data are correctly entered by comparing the data presented in the systematic review with those in the study report.

Methodological quality assessment

The risk of bias of the included trials will be assessed using the Cochrane Risk of Bias 2 (RoB2) tool for randomized trials.

Risk of bias

The assessment of the risk of bias of individual studies was performed as recommended by the Cochrane Collaboration Handbook [17]. The Risk of Bias tool 2 [18] will be used to evaluate the risk of bias according to five domains: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result. Each domain will be considered within one of the three levels, as follows: low risk of bias, some concerns, or high risk of bias [18]. We involved a third reviewer if a

consensus could not be reached. The reviewers will reach concurrence on the final judgment of all the included trials and the result will be displayed in a table or graph.

Assessment of bias in conducting the systematic review

The review will be conducted according to this published protocol and any deviation will be reported in the "differences between protocol and review" section of the systematic review.

Assessment of certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to measure and summarize the overall of the current evidence of each outcome [19]. The GRADE system consists of five items: 1) study limitations – risk of bias; 2) inconsistency of results (heterogeneity); 3) indirectness of evidence; 4) imprecision of the effect estimates, and 5) reporting bias. The quality of the evidence was classified into four categories, as follows: high, moderate, low, and very low; and it was related to the studies that contributed data for the main prespecified outcomes. All analyses were performed using GRADEpro Guideline Development Tool (GRADEpro GDT) software [20]. Two authors will rate independently and a third author will address any discrepancy.

Data synthesis

Review Manager V.5.4 (Cochrane Collaboration) software will be used to conduct the meta-analysis if appropriate – that is: statistically and clinically homogenous. A random-effects model will be used. The mean difference or standardized mean difference will be used to analyze continuous variables with 95% CI. Dichotomous

outcomes will be presented as risk ratios (RR) with 95% CI. Heterogeneity among included trials will be measure using the I^2 statistic. If it's identified as substantial heterogeneity, we will report and explore through a pre-specified subgroup analysis. In addition, sensitivity analysis will be performed through separate analyzes of studies judged to have a high risk of bias or methodological weakness judged to be important. In cases where the combination of data is not possible to allow the meta-analysis, we will carry out only a qualitative synthesis of each included study, of the ongoing studies identified in our search and of the publication bias analysis.

Subgroup analysis

We plan to perform analysis of subgroups, as follows: underlying disease; hypoxemia stage (acute versus chronic); and SpO_2 target (threshold < 92% versus > 92%).

Ethics and dissemination

The ethical approval and additional informed consent application are not required because this systematic review is based on previously published data. The final results will be published in a peer-reviewed journal.

Patient and public involvement

No patient or public involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

Author Contributions

All authors have made significant contributions to this study protocol. The protocol was substantially designed by CGM, AGV, RKN and refined by ACP.

CGM and RKN drafted the manuscript. All authors edited the manuscript, read, and approved the final version.

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Competing of interests

None declared.

Data statement

Not applicable.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Article Summary

Strengths and Limitations

- This study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines.
- The steps of data screening, extraction and methodological quality assessment will be performed by two reviewers independently.
- Standardized methodological evaluation tools will be used to assess the risk of bias of included studies in the review.

- The absence of sufficient high-quality studies, heterogeneity in the interventions, high missing or dropout and small sample size might be the limitations for this systematic review.

Figure legends

Figure 1 – Preferred reporting items for systematic reviews and meta-analyses – PRISMA flow diagram describing the search strategy.

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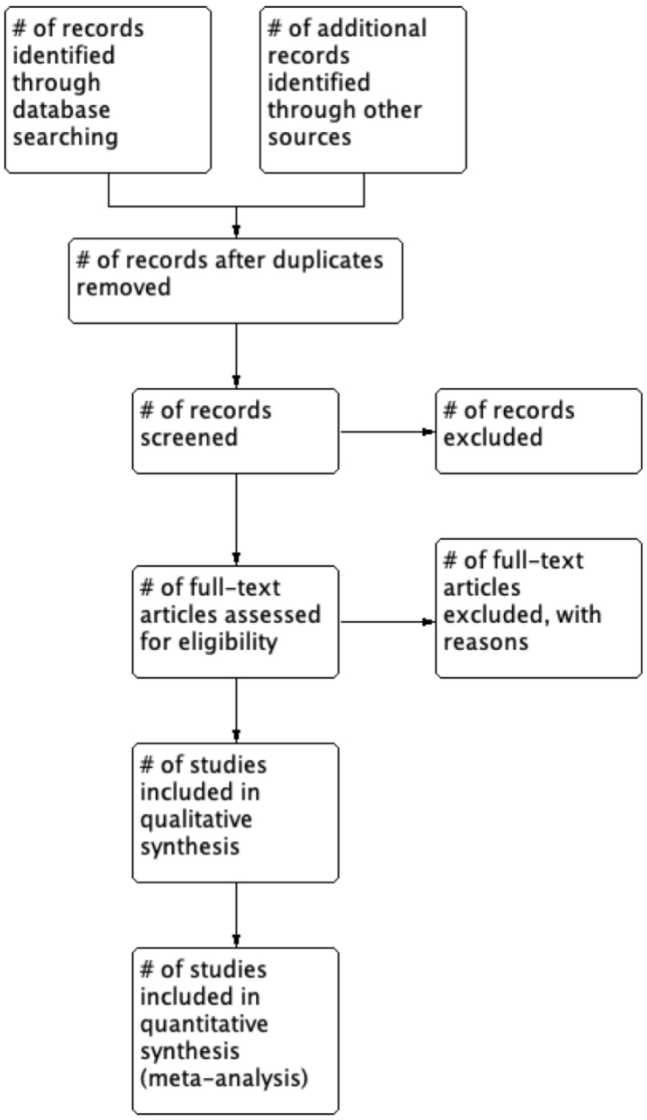
Table 1 – Search strategy for MEDLINE via PubMed.

	Search strategy for PubMed
Number	**Search terms**
#1	"Oxygen Inhalation Therapy"[Mesh] OR "Oxygen"[Mesh] OR oxygen*[tiab] OR Dioxygen[tiab] OR O2[tiab] OR FiO2[tiab]
#2	concentrat*[tiab] OR inspir*[tiab] OR inhal*[tiab] OR level*[tiab] OR tension*[tiab] OR fraction*[tiab] OR arterial*[tiab] OR saturation supply*[tiab] OR supplement*[tiab] OR supplie*[tiab] OR therap*[tiab] OR administr*[tiab] OR dosag*[tiab] OR dose*[tiab] OR dosing*[tiab] OR titrat*[tiab] OR deliver*[tiab]
#3	automat*[tiab] OR algorithms[tiab] OR system*[tiab] OR closed-loop[tiab] OR closed loop[tiab] OR intelligen*[tiab] OR targeted[tiab] OR machine learning[tiab]
#4	adul*[All Fields] OR middle aged[sb] OR age[tw] OR aged[tiab] OR aged[MESH] OR geriatric*[tiab] OR geriatrics[MESH] OR elder*[tiab] OR olding[tiab] OR ageing[tiab] OR aging[tiab] OR aging[MESH] OR "frail elderly"[MESH])
#5	SpO2[tw] OR oxygen saturation[tw] OR Blood Oxygen Level*[tw] OR Saturation of Peripheral Oxygen[tw] OR oxygen weaning[tw] OR FiO2 weaning[tw] OR Length of stay*[tw] OR Cost*[tw] OR Adverse event*[tw] OR adverse effect*[tw] OR Near Misse*[tw] OR Side Effect*[tw] OR Adverse Reaction*[tw] OR Toxicity[tw] OR Mortalit*[tw] OR Fatality Rate*[tw] OR Death[tw] OR Workload*[tw] OR Work Load*[tw] OR process optimization[tw] OR Quality Improvement*[tw]
#6	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6
#8	(animals [mh] NOT humans [mh])
#9	#7 NOT #8

This search strategy was modified as required for other electronic databases.



Preferred reporting items for systematic reviews and meta-analyses – PRISMA flow diagram describing the search strategy.

190x275mm (166 x 166 DPI)

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.

Section and topic	Item No	Checklist item	Page No
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	01
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	04
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	02, 04
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	01
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	09
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	08
Support:			
Sources	5a	Indicate sources of financial or other support for the review	09
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	03, 04
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	04
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	05
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	04,05

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	06, 07
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	06
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	06, 07
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	06, 07
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	06, 07
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	07, 08
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	08, 09
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	08, 09
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	08, 09
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	09
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	08

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Secondary Subject Heading:	Respiratory medicine
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Abstract

Introduction: Oxygen is the most common drug used in critical care patients to correct episodes of hypoxemia. The adoption of new technologies in clinical practice, such as closed-loop systems for an automatic oxygen titration, may improve outcomes and reduce the healthcare professionals' workload at the bedside; however, certainty of the evidence regarding the safety and benefits are still low. We aim to evaluate the effectiveness, efficacy and safety of the closed-loop oxygen control for hypoxemic patients during the hospitalization period by conducting a systematic review and meta-analysis. **Methods and analysis:** MEDLINE, CENTRAL, EMBASE, LILACS, CINAHL and LOVE evidence databases will be searched. Randomized controlled trials and crossover studies investigating the PICO will be included. The primary outcomes will be the time in the SpO_2 target. Secondary outcomes will include time for oxygen weaning time; length of stay; costs; adverse events; mortality; and healthcare professionals workload. Two reviewers will independently screen and extract data and perform quality assessment of included studies. The Cochrane risk of bias tool will be used to assess risk of bias. The RevMan V5.4 software will be used for statistical analysis. Heterogeneity will be analyzed using I^2 statistics. Mean difference or standardized mean difference with 95% CI and *p* value will be used to calculate treatment effect for outcome variables. **Ethics and dissemination:** Ethical approval is not required because this systematic review and meta-analysis is based on previously published data. Final results will be published in peer-reviewed journals and presented at relevant conferences and events. **PROSPERO registration number:** [CRD 42022306033]

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Strengths and Limitations

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- The absence of sufficient high-quality studies, heterogeneity in the interventions, high missing or dropout, and small sample size might be the limitations for this systematic review.

Introduction

Oxygen is vital for cellular metabolism and it is considered the most common drug used in critical care patients to correct episodes of hypoxemia [1,2]. Low levels of oxygen in the arterial blood are frequently associated with impairment of adequate gas exchange [1,2], and prolonged cellular hypoxia promotes rapid and severe organ injuries triggered by natural adaptive mechanisms [2,3]. Thus, supplemental oxygen administration can be considered a lifesaving treatment, and may reduce the morbidity and mortality associated with hypoxemia [1,4].

Despite the benefits of oxygen therapy indication, both hypoxemia and hyperoxia, have potential harmful side effects and complications [5–8]. The literature suggests that safe and acceptable targets of peripheral oxygen saturation (SpO_2) are between 92-98% for patients without lung diseases, and 88-92% for patients with previous lung diseases [9,10]. However, patients' need for oxygen varies during hospital stay, and the manual adjustment to promote adequate oxygen delivery titration has been shown to be ineffective [9]. A precise delivery oxygen method for maintaining the SpO_2 within the target is challenging [10–12]. It is even more challenging when we look at patients requiring invasive mechanical ventilation (IMV) support admitted to the intensive care unit (ICU) who commonly need supplemental oxygen administration during ICU and hospital stay [1,2,4].

The use of artificial intelligence (AI) and machine learning (ML) is increasing in health science to make predictions, improve the interpretation of monitored data, and support decision-making [10]. Closed-loop systems are part of these advances, using a feedback principle to maintain a given variable around a desired set point [10–12]. Delivery oxygen devices based on closed-loop

technology have been developed and utilized in patient care in order to provide a real-time adjustment of oxygen titration, based on patients' SpO_2 preventing episodes of hypoxemia or hyperoxia [11,12]. The adoption of new technologies of AI and ML in clinical practice, may reduce the healthcare professionals' workload at the bedside; however, there is low certainty evidence for their safety and benefits [11,12]. It is still unclear whether closed-loop oxygen control devices could improve clinical outcomes, and with the technological advances, new randomized clinical trials (RCTs) [13–21] have been published since the last two systematics reviews were conducted [11,12]. Thus, the aim of this systematic review is to investigate the effectiveness, efficacy, and safety of the closed-loop oxygen control for hypoxemic patients during hospitalization.

Methods and analysis

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement [22] and followed the recommendations of the Cochrane Collaboration Handbook. The protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO) [23], under registration number CRD42022306033.

Patient and public involvement

No patient or public involved. Only data already existent in the literature and the aforementioned sources will be used in this study. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Search strategy

A search strategy was initially designed for the Medical Literature Analysis and the Retrieval System Online – MEDLINE, via PubMed by an information

specialist, responsible for assisting the authors, searching potential studies for inclusion in their reviews, and for keeping up to date with Cochrane methodological developments in information retrieval. The search strategy was independently peer-reviewed by the information specialist, and afterwards will be adapted for use into five databases, as follows: 1) Cochrane Central Register of Controlled Trials (CENTRAL) – via Wiley; 2) Excerpta Medica dataBASE (EMBASE) – via Elsevier; 3) the Latin American the Caribbean Literature in Health Sciences (LILACS) – via Virtual Health Library; 4) Cumulative Index to Nursing and Allied Health Literature (CINALH) – via Elton Bryson Stephens Company (EBSCO); and 5) LOVE evidence databases. A handsearching will be performed to check preprints, editorials about the included studies, errata of published articles, and references lists from the included studies and any relevant systematic review identified. We will track the randomized controlled trials in progress on a specific website (https://ClinicalTrials.gov) and on the World Health Organization (WHO) website. There will not be restrictions to any specific language, date or type of publication. The detailed search strategy for MEDLINE – via PubMed is shown in **Table 1**. The study selection process will be conducted by two reviewers independently, and any disagreement between the reviewers will be resolved by consensus or by consulting a third reviewer.

Table 1 – Search strategy for MEDLINE via PubMed

Search number	Search terms
#1	"Oxygen Inhalation Therapy"[Mesh] OR "Oxygen"[Mesh] OR oxygen*[tiab] OR Dioxygen[tiab] OR O2[tiab] OR FiO2[tiab]
#2	concentrat*[tiab] OR inspir*[tiab] OR inhal*[tiab] OR level*[tiab] OR tension*[tiab] OR fraction*[tiab] OR arterial*[tiab] OR saturation supply*[tiab] OR supplement*[tiab] OR supplie*[tiab] OR therap*[tiab] OR administr*[tiab] OR dosag*[tiab] OR dose*[tiab] OR dosing*[tiab] OR titrat*[tiab] OR deliver*[tiab]

#3	automat*[tiab] OR algorithms[tiab] OR system*[tiab] OR closed-loop[tiab] OR closed loop[tiab] OR intelligen*[tiab] OR targeted[tiab] OR machine learning[tiab]
#4	adult[All Fields] OR middle aged[sb] OR age[tw] OR (aged[tiab] OR aged[MESH] OR geriatric*[tiab] geriatrics[MESH] OR elder*[tiab] OR olding[tiab] OR ageing[tiab] OR aging[tiab] OR aging[MESH] OR "frail elderly"[MESH])
#5	SpO2[tw] OR oxygen saturation[tw] OR Blood Oxygen Level*[tw] OR Saturation of Peripheral Oxygen[tw] OR oxygen weaning[tw] OR FiO2 weaning[tw] OR Length of stay*[tw] OR Cost*[tw] OR Adverse event*[tw] OR adverse effect*[tw] OR Near Misse*[tw] OR Side Effect*[tw] OR Adverse Reaction*[tw] OR Toxicity[tw] OR Mortalit*[tw] OR Fatality Rate*[tw] OR Death[tw] OR Workload*[tw] OR Work Load*[tw] OR process optimization[tw] OR Quality Improvement*[tw]
#6	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6
#8	(animals [mh] NOT humans [mh])
#9	#7 NOT #8

This search strategy will be modified as required for other electronic databases.

Inclusion criteria

The eligibility criteria were determined using the Population, Intervention, Comparator, and Outcome (PICO) acronym [24]. The studies will be considered eligible based on the following inclusion criteria, as follows: 1) population: hospitalized adult patients requiring supplemental oxygen – either for hypoxemic patients (SpO_2 < 92%) or with acute chronic hypoxemia (SpO_2 < 88%); 2) type of interventions: any devices that allow an automatic oxygen delivery, including invasive and non-invasive devices; low and high flow oxygen devices; 3) type of comparison: manual adjustments of oxygen; 4) type of outcome: time within the SpO_2 target, oxygen weaning time, length of stay, costs, adverse events, mortality, and healthcare professionals workload – process optimization. Two

reviewers (CGM and AGV) will independently assess the titles, abstracts, and full-text published RCTs without language restriction.

Study selection

The reviewers will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. For the selection process we will use Rayyan – a web and mobile app for systematic reviews software [25]. The selection process will be recorded in sufficient detail to complete the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (**Figure 1**). Two review authors (CGM and AGV) will independently screen the titles and abstracts of all the potential studies we identify as a result of the search. All the potential full-texts of the articles that fulfilled eligibility criteria will be included. If a consensus is not reached, a third reviewer (ACP) will be consulted to solve potential disagreements regarding the included articles.

Outcome measures

The primary outcome of interest will be the time spent within the peripheral arterial oxygen saturation target range. Secondary outcomes of interest will be the time for oxygen weaning time, length of stay, costs, adverse events, mortality, and healthcare professional's workload.

Data extraction

Two reviewers (CGM and AGV) will independently extract the data on a standard worksheet. Data will be extracted from each included study utilizing a standardized spreadsheet developed at Microsoft Excel, as follows: authors, year, protocol number, DOI, study type, country of publication; the participants demographics (i.e.: age, gender, inclusion and exclusion criteria, number of

participants, diseases, severity scores, severity of condition, comorbidity, phase of hypoxemia), Interventions – type of device and form of delivery (i.e.: mechanical ventilation or conventional oxygen therapy), duration of intervention, follow-up, Comparators and Outcomes – defined in this review. We will also extract variables, as follows: time spent within the target SpO_2 and other relevant variables to answer the review question (i.e.: oxygen weaning time, length of stay, costs, adverse events, mortality, health professional's workload – process optimization). Additionally, we will extract data from the funding, sponsorship of the included studies and notable conflicts of interest of trial authors. For missing data, we will contact the corresponding authors of the studies through the email provided. In case of crossover studies inclusions, we will consider a paired analysis or if carry-over is thought to be a problem, the first period will be used to perform the analysis. If the data are homogeneous for conducting meta-analyses, one review author will transfer data into the Review Manager (RevMan) version 5.4 software. We will double-check if the data are correctly entered by comparing the data presented in the systematic review with those in the study report.

Methodological quality assessment

The risk of bias of the included trials will be assessed using the Cochrane Risk of Bias 2 (RoB2) tool for randomized trials.

Risk of bias

Assessment of the risk of bias of individual studies was performed as recommended by the Cochrane Collaboration Handbook [26]. The RoB2 [27] will be used to evaluate the risk of bias according to five domains: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome;

and 5) bias in selection of the reported result. Each domain will be considered within one of the three levels, as follows: low risk of bias, some concerns, or high risk of bias [27]. We will involve a third reviewer (ACP) if a consensus cannot be reached. With the concurrence of the reviewers on the final judgment of all the included trials, the result will be displayed in a table or graph.

Assessment of bias in conducting the systematic review

The review will be conducted according to this published protocol and any deviation will be reported in the "differences between protocol and review" section of the systematic review.

Assessment of certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system will be used to measure and summarize the overall current evidence of each outcome [28]. The GRADE system consists of five items: 1) study limitations – risk of bias; 2) inconsistency of results (heterogeneity); 3) indirectness of evidence; 4) imprecision in effect estimates, and 5) reporting bias. The quality of evidence was classified into four categories, as follows: high, moderate, low, and very low; and it was related to the studies that contributed data to the main prespecified outcomes. All analyses were performed using GRADEpro Guideline Development Tool (GRADEpro GDT) software [29]. Two authors will rate it independently and a third author will address any discrepancy found in the study.

Data synthesis

Review Manager V.5.4 (Cochrane Collaboration) software will be used to conduct the meta-analysis if appropriate – that is: statistically and clinically homogeneous. A random-effects model will be used. The mean difference or standardized mean

difference will be used to analyze continuous variables with 95% confidence interval (CI). Dichotomous outcomes will be presented as risk ratios (RR) with 95% CI. Heterogeneity among included trials will be measured using the I^2 statistic. If it is identified as substantial heterogeneity, we will report and explore it through a pre-specified subgroup analysis. In addition, sensitivity analysis will be performed through separate analyses of studies judged to have a high risk of bias or a methodological weakness considered important. In cases where the combination of data does not make it possible to do the meta-analysis, we will carry out only a qualitative synthesis of each included study, of the ongoing studies identified in our search, and of the publication bias analysis.

Subgroup analysis

We plan to perform analysis of subgroups, as follows: underlying disease; hypoxemia stage (acute versus chronic); and SpO_2 target (threshold < 92% versus > 92%).

Ethics and dissemination

Ethical approval and additional informed consent application are not required because this systematic review is based on previously published data. The final results will be published in a peer-reviewed journal.

Author Contributions

Conceptualisation – AGSV, CGM, RKN.

Protocol writing – AGSV, CGM, RKN.

Methodology – AGSV, ACPNP, BMSPG, CGM, RKN.

Project administration – AGSV, ACPNP, CGM, RKN.

Supervision – AGSV, CGM, RKN.

Validation – AGSV, ACPNP, CGM, RKN.

Writing – original draft – AGSV, ACPNP, BMSPG, CGM, RKN.

Writing – review & editing – ACPNP, AGSV, BMSPG, CGM, ESP, RACE, and RKN.

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Competing of interests

None declared.

Data statement

Not applicable.

Patient consent for publication

Not applicable.

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Figure legends

Figure 1 – Preferred reporting items for systematic reviews and meta-analyses – PRISMA flow diagram describing the search strategy.

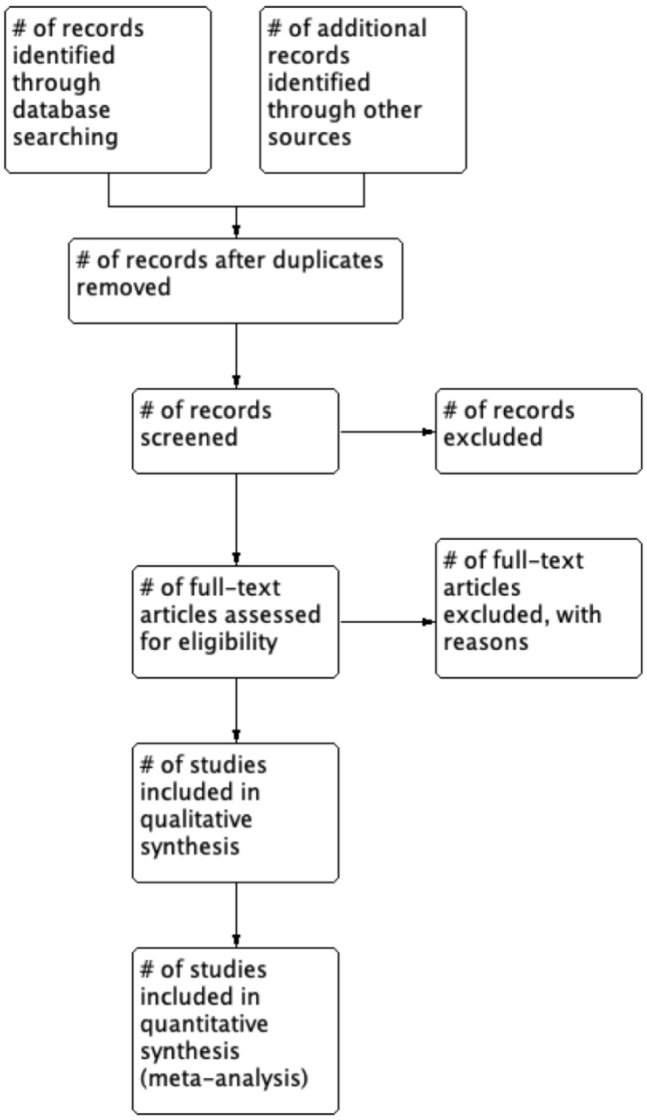

Figure 1 – Preferred reporting items for systematic reviews and meta-analyses – PRISMA flow diagram describing the search strategy.

190x275mm (166 x 166 DPI)

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.

Section and topic	Item No	Checklist item	Page No
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	01
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	04
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	02, 04
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	01
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	09
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	08
Support:			
Sources	5a	Indicate sources of financial or other support for the review	09
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	03, 04
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	04
Methods			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	05
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	04,05

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	13
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	06, 07
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	06
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	06, 07
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	06, 07
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	06, 07
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	07, 08
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	08, 09
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	08, 09
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	08, 09
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	09
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	08