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IMPACTO DA PRESSÃO POSITIVA EXPIRATÓRIA FINAL NA HEMODINÂMICA, HEMATOSE E *DRIVING PRESSURE* EM PARTICIPANTES SEM DOENÇA PULMONAR: UM ESTUDO DE INTERVENÇÃO

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Epígrafe

Scegli um lavoro che ami,
e non dovrai lavorare
neppure um giorno in vita tua.
(Confucio)

RESUMO

A pressão positiva expiratória final (PEEP, do inglês *positive end-expiratory pressure*) é a pressão mantida ao final da expiração e que mantém as unidades alveolares abertas para participarem das trocas gasosas. A PEEP pode reduzir a hipoxemia, porém, a aplicação de níveis elevados pode resultar em riscos hemodinâmicos. Os objetivos foram: realizar (i) uma revisão sistemática da literatura sobre a PEEP e a *driving pressure* (DP); (ii) traçar o perfil epidemiológico dos pacientes da unidade de terapia intensiva (UTI) sob ventilação mecânica invasiva (VMI) (de 2016 a 2019) para os fatores de risco associados ao óbito; (iii) verificar a resposta da hemodinâmica, da hematose e da DP perante a aplicação de três níveis da PEEP em participantes sem doenças pulmonares prévias, submetidos à VMI. Para a revisão sistemática foi realizado uma busca de artigos publicados nos últimos dez anos na plataforma PubMed e publicados até abril de 2021 com os descritores PEEP e DP com o intuito de verificar a influência da PEEP, em seus diferentes níveis, nos desfechos da alta hospitalar, principalmente associados ao DP. O perfil epidemiológico foi analisado nos prontuários eletrônicos dos pacientes internados na UTI sob VMI de 2016 a 2019 de acordo com os dados demográficos, hipótese diagnóstica, tempo de VMI e de hospitalização e PEEP e pressão arterial de oxigênio (PaO_2) de admissão. Por fim, foi realizado um estudo de intervenção, clínico, não randomizado e controlado, com o intuito de verificar o impacto na hemodinâmica, hematose e DP, utilizando diferentes níveis da PEEP no mesmo participante sob VMI. Os resultados foram: (i) um total de 577 artigos foram obtidos como resultado da busca no PubMed, destes, 33 foram analisados. Observou-se importante influência da DP que, quando se apresentou acima de 15 cmH_2O, foi associada a piora do desfecho clínico; já a PEEP mostrou que, valores individualizados, obtidos pela titulação de acordo com a melhor complacência do sistema pulmonar, otimiza a hematose e incrementa o índice de oxigenação. (ii) um total de 1.443 prontuários foram analisados. Foram significativos em relação ao risco para o óbito: a idade, o sexo masculino, o diagnóstico de sepse, a necessidade de cirurgia eletiva, a presença de acidente vascular encefálico, o tempo de internação, a hipoxemia na admissão e a PEEP >8 cmH_2O na admissão. (iii) foram incluídos 150 pacientes e na avaliação dos marcadores associados a hemodinâmica, hematose e DP não foi observada uma resposta estatisticamente significativa perante a modulação da PEEP entre seus diferentes níveis. Podemos concluir que valores ideais de PEEP são controversos na literatura, porém os estudos apontam que valores titulados de acordo com a mecânica ventilatória possuem maior benefício e menor risco de lesão pulmonar. Deve-se evitar a hipoxemia e valores de PEEP >8 cmH_2O na admissão hospitalar, pois esses são fatores de risco para desfecho desfavorável (óbito). Em pacientes sem doença pulmonar, o incremento da PEEP não impactou na hemodinâmica, na hematose e na DP, podendo, valores menores de PEEP serem utilizados com mais segurança na prática clínica.

Palavras-chave: Respiração com Pressão Positiva. Respiração Artificial. Oxigenação. Intubação. Unidade de Terapia Intensiva.

ABSTRACT

The positive end-expiratory pressure (PEEP) is the pressure maintained at the end of expiration, it keeps the alveolar units open to participate in the gas exchanges, thus minimizing hypoxemia, however, the application of high levels of it can increase the hemodynamic risks. The objectives were to perform (i) a search for articles on the PubMed platform, using the descriptors PEEP and driving pressure (DP); (ii) it was performed a retrospective and epidemiologic study, analyzing medical records of inpatients who needed invasive mechanical ventilation (IMV) from 2016 to 2019 to identify the risk factors associated with the risk for death; and (iii) it was evaluated the response of gas exchange, hemodynamics and DP under the application of three levels of PEEP in participants without previous pulmonary diseases, submitted to IMV. A search for articles published in the last ten years until April 2021 was performed on the PubMed platform, using the descriptors PEEP and DP, to verify the influence of PEEP, at its different levels, on the outcomes of hospital discharge, mainly for the DP. To describe the epidemiological profile from our University Hospital it was analyzed the medical records of inpatients who needed IMV from 2016 to 2019. The patients' characteristics considered were demographics data, diagnostic hypothesis, and hospitalization data. It was analyzed the PEEP and partial pressure of oxygen (PaO_2) during the IMV. A controlled, clinical and non-randomized study was carried out in order to verify the impact in gas exchange, hemodynamics and DP using different levels of PEEP in the same participant under IMV. The results were: (i) a total of 577 articles were obtained as a result of the search on PubMed, of these, 33 were analyzed. An important influence of DP was observed, which, when it is above 15 cmH_2O, was associated with worsening of the clinical outcome; on the other hand, PEEP showed that individualized values, obtained by titration according to the best compliance of the respiratory system, optimizes gas exchange and increases the oxygenation index. (ii) a total of 1,443 medical records were analyzed. Among the predictors, the following were significant in relation to the risk for death: age, male sex, diagnosis of sepsis, need for elective surgery, presence of a stroke, length of stay, hypoxemia on admission and PEEP >8 cmH_2O on admission. (iii) data from 150 patients were analyzed. In the evaluation of markers associated with gas exchange, hemodynamics, and DP, a statistically significant response was not observed regarding the modulation of PEEP between its different levels. We could conclude that optimal PEEP values are controversial in the literature, but studies indicate that values titrated according to ventilatory mechanics bring greater benefit and lower risk of lung injury. Hypoxemia and PEEP values above 8 cmH_2O on hospital admission should be avoided, as these are risk factors for an unfavorable outcome. In patients without lung disease, the increase in PEEP did not impact the gas exchange, hemodynamics, and DP. In this context, lower PEEP values may be used more safely in clinical practice.

Keywords: Positive-Pressure Respiration. Artificial Respiration. Oxigenation. Intubation. Intensive Care Units.

Lista de símbolos e abreviações

CO_2 Dióxido de carbono

DP do inglês *Driving pressure*

FiO2 Fração inspirada de oxigênio

O_2 Oxigênio

PaO_2 Pressão arterial de oxigênio

PEEP do inglês *Positive end-expiratory pressure*

SaO_2 Saturação arterial de oxigênio

SpO_2 Saturação periférica de oxigênio

VM Ventilação mecânica

VMI Ventilação mecânica invasiva

SUMÁRIO

1. Introdução

1.1. Ventilação Mecânica

A função essencial da respiração é fornecer oxigênio (O_2) e remover o dióxido de carbono (CO_2) produzido nos tecidos e, desta forma, manter o equilíbrio gasoso do metabolismo humano (1). No entanto, em algumas circunstâncias, o suporte ventilatório é indicado para reduzir a sensação de dispneia, diminuir o trabalho respiratório e melhorar a oxigenação e/ou o *clearance* de CO_2 agindo como efetor para a troca gasosa sendo, desta forma, essencial para a respiração (1,2).

Na prática clínica é um desafio para a equipe que maneja a VM entender a interação entre o que o ventilador mecânico entrega ao parênquima pulmonar e como esse parênquima aceita e recebe tais parâmetros e, essa interação depende, principalmente, de dois fatores: (i) dos valores ofertados pelo operador, tais como volume corrente, pressões (inspiratória e expiratória), fluxo e frequência respiratória; e (ii) das condições do parênquima pulmonar que podem reduzir sua capacidade de troca gasosa, como o aumento de sua heterogeneidade, aumentando as áreas de colapso e de hiperdistensão alveolar (3).

Na insuficiência respiratória aguda, a análise de fatores condicionais da troca gasosa, principalmente, sobre a ventilação mecânica (VM) são cruciais e, possivelmente, poderão contribuir para o melhor desfecho hospitalar, o que inclui o menor tempo de hospitalização e a alta hospitalar, perante a presença da síndrome metabólica e a necessidade de suporte ventilatório.

1.2. Pressão positiva expiratória final

Dentre os parâmetros ventilatórios, a pressão positiva expiratória final (PEEP, do inglês *positive end expiratory pressure*) é a pressão que permanece no alvéolo ao final da expiração e sua aplicação pode incrementar a oxigenação pelo princípio da Lei de Fick; sendo que o aumento da PEEP pode promover o aumento da área de troca gasosa e a redução da espessura da membrana alvéolo capilar, facilitando a difusão dos gases; podendo, dessa forma, aumentar a pressão parcial de oxigênio arterial (PaO_2) e a saturação arterial de oxigênio (SaO_2) (4,5). Na rotina do atendimento, o uso de PEEP viabiliza no melhor recrutamento de alvéolos instáveis e melhora a troca gasosa e a oxigenação tissular e, ao mesmo tempo, a PEEP reduz e redistribui os estresses mecânicos heterogêneos da ventilação corrente (6,7).

Existe uma PEEP fisiológica ocasionada pelo fechamento da epiglote e represamento de ar no sistema respiratório. Essa pressão, de normalmente dois a quatro cmH_2O, impede que ocorram as atelectasias (colapso total ou parcial do pulmão ou do lóbulo pulmonar, decorrente do esvaziamento dos alvéolos) (8).

Pacientes sob VMI apresentam redução da capacidade residual funcional e essa diminuição pode acarretar a atelectasia pulmonar e o *shunt* intrapulmonar (áreas onde a perfusão no pulmão excede a ventilação), o que pode provocar em limitações na difusão do O_2 (9,10).

O uso da PEEP faz sentido por duas razões principais: primeiramente, por recrutar alvéolos instáveis, a PEEP melhora a troca gasosa e a oxigenação tissular; e em segundo lugar, a PEEP reduz e redistribui os estresses mecânicos heterogêneos da ventilação corrente (6,11).

A PEEP era utilizada para amenizar o quadro clínico de hipoxemia em pacientes com síndrome da angústia respiratória aguda logo após a primeira descrição desta síndrome (12). No entanto, posteriormente, níveis elevados da PEEP, juntamente, com a aplicação de manobras de recrutamento foram propostos para melhorar a taxa de sobrevida dos pacientes (13). Entretanto, após estudos translacionais e clínicos terem sido publicados, a efetividade destas manobras continua a ser uma temática ainda controversa quanto sua segurança e sua eficácia (13-16).

1.3. Índice de oxigenação

O índice de oxigenação [razão entre a PaO_2 e a FiO_2 (fração inspirada de oxigênio)] é utilizado em pacientes para avaliar a gravidade do distúrbio ventilatório condicional a uma determinada intervenção terapêutica (17).

Na definição de Berlin para síndrome da angústia respiratória aguda, a estratificação de risco se dá baseada na relação PaO_2/FiO_2 para a avaliação e o diagnóstico inicial da síndrome (18).

A PaO_2 é um dos principais marcadores para avaliar o sucesso do processo de troca gasosa podendo ser um dado obtido na gasometria arterial. O valor de normalidade da PaO_2 para indivíduos saudáveis é de 100 mmHg aos 20 anos e de 80 mmHg aos 70 anos; sendo que é descrita a queda média de quatro mmHg a cada década vivida (2,19). A maior parte do oxigênio sanguíneo é transportado em combinação química com a hemoglobina nos eritrócitos, cada molécula de hemoglobina pode carregar até quatro moléculas de oxigênio, assim sendo, a redução da hemoglobina pode contribuir para a redução da PaO_2 (20) e, neste contexto, ambos marcadores são estritamente associados entre si. Na literatura referida, é descrito que pacientes que respondem com o aumento da PaO_2 com a FiO_2 constante perante o incremento da PEEP tem seu risco de óbito reduzido, sendo o uso da PEEP um indicativo da melhora do desfecho clínico (21,22).

Estudos apontam que a aplicação da PEEP melhora a troca gasosa, no entanto, o incremento efetivo na oxigenação ainda não é bem esclarecido, ou seja, o quanto o nível da PEEP causa de impacto na troca gasosa precisa ainda ser mais bem avaliado com o intuito de se entender o limiar fisiológico associado ao benefício ou malefício do uso da PEEP em numerosas situações clínicas (9,23).

Nesse contexto, na literatura, é claro que valores elevados da PEEP podem acarretar o barotrauma (lesão causada pela variação de pressão no pulmão) ou na instabilidade hemodinâmica, em particular durante a manobra de recrutamento alveolar onde é sabido que ocorre sobrecarga do ventrículo direito. Por outro lado, o reestabelecimento da capacidade residual funcional pelo uso da PEEP resulta na redução dessa sobrecarga e da resistência vascular pulmonar (24-26). Dessa forma, o conhecimento sobre o nível ideal da PEEP e seu desfecho, em cada caso, é crucial. Tal conhecimento é de grande ajuda para manter o nível da PaO_2 dentro do alvo de normalidade estabelecido na literatura como benéfico na manutenção da troca gasosa. Adicionalmente, na atual conjectura para a prática clínica, o aumento no nível da PEEP é realizado visando incrementar a PaO_2, porém isso é feito de forma não padronizada e não se sabe o quanto o aumento de um valor da PEEP incrementa no valor da PaO_2.

1.4. Avaliação da hemodinâmica

Assim como a aplicação da PEEP está associada à melhora na oxigenação (aumento da PaO_2), a aplicação de níveis elevados da mesma pode resultar em riscos hemodinâmicos (12). A presença de elevados valores de pressões intratorácicas implica em menor débito cardíaco e no aumento da resistência vascular pulmonar que podem levar à alteração da função do ventrículo direito (sobrecarga ventricular) (24).

São considerados níveis baixos e/ou fisiológicos da PEEP: de três a sete cmH_2O; níveis moderados: de oito a 12 cmH_2O e, acima de 13 cmH_2O, o nível da PEEP é considerado elevado – fator de risco para a lesão pulmonar (11).

Nesse contexto, na avaliação hemodinâmica, numerosos marcadores podem ser avaliados, dentre eles, destacamos: (i) saturação transcutânea periférica de O_2 da hemoglobina (SpO_2; estimativa da PaO_2 mensurada por um oxímetro); (ii) frequência cardíaca (velocidade do ciclo cardíaco medida pelo número de contrações do coração por minuto); (iii) pressão arterial diastólica ou menor (menor valor verificado durante a aferição de pressão arterial decorrente do repouso do músculo cardíaco para a passagem do sangue); e (iv) pressão arterial sistólica ou máxima (maior valor verificado durante a aferição de pressão arterial decorrente da contração do músculo cardíaco, quando ele bombeia sangue para o corpo).

1.5. *Driving pressure*

Recentemente, a *driving pressure* foi mencionada como um marcador a ser utilizado para otimizar a VM no intuito de melhorar o desfecho de pacientes com síndrome do desconforto respiratório agudo. A *driving pressure* é obtida subtraindo a PEEP da pressão de pausa inspiratória e pode ser determinada pela razão do volume corrente total pela complacência estática do sistema respiratório. Estudos da síndrome do desconforto respiratório agudo concluem que a *driving pressure* é um bom preditor de desfecho clínico do paciente sob intubação (VMI) (27,28).

A associação entre valores de *driving pressure* e o desfecho clínico foi descrito pela primeira vez em 2002. Deste ano em diante, foi denotado que valores acima de 15 cmH_2O de *driving pressure* estão associados a desfechos desfavoráveis, no entanto, que valores abaixo deste *cut-off* podem ser favoráveis a melhor evolução clínica do paciente sob VMI (7).

2. Objetivos

2.1. Objetivos gerais

Descrever a importância da PEEP na prática diária e de sua influência nos marcadores de hemodinâmica e de hematose, bem como na *driving pressure*.

2.2. Objetivos específicos

(i) realizar uma revisão sistemática da literatura (período de 10 anos) considerando a influência dos diferentes níveis da PEEP no uso da VMI. O ponto focal da revisão foi a avaliação do impacto da PEEP na PaO_2 e na *driving pressure*.

(ii) realizar um estudo epidemiológico dos participantes submetidos à VMI na unidade de terapia intensiva do Hospital Universitário São Francisco de Assis (Bragança Paulista) nos últimos cinco anos de seguimento (2016 a 2019) com a descrição de marcadores demográficos, clínicos e laboratoriais, diagnóstico ou hipótese diagnóstica e antecedentes e avaliar a influência da PEEP e da *driving pressure* de admissão no desfecho clínico.

(iii) avaliar os marcadores hemodinâmicos e de hematose, bem como a *driving presure* de acordo com os diferentes níveis da PEEP (seis ou oito ou10 cmH_2O) em participantes submetidos à VMI.

(iv) discutir as práticas de sedação e analgesia - em particular pelo uso dos opioides - utilizadas nos pacientes críticos e as repercussões destas práticas, bem como possíveis dependências que o uso dessas drogas pode causar.

3. Artigos

Capítulo I: Artigo Submetido

Title: Impact of Positive End-Expiratory Pressure (PEEP) and Driving Pressure on the Oxygenation Index and the Outcome of Patients Under Mechanical Ventilation: A Systematic Review

Short title: PEEP and Driving Pressure

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Abstract

Introduction: Mechanical ventilation (MV) is used in severe acute respiratory syndrome to increase the survival rate; however, the inappropriate use of its parameters can lead to lung-induced ventilation injury (LIVI). Thus, it has been studied how to minimize ventilatory injury and how to optimize gas exchange through the use of safe ventilatory parameters. Therefore, this systematic review seeks to elucidate the influence of positive end-expiratory pressure (PEEP) and driving pressure (DP) on the oxygenation index and on the outcome of patients undergoing invasive MV.

Methods: A search for articles was performed on the PubMed platform, using the descriptors PEEP and DP, published until April 31, 2021. The English language and the study in humans were used as filters.

Results: A total of 577 articles were obtained as a result of the search; of these, 544 were excluded and 33 were analyzed, tabulated and included in the review. Most of the studies included in this review (a total of eighteen) analyzed patients diagnosed with adult respiratory distress syndrome and ten studies included patients undergoing abdominal or thoracic surgery and two studies used computational models for intervention and analysis. An important influence of DP was observed, which, when it is above 15 cmH_2O, is associated with a worse clinical outcome; on the other hand, PEEP showed that individualized values obtained by titration according to the best pulmonary compliance (and consequent lower DP) optimize gas exchange and increases the oxygenation index.

Conclusions: Ventilatory mechanics should be considered in the titration of MV parameters. PEEP should be instituted by the best pulmonary compliance, which, in turn, can increase the oxygenation index. Additionally, DP values above 15 cmH_2O were associated with worsening clinical outcome (higher risk of comorbidities and deaths).

Keywords: Driving Pressure; Mechanical Ventilation; Oxygenation Index; Positive End-Expiratory Pressure.

Introduction

Mechanical ventilation (MV) is able to increase the survival rate of patients with acute respiratory failure; however, it can contribute to the emergence of lung lesions caused by alveolar overdistension or by the cyclic opening and closing of small bronchioles or alveoli (1). For this reason, MV and its parameters have been studied with the aim of optimizing gas exchange, with minimal harmful effects (2). In this context, in order to prevent lung-induced ventilation injury (LIVI), the protective strategy has been advocated, using low tidal volumes, high levels of positive end-expiratory pressure (PEEP) and with controlled plateau pressure (or pause pressure inspiratory) (1,3).

PEEP is the pressure that remains in the airways at the end of expiration in patients undergoing MV. It is a parameter used to improve oxygenation, in an attempt to recruit and stabilize the alveolar units (4). Using PEEP for this purpose has been described four decades ago. Since then, studies on its use would allow the health care team to use this therapeutic modality, especially in adult respiratory distress syndrome (ARDS) (5-7). However, an optimal PEEP value in critically ill patients is still controversial, as values above the necessary can lead to hyperdistention and below values, to alveolar collapse (8). In clinical practice, optimal PEEP values, although controversial, depend on individual ventilatory mechanics and its influence on gas exchange, affecting arterial oxygen pressure (PaO_2) value and, consequently, the oxygenation index.

Recently, driving pressure (DP) was mentioned as a potential marker to optimize MV and improve ARDS outcome (9). DP is obtained by subtracting PEEP from the inspiratory pause pressure and can be determined by the ratio of the plateau pressure minus PEEP (DP = Plateau pressure - PEEP) (10). In this context, we can state that, by reducing tidal volume or increasing PEEP, DP is reduced. In the literature, DP in ARDS is considered a sound predictor of clinical outcome and, therefore, it is possible that DP value can improve and optimize ventilatory strategy safety (2,11-13,14).

Considering DP and PEEP as variable tools that are easily accessible at the bedside, clinical practice should benefit from knowledge based on scientific evidence of their influence on clinical outcome, gas exchange and hemodynamic stability for a safe supply of their individualized values, reducing the need to perform tests, especially invasive ones, which can also generate an increase in the cost of hospitalization (15). Additionally, knowledge about safe ventilatory parameter values can provide benefit to patients, since the studied markers, PEEP and DP, are closely related to a higher risk of lung injury when inappropriately offered (16).

In this context, the present literature review on these markers is of significant importance in the routine of patients who need invasive MV (IMV). This fact is more evident at this time of pandemic caused by the new coronavirus (SARS-CoV-2) and which can lead to severe pneumonia followed by respiratory failure, severe hypoxemia and ventilatory changes with the need for IMV (17). Thus, the aim of this systematic review is to verify the relationship between ventilatory parameters PEEP and DP in respiratory mechanics and their impact on mechanically ventilated patients' oxygenation index, hemodynamics, and clinical outcomes.

Methods

In the systematic review, the PubMed-MEDLINE platform was used to search for articles published in the last ten years up to April 31, 2021. In the search for articles, the following descriptors were used:

Search: **(PEEP or positive end-expiratory pressure) and (driving pressure)**.

Filters: **Humans, English**.

Descriptors achieved by PubMed using the search done by the researchers: Most Recent((“positive pressure respiration”[MeSH Terms] OR (“positive pressure”[All Fields] AND “respiration”[All Fields]) OR “positive pressure respiration”[All Fields] OR “peep”[All Fields] OR (“positive pressure respiration”[MeSH Terms] OR (“positive pressure”[All Fields] AND “respiration”[All Fields]) OR “positive pressure respiration”[All Fields] OR (“positive”[All Fields] AND “end”[All Fields] AND “expiratory”[All Fields] AND “pressure”[All Fields]) OR “positive end expiratory pressure”[All Fields])) AND ((“automobile driving”[MeSH Terms] OR (“automobile”[All Fields] AND “driving”[All Fields]) OR “automobile driving”[All Fields] OR “driving”[All Fields] OR “drive”[MeSH Terms] OR “drive”[All Fields] OR “drives”[All Fields] OR “drivings”[All Fields]) AND (“pressure”[MeSH Terms] OR “pressure”[All Fields] OR “pressures”[All Fields] OR “pressure s”[All Fields] OR “pressurisation”[All Fields] OR “pressurised”[All Fields] OR “pressuriser”[All Fields] OR “pressurization”[All Fields] OR “pressurizations”[All Fields] OR “pressurize”[All Fields] OR “pressurized”[All Fields] OR "pressurizer"[All Fields] OR "pressurizes"[All Fields] OR "pressurizing"[All Fields]))) AND ((humans[Filter]) AND (english[Filter]))

In the initial search, 577 articles were obtained, excluding case reports, review articles, meta-analyses, and letters to the editor. After the initial exclusion, 100 articles were included and read in full. The PICO strategy was used using the following markers: (Population) adult patients undergoing IMV or *in silico* models and computer simulators for performing MV; (Intervention) PEEP levels and DP values; (Control) parameters adjusted in relation to the intervention group; (Outcomes) association between PEEP level with oxygenation and DP value with clinical outcome as well as oxygenation description [ratio between PaO_2 and inspiratory oxygen fraction (FiO_2)], LIVI, and/or mortality; (Time) articles published until April 31, 2021.

From the analyzed studies, data on the influence of DP and PEEP were described (i) on the oxygenation index, on PaO_2 and on ventilatory mechanics (pulmonary compliance); (ii) on the incidence of complications related to IMV; and (iii) on the clinical outcome.

Results

A total of 577 articles resulted from the search on the PubMed-MEDLINE platform when DP and PEEP markers were used until April 2021. Of these, 544 were excluded based on the review objectives (143 review articles, 16 case report articles, 73 pediatric and neonatology articles, 67 non-invasive MV articles, 97 obstructive sleep apnea articles, 38 letters to the editor, 13 articles on extracorporeal membrane oxygenation (ECMO), three articles with animals, seven meta-analysis articles, 16 clinical cases, 17 articles on high-frequency MV, 32 articles on ventilatory modalities and 32 articles for other reasons) (**Figure 1**).

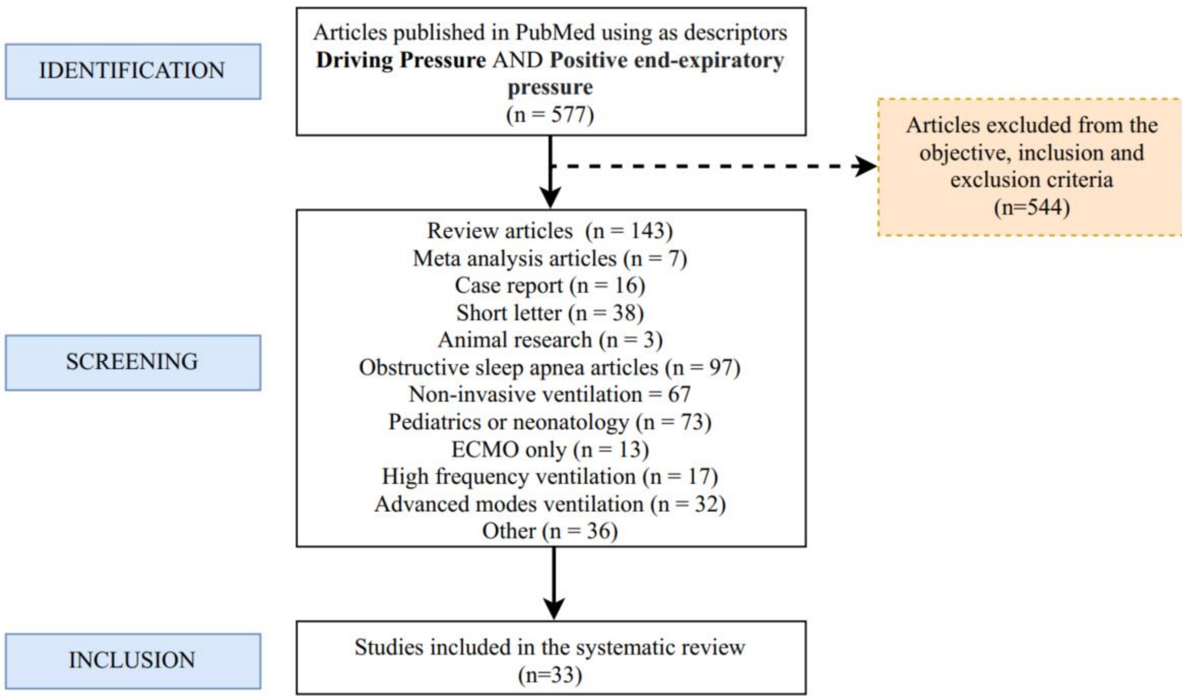

FIGURE 1. Flowchart of study inclusion.

Summing up, **Table 1** describes the name of the main author, year of publication, journal and study design of articles included in this systematic review. **Table 2** shows the description of the objective of the study, methods used, including intervention and inclusion and exclusion criteria of articles included in this systematic review. Finally, **Table 3** shows the summary description of the studies' main findings and their conclusion according to the results.

TABLE 1. Description of the main author, year of publication, journal and study design of articles included in this systematic review

Study	**Year of publication**	**Journal**	**Journal's impact factor**	**Study design**
Das et al. (15)	2019	Respiratory Research	3.890	Clinical and prospective
Grieco et al. (18)	2018	British Journal of Anesthesia	6.880	Clinical and prospective with non-randomized and controlled intervention
Lanspa et al. (11)	2019	Critical Care	7.442	Retrospective cohort
Shono et al. (19)	2019	Anesthesiology	5.060	Randomized and controlled intervention clinic
Sahetya et al. (2)	2019	Critical Care	7.442	Prospective cohort
Richard et al. (20)	2019	Intensive Care Medicine	17.679	Observational multicenter
Bellani et al. (21)	2019	Anesthesiology	5.060	Retrospective cohort
Zampieri et al. (22)	2019	British Journal of Anesthesia	6.880	Post hoc RTC (Randomized Controlled Trial)
Park et al. (23)	2019	Anesthesiology	5.060	Double-blind randomized controlled
Rauseo et al. (24)	2018	Anesthesiology	5.060	Clinical, controlled, randomized
Pereira et al. (25)	2018	Anesthesiology	5.060	Pilot, controlled, randomized
Chalkias et al. (26)	2018	Heart and Lung	1.840	Observational prospective
De Jong et al. (27)	2018	Intensive Care Medicine	17.679	Unicentric retrospective
Gogniat et al. (28)	2018	Journal of Critical Care	2.685	Intervention and experimental
Schmidt et al. (29)	2017	Chest	7.652	Retrospective cohort
D'Antini et al. (30)	2018	*Minerva Anestesiologica*	2.498	Controlled, non-randomized intervention clinic
Ferrando et al. (17)	2017	Plos One	2.766	Pilot, randomized, controlled clinic
Villar et al. (31)	2017	Critical care medicine	7.442	Observational retrospective

Guérin et al. (32)	2016	Critical Care	7.442	Secondary analysis of patient data from two randomized controlled trials
Chiumello et al. (3)	2016	Critical Care	7.442	Prospective with literature data
Rotman et al. (33)	2016	Anesthesiology	5.060	Prospective cohort
Baedorf Kassis et al. (34)	2016	Intensive Care Medicine	17.679	Cohort observational retrospective
Kamarek et al. (35)	2016	Critical care medicine	7.442	Pilot, multicenter, prospective, randomized, controlled
Beitler et al. (36)	2016	Critical care medicine	7.442	Clinical, prospective, randomized, controlled intervention
Cinnella et al. (37)	2015	Anesthesiology	5.060	Clinical, prospective, non-randomized, controlled intervention
Amato et al. (10)	2015	New England Journal of Medicine	16.591	Observational with post hoc analysis
Das et al. (38)	2015	Critical Care	7.442	Experimental using computer simulator
Mauri T et al. (39)	2013	Critical care medicine	7.442	Intervention, prospective, randomized, controlled
Gernoth et al. (40)	2009	Critical Care	7.442	Intervention, prospective, clinical, non-randomized, controlled
Szakmany et al. (41)	2004	Anesthesiology and Intensive Care Journal	1.539	Clinical and prospective
Biker et al. (42)	2010	Critical Care	7.442	Clinical, prospective with intervention
Sahetya et al. (44)	2019	Respiratory Care	2.258	Prospective, physiological, pilot
Fernadez-Bustamante (43)	2020	British Journal of Anesthesiology	9.166	Prospective, multicenter, pilot study

TABLE 2. Description of objectives and methods used (including intervention) the inclusion and exclusion criteria of studies included in this systematic review to identify the impact of positive end-expiratory pressure and driving pressure on the oxygenation index and outcome of patients under mechanical ventilation

Study	Objectives	Methods	Inclusion criteria	Exclusion criteria	Intervention
Das et al. (15)	Review the influence of driving pressure (DP) on LIVI in *in silico* models.	Multi-compartment computational model that simulated the integration of heart and lung disease by analyzing data from 25 adult patients with acute respiratory distress syndrome (ARDS). The model was developed to represent the *in vivo* cardiorespiratory dynamics, comprising the conductive airways and 100 parallel alveolar compartments, which responded according to stiffness, applied pressures, airway and blood vessel resistance. The study allowed the replicability of the ventilation perfusion relationship. The model included physiological reflex mechanisms such as hypoxic pulmonary vasoconstriction. The	Data from 25 patients with ARDS were used in a computer simulator of an *in-silico* model.	Not reported.	Of the 25 patients with ARDS, according to severity, 13 were classified as severe, 7 as moderate and 6 as mild. Patients' body weight was 70 kg and all were considered to be deeply sedated. With a positive end-expiratory pressure (PEEP) of 10 cmH_2O, arterial blood gas data, cardiac index and hemodynamic changes during the alveolar recruitment maneuver were replicated. To assess LIVI, the values of DP, static compliance, dynamic strain and mechanical power during the alveolar recruitment maneuver were calculated. In

		diagnosis of ARDS was performed according to the Berlin criteria.			the simulation process, data was recorded every 10 milliseconds.
Grieco et al. (18)	Verify whether compliance and DP reflect on aerated lung volume and dynamic strain during general anesthesia in non-obese patients.	Twenty non-obese patients underwent open abdominal surgery and received 3 PEEP levels (2, 7 and 12 cmH_2O) with constant tidal volume in a hospital in Italy, between March 2017 and January 2018.	Patients without obesity (body mass index < 30), classified in ASA (American Society of Anesthesiologists) 1 and 2, without cardiac and pulmonary comorbidities and who underwent open abdominal surgery with an estimated time above 150 min.	Pregnancy and liver surgery.	Participants received 100% oxygen via a reservoir mask 3 min before anesthetic induction. Orotracheal intubation was performed after verifying the total paralysis of the respiratory muscles. Ventilatory parameters used were: tidal volume of 7 mL/kg of predicted weight, respiratory rate to maintain capnography between 3 and 4.3 KPa, and initial inspired oxygen fraction (FiO_2) of 40%, which could be increased to maintain peripheral oxygen saturation (SpO_2) above 92%. The three PEEP values during surgery were maintained for 40 min and the first value was applied 40 min after the beginning of the procedure. The following

					measurements were taken for each PEEP value: static compliance, lung volume, arterial blood gas values and alveolar dead space fraction.
Lanspa et al. (11)	Assess the influence of DP and tidal volume in patients with respiratory failure without adult respiratory distress syndrome (ARDS).	Patients under invasive mechanical ventilation (IMV) in medical, surgical, cardiac, and trauma Intensive Care Units (ICUs) of 12 hospitals in Utah and Idaho for two years. Two cohorts: ARDS and non-ARDS patients (according to the Berlin definition).	18 years or older, under IMV for at least 24 hours in controlled volume, controlled pressure and controlled volume with regulated pressure modes.	Pressure controlled modes, spontaneous modes, patients on prolonged IMV and with extreme or underreported tidal volume values.	Retrospective cohort study
Shono et al. (19)	Observe the effect of applying PEEP of 15 cmH_2O on the distribution of ventilation during robotic	49 patients were randomized and divided into two groups: PEEP of 5 cmH_2O (26 patients); PEEP of 15 (23 patients) cmH_2O. Patients received the same anesthesia protocol, were ventilated with pressure mode, reaching a tidal volume of 6-8 mL/kg of predicted	Patients aged 18 years or older, and with ASA classification 1 or 2.	Chronic lung disease and heart disease.	The distribution of pulmonary ventilation was measured by an electrical impedance tomograph at various times: (in the supine position for the first moment) 10 min after anesthetic induction, 10 min after recruitment maneuver - before

	laparoscopic prostatectomy.	weight. FiO_2 was measured to maintain SpO_2 above 94% and the frequency respiratory was titrated to maintain a concentration of CO_2 at the end of expiration ($EtCO_2$) between 35 and 45 cmH_2O. Vasoactive drug was administered in the presence of arterial hypotension. Patients after surgery were referred to the recovery room and received analgesia. Lung function was assessed by a physical therapist and a pain scale (scored from zero to ten) was used.			pneumoperitoneum; (Trendeleburg position at 25^{o} at the second moment) 20, 60 and 120 min, after pneumoperitoneum by an intra-abdominal device with 12 cmH_2O; (supine position at the third moment) 10 min after deflating the pneumoperitoneum pressure device and 10 min after extubation.
Sahetya et al. (2)	Verify whether higher DP and plateau pressure values are associated with a worse outcome in patients without ARDS.	Data from 6,179 critically ill patients from 59 US ICUs were used. DP and plateau pressure variables were assessed in 1,132 mechanically ventilated patients and associated with in-hospital mortality. Analysis was stratified according to ARDS status (classified by the American European Consensus Conference).	Patients admitted to ICUs, under MV, aged 18 years and older.	Patients without MV, without ARDS classification, without plateau pressure and/or DP values, or with non-compatible values for assessed markers.	Biostatistical methods were used to assess the relationship between plateau pressures and DP in hospital mortality of patients undergoing MV with and without ARDS. For analysis, 1,132 patients were included; of these, 822 without ARDS and 310 with ARDS, both groups had pneumonia as

		DP, plateau pressure (by an inspiratory pause of 0.5 sec) and PEEP (set on the mechanical ventilator) were measured.			the cause of mechanical ventilation (MV) and most of the individuals were of clinical and non-surgical origin.
Richard et al. (20)	Assess if the use of a tidal volume below 6 mL/Kg reduces DP.	Data collected: anthropometric and demographic, admission category, immunodeficiency, time since ARDS diagnosis, Simplified Acute Physiology Score II (SAPS-II), Richmond Agitation Sedation Scale (RASS), vasopressors and sedatives, ventilatory parameters, arterial blood gases, Sepsis- related Organ Failure Assessment (SOFA), echocardiographic data. Measurements: Total PEEP, intrinsic PEEP, DP and mechanical power. Follow-up and outcomes: follow-up was carried out until day 90 after inclusion; endpoints: 1. difference in DP between day of inclusion and day 2, 2. ratio of patients reaching tidal volume <4.2 mL/kg in the first two days, 3.	Patients aged 18 years or older, from 11 ICUs, under IMV, diagnosed with ARDS according to the Berlin definition and the relationship between arterial oxygen pressure (PaO_2) and FiO_2 (P/F) <150 mmHg.	ARDS diagnosis for more than 24 hours, IMV for more than 48 hours, intracranial hypertension, chronic obstructive pulmonary disease (CODP), undrained pneumothorax, morbid obesity, chemotherapy-induced neutropenia, recent bone marrow transplant, sickle cell anemia, burn of 30 % or more of body surface, Child C liver cirrhosis, pregnancy, extracorporeal	After inclusion, patients were volume-controlled ventilated and had the volume reduced by 1 in 1 mL until reaching 4 mL/kg of predicted weight with the goal of the following targets: plateau pressure less than 30 cmH_2O, PaO_2 between 55 and 80 mmHg, pH between 7.20 and 7.55, SpO_2 between 88 and 95%. The following adjunct therapies for ARDS were considered: use of neuromuscular blocker (NMB) for 48h, use of the prone position for at least 16h with P/F <150 mmHg, considered successful when supine with PEEP <10 cmH_2O e FiO_2 <60% with P/F >150 mmHg, from the

		change in ventilatory parameters, vasopressors, sedatives in first two days, 4. echocardiographic changes, pneumothorax and adverse events, 5. day 90 outcome.		membrane oxygenation (ECMO) treatment, prior study inclusion.	third day onwards, weaning from PEEP was effective as long as P/F >150 mmHg in the supine position. After completing these steps, ventilatory parameters were adjusted in volume-controlled ventilation or pressure support ventilation to 6-8 mL/kg of predicted weight.
Bellani et al. (21)	Monitor whether DP and respiratory system compliance are associated with increased mortality during spontaneous ventilatory support.	Plateau pressure was measured spontaneously by an inspiratory pause of 2 sec, in the absence of visible chest movement, flow curve at zero line and flat plateau line. Using computed tomography, the total lung volume (aerated area) was calculated.	Patients aged ≥18 years, diagnosed with ARDS according to the Berlin classification, submitted to MV for at least 3 consecutive days in spontaneous mode after at least 1 day in controlled care mode.	Pregnancy, bronchopleural fistula and pneumothorax.	The following were analyzed: (i) association between ventilatory parameters of the first 3 days in spontaneous mode and the mortality rate in ICUs; and (ii) association between compliance and the volume calculated by computed tomography in spontaneous mode.

Zampieri et al. (22)	Verify the heterogeneity of the effect of the alveolar recruitment maneuver (application of high PEEP values) in patients with ARDS.	Data from 1,010 patients included in the ART study were analyzed (this is a secondary post hoc analysis of the ART study).	The same inclusion criteria as the ART study were used (this is a secondary post hoc analysis of this study). Patients diagnosed with ARDS according to the American European Consensus Conference submitted to IMV within 72 hours.	The same exclusion criteria of the ART (post hoc) study were used: age <18 years, use of rising vasopressors with mean blood pressure less than 65 mmHg, pneumothorax, subcutaneous emphysema or pneumomediastinum, patients in palliative care, previously included or contraindicated for hypercapnia.	From the analysis of the ART study participants, 28-day mortality data were obtained according to the treatment group (ART or ARDSNet). Patients were divided into three groups: (Group 1) cause of ARDS was pneumonia and vasopressor use; (Group 2) variable cause of ARDS and no vasopressor use; (Group 3) use of vasopressors and ARDS not caused by pneumonia. Variables analyzed were: SAPS-III, P/F and DP.
Park et al. (23)	Review the influence of DP on pulmonary complications in the postoperative period of	A total of 292 patients who underwent elective thoracic surgery and who were randomized and divided into two groups (protective ventilation group and DP group) were included.	Patients aged ≥19 years who underwent elective thoracic surgery and single lung ventilation.	Patients with ASA index ≥IV, with contraindication to the use of PEEP (bronchopleural fistula, hypovolemic shock, high	Ventilatory strategies: protective ventilation group - 100% FiO_2, tidal volume of 6 mL/kg of predicted weight with inspiratory pause of 30%, PEEP of 5 cmH_2O, ratio between inspiration and expiration (I:E)

	thoracic surgery.			intracranial pressure, right ventricular failure), or patients who refused to participate in the study. As discontinuity criteria: severe intraoperative bleeding (>500 mL), severe hypotension during the procedure and change of surgical plan.	of 1:2, respiratory rate between 10 and 15 (for arterial pressure of carbon dioxide ($PaCO_2$) between 35-40 mmHg). DP Group: 100% FiO_2, tidal volume of 6 mL/kg of predicted weight, respiratory rate of 12 with DP was calculated with PEEP of 2 to 10 cmH_2O after 10 cycles at each level, adopting the lowest DP value.
Rauseo et al. (24)	Verify how the alveolar recruitment strategy followed by decremental PEEP titration can influence pulmonary	The mechanics of the lung and chest wall of 13 patients who underwent left lobectomy were assessed. The considered markers were: transpulmonary pressure, DP, gas exchange and hemodynamic parameters. Two moments were assessed: MV with zero PEEP and MV after open lung ventilation (OLA) strategy – where the alveolar	Patients aged >18 years, undergoing thoracic surgery and selective ventilation with a minimum duration of 60 min.	Pulmonary reduction surgeries, pneumectomy, severe CODP, pneumatocele, decompensated heart disease and acute or chronic pleural diseases.	After sedation and monitoring, patients were intubated with a double-lumen cannula and ventilated in one lung with a Fabius respirator with a tidal volume of 6/8 mL/kg of weight, respiratory rate of 12-14 ipm, inspiratory pause time of 33% and FiO_2 for SpO_2 >95%. Then, the modality was changed to

	mechanics and gas exchange.	recruitment maneuver is performed followed by decremental PEEP titration.			pressure-controlled ventilation, with an inspiratory pressure of 20 cmH_2O above PEEP. PEEP was increased to 5, 10, 15 and 20 cmH_2O every 6 breaths; then, with pressure controlled at 15 cmH_2O above PEEP, titration was performed, starting with 15 cmH_2O of PEEP and reducing every 2 cmH_2O every 2 min and calculating compliance static. After PEEP titration, another recruitment maneuver was performed and, at the end of the intervention, the modality used was volume-controlled ventilation with the PEEP value chosen to optimize the best compliance.
Pereira et al. (25)	Assess the impact of PEEP measured by electrical impedance	A total of 40 patients, undergoing general anesthesia, were ventilated with a PEEP of 4 cmH_2O. PEEP titration was performed by electrical impedance tomography and alveolar	Patients undergoing elective abdominal surgery between	Not defined by authors.	After alveolar recruitment maneuver, patients were randomized into two groups of PEEP value (4 cmH_2O and titrated PEEP by electrical

	tomography versus fixed PEEP of 4 cmH_2O in patients with healthy lung undergoing abdominal surgery.	recruitment maneuver. After this intervention, patients were randomized and divided into two groups: (group 1, n=10) PEEP of 4 cmH_2O; (group 2, n=10) titrated PEEP.	August 2014 and April 2016.		impedance tomography) within two types of abdominal surgery (open or video). After the surgical procedure, where PEEP and FiO_2 values were not modified, patients were extubated and underwent a chest computed tomography scan to assess the collapsed and hyperdistended areas.
Chalkias et al. (26)	Examine the feasibility of a modified ARDSnet protocol in patients with sepsis and severe ARDS (according to the Berlin classification) undergoing surgery.	Patients were intubated in the operating room and initial ventilation was titrated with a tidal volume of 6 mL/kg of predicted weight, FiO_2 of 100%, constant flow, I:E of 1:2 and PEEP of 5 cmH_2O. After 10 min of MV, ARDS was diagnosed by P/F, then the tidal volume was increased to 8 mL/kg and the other parameters adjusted according to the ARDS protocol. Optimal PEEP was titrated using 3 levels with hemodynamic stability. During surgery, when	Patients in septic shock and with complications from severe ARDS who required urgent abdominal surgery, aged ≥18 years old, from a hospital located in Greece from November 2013 to May 2017.	Not informed by authors.	The anesthetist team was informed 30 min before surgery about patients' diagnosis. Patients were intubated in the operating room using the rapid sequence sedation protocol and previously pre-oxygenated. In the initial ventilation parameters, the following was adopted: volume-controlled ventilation mode, tidal volume of 6 mL/kg of predicted weight, PEEP of 5 cmH_2O, FiO_2 of 100%, I:E of 1:2, flow and

	necessary, an alveolar recruitment maneuver was performed by increasing the pressure (40-45 cmH_2O) for 20 to 30 sec. Patients were monitored during the procedure and exams were carried out using a central venous catheter and an invasive arterial monitoring catheter. Patients were referred to ICUs at the end of surgery with the abdomen closed. The 90-day follow-up was carried out by telephone contact. The assessed outcomes were in follow-up after 90 days and the adverse events in the postoperative period.	constant respiratory rate to keep partial pressure of carbon dioxide (pCO_2) within blood gas reference values. Predicted weight calculation: (height (cm) - 152.4) x 0.91+50 (men) or +45.5 (women). 10 min after MV onset, severe ARDS was confirmed by P/F. Then, the tidal volume was increased to 8 mL/kg of predicted weight and the other parameters adjusted according to the ARDSNet protocol. Titration of PEEP was performed using two or three PEEP levels for 15 min each level, without changing the other parameters. In order to recruit alveoli during surgery, patients underwent increased airway pressure to 40-45 cmH_2O for 20 sec, whenever necessary. The primary outcome was in-hospital

					survival at 90 days and the secondary were the presence of ICU intraoperative adverse events and length of stay.
De Jong et al. (27)	Examine the influence of obesity on DP, plateau pressure and respiratory system compliance as well as on mortality after 90 days of ICU stay.	A retrospective analysis of prospective data of patients admitted to an ICU of a university hospital diagnosed with ARDS from January 2008 to May 2017 was performed.	ARDS patients according to the Berlin criteria.	Not defined by authors.	Patients were ventilated according to a protective strategy defined in the literature. Data were collected from electronic medical records and the following endpoints were studied: mortality in the 90-day follow-up, ICU mortality, time on IMV, need for non-invasive MV after extubation, occurrence of pneumothorax and ventilator-associated pneumonia, and need for a prone position.
Gogniat et al. (28)	Describe the effect of PEEP on the dead space ratio (obtained by the Bohr equation) and its	Patients were monitored and placed in the supine position, sedated with propofol and remifentanil, with baseline ventilatory parameters for volume-controlled ventilation with a tidal volume of 6 mL/kg of predicted weight, respiratory rate	Patients diagnosed with ARDS according to the Berlin definition, aged ≥18 years, under	Hemodynamic instability, heart failure, chest wall abnormalities, and CODPs.	First FiO_2 was adjusted to 100% in order to decrease hypoxemia, data were collected after 15 min of baseline ventilation. After this time, 4 PEEP values (0, 6, 10 and 16 cmH_2O) were applied for 10 min. The protocol was

	subcomponents in mechanically ventilated patients with ARDS.	for pH >7.30 without causing intrinsic PEEP, I:E of 1:2, PEEP of 10 cmH_2O, FiO_2 of 50% (or more when SpO_2 <90%) and 15% of inspiratory pause. Fluid therapy and vasoactive drugs were used to maintain mean arterial pressure >60 mmHg.	IMV for at least 12 hours.		discontinued when SpO_2 <90%. Data collected: hemodynamic, respiratory, arterial blood gases and tidal volume in capnography at the end of each PEEP step.
Schmidt et al. (29)	Determine the association between DP and the outcome of patients under MV and without a diagnosis of ARDS on day 1 of ventilation.	Retrospective analysis of a cohort of 622 MV patients without a diagnosis of ARDS on the first day of ventilation in 5 ICUs of a US tertiary center. The primary outcome considered was mortality. The dataset was first validated by testing the model on 543 patients diagnosed with ARDS.	Patients aged ≥15 years under IMV for at least 48 hours in volume-controlled ventilation or pressure-controlled ventilation modalities.	Patients with ARDS according to the Berlin classification on day 1 of MV.	The independent variables of the study were: SAPS on admission, age, diagnosis on admission, Elixhauser comorbidity index on admission, highest pCO_2 value on day 1 of MV and lowest P/F value. Mathematically linked variables were excluded. The outcomes considered were in-hospital mortality and mortality in the 6-month follow-up.
D’Antini et al. (30)	Observe the pulmonary mechanics and oxygenation	Twenty patients were included during laparoscopic cholecystectomy. Data on pulmonary mechanics and	Patients aged ≥18 years, with ASA I or II criteria.	Patients with previous heart and/or lung diseases and/or obesity.	After anesthetized and monitored, the patient underwent an alveolar recruitment maneuver (PEEP of

	response after application of alveolar recruitment maneuver followed by decremental PEEP titration during laparoscopic cholecystectomy and verify its impact on hemodynamic stability.	hemodynamics were collected at the beginning of the procedure, after the alveolar recruitment maneuver and PEEP titration, and at the end of the procedure.			5, 10, 15 and 20 cmH_2O) followed by PEEP titration.
Ferrando et al. (17)	Compare the effects on DP by adding the alveolar recruitment maneuver in low tidal volume ventilation, with	Patients undergoing major abdominal surgery were ventilated with a tidal volume of 6 mL/kg of predicted weight and a PEEP of 5 cmH_2O. Afterwards, they underwent an alveolar recruitment maneuver and were then randomized into two groups: (i) PEEP of 5 cmH_2O and (ii) titrated	Patients undergoing major abdominal surgery (pancreatectomy, duodenectomy, gastrectomy and liver resection),	Age under 18 years, ASA IV criteria, previous respiratory disease or laparoscopy surgery.	Patients received the same anesthesia and monitoring protocol and were ventilated with the following parameters: tidal volume of 6 mL/kg of predicted weight, PEEP of 5 cmH_2O, FiO_2 of 50%, I:E of 1:2, 10% inspiratory pause and respiratory rate to maintain

	or without optimal PEEP titration in patients without previous lung disease under general anesthesia.	PEEP (according to the best compliance). The effects on DP and pulmonary efficiency were measured by volumetric capnography. The study was carried out at a university hospital in Spain from July to October 2014. Randomization was performed by computer.	with ASA criteria I, II or III.		$EtCO_2$ ~35-45 mmHg. SpO_2 and $EtCO_2$ were collected in the monitor; equal pressure point, plateau pressure, DP, compliance and resistance were calculated from ventilatory parameters; ventilatory efficiency was obtained using the dead space concept (Bohr's equation). Arterial blood gases were collected before and at the end of surgery. Alveolar recruitment maneuver: PEEP of 5, 10, 15 and 20 cmH_2O with inspiratory pressure of 15 cmH_2O, for 15 cycles at each PEEP level. Titration: PEEP of 20, 18, 16, 14, 12, 10, 8 and 6 cmH_2O, calculating the best compliance at each level.
Villar et al. (31)	Assess whether DP is a better marker for predicting	Secondary analysis of data collected from three previous observational studies. Mortality risk was quantified based on quantiles of	Patients whose data were collected in three previous studies.	High frequency ventilation and use of ECMO.	Patients were diagnosed with ARDS according to the Berlin classification and were ventilated with a protective

	outcome in patients diagnosed with ARDS.	tidal volume, PEEP, plateau pressure and DP in the first 24 hours of MV after the diagnosis of ARDS, regardless of age, treatment or specific disease process.			strategy (tidal volume 4 to 8 mL/kg of predicted weight), plateau pressure <30 cmH_2O, respiratory rate for pCO_2 ~35-50 mmHg, moderate to high PEEP value to maintain PaO_2 >60 mmHg and SpO_2 >90%. The study was carried out with the derivation model and the validation model.
Guérin et al. (32)	Investigate the impact of tidal volume variation on DP and risk factors for compliance and plateau pressure on mortality.	The following variables were included: tidal volume, PEEP, DP, plateau pressure, compliance and respiratory rate, which were measured 24 hours after randomization and compared with survivors and non-survivors on day 90.	Patients diagnosed with ARDS undergoing protective MV (tidal volume of 6 mL/kg of predicted weight).	Not defined by authors.	Not defined by authors.
Chiumello et al. (3)	Assess the impact of DP on pulmonary stress.	A total of 150 patients were included, 21 from a "new" prospective study that assessed the relationship between recruitment and PEEP by computed tomography	Not reported.	Not reported.	With patients sedated and anaesthetized, volume MV (6-8 mL/kg of predicted weight) was performed with FiO_2, tidal volume and respiratory rate

		and 129 from three other previous studies. Patients were deeply sedated and anaesthetized and were volume ventilated (6-8 mL/kg predicted weight) with FiO_2, tidal volume and respiratory rate constant during the protocol. Before the application of PEEP, patients underwent an alveolar recruitment maneuver and then PEEP of 5 and 15 cmH_2O were used for 20 min each. Measures taken: arterial blood gas, esophageal pressure by esophageal balloon, DP, pulmonary stress and elastance.			unchanged during the protocol. Before applying PEEP at values of 5 and 15 cmH_2O (for 20 min each), the patients underwent an alveolar recruitment maneuver (pressure-controlled ventilation mode) and they were divided into two groups: DP <15 cmH_2O and DP $\geq$15 cmH_2O.
Rotman et al. (33)	Assess the effects on the inflammatory response, aeration and lung function of two protective ventilatory strategies (low	Study carried out in a hospital in Rio de Janeiro - Brazil and which included a total of 15 participants.	Patients diagnosed with ARDS, undergoing protective MV (tidal volume of 6 mL/kg of predicted weight), PEEP of 5	Patients with more than 48 hours of ARDS diagnosis, pneumothorax, pneumomediastinum, bronchopleural fistula, subcutaneous emphysema, intracranial	Patients received the same anesthesia and monitoring protocol and were positioned in dorsal decubitus with an elevation of 30° at the head and ventilated with the same equipment, according to low PEEP table of the ARDS-network study, with a tidal

	PEEP and titrated PEEP) in patients diagnosed with early-stage ARDS.		cmH_2O and FiO_2 of 100%, hemodynamically stable and with lactate <3 mmol/L in the first 6 hours of MV.	hypertension, pregnant women, body weight >140 kg or with pre-existing disease with risk of death within 6 months.	volume of 6 mL/kg of predicted weight and plateau pressure below 30 cmH_2O for 24 hours. After this period, arterial blood gases and respiratory variables were collected and a chest tomography was performed without disconnecting the ventilator. After 24 hours, the first 9 patients with P/F <350 mmHg were ventilated according to OLA (alveolar recruitment maneuver + decremental PEEP titration) and the other 6 according to low PEEP table of the ARDS-network study for another 24 hours. At the end of this period, arterial blood gas, respiratory variables and chest tomography collections were repeated.
Baedorf Kassis et al. (34)	Verify the relationship between the	A total of 56 patients were analyzed at a Boston medical center (USA) and had a diagnosis of acute	Patients with acute respiratory failure or ARDS.	Not reported.	Patients were positioned in dorsal decubitus with the head elevated at 30° and underwent

	respiratory system and transpulmonary DP, pulmonary mechanics and 28-day mortality.	respiratory failure or ARDS according to the American-European Consensus Conference. Participants were divided into two groups (control and intervention). The following markers were measured: tidal volume, flow, inspiratory and expiratory pause pressure, PEEP, intrathoracic pressure by esophageal balloon. Moreover, DP was calculated by subtracting the inspiratory pause pressure from PEEP and intrathoracic pressure was the difference between the airway pressure and the esophageal balloon pressure, elastance was obtained by the airway pressure minus the expiratory pause pressure divided by the tidal volume. Measurements were taken at the same time at the 5th min and 24 hours on MV.			an alveolar recruitment maneuver for 30 sec and the tidal volume was fixed at 6 mL/kg of predicted weight. Patients in the intervention group had PEEP adjusted to achieve an intrathoracic pressure of 0-10 cmH_2O and FiO_2 titrated according to the EPvent study. The control group had PEEP titrated according to the ARDSNet study low PEEP table.
Kamarek et al. (35)	Compare the ARDSNetwok	The study was carried out in 20 ICUs and included patients with	Patients aged ≥18 years, diagnosed	Age <18 years, weight <35 kg, body	ARDSNet Group (101 participants): ventilated with a

	low PEEP protocol with PEEP titrated by OLA in patients with ARDS classified as moderate or severe.	ARDS. Patients were ventilated according to the ARDSNet protocol. Baseline arterial blood gases were collected with a 100% FiO_2 and after collection, patients were randomized to the ARDSNet or OLA groups.	with ARDS according to the American-European Consensus and admitted to participating ICUs under MV for at least 96 hours.	mass index greater than 50 kg/m^2, intubation due to exacerbation of CODP, asthma or cystic fibrosis, high intracranial pressure, patients immunosuppressed by radiotherapy or chemotherapy, severe heart disease.	tidal volume of 6-8 mL/kg of predicted weight, respiratory rate for pCO_2 between 35-60 mmHg, PEEP and FiO_2 according to ARDSnet low PEEP table, pressure plateau <30 cmH_2O. OLA group (99 participants): tidal volume of 6 mL/kg of predicted weight, respiratory rate for pCO_2 between 35-60 mmHg, Titrated PEEP in decrement, FiO_2 for SpO_2 between 88-95%, plateau pressure <30 cmH_2O.
Beitler et al. (36)	Determine how the tidal volume demanded during the recruitment maneuver is inversely associated with pulmonary stress and	Analysis of the ARDS clinical study with PEEP titrated by esophageal pressure.	Patients diagnosed with ARDS undergoing MV.	Occurrence of air leak during alveolar recruitment maneuver.	At the beginning of the intervention, patients underwent 30 sec of sustained breathing with a pressure of 40 cmH_2O (alveolar recruitment maneuver), deeply sedated or anaesthetized. Airflow, airway pressure and esophageal pressure were collected during the procedure. To obtain the

	mortality in patients with ARDS.				tidal volume in the alveolar recruitment maneuver, the flow vs. curve was used. time. Pulmonary stress was obtained by the transpulmonary pressure at the end of inspiration and by the difference between the end-inspiratory and expiratory pressures.
Cinnella et al. (37)	Test how the application of the OLA strategy improves the distribution of aerated areas and lung mechanics.	Patients were ventilated according to the ARDSNet strategy. In a second moment, the OLA strategy (alveolar recruitment maneuver followed by PEEP titration) was applied. Respiratory mechanics, cardiac indices, electrical impedance tomography and esophageal pressure measurements were performed before and 20 min after the application of the OLA strategy.	Patients aged >18 years, diagnosed with moderate early-stage ARDS (according to the Berlin criteria), under continuous use of intravenous sedation and analgesia, with a Ramsay scale between 3 and 4.	Hemodynamic instability, pneumothorax, intracranial hypertension, pregnancy, burns that reached more than 30% of the body surface, any condition that contraindicated hypercapnia, lung transplantation, alveolar hemorrhage, impossibility of	Data on respiratory mechanics, hemodynamics, arterial blood gases and electrical impedance tomography were collected from patients ventilated using the ARDSNet strategy. The ventilator was set to pressure mode, with I:E of 1:1, respiratory rate of 10, FiO_2 of 100%, DP <15 cmH_2O and PEEP of 25 (1 min), in 35 (1 min) and 45 (2 min). After this maneuver, volume was adjusted with an initial PEEP of 23 cmH_2O and a reduction of every

				using electrical impedance tomography, irreversible or malignant diseases, patient refusal.	3 cmH_2O for 5 min each level. Compliance was calculated at each level and PEEP was titrated by the best compliance plus 2 cmH_2O. After 20 min of intervention, initial measurements were repeated. After intervention, patients were ventilated with initial adjustments (ADRSNet).
Amato et al. (10)	Verify the influence of DP on the survival rate of patients with ARDS and compare the result with the variables tidal volume and PEEP.	Data from 3,562 patients from 9 previous randomized studies were analyzed. The isolated effects on DP after changes in ventilatory parameters were estimated and DP was analyzed as an independent variable in the survival rate.	Patients previously included in nine randomized clinical trials.	Not reported.	Through a statistical analysis tool known as multilevel mediation analysis, DP was assessed as an independent marker for survival. In the mediation analysis, the isolated effect of change in DP secondary to changes in ventilatory parameters aimed at minimizing the injury according to the severity of the lung disease was estimated.

Das et al. (38)	Analyze how 3 different recruitment maneuvers act on the pulmonary physiological response and investigate how different PEEP levels contribute to the effective maintenance of alveolar recruitment.	The model simulates a lung with 100 alveolar compartments, with each compartment responding to parameter changes according to lung elastance and compliance. The three recruitment maneuvers used were previously described in the literature.	The study used a computer simulator.	Not reported.	Three recruitment maneuvers were applied: maximum recruitment strategy, sustained inflation maneuver and prolonged recruitment maneuver.
Mauri et al. (39)	Verify the influence of two PEEP levels (low and high) on the distribution of tidal volume in different areas of the lung by	Patients with a diagnosis of ARDS admitted to a general and neurosurgical ICU in Italy, who were ventilated in the modality of ventilation with pressure support, participated in the study. Clinical and demographic data were collected (gender, age, body mass index, predicted weight, SAPS-II	Patients diagnosed with ARDS admitted to a general and neurosurgical ICU in Italy.	Patients aged <18 years, pregnant women, contraindication to the use of electrical impedance tomography, inability to correctly position the bed	In each patient, 3 different ventilatory parameters were randomly applied in the pressure support ventilation mode, with a duration of 20 min for each parameter. FiO_2, sensitivity and inspiratory rise time were kept unchanged during the protocol. Parameters:

	electrical impedance tomography in patients with ARDS under MV in pressure support ventilation mode.	score, SOPA score, ARDS etiology, days on MV, lung injury score and in-hospital mortality). Electrical impedance tomography was used during intervention with patients in the supine position and 16 electrodes.		electrical impedance tomography or its electrodes in patients and severe cardiovascular instability.	1. Pressure support ventilation + clinically selected PEEP. 2. Clinically selected pressure support ventilation + (previous PEEP + 5 cmH_2O). 3. Ventilation with high- and low-pressure support (according to p01 measurement - airway occlusion pressure) + clinically selected PEEP. Total volume distribution data were collected from electrical impedance tomography.
Gernoth et al. (40)	Investigate hemodynamic and respiratory changes during decremental PEEP titration in patients with ARDS.	Software was incorporated into the mechanical ventilator for measurements. Patients underwent alveolar recruitment maneuver followed by decremental PEEP titration. Optimal PEEP was defined as the best dynamic compliance + 2 cmH_2O. Hemodynamic, respiratory mechanics and gas exchange data were recorded during intervention. A transesophageal echocardiogram	Patients with ARDS and undergoing MV.	Patients aged <18 years, with MV over 96 hours, pregnant women, aortic or femoral aneurysm, cardiac malformations, arrhythmias, immunosuppression and end-stage organ failure.	For the intervention, patients were stable, sedated (RASS scale of -5) without the use of NMBs, with the following ventilatory parameters: pressure modality for a tidal volume of 5 to 8 mL/kg of predicted weight, I:E of 1:1, respiratory rate to maintain pH >7.20. PEEP was chosen for the best oxygenation at first. Vasoactive drugs were

		was performed at the beginning and at the end of the procedure.			used to maintain hemodynamic stability when necessary. Alveolar recruitment maneuver: PEEP of 20 cmH_2O with final inspiratory pressure of 40, 45 and 50 cmH_2O for 2 min each. Subsequently, a decremental titration was performed from a PEEP of 20 cmH_2O, with a reduction of every 2 cmH_2O for 2 min each PEEP. During titration, dynamic compliance was recorded and optimal PEEP was defined as the best compliance, adding 2 cmH_2O to its value. The analyzed data were recorded in 3 moments: with the initial parameters, 2 min after the alveolar recruitment maneuver and at the end of titration (with optimal PEEP).
Szakmany et al. (41)	Assess the relationship	Twenty-three patients diagnosed with ARDS under IMV due to	Patients with ARDS due to	Age <18 years, participant in	Patients were sedated without NMB, ventilated in pressure-

	between P/F and extravascular pulmonary fluid in patients diagnosed with ARDS due to septic shock.	septic shock (with onset within 24 hours) from January 2001 to February 2002 participated in the study.	septic shock (within 24 hours of onset). ARDS with P/F <300 mmHg.	previous studies for less than 30 days, morbid obesity, pregnant women, neuromuscular disease that progressed with impairment of respiratory drive, elevated intracranial pressure, chronic heart disease, CODP, portal hypertension, immunodeficiency, under renal replacement therapy, insulin dependent diabetes and liver cirrhosis.	controlled mode with PEEP individually adjusted according to PaO_2 obtained from arterial blood gases. If PaO2 <80 mmHg, PEEP was increased from 2.5 in 2.5 cmH_2O to a value of 15 cmH_2O, with FiO_2 of up to 80%. If PaO_2 was not satisfactory, PEEP was increased up to 20 cmH_2O and FiO_2 up to 100%. Monitoring was performed every 8 hours for 72 hours with a thermodilution arterial catheter (to measure extravascular pulmonary fluid) and by collecting arterial blood gases. The cut-off point for high PEEP and low PEEP was 10 cmH_2O.
Biker et al. (42)	Assess the distribution of ventilation by bedside	Electrical impedance tomography images were obtained and P/F calculated by arterial blood gases of 14 patients under IMV in an ICU.	Patients under IMV, with or without pulmonary	Pneumothorax, severe airway obstruction due to CODP, lung	Obtain the electrical impedance tomography images, 16 electrodes were placed between the fifth and sixth intercostal

	electrical impedance tomography of patients under MV, inside ICUs, with or without pulmonary involvement, during the standardized reduction in PEEP.		involvement, admitted to an ICU.	transplantation, chest deformities, and hemodynamic instability.	space. Participants were assessed by chest X-ray and subsequently separated into two groups: without pulmonary involvement and with pulmonary involvement. Patients were sedated and ventilated in the pressure-controlled mode with constant DP (12 cmH_2O) in the group without pulmonary involvement and 16 cmH_2O in the group with pulmonary involvement). PEEP values used were: 15, 10, 5 and zero cmH_2O and, for each PEEP value, a mapping of the ventilatory distribution and arterial blood gases were performed.
Fernandez-Bustamante et al. (43)	Analyze the impact of periodic PEEP adjustments during	Prospective, randomized and controlled study that compared 3 different PEEP application protocols in the intraoperative period of abdominal surgery, where	Patients aged >18 years, undergoing elective abdominal surgery, at risk of	Patients with predefined cardiopulmonary diseases or other serious conditions.	All participants were ventilated in volume-controlled ventilation mode with protective parameters: tidal volume of 6-8 mL/kg of predicted weight,

	abdominal surgery on respiratory mechanics (compliance, DP, and transpulmonary pressure) and to assess the influence of individualization of PEEP on lung injury biomarkers.	2 groups were intervention (with 2 PEEP titration protocols) and the third group was control (with PEEP kept constant throughout the procedure).	postoperative pulmonary complications (according to risk score >26 by ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) were eligible.		inspiratory pause of 20%, FiO_2 to maintain saturation >92%. An esophageal balloon was positioned to monitor esophageal and transpulmonary pressures continuously during the procedure. After randomization, patients were divided into three groups: (1. Control) PEEP of 2 cmH_2O and absence of intraoperative recruitment maneuver; (2) alveolar recruitment maneuver (up to PEEP of 20 cmH_2O), followed by decremental PEEP titration (titrated by best compliance); (3) end-expiratory transpulmonary positive pressure group, where PEEP was titrated by adding 1 cmH_2O according to the best PEEP value found by the best esophageal pressure. Lung injury biomarkers were

					collected by analyzing blood samples at 3 times: beginning of surgery, end of surgery and 24 hours after the surgical procedure.
Sahetya et al. (44)	Demonstrate the feasibility of a DP estimation protocol in which PEEP was adjusted according to the lowest DP; to characterize the difference between PEEP titrated by the lowest DP with low ARDSNet study $PEEP/FiO_2$ table; demonstrate the time needed to	A prospective pilot study was conducted in the ICU of Johns Hopkins Hospital in Maryland. Ten individuals were ventilated with PEEP adjusted according to low ARDSNet study $PEEP/FiO_2$ table. After this initial adjustment, they underwent PEEP adjustment according to the lowest DP.	Patients aged ≥18 years, admitted to ICUs and undergoing IMV with the following criteria: ARDS (Berlin criteria), intubation less than 7 days, with PEEP ≥8.	Patients were excluded due to certain criteria: elevated intracranial pressure, heart failure, barotrauma for less than 10 days, severe refractory hypoxemia, plateau pressure ≥35 cmH_2O or refusal to participate.	Patients were ventilated in volume-assisted control mode, in the dorsal position with a 30º head elevation. The tidal volume adopted was 6 mL/kg of predicted weight (tidal volume maintained throughout intervention). The initial PEEP was determined according to low ARDS network $FiO_2/PEEP$ table. The initial DP was obtained after 30 min of this adjustment with an inspiratory pause of at least 0.5 second. PEEP was increased by 4 cmH_2O from the initial value, if there was an increase in DP, PEEP was then reduced by 4 cmH_2O from the initial value.

stabilize DP after PEEP change.	Thus, PEEP was changed to search for the lowest DP. For each DP measurement, a time of 10 respiratory cycles was awaited. After this intervention, participants were divided into two groups: (i) PEEP titrated by the lowest DP when titrated PEEP was different from the initial one; (ii) Initial PEEP was equal to the one titled by the lowest DP. Participants were followed 48 hours after intervention for adverse events: pneumothorax, pneumomediastinum, severe hypoxemia requiring rescue therapy (ECMO), inhaled vasodilator, severe acute hypotension and cardiac arrhythmias.

Of the articles selected for full reading, 19 were carried out in Europe (3,15,17,18,20,21,24,26,27,30,31,32,37,38,39,40,41,42,43), six in North America (2,11,29,34,36,44), 2 in Asia (18.23), four in South America (10,22,28,33) and two in different regions worldwide (25,35). Two articles from the United Kingdom did not carry out the study in humans, but in an *in-silico* model and with the use of a computerized simulator. The *in-silico* model was used to assess the influence of DP on LIVI and to verify the effective maintenance of three different alveolar recruitment maneuvers (15,38).

Twenty studies were prospective (2,3,15,18,19,24,26,28,30,32,33,36,37,38,39,40,41,42,43), six were retrospective (11, 21,27,29,31,34), two were post-hoc analysis (10,22), one was double blind (23), one was observational multicenter (20) and four were pilot studies (17,25,35,44).

Among the diagnoses of the patients assessed, most studies reported the outcome in individuals with ARDS, totaling 5,860 data analyzed (2,10,11, 20,21,22,26,27,28,31,32,33,34,35,36,37,40,41,44), and only one study addressed patients without a diagnosis of ARDS under IMV (29). Concomitantly, three studies used electrical impedance tomography (EIT) to verify the pulmonary volume distribution, with a total of 73 individuals analyzed (19,39,42). Eight studies included individuals undergoing surgery, six of them abdominal surgeries totaling 160 individuals assessed (17,18,25,26,30,43) and two thoracic surgeries, including 305 patients (23,24). A study with 150 participants analyzed only data from the literature (3).

The studies that used a computerized simulator emphasized the easiness in carrying out the measurements of the markers using this technology, and both concluded that high DP values can increase the risk of mortality in patients with ARDS (15,38). A study by Das et al. (2019) used data from 25 patients with ARDS to assess, through *in silico* models, the influence of DP on ventilatory mechanics and demonstrated that the higher the DP value, the worse the ventilatory mechanics and clinical outcome. The authors also highlighted the difficulty in measuring these findings directly in patients, since the importance of ventilation through the use of the protective strategy is well established (15). Concomitantly, in a study by Das et al. (2015), three alveolar recruitment techniques were compared in five “virtual patients” using a computer simulator and it was determined that titrating PEEP after alveolar recruitment maneuver allows recruitment to be effective for a longer period (15,38).

The articles that assessed patients with ARDS concluded that high DP is associated with the worst outcome both in terms of mortality and lung injury (21,31,32,33). Regarding studies involving abdominal surgeries, it was shown that alveolar recruitment maneuvers performed during the intraoperative period optimized oxygenation during surgery but showed no effect on the postoperative follow-up (17,18,25,26,30,43). For example, in 2019, Sahetya et al. assessed the influence of DP in a prospective observational cohort study with a sample of 1,132 individuals under MV, where 822 did not have ARDS (mortality of 27.3%) and 310 had ARDS (mortality of 38.7%). In this study, it was concluded that the probability of mortality increases linearly with the increase in DP, as the difference in DP values between the groups was only two cmH_2O; concomitantly, it was described that DP should be considered an important marker in protective ventilatory strategy assessment in patients under IMV regardless of ARDS (2). However, a study by Lanspa et al. (2019), which included data from 2,641 individuals with and without ARDS, in which 48% had a diagnosis of ARDS, described that DP did not influence the mortality of patients without ARDS, but that increased tidal volume raised mortality (OR of 1.18 for each increment of one mL/kg) in this group. In contrast, it was described that high DP was associated with an increased probability of death in patients diagnosed with ARDS (11).

Studies performed in thoracic surgery included a total of 305 patients; both were performed by an intervention protocol, one of them being randomized double-blind (with a sample number of 292 individuals) (23,24). In a study by Rauseo et al. (2018), the influence of the alveolar recruitment maneuver followed by PEEP titration as a therapeutic strategy was described. It was noted that the protocol improved the oxygenation index and pulmonary compliance without changing hemodynamics, suggesting that the lower the DP, the better the oxygenation index (24). Moreover, a study by Park et al. (2019) compared the protective ventilatory strategy with a PEEP of five cmH_2O and alveolar recruitment with PEEP titrated by the lowest DP and alveolar recruitment and demonstrated that the ventilation guided by the lowest DP courses with the lower incidence (6.9% versus 15%) of pulmonary complications in the postoperative period (23).

A study carried out by Cinnella et al. (2015) included 15 individuals and demonstrated a reduction in DP of approximately two cmH_2O after the alveolar recruitment maneuver can cause an improvement in the distribution of regional ventilation, visualized by means of EIT. Thus, EIT was described as an effective bedside technique to verify air distribution and better pulmonary compliance (37).

A study conducted by Baedorf Kassis et al. (2016) concluded that DP can be a sound bedside prognostic predictor (34). Two studies compared the use of a PEEP table and FiO_2 with titrated PEEP and both concluded that ventilation with titrated PEEP results in improved oxygenation and reduces the incidence of lung injury, favoring a better clinical outcome for patients (3,24).

Discussion

The lung's main function is to carry out gas exchange, which, in turn, is carried out in the terminal respiratory unit, where the alveolar ducts that are covered by alveoli are found (**Figure 2A**). The interior of the alveoli is occupied by air and its exterior is permeated by blood vessels (**Figure 2B),** the movement of gases between the alveoli and blood vessels is accomplished through simple diffusion, so air flows on one side through the airways and on the other through the blood vessels (**Figure 2C**). There are about 500 million alveoli in the human lung, whose total area is approximately 85 square meters. The alveolar capillary membrane is very thin (about 0.3 micrometers thick), allowing a satisfactory gas exchange capacity according to Fick's law of diffusion (which states that the volume of gas per unit of time moving across a tissue sheet is directly proportional to the surface area of the sheet, the diffusivity, and the difference in gas concentration between the two sides, but is inversely proportional to the tissue thickness) (**Figure 2D**). In a situation in which the alveolus is exposed to pressure above or below what is necessary, the exchange area is reduced, making gas exchange less favorable (**Figure 2E** and **2F**). However, despite advances in the knowledge acquired inherent to studies on respiratory dynamics during IMV, much still needs to be pointed out about the importance of some markers, which include DP and PEEP and their real role in gas exchange and in patient management.

As described in the literature, microprocessor-based mechanical ventilations, developed in the 1980s, made it possible to carry out important measures regarding respiratory mechanics, which were previously unavailable (45). Since then, researchers have sought answers to important questions related to the influence that some ventilatory parameters exert on patients' clinical outcome, gas exchange and hemodynamic stability; an example of these measures is the plateau pressure, measured after a brief manual inspiratory pause, whose result, when subtracted from PEEP value, is DP, which proved to be a significant marker in mortality risk stratification (10,31,34).

Considered a parameter that directly influences gas exchange and, consequently, the oxygenation index, PEEP, which has as its main objective to stabilize alveolar units and prevent their collapse, has its values still controversial in the literature and has been studied in order to verify its influence on respiratory mechanics and clinical outcome (4). Inadequate PEEP levels can lead to lung injury by two mechanisms: (i) overdistension; and/or (ii) cyclic opening and closing of small airways and alveoli - atelectrauma (4,46). Concomitantly, alveolar overdistension pressure, known as DP, has a direct influence on pulmonary compliance and is influenced by tidal volume, plateau pressure (or inspiratory pause pressure) and PEEP, as shown below (3):

Cstat (pulmonary static compliance) = TV (tidal volume)/DP.

DP = TV / Cstat

DP = Plateau pressure - PEEP, plateau pressure being obtained after a manual inspiratory pause of 1 to 2 seconds (**Figure 2G**).

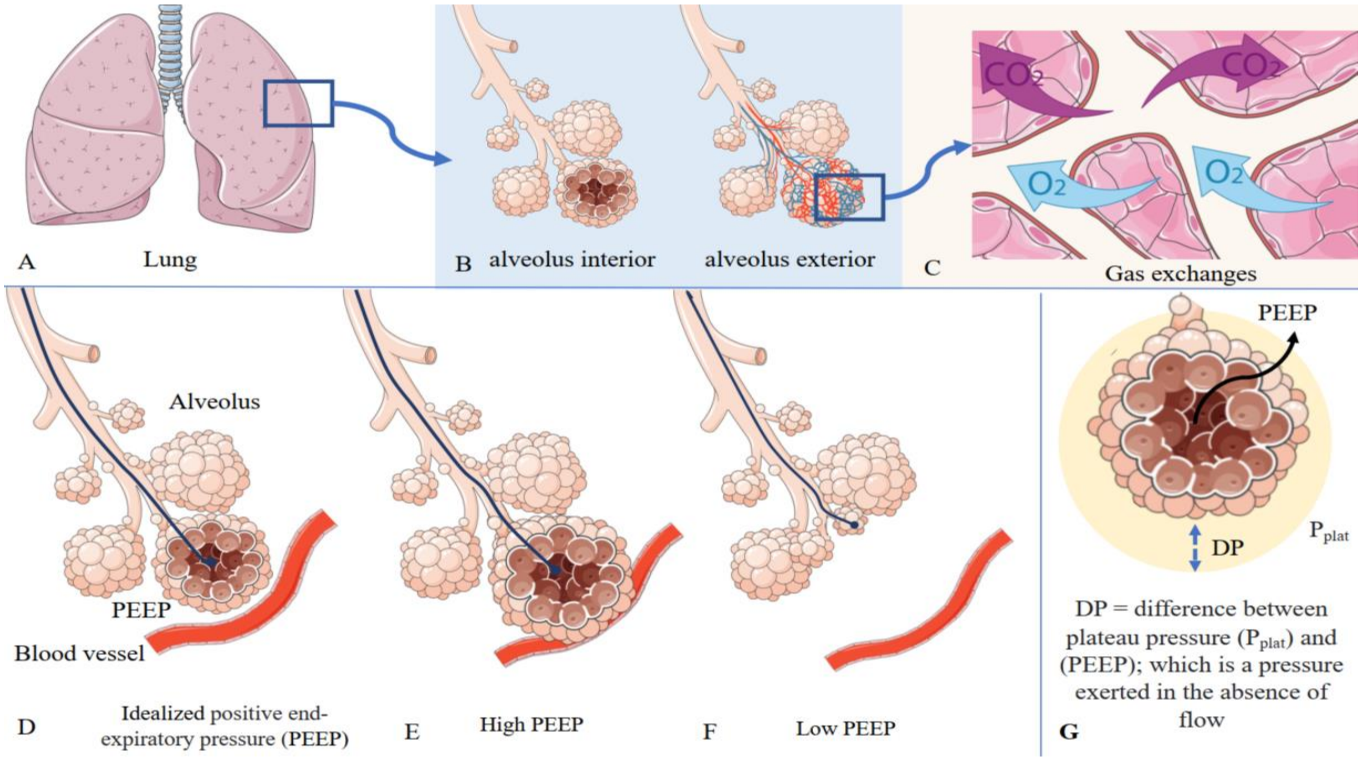

FIGURE 2. Description of the morphological and physiological aspects of the lung associated with gas exchange pattern involved in final expiratory positive pressure (PEEP) and driving pressure (DP). **(A)** Structure of the lung and its pulmonary lobes. **(B)** In the diagram, the alveoli and their interior occupied by air are shown on the left; on the right, the alveoli and their exterior permeated by blood vessels are shown. **(C)** Gas exchange pattern performed by simple diffusion: air flows from one side through the airways and the other through blood vessels. **(D)** Gas exchange pattern detailing, considering that, for gas exchange to occur satisfactorily, it is necessary that the blood gas barrier promotes favorable conditions, i.e., that its area is large and its thickness small, respecting Fick's law. **(E)** Unfavorable gas exchange area due to compression by the alveoli to blood vessels (situation of PEEP in excess of necessary). **(F)** Unfavorable gas exchange area due to increased distance between alveoli and blood vessels (situation of PEEP below necessary). **(G)** Driving pressure: alveolar overdistension pressure, is the pressure exerted on the alveolar wall in the absence of airflow, mathematically, and the difference between the inspiratory pause pressure (situation in which there is no flow) and PEEP.

Understanding these issues, Guérin et al. (2016) demonstrated that DP is a reliable variable in predicting LIVI, being directly influenced by the variation in tidal volume and PEEP.

Regarding the choice of optimal PEEP level, an important study had the leading role of secondary analyzes that aimed to compare two ventilatory strategies and their clinical outcomes (22). These strategies are known as ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial) and ARDSNet protocol (which uses a PEEP table versus FiO_2 level - fraction of oxygen inspired). The ART strategy is a maximal alveolar recruitment maneuver followed by PEEP titration, adjusted according to the best pulmonary static compliance and aims to minimize the cyclic opening and closing of small airways and alveoli, thus reducing the incidence of LIVI. Although titrated PEEP has shown improvement in oxygenation and regional ventilatory distribution, it has also been associated with reduced DP in some studies (10,22), without causing visible hemodynamic changes in the bedside cardiac monitor. Concomitantly, a study by Gernoth et al. (2009) demonstrated that this maximum recruitment technique, which uses very high PEEP values (reaching 45 cmH_2O), affects right ventricular function (40). In the literature, the improvement in compliance after maximal alveolar recruitment maneuver is attributed to optimization of the regional ventilation distribution, i.e., having more recruited alveoli, tidal volume is better distributed, requiring less distension pressure, thus reducing the incidence of LIVI (37,47).

Limitations

Most clinical intervention studies have a small sample size. This fact can be attributed to the limitation in the use of ventilatory parameter values (such as PEEP, tidal volume, and consequent peak pressure, plateau pressure and DP) above the recommended, offering risks for individuals. Thus, *in silico*, lung-on-a-chip models and computational simulators can be alternatives to optimize studies on ventilatory parameters. Additionally, by assigning the bookmarks to the PubMed platform, the detailed search showed unspecific results and not consistent with the theme.

Highlights

(i) PEEP and DP can be considered important markers to determine respiratory mechanics and gas exchange, being easily accessible markers in clinical practice;

(ii) DP as a sound predictor of clinical outcome;

(iii) PEEP titration should preferably be individualized and in accordance with respiratory mechanics.

Conclusion

MV, over the years, has helped to reduce the mortality rate by promoting respiratory muscle rest and gas exchange optimization; however, this tool can cause damage to lung structures due to the imposition of positive pressures on the parenchyma, which can cause alveolar collapse and hyperdistention. Inadequate PEEP values and high plateau pressure values are two important factors influencing healthy LIVI. Additionally, the literature describes optimal PEEP values as still controversial, perhaps because studies indicate that the best strategy for choosing it would be titration guided by the best compliance, which indicates that ventilatory mechanics is of fundamental importance in the adjustment of mechanical ventilator parameters. Another strong evidence regarding the importance of knowledge of ventilatory mechanics is the fact that DP shows a significant influence on the clinical outcome of patients under IMV. Thus, it is inferred that the different PEEP values are due to the individuality of ventilatory mechanics in each patient, assuming that it is influenced according to the physiology associated with each disease.

Declarations

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Capítulo II: Artigo Submetido

Title: Epidemiological Profile and Risk Factors Associated with Death in Patients Receiving Invasive Mechanical Ventilation in an Adult Intensive Care Unit from Brazil: A Retrospective Study

Running title: Intubation and Risk of Death

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Abstract

Introduction: Understanding the epidemiological profile and risk factors associated with invasive mechanical ventilation (IMV) is important to better manage the patients and improve health services. Therefore, the objective of this study was to describe the epidemiological profile of adult patients in intensive care (ICU) that required IMV in hospital treatment and evaluate the risks associated with death and the influence of positive end-expiratory pressure (PEEP) and oxygen arterial pressure (PaO_2) at admission in the clinical outcome.

Methods: A retrospective and epidemiological study was conducted analyzing medical records of inpatients who received IMV from January 2016 to December 2019. The patients' characteristics considered in the analysis were demographic data, diagnostic hypothesis, and hospitalization data. PEEP and PaO_2 during IMV were analyzed. The patients' characteristics were associated with the risk of death using a multivariate binary logistic regression analysis and alpha=0.05.

Results: The total number of medical records analyzed was 1,443 and out of those 570 (39.5%) recorded the patients' death. The binary logistic regression was significant when the patients' risk of death was predicted [$X^2_{(9)}$=288.335; P-value<0.001], with a 73.0% prediction global percentage. Among predictors, the most significant in relation to death risk were: age [elderly ≥65 years old; OR=2.226 (95%CI=1.728-2.867)]; male sex (OR=0.754; 95%CI=0.593-0.959); sepsis diagnosis (OR=1.961; 95%CI=1.481-2.595); need for elective surgery (OR=0.469; 95%CI=0.362-0.608); presence of cerebrovascular accident (OR=2.304; 95%CI=1.502-3.534); time of hospital care (OR=0.946; 95%CI=0.935-0.956); hypoxemia at admission (OR=1.635; 95%CI=1.024-2.611), and PEEP >8 cmH_2O at admission (OR=2.153; 95%CI=1.426-3.250).

Conclusion: The death rate of the studied ICU was equivalent to that of other similar units. Regarding risk predictors, most of them are modifiable through management optimization and the promotion of better health access. PEEP use must be cautious and personalized, since it was shown to increase death risk when used with values >8 cmH_2O at admission.

Keywords: Epidemiological Profile; Intensive Care Unit; Mechanical Ventilation

1. Introduction

The intensive care unit (ICU) of a hospital provides advanced life support to critical patients presenting different severity levels [1]. It is, therefore, a specialized facility to monitor and stabilize the patients' clinical aspects [2]. In such context, critical patients admitted in an ICU might require the use of invasive mechanical ventilation (IMV) to maintain patent airways, improve oxygenation, and prevent aspiration [3,4]. IMV is a complex resource and the expertise of the team managing it might generate better results. However, around 38% of the patients that require IMV still die [5]. For this reason, knowing the factors that lead to the outcomes of patients under IMV in ICU is vital to better inform the professionals' conduct and advise their families [6]. Understanding the profile of patients under IMV might lead to decisions such as getting access to technologies, training human resources, and reevaluating care processes, which could allow the structural adjustment of the unit according to the demographic and morbidity characteristics of the population assisted [7].

Since the appearance of ICU in the mid-1854, the mortality of patients that required care in such units has decreased [8]. However, some factors can still be considered to present death risk such as male sex, age (elderly), presence of comorbidities (e.g., systemic arterial hypertension, diabetes mellitus, smoking and drinking habits, obesity), admission diagnosis (e.g., polytrauma, traumatic brain lesion, sepsis, neurological disorders, cerebrovascular accident, cardiopathy), and ventilatory parameter values at admission, including the Positive End Expiratory Pressure (PEEP) value, which influences the dissolved oxygen partial pressure in arterial blood (PaO_2) [9-14].

Curiously, in the United States, the main causes of ICU admission are respiratory insufficiency, myocardial acute infarction, intracranial hemorrhage or brain infarction, percutaneous cardiovascular procedures, and septicemia or sepsis. In Brazil, however, different data was obtained. An epidemiological study carried out at the Clinical Hospital of Marília reported that the main causes of hospital admission were circulatory system diseases, lesions, poisoning and neoplasias. Similar results were found in a hospital in the state of Santa Catarina and, according to the AMIB (Brazilian Intensive Medicine Association) most admissions in Brazilian ICU have clinical origin, followed by elective surgeries [8,15-18]. Even if epidemiological characteristics in different countries might differ, it remains clear that patients admitted in ICU require greater care, and MV is usually the main medical support in such events [18].

Regarding ventilatory parameters at admission, different strategies can be employed. However, the literature recommends the use of protective parameters (low current volumes along with driving pressure and mechanical power limitation) [3,19,20]. When considering ventilatory parameters, although PEEP is used aiming to improve oxygenation and stabilize alveolar units, its ideal value is still controversial [21,22]. However, some reports suggest that PEEP ideal values might prevent pulmonary lesion due to the cyclic opening and closing of alveoli, and that higher values than those required might cause lesion due to alveolar hyperdistention [23].

The use of 8 cmH_2O initial PEEP as "prophylactic PEEP" has been described in some studies as a preventive and compensatory value of the functional residual capacity resulting from orotracheal intubation. However, when this value is applied to normal lungs, there is no evidence of improvement of the outcome or time of hospital stay [23,24]. Therefore, the best choice of PEEP value must be made according to individual ventilatory mechanics [25]. At the same time, PaO_2 characterizes the degree of hypoxemia and hyperoxemia [26], and both might have some influence in the clinical outcome and time of hospital stay, since hypoxemia reduces oxygen supply to tissues and its cause might have different origins, namely, unbalance in the ventilation/perfusion rate, pulmonary shunt, hypoventilation. Hyperoxemia, in turn, might cause non-cardiogenic pulmonary edema, formation of hyalin membrane, neutrophilic infiltration, type I pneumocyte damage, type II pneumocyte hyperplasia, alveolar hemorrhage, and increase in the alveolar sept thickness [27,28].

Taking all that into consideration, this study aimed to describe the epidemiological profile of adult patients admitted in the ICU and receiving IMV at a University Hospital and evaluate the characteristics of the population investigated as risk factors for death and the influence of PEEP and PaO_2 at admission in the clinical outcome.

2. Methods

A retrospective and epidemiologic study was carried out of electronic medical records described in the Philips Tasy system (Philips Healthcare®), Barueri, São Paulo, Brazil, which records the diagnosis, laboratorial data, monitoring of ventilatory support and clinical evolution of inpatients who required IMV. The patients were included from January 2016 to December 2019 and were assisted at the University Hospital São Francisco de Assis na Providência de Deus ICU, located in Bragança Paulista, São Paulo, Brazil. The ICU has 20 beds for the treatment of critical patients from 15 years old (y.o.) onwards. The time-period was selected to avoid the Coronavirus Disease (COVID)-19 impact on our data, because our University Hospital was a referral center to treat severe cases of SARS-CoV-2 infection.

The patients' characteristics considered in our epidemiological study were: (i) age [years and grouped as adult (18-64 y.o.) or elderly (>65 y.o.)], (ii) sex (male and female), (iii) body mass index (BMI) [Kg/m^2; underweight (<18.5 Kg/m^2), normal weight (18.5-24.9 Kg/m^2), overweight (25-29.9 Kg/m^2), obesity grade I (30-34.9 Kg/m^2), obesity grade II (35-39.9 Kg/m^2) and obesity grade III (>40 Kg/m^2)], (iv) diagnostic (traumatic brain injury, polytraumas, sepsis, elective surgery, acute myocardial infarction, stroke, dyslipidemia, subarachnoid hemorrhage, neuromuscular disease, smoking habits, and others); (v) patient origin from clinics or surgery; (vi) previous history of comorbidities (smoking, alcoholism, cardiopathy, pneumopathy, neurologic sequelae, use of drugs, systemic arterial hypertension, diabetes mellitus, dyslipidemia, and others); (vii) PEEP values at admission in the ICU and during IMV (absolute value and the categorization using the 8 cmH_2O points as parameter); (viii) PaO_2 values at admission in the ICU and during IMV (absolute value and the categorization using the following distribution: hypoxia (<80 mmHg), normal (between 80 and 100 mmHg), and hyperoxia (>100 mmHg); (ix) length of hospital stay; (x) length of IMV; (xi) presence of acquired pneumonia; (xii) presence of tracheostomy during hospital stay; and (xiii) outcome (discharge and death).

Descriptive analysis was performed using two approaches. (i) categorical markers – N (%): sample size (percentage); (ii) numeric markers – mean (standard deviation) and a 95% confidence interval (95%CI) of the mean or median (interquartile range) and 95%CI to the median, according to the data distribution, parametric or non-parametric, respectively. The normality of the numeric data was evaluated employing the following methods: (i) analysis of descriptive measures for central tendency; (ii) plot method (normal Q-Q plot, trendless Q-Q plot, and boxplot); (iii) statistical tests (normality tests): Kolmorov-Smirnov, and Shapiro-Wilk.

The presence of death (categorical data) was associated with the values of the markers with numerical distribution by using the T-test or the Mann-Whitney test. Concomitantly, the presence of death was associated with markers with categorical distribution by using Fisher's Exact test or Qui-square test; also, the relative risk (RR) and the 95%CI were calculated. Pearson's correlation coefficient between PaO_2 and PEEP levels was also evaluated to denote the mutual response between them.

The survival curve of patients who received IMV according to PEEP at admission and according to the classification of PaO_2 as normal, hypoxia and hyperoxia at admission was performed. The statistical analysis was performed by the Log-Rank (Mantel-Cose) test. The Hazard ratio was calculated using the PEEP ≤8 cmH_2O as the numerator.

The binary logistic regression by the forward stepwise method (likelihood ratio) included the patients' characteristics that presented P-value ≤0.05 in the univariate analysis. However, the patients' characteristics which presented association between each other were excluded, since they could present a multicollinearity effect, also, in our model, BMI and the day the pneumonia associated with mechanical ventilation was diagnosed were excluded, due to a high number of missing data. Death was considered as a dependent variable, whereas the other patients' characteristics, were allocated as predictors of risk of death.

A 0.05 alpha was used and no technique was applied to stipulate the missing data values. The statistical analysis was carried out using the Statistical Package for the Social Sciences version 24.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp) software and in the MedCalc 15.0 (MedCalc for Windows, version 15.0; MedCalc Software, Ostend, Belgium). Concomitantly, the GraphPad Prism version 8.0 was used for figures.

The research was approved by the Ethics Committee of São Francisco University [CAAE #29718820.9.0000.5514]. The waiver of the Informed Consent Term was obtained, since only the data from the patients' medical records were obtained without the individual description of the patient.

3. Results

3.1. Epidemiological profile of patients receiving IMV

A total of 3,213 medical records were evaluated from patients who were admitted to the ICU. Out of which 1,681 patients were excluded since they did not require IMV, and 68 were also excluded since the clinical data was missing. In the initial analysis, 1,464 patients were included for having received IMV, however, 21 were later excluded since they were transferred to a different ICU. Thus, a total of 1,442 patients were included in our analysis (**Figure 1**).

Higher frequency of male patients (n=901; 62.4%), adults (n=914; 63.3%), with normal BMI (n=423; 29.3%) or overweight (n=372; 25.8%) was observed (**Table 1**). Among the previous history of comorbidities, the most prevalent were diabetes mellitus (n=325; 22.5%), systemic arterial hypertension (n=653; 45.3%), smoking (n=388; 26.9%), alcoholism (n=221; 15.3%), pneumopathy (n=131; 9.1%), cardiopathy (n=310; 21.5%), and neurologic sequel (n=171; 11.9%) (**Table 1, Supplementary material – Table 1**).

A total of 923 (64%) patients were referred to the ICU by the surgery department and the main reason for the admissions were traumatic brain injury (n=197; 13.7%), polytrauma (n=210; 14.6%), sepsis (n=375; 26%), the need for elective surgery (n=616; 42.7%), and cardiopathy (n=222; 15.4%) (**Table 1, Supplementary material – Table 1**). Pneumonia associated with MV was observed in 410 (28.4%) patients, and the need for tracheostomy in 332 (23%) patients; death of 570 (39.5%) patients was recorded.

3.2. Risk factors associated with death in patients receiving IMV

Several patients' characteristics were associated with enhanced lethality such as older age (RR=1.512 [95%CI=1.334-1.713]), enhanced BMI, grade II and III obesity (RR=1.426 [95%CI=1.029-1.977]) and obesity grade I (RR=1.354 [95%CI=1.085-1.357]), which presented higher risk of death (**Figure 1**). Individuals with previous history of comorbidities of diabetes mellitus (RR=1.262 [95%CI=1.099-1.449]), systemic arterial hypertension (RR=1.271 [95%CI=1.119-1.443]) and kidney disease (RR=1.554 [95%CI=1.251-1.931]) were also at higher risk of death (**Supplementary material – Table 2; Figure 1**). Male sex was associated with decreased risk of death when compared to female (RR=0.776 [95%CI=0.683-0.880]) (**Supplementary material – Table 3; Figure 1)**.

In our data, older age and higher BMI were observed in the patients who died, also, these patients were hospitalized for more days and had the diagnosis of pneumonia associated with MV earlier when compared to patients who did not die (**Figure 2**). On the other hand, the lowest risk of death was associated with use of drugs and alcoholism, and this finding might be explained by the younger age of the patients in this group (data not shown). The presence of pneumonia caused by MV was associated with longer hospital stay (**Figure 3**)

Several diagnoses were associated with enhanced lethality such as those from clinical origin (RR=1.387 [95%CI=1.223-1.573]), sepsis (RR=1.391 [95%CI=1.222-1.583]), stroke (RR=1.480 [95%CI=1.246-1.757]), and kidney disease (RR=1.485 [95%CI=1.094-2.017]) (**Supplementary material – Table 4; Figure 1**). However, patients with traumatic brain injury (RR=0.744 [95%CI=0.596-0.928]) and/or polytrauma (RR=0.665 [95%CI=0.290-0.836]) or those who needed elective surgery (RR=0.677 [95%CI=0.589-0.778]) and those who needed tracheostomy (RR=0.644 [95%CI=0.535-0.776]) presented decreased risk of death (**Supplementary material – Table 4; Figure 1**), nevertheless, patients who suffered traumatic brain injury and/or polytrauma were younger (data not shown).

3.3. Risk of death associated with PEEP and PaO_2

In our data, PEEP >8 cmH_2O at admission was associated with higher risk of death (RR=1.621 [95%CI=1.393-1.887]). Higher risk of death was also observed in patients with hypoxemia at admission (RR=1.365 [95%CI=1.126-1.655]). In contrast, lower risk of death was observed in those with hyperoxia (RR=0.813 [95%CI=0.693-0.954]) at admission (**Supplementary material – Table 4; Figure 1**).

In the analysis of the 20 first days of intubation, the patients who died required longer ventilatory support and presented higher PEEP values throughout the 20 first days, when compared to those who were discharged, except on the 15^{th} day of hospitalization (**Figure 4**). Curiously, the same did not happen with PaO_2, which presented lower values in the patients who died only between the day of intubation until the 5^{th} day of follow up, as well as between the 7^{th} and 10^{th} day of intubation (**Figure 5**). The categorization of the patients according to the PEEP and the outcome for the 20 days of intubation is presented in **Figure 6.** It seems relevant to point out that patients who died had more time on PEEP >8 cmH_2O.

In the Pearson correlation between numeric markers (PEEP at admission, PaO_2 at admission, IMV duration, hospital stay, time until the pneumonia diagnosis, BMI, and age) no significant correlation was observed, except for the correlation between the IMV duration and hospital stay (CC=0.70; P-value<0.001), as well as the time until the pneumonia diagnosis associated with IMV (CC=0.41; P-value<0.001) and hospital stay (CC=0.35; P-value<0.001) (**Supplementary material – Figure 1**).

3.4. Survival analysis

In the survival analysis, PEEP >8 cmH_2O at admission was seen to be associated with a survival of 26 days, in contrast, in patients with PEEP ≤8 cmH_2O the survival was 41 days (P-value<0.001), a Hazard ratio of 1.713 (95%CI=1.340-2.345) was observed. Regarding the PaO_2 classification, values of 40, 27 and 22 were found, respectively for hyperoxia, normal and hypoxemia (P-value<0.001) (**Figure 7**).

3.5. Multivariate binary logistic regression analysis

In our model, the BMI and the day the diagnosis of pneumonia associated with mechanical ventilation was made were excluded, due to a high number of missing data, also, the previous diagnosis of kidney disease, kidney disease at admission, and use of drugs were also excluded.

The multivariate analysis by the binary logistic regression performed by the forward stepwise method (likelihood ratio) was significant to determine whether the patients' characteristics evaluated were likely to predict death [$X^2_{(9)}$=288.335; P-value <0.001; Nagelkerke R^2=0.245], with an overall prediction percentage of 73.0% for the best equation. Predictors that were significant to predict the risk of death included older age [elderly ≥65 y.o.; OR=2.226 (95%CI=1.728-2.867)]; male (OR=0.754; 95%CI=0.593-0.959); sepsis (OR=1.961; 95%CI=1.481-2.595); need for elective surgery (OR=0.469; 95%CI=0.362-0.608); stroke (OR=2.304; 95%CI=1.502-3.534); hospital stay (OR=0.946; 95%CI=0.935-0.956); hypoxemia (OR=1.635; 95%CI=1.024-2.611) and PEEP >8 cmH_2O at admission (OR=2.153; 95%CI=1.426-3.250). In contrast, hyperoxia could not predict the risk of death (**Table 2**)

4. Discussion

This study described the death of 570 patients (39.5%). Higher risk of this outcome was observed in patients that presented older age, sepsis diagnosis, presence of cerebrovascular accident, hypoxemia at admission, and the use of PEEP >8 cmH_2O at admission. The epidemiological profile of patients admitted in the adult ICU of the university hospital shows mainly adult male patients, with previous history of diabetes mellitus, systematic arterial hypertension, alcoholism and smoking habits. Those patients were usually referred to the ICU by the surgical team, including those undergoing elective surgeries (42.7%). Main causes of admission in the ICU included traumatic brain injury, polytrauma, and sepsis. During the follow-up period, 410 (28.4%) patients presented pneumonia associated with ventilation.

4.1. Epidemiological profile of patients receiving IMV and death risk

This study found a 39.5% death rate and this value is only associated with patients that received IMV. In the literature, a multicenter study that analyzed data from 361 ICU located in the United States, Europe and Latin America and included 5,183 individuals receiving MV reported a 52% death rate in patients that required MV due to respiratory insufficiency [7]. That study presented demographic characteristics very similar to the ones in our study, which showed prevalence of male patients, mean age of 59 years, and the main causes of MV were surgery followed by pneumonia, cardiopathy, sepsis, and trauma. Those authors also reported that the factor that leads to the need for MV might influence the outcome. In Brazil, most patients in ICU are male (50.78%) [16]. This value is similar to the ones found in the United States (51.5%) and the United Kingdom (57.2%) [29,30]. As for the age range, both in Brazil and the United States, adult individuals prevail [16,29].

In this study, the presence of older age, obesity, systemic arterial hypertension, diabetes mellitus, and kidney insufficiency were associated to higher likelihood of death. This data is in accordance with the literature [7,19]. Curiously, these markers seem to be part of the profile of the patients assisted in Brazil, since, according to the Brazilian Intensive Medicine Association, the most frequent comorbidities found in patients admitted in ICU in the country include systemic arterial hypertension (66.40%), diabetes mellitus (32.82%), and kidney insufficiency (11.63%). The prevalence of male patients was also reported (51.30%) by that institution [16]. Such comorbidities might lead to the risk of ICU admission, in which diabetes mellitus, for example, is associated with increased risk of infection in several sites (skin, nervous system, bones, and articulations) [69]. Systemic arterial hypertension, in turn, is the most important morbidity and mortality risk factor in the world, and is associated with increased risk of cardiovascular diseases [31]. Finally, kidney insufficiency presents a 57% increase in the mortality risk of critical patients due to its consequences, namely, metabolic acidosis, electrolytic unbalance, and uremic toxicity [32].

Obesity is also a predictor of both death and longer hospital stay, since it might have consequences in several organs, mainly lungs and heart. In addition, it requires a differentiated MV management and higher ventilatory weaning expertise [32]. The literature reports a relevant study carried out in the United Kingdom including over 3.6 million individuals, which pointed out higher death incidence in patients with BMI over the band considered healthy [BMI >30 Kg/m^2 (obesity)]. However, that study identified the influence of age and BMI together and reported that low BMI increases death risk in young individuals, while higher BMI might have a protective effect in older people (which might be associated with higher nutritional reserve) [33]. However, other studies have reported that obesity influences mainly the time of hospital stay rather than death risk [32,34]. Clearly, the obesity role in the outcome of patients admitted in the ICU and mainly in those that require IMV still needs further studies, since a new pandemic of obese individuals has been observed worldwide [35].

It seems relevant to emphasize that comorbidities not always develop individually. Therefore, when considered together, they might increase even more the likelihood of negative outcomes; however, it is also important to highlight that, in some cases, the risk factors are modifiable and might be reduced by public health policies, awareness raising, and better access to health services, with the implementation of actions such as campaigns incentivizing healthy eating habits, regular practice of physical exercises, adherence to disease control measures, and stopping smoking and consuming alcohol. These actions aim at the reduction of the incidence of obesity, systemic arterial hypertension, diabetes mellitus and, consequently, might reduce the occurrence of cardiovascular events [36].

Regarding diagnosis at admission, our study shows that patients in treatment that present diagnosis of sepsis, cerebrovascular accident, and kidney disorders also present higher death risk when compared to individuals with diagnosis of traumatic brain injury, polytrauma, elective surgeries, and those that evolved to tracheostomy. Some findings in our study disagree with those in the literature, since patients with traumatic brain injury and/or polytrauma were younger than other patients. For example, cerebrovascular accident along with the need for MV presents high mortality rate (56.6%) and tends to predominate among male patients (52.7%) with mean age of 60 years [37,38]. This data is confirmed in our study, which showed that male sex, diagnosis of cerebrovascular accident, and age are more frequent among our patients; however, in our data, male sex was not a death predictor.

When considering death risk markers, sepsis is responsible for ~30-60% deaths in ICU [39]. The highest death risk due to sepsis results from organ failure caused by the host's deregulated response to the infection. Despite all efforts made to prevent infections and treat patients affected by them, sepsis is still one of the most common causes of death worldwide, with varied rates according to the region (South Africa and Asia are the most affected regions), age (older age is more associated with death risk), and sex (male) [40-42]. As for treatment, empirical antimicrobial therapy is still the base treatment, and its start is indicated in the first 6 hours of the diagnosis, and each hour of delay represents a 6% increase in the death risk. The prescription of unsuitable antimicrobial drugs also increases death rates, and bacteria resistance to the antibiotic medication has also been observed. In addition, antibiotic medicine might eliminate the bacteria from the blood plasma, however, it might not be efficient to prevent the pathogen proliferation in the erythrocyte, which might be the cause of inefficiency of some treatments against sepsis [43]. The sepsis profile described is similar to the profile observed in patients that were assisted at the University Hospital where this study was carried out.

Elective surgeries that require ICU admission represent 9.7% of this treatment. Out of those, around 50.4% also present some postoperative complications such as pulmonary embolism and cardiac arrest, with a mortality rate ranging between 2.4 and 9.7% [44]. In this study and in the literature, lower death risk after elective surgery might be associated with the preparation that precedes the procedure.

4.2. Death risk associated with PEEP and PaO_2

This study described the highest death risk of patients receiving ventilation with PEEP >8 cmH_2O and that maintained hypoxemia. On the other hand, patients with hyperoxemia showed lower death risk. Some studies have pointed out that PEEP does not reduce the incidence of pulmonary complications and that for this reason, it should not be considered a protective factor for a favorable outcome. In addition, in some cases, PEEP might increase oxygenation; however, in other cases, it might lead to static stretching which might result in lesions [21,45]. A study found in the literature carried out the analysis of surgical patients and showed that PEEP use resulted in a 5% death risk reduction due to decreased postoperative pulmonary complications such as atelectasis and hypoxemia. However, those findings were inconclusive due to research limitations (small sample) [47]. Concomitantly, we observed higher survival rate in patients that used PEEP $\leq$8 cmH_2O. However, in the literature, the outcome does not seem to be associated with the PEEP cut-off point [24,25]. Gatinoni and co-workers (2015) concluded that there is not a PEEP correct value, and that it must be titrated taking into consideration several factors (oxygenation and hemodynamics, for example) [22].

In extreme cases, hypoxemia might lead to organ failure [48], while hyperoxemia might lead to acute hyperoxic acute lung injury, damaging the epithelium and endothelium due to the release of pro-inflammatory cytokines (TNF-a and gamma interferon (IFN-g)), which might start a pulmonary injury process. [27,49]. Although hyperoxemia in the first 24h of hospital admission does not seem to increase death risk in severe trauma patients [50], it is associated with higher death risk in patients with cardiorespiratory arrest [51]. The use of supplementary oxygen in patients with hyperoxemia (PaO_2 over 150 mmHg) was associated with the worst clinical outcome, possibly due to vasoconstriction, reduction in the coronary blood flow and cardiac output, release of free radicals, and microvascular perfusion modulation [49,52].

Despite the general reduction in death risk in patients with PaO_2 over 150 mmHg in the first 24h of ICU admission, high PaO_2 values should not be recommended when the etiology of the tissue oxygenation decrease is not known (e.g., due to hampered transportation), thus, it might not be wise to state that high levels of arterial oxygenation are always beneficial or might cause deleterious side effects [53].

4.4. Multivariate binary logistic regression analysis

This analysis enabled the identification of markers that were death risk predictors, which included female sex, elderly, sepsis, cerebrovascular accident, hypoxemia, and PEEP >8 cmH_2O ventilation. Concomitantly, patients undergoing elective surgery and male sex presented lower chances of death.

In our study, the fact that it was developed at a trauma referral center in the region where it is located could lead to an increase in the death risk in male patients, which would confirm other epidemiological studies on trauma centers in Brazil (located in the states of Parana, Bahia, and Paraiba). However, male sex was associated with the lowest death incidence. A fact that could explain our findings is that these male patients might have had their age as the main protective factor, since they were all younger patients (data not presented).

Among the elderly, traumatic brain injury might increase mortality when associated with a number of comorbidities such as falls, which can even contribute to the cause of trauma [54-56]. A cohort retrospective study that analyzed data from 8,598 patients, reported that most of the ICU admissions were of male patients. However, when comparing hospital stay, the analysis did not show difference between genders, but the hospital discharge rate was higher for female patients [57]. In addition, older patients are more vulnerable and might develop multiple organ failure faster, which might lead to an increased death rate in that population [58].

Sepsis is accountable for 25% of ICU admissions in Brazil and shows high mortality rates, which might reach 65%, while the sepsis mortality mean around the world might reach 40% [59]. For being an organ failure caused by deregulated and unsuitable host's response to infection, sepsis is potentially fatal and its mortality rate is higher in environments of low or medium resources [60].

Elective surgeries usually present low mortality rate (between 1% and 4%) and preoperative care procedures are considered essential to provide a safe surgical treatment. However, the ideal level of such care has not been defined yet and death still occurs, mainly due to postoperative complications, as for example, pulmonary embolism and cardiac arrest [44].

Both hypoxemia and the use of PEEP >8 cmH_2O were factors that increased mortality rates in our analysis. A study developed with rats that analyzed PEEP as a way of preventing postoperative pulmonary complications reported that the use of PEEP >8 cmH_2O prevented such complications [61]. However, that study reported a postoperative analysis only. In addition, regarding PaO_2, health professionals are most concerned with hypoxemia than with the deleterious effects of hyperoxemia. For this reason, PaO_2 at admission is most times over than that recommended. However, the mortality curve related to PaO_2 at admission presents a U shape, that is, the mortality risk increases as much with low PaO_2 as with high, and it seems relevant to highlight that PaO_2 is influenced by both the oxygen supplementary offer and the PEEP [62].

Although PEEP reduces the collapse of alveolar units and the incidence of atelectasis, one of the factors causing hypoxemia [63], the use of high PEEP values might lead to injury induced by static stretching of alveolar units, mainly when the time in MV is considered, since it is usually longer in patients of clinical or trauma origin [21,64]. The PEEP ideal value remains an unanswered question and if underestimated, it might collapse the alveoli hampering gas exchange. On the other hand, if overestimated, it might lead to alveolar hyperdistention, which also hampers gas exchange and the venous return [22,23]. Therefore, PEEP titration must be compared to the drug administration and it must be applied rationally based on the patient's condition.

PEEP increases linearly the mechanical power, which is the energy delivered to the alveolus as a consequence of the ventilatory parameters set [65]. The mechanical power equation might help the clinical team to estimate injuries associated to MV by observing the variables present in its formula (current volume, respiratory rate, and inspiratory time) and, since PEEP increases the mechanical power volume linearly, it also increases the risk of injury associated with ventilation and, consequently, the death risk [66]. Our study showed increased death risk with PEEP >8 cmH_2O, which might be associated with lesions caused by the ventilation, which is in agreement with the literature.

A recent study incorporated PEEP to the PaO_2/FiO_2 ratio with the purpose of evaluating the mortality predisposition of patients receiving MV and was seen to be a good marker. That study also reported that PEEP incorporated to the PaO_2/FiO_2 ratio alters the classification of gas exchange severity in critical patients [67]. The pandemic caused by the new coronavirus raised great interest in PEEP due to the fact that this disease affects lungs severely in some cases leading to a condition similar to that of the acute respiratory discomfort syndrome, requiring better MV performance [68].

5. Limitations

The limitations of our study include a small sample and missing data such as the absence of severity score and some BMI, and pneumonia associated with ventilation. This was an observational study, which might lead to confounding factors. In addition, due to the COVID-19 pandemic, the 2020 and 2021 data were not included, since the pandemic modulated and affected ICU admissions, including referred ICU [70-73].

6. Conclusions

Our study reported a 39.5% death rate and the predictors listed were sex (female), age (elderly), sepsis diagnosis at admission, cerebrovascular accident, hypoxemia, and the use of PEEP over 8 cmH_2O. The death rate found was similar to that reported by other centers. Although there are predictor factors that cannot be altered, there are those that can be managed, therefore, reducing their influence in the outcome. Regarding PEEP, it was seen to be a bedside tool that can be titrated to improve the clinical outcome. Preventing the occurrence of hypoxemia through the correct oxygen offer and PEEP can also reduce mortality rates, mainly considering that PEEP can be titrated and personalized to each patient. Specific campaigns and providing the population with access to preventive health services might reduce the incidence of cerebrovascular accidents and infections in addition to controlling the prevalence of other factors, such as diabetes mellitus and systemic arterial hypertension, which were frequent in our analysis.

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TABLE 1. Characteristics of the patients in the intensive care unit during the study period (2016-2019)

Patients' characteristics		**Patients – N/1,443 (%)**
Age (years)		56.71±17.55; 59 (46-79)
Age group		
	Adult (18 to 64 y.o.)	914 (63.3)
	Elderly (>65 y.o.)	529 (36.7)
Sex		
	Female	542 (37.6)
	Male	901 (62.4)
		25.92±5.36; 25.60 (22.6-28.8)
Body Mass Index (Kg/m^2)		
	Underweight	55 (3.8)
	Normal weight	423 (29.3)
	Overweight	372 (25.8)
	Obesity grade I	139 (9.6)
	Obesity grade II	27 (1.9)
	Obesity grade III	19 (1.3)
	Not informed	408 (28,3)
Origin		
	Surgery	923 (64.0)
	Clinic	520 (36.0)
Previous history of comorbidities		
	Diabetes mellitus	325 (22.5)
	Hypertension	653 (45.3)
	Smoking	388 (26.9)
	Alcoholism	221 (15.3)
	Other drugs	49 (3.4)
	Dyslipidemia	108 (7.5)
	Pneumopathy	131 (9.1)
	Cardiopathy	310 (21.5)
	Neoplasia	70 (4.9)
	Thyroidopathy	70 (4.9)

	Kidney disorder	60 (4.2)
	Hepatopathy	18 (1.2)
	Neurological sequel	171 (11.9)
	Immunodepression	25 (1.7)
	Gastrointestinal disorder	16 (1.1)
	Other personal background	45 (3.1)
Diagnostic		
	Traumatic brain injury	197 (13.7)
	Polytrauma	210 (14.6)
	Sepsis	375 (26.0)
	Elective surgery	616 (42.7)
	Acute myocardial infarction	89 (6.2)
	Stroke	121 (8.4)
	Subarachnoid hemorrhage	104 (7.2)
	Neoplasia	23 (1.6)
	Neurologic and Psychiatry disorders	69 (4.8)
	Cardiopathy	222 (15.4)
	Nephropathy	31 (2.1)
	Other	49 (3.4)
Days of hypoxia		2.57±2.09; 2 (1-3)
Normal days		2.74±2.0; 2 (1-4)
Days of hyperoxia		5.23±4.32; 4 (2-8)
Pneumonia associated with invasive mechanical ventilation		410 (28.4)
Day of hospitalization on which pneumonia was diagnosed		
Tracheostomy		332 (23.0)
Deaths		570 (39.5)

TABLE 2. Multivariate binary logistic regression analysis to predict death of adult and old patients admitted in an intensive care treatment unit.

Predictors	**B**	**E.P.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95%CI**	
							Lower limit	**Upper limit**
Age (elderly)	0.800	0.129	38.329	1	<0.001	2.226	1.728	2.867
Sex (Male)	-0.283	0.123	5.307	1	0.021	0.754	0.593	0.959
Sepsis (Positive)	0.673	0.143	22.136	1	<0.001	1.961	1.481	2.595
Elective surgery (Presence)	-0.757	0.132	32.774	1	<0.001	0.469	0.362	0.608
Cerebrovascular accident (Positive)	0.834	0.218	14.615	1	<0.001	2.304	1.502	3.534
Hospital stay (days)	-0.056	0.006	99.131	1	<0.001	0.946	0.935	0.956
PaO_2 (normal)			14.712	2	0.001			
PaO_2 (Hyperoxemia)	-0.273	0.157	3.016	1	0.082	0.761	0.560	1.036
PaO_2 (Hypoxemia)	0.492	0.239	4.245	1	0.039	1.635	1.024	2.611
PEEP (>8 cmH_2O)	0.767	0.210	13.320	1	<0.001	2.153	1.426	3.250
Constant	0.525	0.200	6.853	1	0.009	1.690		

Variables not inserted in the equation using the forward stepwise method: patient's origin (surgery or clinic); traumatic brain injury; polytrauma; cerebrovascular accident; presence of pneumonia; need for tracheostomy; diabetes mellitus, systemic arterial hypertension, and alcoholism. B, regression coefficient estimated for the predictor; EP, regression coefficient standard error; df, degrees of freedom; Exp(B), predictor odds ratio; CI, confidence interval; PEEP, positive end-expiratory pressure; PaO_2, oxygen arterial pressure.

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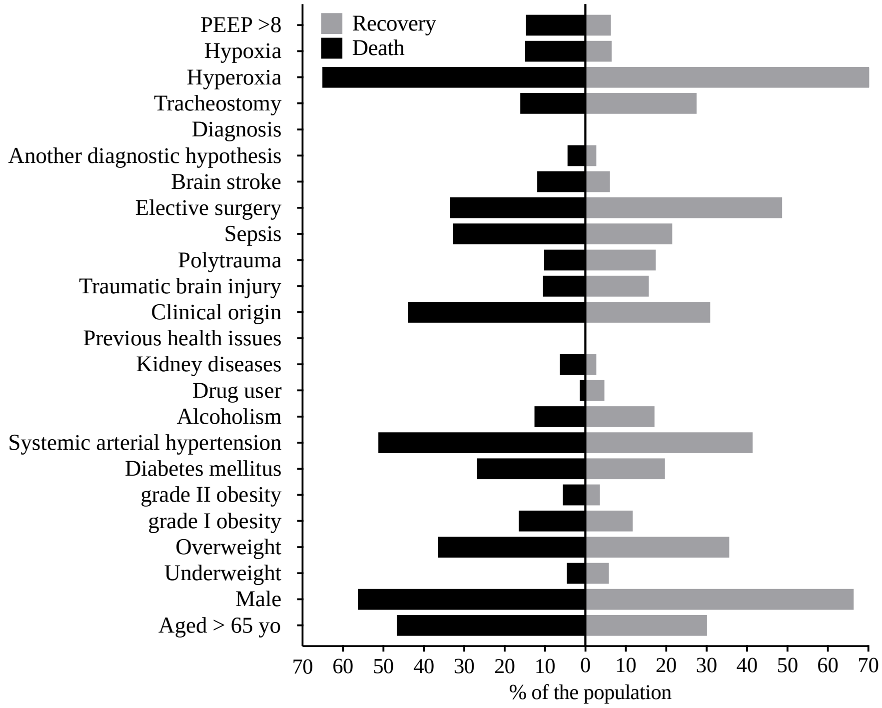

FIGURE 1. Markers that presented statistical significance in the association between patients that died and those that were discharged from hospital. This figure shows the percentage of individuals that presented a marker according to the outcome, as well as the relative risk, whose reference was the percentage of individuals in the group that were discharged from the hospital against the group of patients that died. RR, relative risk; 95%CI, 95% confidence interval. The statistical analysis was carried out using the Fisher Exact test or the Chi-square test and 0.05 alpha.

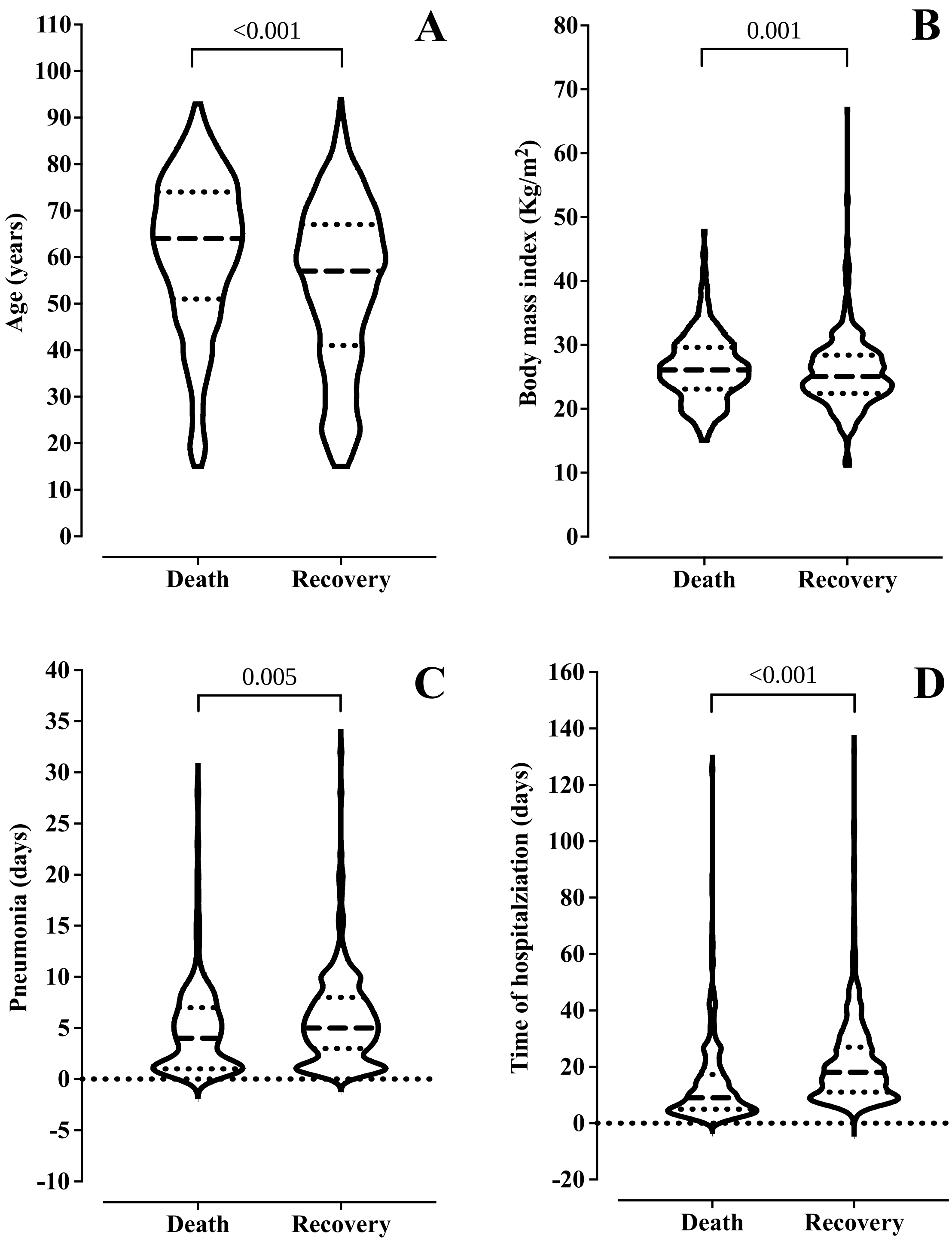

FIGURE 2. Association between clinical outcome and age (**Figure A**), body mass index (**Figure B**), pneumonia associated with mechanical ventilation (**Figure C**), and hospital stay (**Figure D**). The statistical analysis was carried out using the Mann-Whitney Test and a 0.05 alpha.

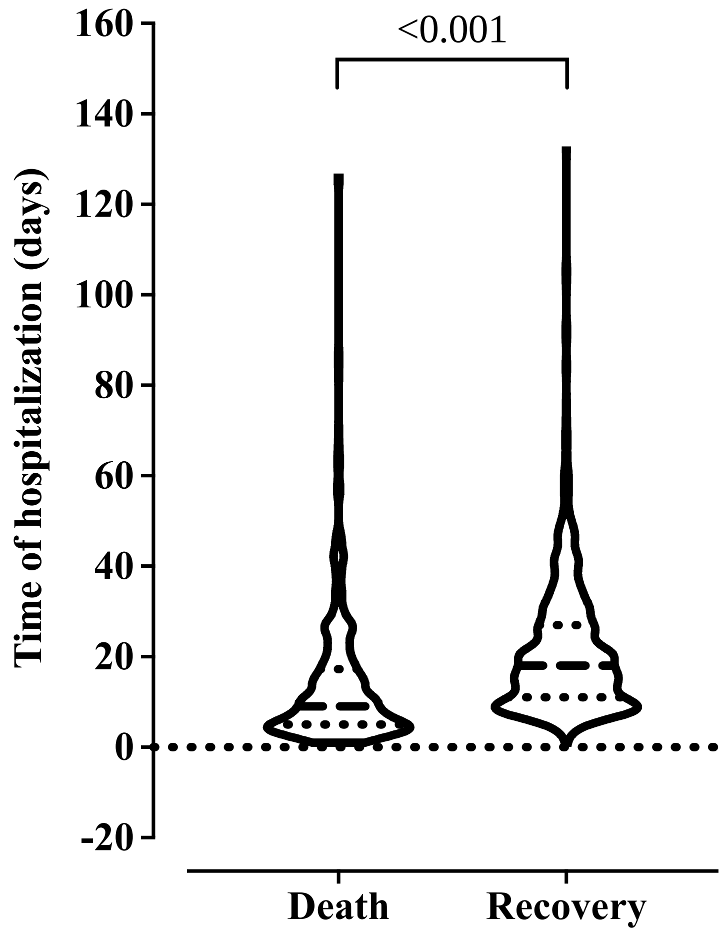

FIGURE 3. Association between the risk of developing pneumonia associated with mechanical ventilation according to the mechanical ventilation time. The statistical analysis was carried out using the Mann-Whitney test and a 0.05 alpha.

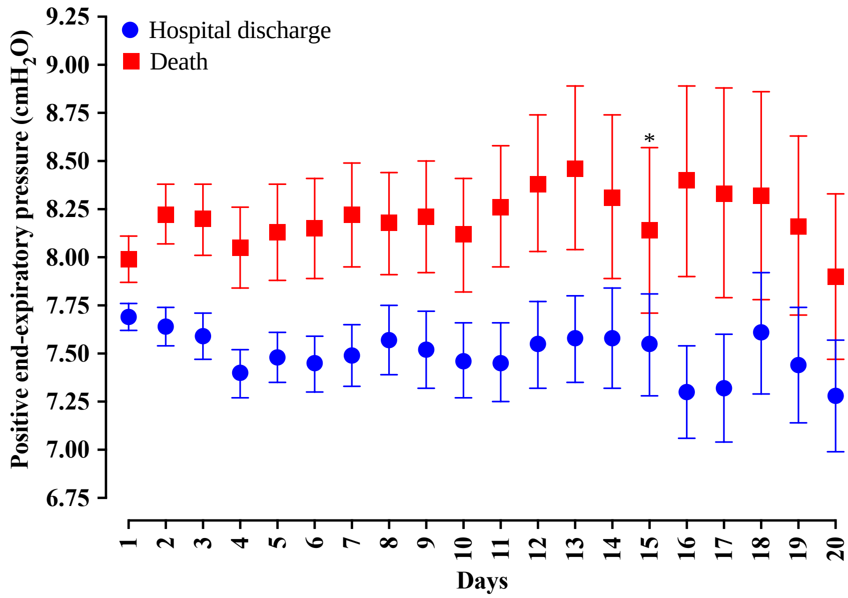

FIGURE 4. Distribution of the positive end-expiratory pressure (PEEP) values according to the days of mechanical ventilation. In blue, individuals that were discharged. In red, individuals that died. The statistical analysis was carried out using the Mann-Whitney test and a 0.05 alpha. *, P-value>0.05.

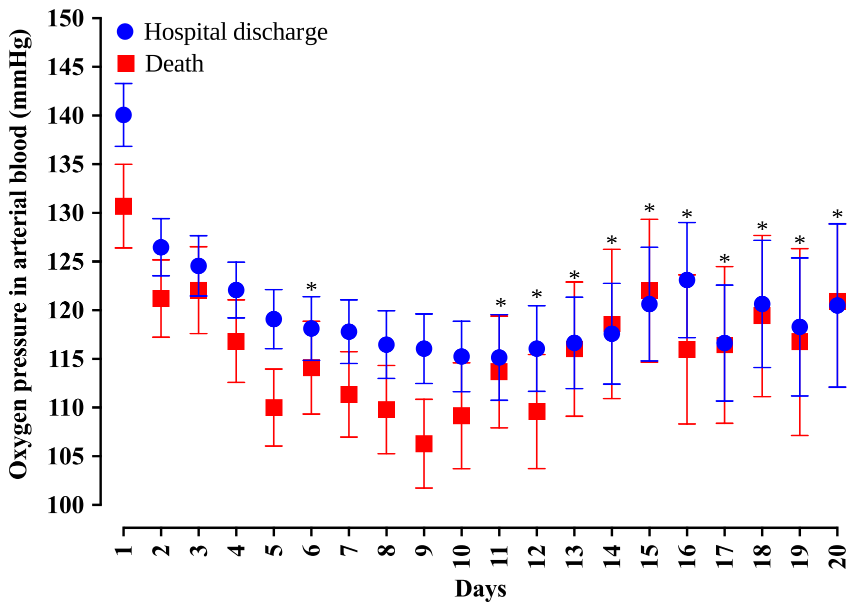

FIGURE 5. Distribution of the oxygen arterial pressure (PaO_2) values according to the days of mechanical ventilation. In blue, individuals that were discharged. In red, individuals that died. The statistical analysis was carried out using the Mann-Whitney test and a 0.05 alpha. *, P-value>0.05.

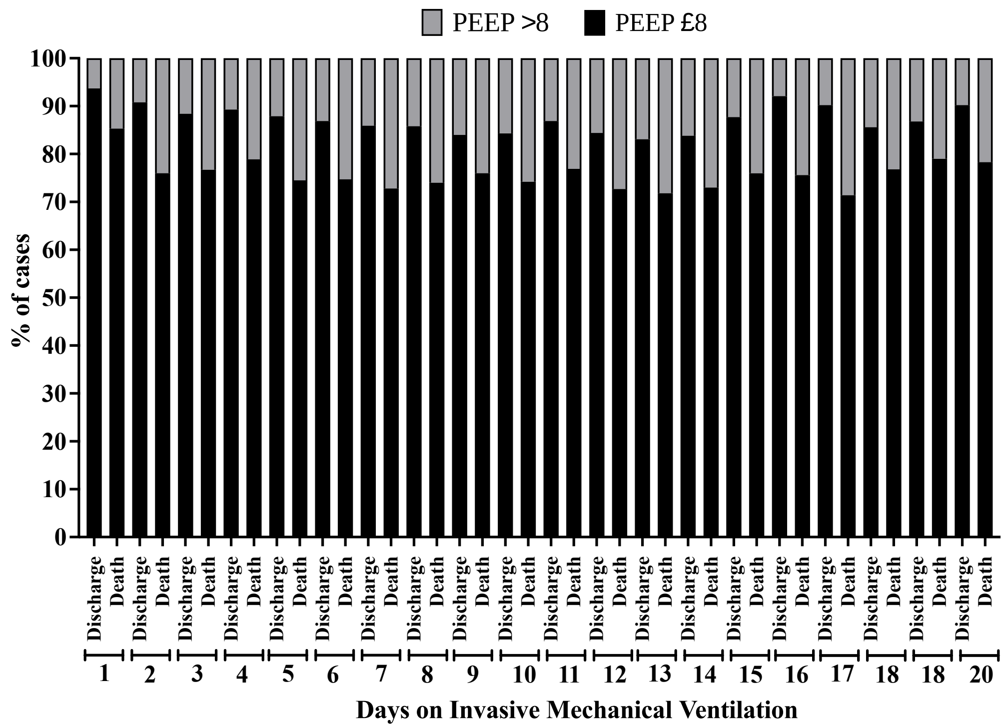

FIGURE 6. Percentage of patients according to the clinical outcome distributed by the positive end-expiratory pressure (PEEP) value (≤8 cmH_2O or >8 cmH_2O) and according to the time of invasive mechanical ventilation (days 1 to 20).

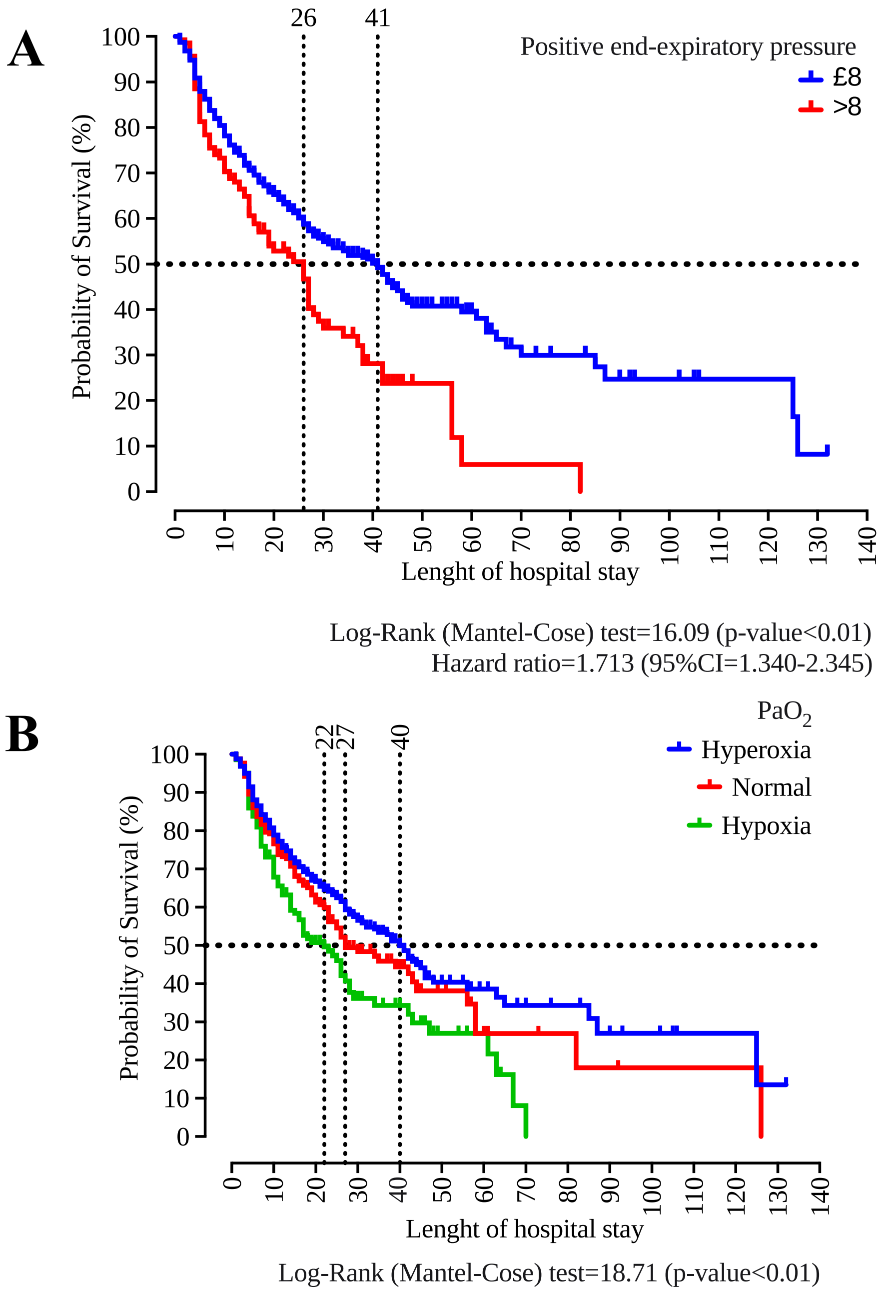

FIGURE 7. Survival curve of patients that were intubated at the university hospital according to the positive end-expiratory pressure (PEEP) and according to the oxygen arterial pressure (PaO_2) classification as normal, hypoxemia and hyperoxemia. The statistical analysis was carried out using the Log-Rank (Mantel-Cose) test. The Hazard ratio was calculated using the PEEP ≤ 8 cmH_2O as the numerator parameter and a 0.05 alpha.

Supplementary Material – Table 1. Previous history of comorbidities of the patients in the intensive care unit during the study period (2016-2019).

Characteristics	**Patient - N**
Miscarriage	1
Amputation	2
Anemia	5
Sickle cell anemia	1
Obstructive sleep apnea	3
Sleep apnea	1
Arthrosis	5
Arthrosis and anemia	1
Transient ischemic attack	1
Hearing deficiency	1
Malnutrition	3
Malnutrition and anemia	1
Sacral scab	1
Fibromyalgia	1
Glaucoma	3
Ectopic pregnancy	1
Leprosy	1
Hernia	1
Hysterectomy	1
Prostatectomy	1
Puerperal	1
Down syndrome	1
Deafness	1
Tracheostomy	1
Traumatic brain injury	1
Thrombocytosis	1
Pulmonary thromboembolism	1
Deep vein thrombosis	3

Supplementary Material – Table 2. Diagnosis of the patients in the intensive care unit during the study period

Diagnosis	**Patient - N**
Abscess	1
Miscarriage	1
Drowning	1
Asthma	1
Colostomy	1
Diabetes Insipidus	1
Multiple organ disfunction	1
Diverticulitis	1
Neuromuscular disease	3
Chronic obstructive pulmonary disease	2
Chest drainage	3
Pulmonary emphysema	1
Wegner’s granulomatosis	1
High digestive bleeding	1
Lower gastrointestinal bleeding	1
HIV	1
Urinary infection	3
Intoxication	1
Cardiorespiratory arrest	2
Pneumocystosis	1
Pneumothorax	1
Lowered level of consciousness	1
Motor sequelae	2
Systemic inflammatory response syndrome	1
SARS and Multiple organ disfunction	1
Pulmonary thromboembolism	3
thrombophilia	1
Not informed	11

TABLE 3. Association between demographic markers and personal background of patients admitted in the intensive care unit as death risk factor.

Patient's characteristics	Groups	Deaths - N (%)	Discharges - N (%)	Total - N	p-value	RR	95%CI
Age group	Adult	304 (53.3)	610 (69.9)	914	0.001	Reference	-
	Elderly	266 (46.7)	263 (30.1)	529		1.512	1.334-1.713
Gender	Female	249 (43.7)	293 (33.6)	542	0.001	Reference	-
	Male	321 (56.3)	580 (66.4)	901		0.776	0.683-0.880
Body mass index	Underweight	18 (4.6)	37 (5.8)	55	0.046	0.955	0.639-1.426
	Normal weight	145 (36.8)	278 (43.4)	423		Reference	-
	Overweight	144 (36.5)	228 (35.6)	372		1.129	0.940-1.357
	Obesity grade I	65 (16.5)	74 (11.5)	139		1.354	1.085-1.690
	Obesity grade II and III	22 (5.6)	24 (3.7)	46		1.426	1.02-1.977
Personal background							
Diabetes mellitus	Absent	417 (73.2)	701 (80.3)	1.118	0.002	Reference	-
	Present	153 (26.8)	172 (19.7)	325		1.262	1.099-1.449
Hypertension	Absent	278 (48.8)	512 (58.6)	790	0.001	Reference	-
	Present	292 (51.2)	361 (41.4)	653		1.271	1.119-1.443
Smoking	Absent	426 (74.7)	629 (72.1)	1,055	0.275	Reference	-
	Present	144 (25.3)	244 (27.9)	388		0.919	0.792-1.067
Alcoholism*	Absent	498 (87.4)	724 (82.9)	1,222	0.025	Reference	-
	Present	72 (12,6)	149 (17,1)	221		0.799	0.654-0.978
Other drugs*	Absent	562 (98.6)	832 (95.3)	1,394	0.001	Reference	-
	Present	8 (1,4)	41 (4.7)	49		0.405	0.214-0.766

Dyslipidemia	Absent	529 (92.8)	806 (92.3)	1,335	0.760	Reference	-
	Present	41 (7.2)	67 (7.7)	108		0.958	0.746-1.230
Pneumopathy	Absent	508 (89.1)	804 (92.1)	1,312	0.061	Reference	-
	Present	62 (10.9)	69 (7.9)	131		1.222	1.008-1.483
Cardiopathy	Absent	434 (76.1)	699 (80.1)	1,133	0.077	Reference	-
	Present	136 (23,9)	174 (19.9)	310		1.145	0.990-1.325
Neoplasia	Absent	537 (94.2)	836 (95.8)	1,373	0.210	Reference	-
	Present	33 (5.8)	37 (4.2)	70		1.205	0.933-1.558
Thyreopathy	Absent	535 (93.9)	838 (96,0)	1,373	0.079	Reference	-
	Present	35 (6.1)	35 (4,0)	70		1.283	1.006-1.637
Kidney disease	Absent	534 (93.7)	849 (97.3)	1,383	0.001	Reference	-
	Present	36 (6,3)	24 (2.7)	60		1.554	1.251-1.931
Hepatopathy	Absent	561 (98.4)	864 (99.0)	1,425	0.467	Reference	-
	Present	9 (1.6)	9 (1.0)	18		1.270	0.797-2.025
Neurologic Sequel	Absent	511 (89.6)	761 (87.2)	1,272	0.158	Reference	-
	Present	59 (10.4)	112 (12.8)	171		0.859	0.691-1.067
Immunosupression	Absent	557 (97.7)	861 (98.6)	1,418	0.219	Reference	-
	Present	13 (2.3)	12 (1.4)	25		1.324	0.903-1.940
Gastrointestinal	Absent	565 (99.1)	862 (98.7)	1,427	0.612	Reference	-
disorder	Present	5 (0.9)	11 (1.3)	16		0.789	0.381-1.697
Other	Absent	553 (97.0)	845 (96.8)	1,398	0.878	Reference	-
	Present	17 (3.0)	28 (3.2)	45		0.955	0.653-1.397

Patient's age was associated with the presence of drug use [p-value<0.001; (Yes) 35.12±11.42, 34 (26.5 to 40); (No) 57.47±17.24; 60 (47 to 70)] and alcoholism [p-value=0.013; (Yes) 55.43±13.37, 57 (47 to 64); (No) 56.95±18.20; 60 (45 to 70)], and individuals who presented drug use and alcoholism were younger. N, number of individuals; RR, relative risk; 95%CI, 95% confidence interval.

TABLE 3. Association between patient's origin, diagnosis indicating intubation, presence of pneumonia associated with invasive mechanical ventilation, need for tracheostomy and intubation markers of patients admitted in the intensive care unit as death risk factor.

Patient's characteristics	**Group**	**Death – N (%)**	**Discharge – N (%)**	**Total – N**	**p-value**	**RR**	**95%CI**
Origin	Surgery	320 (56.1)	603 (69.1)	923	0.001	Reference	-
	Clinic	250 (43.9)	270 (30.9)	520		1.387	1.223-1.573
Diagnosis							
Traumatic brain injury	Absent	510 (89.5)	736 (84.3)	1,246	0.006	Reference	-
	Present	60 (10.5)	137 (15.7)	197		0.744	0.596-0.928
Polytrauma	Absent	512 (89.8)	721 (82.6)	1,233	0.001	Reference	-
	Present	58 (10.2)	152 (717.4)	210		0.665	0.290-0.836
Sepsis	Absent	383 (67.2)	685 (78.5)	1,068	0.001	Reference	-
	Present	187 (32.8)	188 (21.5)	375		1.391	1.222-1.583
Elective Surgery	Absent	379 (66.5)	448 (51.3)	827	0.001	Reference	-
	Present	191 (33.5)	425 (48.7)	616		0.677	0.589-0.778
Acute Myocardial Infarction	Absent	527 (92.5)	827 (94.7)	1,354	0.093	Reference	-
	Present	43 (7.5)	46 (5.3)	89		1.241	0.991-1.555
Stroke	Absent	502 (88.1)	820 (93.9)	1,322	0.001	Reference	-
	Present	68 (11.9)	53 (6.1)	121		1.480	1.246-1.757
Subarachnoid hemorrhage	Absent	520 (91.2)	819 (93.8)	1,339	0.076	Reference	-
	Present	50 (8.8)	54 (6.2)	104		1.238	1.003-1.528
Neoplasia	Absent	562 (98.6)	858 (98.3)	1,420	0.675	Reference	-
	Present	8 (1.4)	15 (1.7)	23		0.879	0.500-1.544
	Absent	550 (96.5)	824 (94.4)	1,374	0.077	Reference	-
Neurologic and psychiatric disease	Present	20 (3.5)	49 (5.6)	69		0.724	0.498-1.053

Cardiopathy	Absent	471 (82.6)	750 (85.9)	1,221	0.101	Reference	-
	Present	99 (17.4)	123 (14.1)	222		1.156	0.982-1.730
Kidney disorder	Absent	552 (96.8)	860 (98.5)	1,412	0.040	Reference	-
	Present	18 (3.2)	13 (1.5)	31		1.485	1.094-2.017
Other	Absent	545 (95.6)	849 (97.3)	1,394	0.103	Reference	-
	Present	25 (4.4)	24 (2.7)	49		1.305	0.984-1.730
Pneumonia associated with invasive mechanical ventilation	Absent	412 (72.3)	621 (71.1)	1,033	0.676	Reference	-
	Present	158 (27.7)	252 (28.9)	410		0.966	0.837-1.115
Tracheostomy	Absent	478 (83.9)	633 (72.5)	1,111	0.001	Reference	-
	Present	92 (16.1)	240 (27.53)	332		0.644	0.535-0.776
	Hypoxia	85 (14.9)	57 (6.5)	142	<0.001	1.365	1.126-1.655
	Normal	114 (20)	146 (16.7)	260		Reference	-
Oxygen blood pressure (PaO_2)	Hyperoxia	371 (65.1)	670 (76.7)	1,041		0.813	0.693-0.954
Positive end-expiratory pressure	≤8	486 (85.3)	818 (93.7)	1,304	<0.001	Reference	-
	>8	84 (14.7)	55 (6.3)	139		1.621	1.393-1.887

The patients' age was associated with the presence of traumatic brain injury [p-value<0.001; (Yes) 40.87±17.06, 38 (25 to 36); (No) 59.22±16.28; 61 (50 to 71)] and polytrauma [p-value<0.01; (Yes) 38.73±16.62, 34 (24.75 to 51); (No) 59.78±15.78; 61 (51 to 71)], and individuals who presented drug use and alcoholism were younger. N, number of individuals; RR, relative risk; 95%CI, 95% confidence interval.

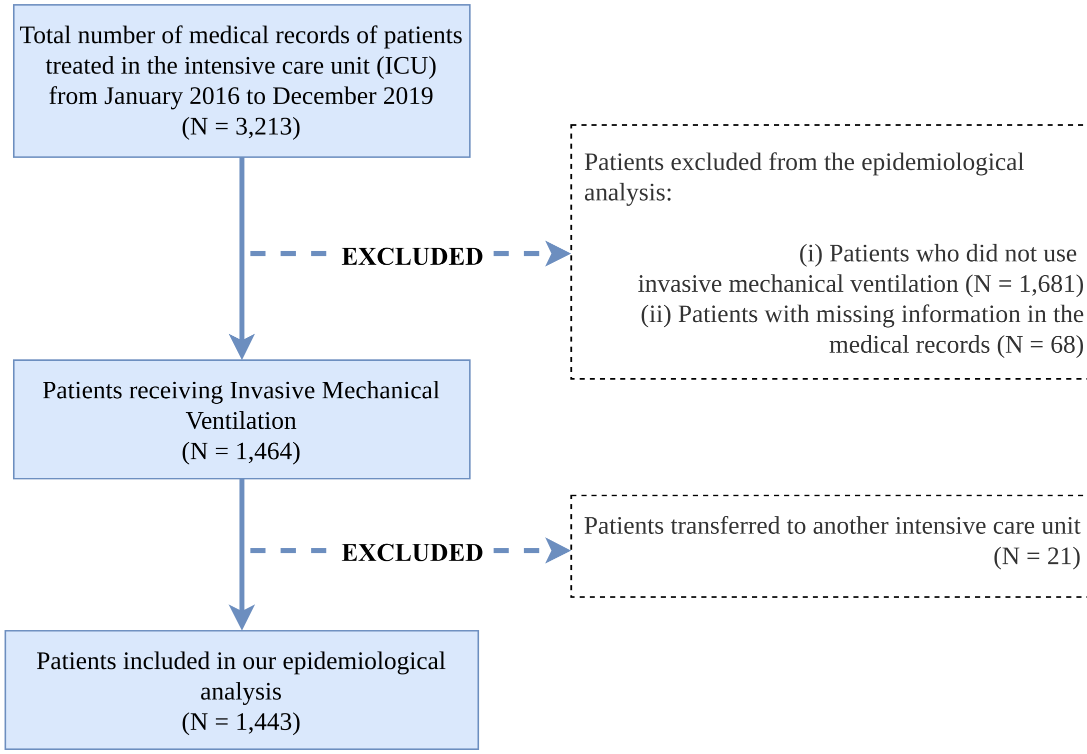

FIGURE 1. Flowchart of medical record analysis and inclusion of intubated patients in the intensive care unit of a university hospital in São Paulo State, Brazil.

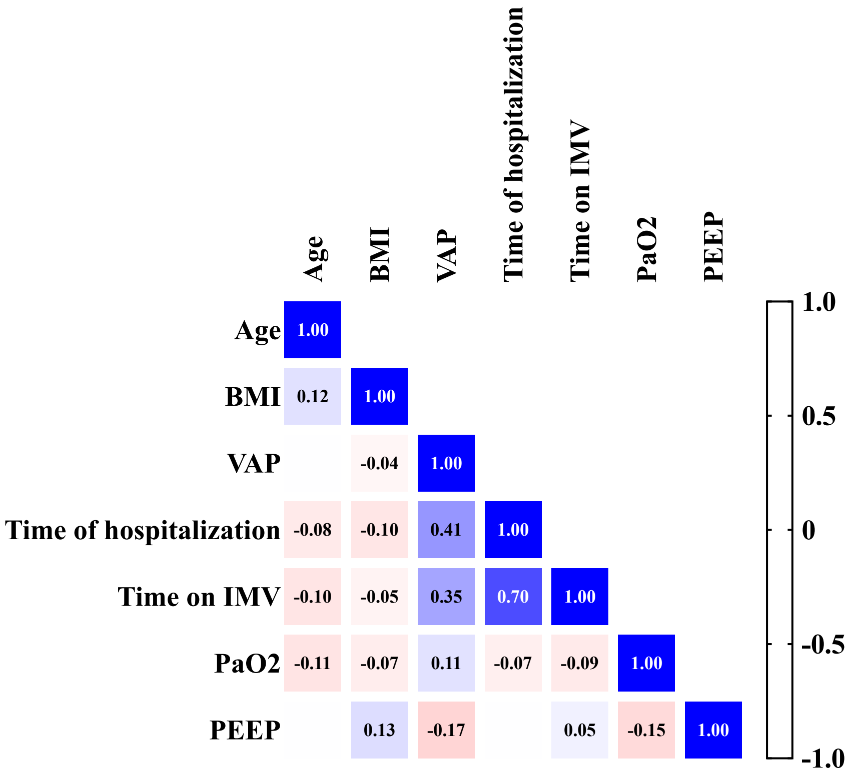

FIGURE 2. Pearson's correlation between markers with numeric distribution [positive end-expiratory pressure (PEEP) at admission, oxygen arterial pressure (PaO_2) at admission, time receiving invasive mechanical ventilation (IMV), hospitalization (hospital stay) time, time up to the diagnosis of ventilation-associated pneumonia (VAP), body mass index (BMI), and age] included in the study. 0.05 alpha.

Capítulo III: Artigo submetido

Article type: Short Communication

Title: Impact of Positive End-expiratory Pressure on Hemodynamics, Gas exchange and Driving Pressure of Patients under Invasive Mechanical Ventilation Without Previous Lung Disease: An Intervention Study

Short title: PEEP and Intubation

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Declarations

Ethics approval and consent to participate: The study was approved by the ethics committee from the institution (CAAE: 29718820.9.0000.5514; Technical Opinion: #3.939.784).

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Abstract

Introduction: Positive End-expiratory Pressure (PEEP) is used to optimize gas exchange and improve oxygenation. However, in patients that do not present lung diseases the real impact of this factor on their hemodynamics, gas exchange, and driving pressure is still unknown. Thus, this study aimed to evaluate the impact of three different levels of PEEP on these markers in individuals without previous lung disease.

Methods: A prospective and interventional study was carried out in patients without previous lung disease under mechanical ventilation. The ventilation provided to the patients presented a current volume of 6-8 mL/Kg predicted body weight, and a fixed oxygen inspired fraction for the oxygen arterial saturation (SaO_2) with a >90% target. The patients were subjected to three PEEP levels (6, 8, and 10 cmH_2O) for 30 min each. The items evaluated were: arterial oxygen partial pressure (PaO_2), carbon dioxide arterial pressure ($PaCO_2$), a SaO_2, oxygenation index, systolic, diastolic, and mean arterial pressure, driving pressure, and static complacency. The statistical analysis was carried out using the generalized linear model, with a 0.05 alpha.

Results: The data of 150 patients was analyzed, and out of those, 80 (53.3%) died. Highest prevalence was seen in male patients, 97 (64.7%) after surgery 98 (65.3%), and the most frequent cause of hospitalization was polytrauma, (37; 24.7%). When evaluating the markers associated with hemodynamics, gas exchange, and driving pressure, no statistically significant response was observed regarding the PEEP modulation between its different levels. However, in absolute terms, increase PEEP correlated with systolic arterial pressure reduction in both groups (from 129 to 125 mmHg in the hospital discharge group, and from 129 to 127 mmHg in the death group) (P-value=0.675), the diastolic arterial pressure was not altered in any of the groups (keeping a 63 mmHg mean value), while the mean arterial pressure decreased from 85 to 83 mmHg in the hospital discharge group and from 85 to 84 mmHg in the death group (P-value=0.484). Regarding PaO_2, the hospital discharge group presented a reduction (from 120 to 115 mmHg), while the death group showed a slight increase (from 122 to 124 mmHg) (P-value=0.359). Increased PEEP did not impact $PaCO_2$ or SaO_2 in any of the groups. Likewise, driving pressure was not altered with the PEEP increase and, consequently, the static complacency remained unchanged.

Conclusion: Increased PEEP in individuals without previous lung disease and under mechanical ventilation was not associated with alterations in the hemodynamics, gas exchange or driving pressure.

Keywords: positive end-expiratory pressure; hemodynamics; gas exchange; driving pressure; oxygenation index; mechanical ventilation.

Introduction

One of the challenges in the clinical practice for the mechanical ventilation (MV) management team is to understand the interaction between what is delivered by the mechanical ventilator to the lung parenchyma and how the parenchyma accepts and receives such parameters, and such interactions depend mainly on two factors: (i) values offered by the operator such as current volume, pressures (inspiratory and expiratory), and respiratory flow and frequency; (ii) lung parenchyma conditions that might reduce its gas exchange capacity such as increase in its heterogeneity, increasing collapse and alveolar hyperdistention areas (1). The use of protective parameters such as current volume limitation (6 mL/Kg predicted body weight) and plateau pressure (up to 30 cmH_2O) in MV help to reduce the risk of lesions resulting from intubation (2). However, the literature still lacks a coherent interpretation of how these parameters must be set in the ventilator so that greater functional gain is achieved by the patients with lower number of injuries.

Among the ventilatory parameters, positive end-expiratory pressure (PEEP) is the pressure that remains in the alveolus at the end of the expiration and its application might increase oxygenation according to the Fick Law principle. Since an increase in the PEEP might promote increase in the gas exchange area and reduction in the capillary alveolus membrane thickness, it might facilitate gas diffusion, and, therefore, increase the arterial oxygen partial pressure (PaO_2), and the oxygen arterial saturation (SaO_2) (3,4). In routine care, the PEEP use enables a better recruitment of unstable alveoli and improves gas exchange and tissular oxygenation, and at the same time, reduces and redistributes heterogeneous mechanical stresses of the current ventilation (5,6).

However, PEEP might optimize or worsen the performance of lung functions, and this dichotomy results in the search of a reliable marker for the choice of an ideal PEEP value. In such context, the respiratory system complacency has been considered a good marker to be used during hospital treatment (7). Complacency is the parameter that evaluates the respiratory system elasticity through the understanding of the lung tissue expansion capacity and, during MV, the static complacency measured by the application of an inspiratory pause is estimated from the ratio between the alveolar current volume and the driving pressure (plateau pressure – PEEP) [Cst=VC/DP] (8). Therefore, in the presence of PEEP that minimizes the driving pressure, the complacency optimization is possible. However, when values above the necessary ones are applied, PEEP might have negative effects such as reduction in the cardiac debt and right ventricle performance, resulting in worsened gas exchange effectiveness, which might provoke a PaO_2 decrease (9). Currently, driving pressure, which can be modulated by the PEEP, has been reported as a mortality risk marker, and although a consensus has not been reached, the suggestion is to keep the driving pressure value up to 15 cmH_2O in patients with acute respiratory distress syndrome (10,11).

Due to the PEEP importance in the clinical practice, this study aims to evaluate the impact of three different levels of this marker on the hemodynamics, gas exchange, and driving pressure of individuals without previous lung disease admitted for treatment in a university hospital.

Methods

The study evaluated a population of participants admitted to the adult intensive care unit of the São Francisco de Assis na Providência de Deus University Hospital, in Bragança Paulista, state of São Paulo, Brazil that were subjected to invasive mechanical ventilation (IMV). Only patients that did not present previous lung disease were included (after analysis by a multiprofessional team). They could be male or female, clinical or surgical, and had to be over 18 years old. The data collected included: sex, age, diagnosis, hospitalization time, and time in the invasive mechanical ventilation, personal background, height (in cm), body mass index (BMI, Kg/m^2), clinical outcome (hospital discharge or death), and type of ventilatory support.

This intervention, clinical, non-randomized or controlled study was carried out aiming to evaluate the impact of different PEEP levels (6, 8, and 10 cmH_2O) in the same patient under IMV on PaO_2, carbon dioxide arterial pressure ($PaCO_2$), SaO_2, oxygenation index (PaO_2/FiO_2), systolic, diastolic and mean arterial pressure, driving pressure, and Cst. The evaluation of PaO_2, $PaCO_2$, and SaO_2 was carried out using arterial blood gas test collected through peripheral arterial access performed by the nurse in the health unit after request by the medical doctor. The study included patients without previous lung disease history and for this reason, the PEEP levels employed did not exceed 10 cmH_2O.

The study excluded patients that presented hemodynamic instability, pneumothorax, or undrained pleural effusion, and the absence of peripheral arterial access. If any hemodynamic instability was noticed during collection, it was interrupted.

The values of different markers were collected at the three different PEEP levels in the first twenty-four hours of admission to the ICU, after the participant had remained for 30 minutes in each level and with a fixed FiO_2 (titrated for SpO_2 >90% and unchanged during collection), current volume of 6-8 mL/Kg predicted body weight (with estimated height supplied by the sector nutritionist), plateau pressure below 30 cmH_2O, and respiratory frequency for pH above 7.20.

The statistical analysis was aided by the software IBM SPSS Statistics for Macintosh, Version 27.0. The descriptive analysis presents data by mean and standard deviation or by relative and absolute frequency. The inference analysis was carried out employing the generalized linear model containing the different PEEP levels as factors among the patients, and the markers PaO_2, $PaCO_2$, SaO_2, oxygenation index, systolic, diastolic, and mean arterial pressure, driving pressure, and Cst as dependent data. In the model, the outcome (death or hospital discharge) was conditioned as an analysis factor among individuals. The covariables included were: patients' sex, age, and BMI. A 0.05 alpha was considered as significant in all analyses carried out.

Results

A hundred and fifty patients were included in the study and out of those, 97 (64.7%) were men, and (65.3%) from surgical origin. The main causes of hospitalization were polytrauma (37; 24.7%), traumatic brain injury (30; 20%), sepsis (23; 15,3%), and need for elective surgery (41; 27,3%). Among the patients, 47 (31,1%) developed pneumonia associated with ventilation, and 59 (39.3%) evolved into the need for tracheostomy (**Table 1**).

The most frequent personal background was systemic arterial hypertension (52; 34.7%), followed by diabetes mellitus (32; 21.3%), smoking and cardiopathy (27; 18% each), and drinking habits (25; 16.7%). The most used type of ventilation was the control volume assist ventilation (138; 92%). Eighty patients (53.3%) died (**Table 1**).

TABLE 1. Characteristics of the patients included in the study.

Markers	**Data**	**N (%)**
Sex	Female	53 (35.3%)
	Male	97 (64.7%)
Cause of hospitalization		
	Traumatic brain injuty	30 (20%)
	Polytrauma	37 (24.7%)
	Sepsis	23 (15.3%)
	Elective surgery	41 (27.3%)
	Acute myocardial infarction	2 (1.3%)
	Cerebrovascular accident	15 (10%)
	Subarachnoid hemorrhage	14 (9.3%)
	Diabetes types 1 and 2	3 (2.0%)
	Obesity	6 (4.0%)
	Neurological and psychiatric disorder	17 (11.3%)
	Cardiopathy	16 (10.7%)
	Motor Sequelae	1 (0.7%)
Patients' origin	Surgical	98 (65.3%)
	Clinical	52 (34.7%)
Pneumonia associated with the ventilator	Present	47 (31.1%)
	Absent	103 (68.7%)
Need for tracheostomy	Yes	59 (39.3%)
	No	91 (60.7%)
Outcome	Hospital discharge	70 (46.7%)
	Death	80 (53.3%)
Comorbidities		
	Diabetes mellitus	32 (21.3%)
	Systemic arterial hypertension	52 (34.7%)
	Smoking	27 (18.0%)
	Drinking	25 (16.7%)
	Drug addiction	13 (8.7%)
	Dyslipidemia	9 (6.0%)

	Pneumopathy	2 (1.3%)
	Cardiopathy	27 (18.0%)
	Neurological sequelae	5 (3.3%)
	Others	43 (35.3%)
Types of ventilation	Pressure control ventilation	12 (8.0%)
	Volume control ventilation	138 (92.0%)

The association between PEEP and the markers evaluated in the study, namely, PaO_2, $PaCO_2$, SaO_2, oxygenation index, systolic, diastolic and mean arterial pressure, driving pressure, and Cst according to the clinical outcome (hospital discharge and death) is presented (**Table 2)**. When evaluating the markers associated with hemodynamics, gas exchange, and driving pressure, no statistically significant response was observed in relation to the PEEP modulation at its different levels.

TABLE 2. GLM analysis to determine the interaction factor between PEEP levels and death of patients intubated at the University Hospital that were included in the study.

Marker	Outcome	PEEP 6	PEEP 8	PEEP 10	F	P-value
Systolic arterial pressure	Hospital discharge	129.24±24.85	127.77±23.93	125.40±20.53	0.336	0.675
	Death	129.25±28.27	130.09±29.60	127.33±29.18		
Diastolic arterial pressure	Hospital discharge	64.13±12.70	64.73±12.02	63.94±11.13	1.036	0.355
	Death	63.19±11.81	66.29±14.96	63.81±12.23		
Mean arterial pressure	Hospital discharge	85.49±13.82	84.69±12.97	83.51±11.48	0.710	0.484
	Death	85.30±15.18	86.88±16.97	84.89±16.78		
SaO_2	Hospital discharge	97.84±2.29	97.84±2.06	97.87±1.86	0.062	0.935
	Death	97.74±2.30	97.63±2.51	97.70±2.50		
PaO_2	Hospital discharge	120.40±32.30	116.61±28.59	115.76±29.70	0.990	0.359
	Death	122.26±40.80	121.03±39.00	124.60±43.94		
$PaCO_2$	Hospital discharge	41.43±6.72	41.69±6.11	42.86±6.01	0.883	0.411
	Death	41.79±7.04	42.04±7.35	42.26±6.84		
Oxygenation index	Hospital discharge	386.97±143.60	374.49±125.39	370.20±124.94	0.529	0.555
	Death	361.08±137.48	356.52±129.71	360.95±132.09		
Driving pressure	Hospital discharge	9.81±2.80	9.69±3.06	9.86±3.06	0.501	0.595
	Death	10.41±3.50	10.06±3.16	10.11±3.58		
Static complacency	Hospital discharge	47.51±16.53	48.64±18.00	49.25±21.71	0.209	0.781
	Death	46.18±18.83	47.99±21.99	49.39±25.09		

PaO_2, O_2 arterial pressure; $PaCo_2$, carbon dioxide arterial pressure; SaO_2, O_2 arterial saturation.

Factors among individuals, and different PEEP levels, and dependent data such as ventilatory markers (PaO_2, $PaCO_2$, SpO_2, oxygenation index, systolic, diastolic, and mean arterial pressure, driving pressure, static complacency, and oxygenation index).

In this model, the outcome (death or hospital discharge) was conditioned as a factor of analysis between the individuals. Data such as sex, age, and the patients' BMI was included as covariables. A 0.05 alpha was considered as significant in all analysis carried out.

As for the hemodynamic markers in the population that evolved into hospital discharge, in absolute terms, the systolic arterial pressure decreased according to the increased PEEP and ranged from 129 mmHg at the 6 cmH_2O PEEP to 125 mmHg at the 10 cmH_2O PEEP (P-value=0.675). The diastolic arterial pressure, in turn, kept the average 64 mmHg at the three PEEP levels (P-value=0.355). However, the mean arterial pressure decreased 1 (um) mmHg at each PEEP level, ranging between 85 and 83 mmHg (P-value=0.484). The patients that died also showed a decrease in the systolic arterial pressure from 129 mmHg at the 6 cmH_2O PEEP to 127 mmHg at the 10 cmH_2O PEEP (P-value=0.675), while the diastolic arterial pressure kept an average of 63 mmHg (P-value=0.355), and the mean arterial pressure decreased from 85 mmHg at the 6 cmH_2O PEEP to 84 mmHg at the 10 cmH_2O PEEP (P-value=0.484).

When analyzing the arterial blood gas test markers, PaO_2 showed decreased values when the PEEP was increased in the population that evolved into hospital discharge (from 120 mmHg at the 6 mmHg PEEP to 115 mmHg at the 10 mmHg PEEP), while in the group that evolved into death, an increase was observed in the PaO_2 from 122 mmHg at the 6 cmH_2O mmHg to 124 mmHg at the 10 cmH_2O mmHg. However, no statistical significance was observed in any of the cases (P-value=0.359). As for the $PaCO_2$, the same value was kept at the PEEP three levels in both groups (death and hospital discharge) (41 mmHg; P-value=0.411), while SaO_2 presented a 97% value at the PEEP three levels (P-value=0.935).

Regarding the oxygenation index, it was seen to decrease as PEEP increased (from 386 at the 6 cmH_2O PEEP to 370 at the 10 cmH_2O PEEP, in the hospital discharge group, and 361 at the 6 cmH_2O PEEP to 360 at the 10 cmH_2O PEEP in the death group; P-value=0.555). Driving pressure was not altered at any of the PEEP three levels, remaining at 9 cmH_2O in the hospital discharge population, and at 10 cmH_2O in the death population (P-value=0.595) and, since the current volume was kept during the intervention, the Cst also remained unchanged at the three PEEP levels, with a 48 mL/cmH_2O mean value, observed in both groups (hospital discharge and death) (P-value=0.781).

Discussion

The data of 150 participants was analyzed and showed the prevalence of male patients, referred to the ICU after surgery, and whose hospitalization cause was polytrauma. This data confirms the profile of the collections center, that is a referral hospital for trauma in its region. As for the PEEP, its use is recommended to avoid the effects of orotracheal intubations, which might result in loss of lung volume and functional residual capacity. (12). In such context, the use of 8 cmH_2O PEEP as preventive care in the clinical practice is common. However, this value is still challenged by some authors that have reported the use of a lower PEEP level (5 cmH_2O) in patients that require orotracheal intubation for causes not related with pneumopathies, which is suggested to be safe and preventive regarding ventilation induced lesions (12,13,14). Curiously, among the markers evaluated in the study, none was responsive to the PEEP value changes, and the outcome resulting from the application of different PEEP levels was the same for the hemodynamics, gas exchange and driving pressure markers.

Despite the absence of statistical significance, when analyzing PEEP impact on the hemodynamics, we could observe a decrease, in absolute terms, in the systolic and mean arterial pressure. The pressures generated by the application of positive pressures, both inspiratory and expiratory during IVM have direct results in the right and left ventricular functions, and might present hemodynamic consequences such as arterial pressure decrease and cardiac rate alterations (15). Lung exposure to the positive pressure imposed by the mechanical ventilation use generates lung volume changes, which provoke significant alterations in the resistance and pulmonary vascular capacitance. Sharp volume variations might provoke heart compression in the mediastinum, and consequently, relevant hemodynamic alterations associated with the patients' worsened clinical outcome (16). Reduction in the arterial pressure is observed in the clinical practice upon sharp PEEP variations. In our study, the PEEP levels applied during the intervention were low and close one to another. This might be one of the reasons why it was not possible to observe statistical difference in the artertial pressure alteration.

When PaO_2 was analyzed, the study showed a lower value of this marker at the lowest PEEP level used during the intervention. However, no statistical significance was observed, which is not in accordance with the clinical practice, where it is common to increase the PEEP value with the purpose of raising the PaO_2 and, consequently, improving the oxygenation index. Such practice (PEEP increase to reach higher PaO_2 values) is mostly used in patients with a diagnosis of acute respiratory distress syndrome that have proved evidence (17,18,19). For this reason, following the same reasoning, critical patient care teams tend to keep this intervention. Thus, the literature provides better support for the interpretation of the PEEP association with PAO_2 in the presence of acute respiratory distress syndrome (11,20,21). However, little information is found in the literature in relation to studies with patients that do not present pneumopathies. Among these studies, one concluded that the PEEP titrated by the lowest driving pressure provoked fewer lesions to the lungs of patients without pneumopathies. However, it did not show any association with mortality resulting from intubation (22). This study objective was to evaluate PEEP impact on hemodynamics, gas exchange and driving pressure of individuals without previous lung disease, and thus the use of PEEP levels above those chosen for the intervention were not necessary. In this context, and considering our findings, we can instruct the clinical staff to use lower PEEP during ventilatory management without impacting negatively the markers evaluated.

This study did not find significant alteration in the driving pressure value at different PEEP levels, which can be a possible cause for not increasing oxygenation, since the driving pressure has been considered a reliable bedside variable to predict ventilation induced lesion, mortality, and oxygenation. However, its impact on the oxygenation only occurs when the PEEP increase reduces it value and, consequently, reduces the dead space, optimizing the gas exchange. In addition, by increasing the PEEP we can evaluate the potential alveolar recruitment by the driving pressure alteration, that is, if the driving pressure increases with the PEEP increase, we are dealing with a lung with low recruitment potential, which indicates that this patient will probably not benefit from the increased PEEP (23,24,25,26,27). In this context, our intervention showed that for the same driving pressure value at the three different PEEP levels, we should opt for the lowest PEEP aiming to protect the alveoli from possible lesions, minimizing the stress due to the alveolus cyclic opening and closing.

The main limitations of our study were: small sample size, close PEEP values used in the intervention, which might not have influenced the sample, since it included patients without previous lung disease and without hypoxemia, a condition in which the PEEP could have influenced. For further studies, we suggest this type of intervention mainly in groups presenting hypoxemia. Also, our study presented a cohort of patients with heterogeneous characteristics that, despite representing the routine care provided to patients in the University Hospital, makes it difficult to understand specific processes regarding the respiratory physiology and PEEP response.

Conclusion

In individuals without pneumopathies that required IMV, increased PEEP was not associated with alterations in hemodynamics, gas exchange, and driving pressure. Therefore, these values can be safely used in the bedside care. Our results also suggest the use of lower PEEP levels, aiming to optimize a protective ventilation in patients subjected to IMV.

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Capítulo IV: Artigo Submetido

Title: Opioids in COVID-19: two sides of a coin

Running title: Opioids in COVID-19 in Brazil

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Abstract

Introduction: The treatment of most severe COVID-19 patients included the large-scale use of sedatives and analgesics – possibly in higher doses than usual – which was reported in the literature. The use of drugs that decrease mortality is necessary and opioids are important agents in procedures such as orotracheal intubation. However, these drugs seem to have been overestimated in the COVID-19 pandemic. We performed a review of the PubMed-Medline database to evaluate the use of opioids during this period. The following descriptors were used to enhance the search for papers: "Opioids", "COVID-19", "COVID-19 pandemic", "SARS-CoV-2", "Opioid use disorder", "Opioid dependence" and the names of the drugs used. We also evaluated the distribution of COVID-19 patients in Brazil and the applicability of opioids in our country during the pandemic.

Results: Several positive points were found in the use of opioids in the COVID-19 pandemic, for instance, they can be used for analgesia in orotracheal intubation, for chronic pain management, and as coadjutant in the management of acute intensification of pain. However, high doses of opioids might exacerbate the respiratory depression found in COVID-19 patients, their chronic use can trigger opioid tolerance and the higher doses used during the pandemic might result in greater adverse effects. Unfortunately, the pandemic also affected individuals with opioid use disorder, not only those individuals are at higher risk of mortality, hospitalization and need for ventilatory support, but measures taken to decrease the SARS-CoV-2 spread such as social isolation, might negatively affect the treatment for opioid use disorder. In Brazil, only morphine, remifentanil and fentanyl are available in the basic health care system for the treatment of COVID-19 patients. Out of the 5,273,598 opioid units used in this period all over the country, morphine, fentanyl, and remifentanil, accounted for, respectively, 559,270 (10.6%), 4,624,328 (87.6%), and 90,000 (1.8%) units. Many Brazilian regions with high number of confirmed cases of COVID-19 had few units of opioids available, as the Southeast region, with a 0.23 units of opioids per confirmed COVID-19 case, and the South region, with 0.05 units. In the COVID-19 pandemic scenario, positive points related to opioids were mainly the occurrence of analgesia, to facilitate intubation and their use as coadjutants in the management of acute intensification of pain, whereas the negative points were indiscriminate use, the presence of human immunosuppressor response and increased adverse effects due to higher doses of the drug.

Conclusions: The importance of rational and individualized use of analgesic hypnotics and sedative anesthetics should be considered at all times, especially in situations of high demand such as the COVID-19 pandemic.

Keywords: COVID-19; Opioids; Pandemic; SARS-CoV-2; Treatment; Analgesics; Fentanyl; Remifentanil; Sufentanil; Alfentanil; Opioid use disorder; Opioid dependence; Morphine; Hydromorphone; Methadone

1. Introduction

The infection caused by the SARS-CoV-2 might affect different systems such as the gastrointestinal, central nervous, renal, cardiovascular and respiratory (Zhang et al., 2020). The most common symptoms include fever, cough, fatigue, and sputum production (Guan et al., 2020). At the same time, pneumonia associated with the COVID-19 might complicate due to the development of severe acute respiratory syndrome, and these patients might require admission in the intensive care unit (ICU), and be subjected to invasive mechanical ventilation (IMV) (Ammar et al., 2021).

In ICU patients under IMV, pain is one of the main reasons for restlessness, and moderate to deep levels of analgesia and sedation might be required as well as the use of neuromuscular blockade (NMB), to reduce the risk of cough, prevent asynchronous breath, and reduce the respiratory drive, which are harmful to the patient, and optimize ventilation, promoting suitable pain relief, and also preventing the activation of the sympathetic nervous system (Pandharipande et al., 2014; Allen et al., 2021; Ammar et al., 2021; Chaves-Cardona et al., 2021). Historically, the opioids are the most used class of drugs to perform sedation and analgesia in patients who need IMV. However, these drugs might be used carefully, since one of their most common side effects is the presence of respiratory depression, which can intensify the respiratory symptoms from COVID-19 such as shortness of breath (Roan et al., 2018; Ammar et al., 2021).

Even though the use of opioids might be necessary to help the ventilation of critically ill patients, prolonged use of sedatives in patients with respiratory insufficiency presents several adverse effects such as increase in hospital mortality, longer hospital treatment time, longer periods of IMV use and an dose dependent enhanced risk for delirium (Xing et al., 2015; Page, 2021). Additionally, the conditions described might indicate the patients' worst prognosis and contribute to an increase in care costs, and interfere in their quality of life and survival rate after hospital discharge (Kotfis et al., 2020; Pun et al., 2021). It seems relevant to highlight that opioid have been widely used in critical COVID-19 patients under IMV. The literature suggests that patient subjected to IMV due to the COVID-19, often received higher doses of sedatives and analgesics when compared to patients with other clinical condition (Kapp et al., 2020; Page, 2021; Pun et al., 2021).

Another fact regarding this period is that the pandemic affected the individuals who already presented opioid use disorders in several different manners. For instance, recent studies observed that these individuals are at higher risk of COVID-19 infection, death, hospitalization, and need for ventilation (Baillargeon et al., 2021; Wang et al., 2021). Unfortunately, the impact of the COVID-19 was not limited to the worst outcomes of the disease. These individuals with opioid use disorder might be more susceptible to loss of income, isolation, lack of rewarding activities, fear and anxiety, which ultimately can enhance the risk of substance abuse (Columb et al., 2020; Khatri and Perrone, 2020; Mota, 2020; Henderson et al., 2021). One might also speculate that the pandemic provided less access to safe places to use opioids, leading to a high rate of overdose related calls to the paramedics (Galarneau et al., 2021). Thus, it is extremely important to revise the impact of opioid use during the COVID-19 in several aspects to improve the scientific evidence for other pandemics as well as to be prepared for the pos-pandemic period.

The objective of this narrative review was to discuss sedation and analgesia practices – particularly the use of opioids – in critical patients and the repercussion of these practices. It also aimed to carry out a review on the impact of the pandemic on individuals with opioid use disorder.

In this review, the PubMed-Medline database was surveyed regarding studies related to opioids and the COVID-19 published in the period from 2019 to 2021. The following descriptors were used to enhance the search for papers: “Opioids”, “Opioid use disorder”, “Opioid dependence”, “COVID-19”, “COVID-19 pandemic”, “SARS-CoV-2”, “SARS-CoV-2 infection”, and opioids [“Morphine”, “Oxycodone” “Fentanyl”, Hydrocodone”, “Methadone”, “Remifentanil”, “Sufentanil”, and “Alfentanil”]. Brazilian databases were also surveyed such as that made available by the Brazilian Health Ministry (https://covid.saude.gov.br/), to evaluate the Brazilian characteristics related to the COVID-19, including the number of confirmed cases, the number of deaths due to the COVID-19, incidence of the disease per 100,000 inhabitants, and mortality due to this disease per 100,000 inhabitants. Additionally, the study analyzed the distribution and number of opioids used all over the country according to the newsletter published by the Health Ministry. We also estimated the total opioid use per confirmed COVID-19 cases, which was a ratio between total opioids and confirmed cases of COVID-19; and total opioids per death due to the COVID-19, which was a ratio between total opioids and deaths due to the COVID-19. In such scenario, we included a narrative review demonstrating the pros and cons of opioid use during the COVID-19 pandemic.

2. Results and discussion

2.1. Physiological effects of opioids in COVID-19 and the physiology of dependence

Opioids might inhibit the release of neurotransmitters such as the Glutamate and the P substance released by the dorsal root ganglion at the level of the spinal and cerebral marrow through the activation of G proteins that inhibit the adenylate cyclase and regulate ionic canals through their bond to opioid receptors. In that context, three opioid receptors were established: mu, delta and kappa, which are metabotropic receptors that bond to the G protein, with different biomolecular structure, but with interrelated functions (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009; Friedman and Nabong, 2020). These receptors can be found in high concentrations in supraspinal regions, such as the limbic area and regions related to neurohormonal secretion, as the hypothalamus, and most of these receptors are pre synaptic (Friedman and Nabong, 2020).

Agonist opioids of the delta and mu receptors present an analgesic action, while the agonist opioids of the delta receptor seem to present lesser side effects after long periods of use. Interestingly, the mu receptor is the main receptor for opioid agonists used in pain management (Friedman and Nabong, 2020). The kappa receptor, in turn, might induce dopamine release and cooperate with the development of hallucination and dysphoria behaviors, also, high concentrations of kappa receptors can be found in the spinal cord, and are thought to play a central role in the development of hyperalgesia. One can speculate that this might limit the development of drugs that interact with this receptor (Chavkin, 2011; Friedman and Nabong, 2020). Opioids show a high distribution volume and high liposolubility. Consequently, a short infusion bolus, for example, might have significant effects on plasma concentrations (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009) (**Figure 1**). Moreover, some of these medicines present very short plasma half-lives such as the remifentanil and the alfentanil (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Ammar et al., 2021).

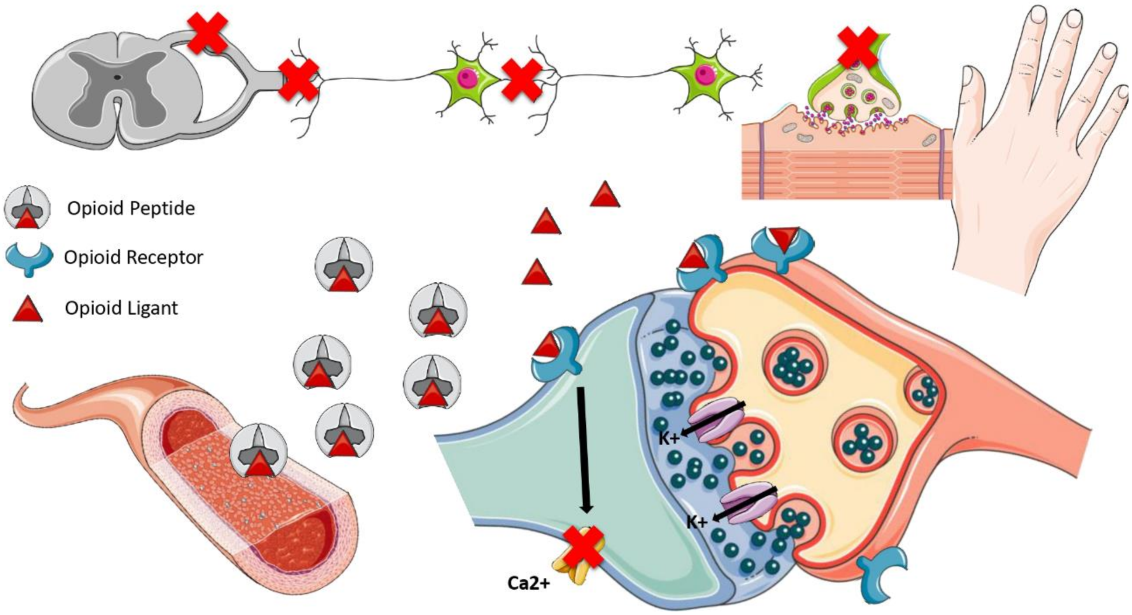

FIGURE 1. Pharmacodynamics of opioids. Opioids inhibit the release of Glutamate and Substance P by the dorsal ganglion neuron in the spinal cord and brain through the activation of G proteins, which inhibit adenylate cyclase and regulate ion channels by binding to opioid receptors. Once the opioid binds to the receptor, potassium influx and calcium channel blockage in the synaptic cleft occurs. Three opioid receptors: mu, delta and kappa, which are metabotropic receptors and bind to G protein, are responsible for the analgesic effect. Delta and mu receptor agonist opioids have mainly analgesic action, and delta receptor agonist opioids seem to present fewer side effects after a long period of use. The Kappa receptor can induce dopamine release and contribute to the development of hallucination and dysphoria behaviors. Opioids have a high volume of distribution due to their high liposolubility. Therefore, a short infusion bolus, for example, may have significant effects on plasma concentrations (Henriksen and Willoch, 2008; Bruijnzeel, 2009; Stein and Lang, 2009).

Interestingly, the brainstream has a great concentration of Mu opioid receptors in areas involved with the control of breathing and the respiratory frequency, in which, if activated they may interfere of the process of breathing (Boom et al., 2012). Although the mechanism involved with respiratory depression is complex, opioids might increase hypercapnia and reduce tidal and minute volume, leading to slow and irregular breathing, which in severe cases can progress to fatal apnea (Leino et al., 1999; Boom et al., 2012). Furthermore, a great number of opioid receptors can be also found in the pre-Bötzinger complex, which is an important area related to the inspiration and has been recently described in humans. The activation of opioid receptors in this particular area might play a role in respiratory depression (Pattinson, 2008; Montandon et al., 2011; Schwarzacher et al., 2011; Boom et al., 2012) (**Figure 2**).

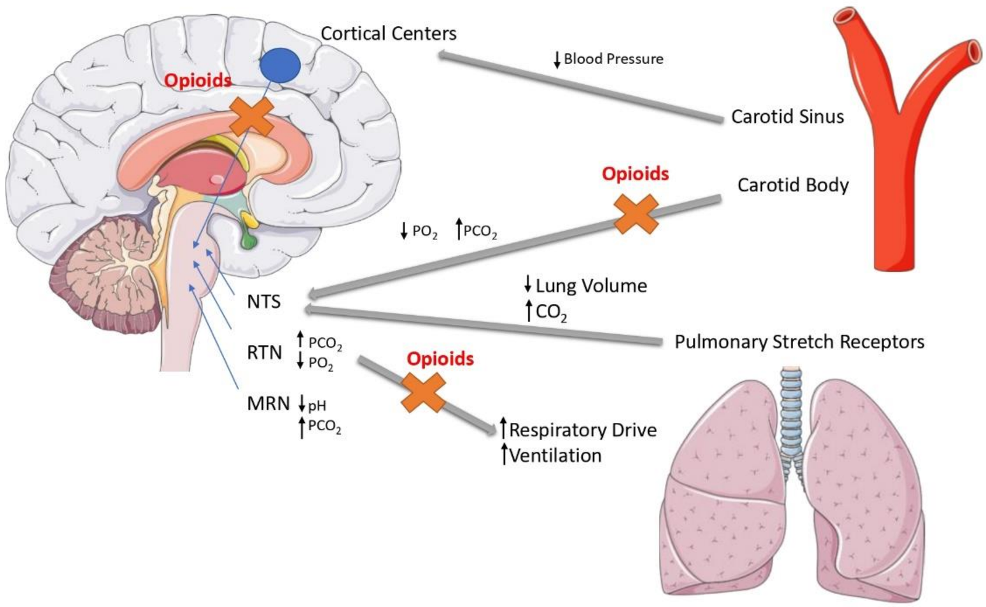

FIGURE 2. Opioid-induced respiratory depression mechanisms. Opioid-induced analgesia and respiratory depression arise from stimulation of μ-opioid receptors (MORs). MORs are expressed in neurons involved in the control of breathing, primarily located in the brainstem, particularly in the Nucleus Tractus Solitarius (NTS), Retrotrapezoid Nucleus (RTN) and Median Raphe Nuclei (MRN) (Boom et al., 2012)

Unfortunately, opioids can also cause dependence due to their interaction with Mu receptors in the brain, resulting in activation of the reward mesolimbic system, which is also activated in several other daily activities such as sex and eating. The activation of the mesolimbic system, in turn, is responsible for the activation of the tegmental ventral area, located in the mesencephalon, which acts by releasing dopamine in the accumbens nucleus, which provides a feeling of pleasure (Kosten and George, 2002). Another factor that might result in dependence is the opioid action on the locus coeruleus. Normally, the locus coeruleus produces noradrenalin, an excitatory neurotransmitter that regulates several functions such as the respiratory frequency and blood pressure. However, opioids can act on the Mu receptors in this region, which reduces the noradrenalin secretion, leading to metabolic alteration that include reduced respiratory frequency and arterial pressure. As a consequence of the chronic ingestion of opioids, the locus coeruleus increases its noradrenalin secretion in an attempt to manage the opioid effect. Therefore, when a reduction in the concentration of opioids in the nervous system occurs and greater noradrenalin concentration is observed, several symptoms of the withdrawal syndrome such as anxiety and the presence of muscle cramps might appear (Kosten and George, 2002).

Regarding the physiological effects of opioids, we observed several positive points, as the mechanisms involved in analgesia, and those involved in the IMV. However, some negative points were also observed such as chest wall rigidity, which can increase the respiratory depression, and the mechanism related to opioid dependence.

Additionally, even if opioids belong to the same class of drugs, they present distinct pharmacodynamic, pharmacokinetic mechanisms and molecular structure (**Table 1**)**.**

2.2. Opioids used in patients' sedation

Pulmonary impairment is one of the main pathophysiological mechanisms of the COVID-19. Patients with this disease might present pain and suffering, not only due to the illness, but also as a result of invasive procedures such as the IMV, required by around 69% of the COVID-19 patients admitted in ICU (Devlin et al., 2018; Ammar et al., 2021; Chang et al., 2021). Analgesia, mainly using opioids, in this type of patients becomes usual, in order to provide them with comfort and also enable the accomplishment of further procedures such as orotracheal intubation (Allen et al., 2021). In the literature, opioids such as fentanyl, morphine, and hydromorphone are the main drugs used to treat ICU patients (Ammar et al., 2021). Our review summarizes the characteristics of the main opioids used in the treatment of COVID-19 patients (**Table 1**).

Fentanyl outstands as the most used opioid in the analgesia of conventional diseases. However, it is necessary to be cautious when using it through intravenous administration, since one of its main adverse effects is chest wall rigidity increase leading to respiratory depression (Roan et al., 2018; Ammar et al., 2021), which is recurrent in COVID-19 patients. Another drug that can be used to alleviate the discomfort caused by dyspnea is morphine (Ammar et al., 2021). Hydromorphone, in turn, can be used to substitute morphine or fentanyl, whenever the health service does not have the other medications, however, this opioid presents higher dosage error rate, when compared to other opioids, for this reason, health professionals must use it with caution to prevent overdoses of this medication (Ammar et al., 2021).

Other options of opioid analgesics for the treatment of COVID-19 patients include remifentanil, sufentanil, and alfentanil, which are drugs used in the hospital practice. However, they show some limitations that reduce their use in large scale situations. Remifentanil is associated to higher risk of hypotension, when compared to fentanyl, and has a shorter half-life, which might reduce the duration of its analgesic effect. Sufentanil and alfentanil are less frequently used in ICU also due to their short half-life. In addition, sufentanil might accumulate progressively when used in continuous and prolonged infusions. As for alfentanil, there are few reports of its use in continuous infusion by intensive care teams (Egan et al., 1993; Joshi et al., 2002; Ammar et al., 2021). However, these drugs are still considered options when the most commonly used drugs (morphine, hydromorphone, and fentanyl) are not available in the health service.

The advantages observed include the fact that many opioids such as fentanyl, hydromorphone, morphine, sufentanil, remifentanil, alfentanil can be used in order to help in the IMV, and they are important to manage COVID-19 patients. However, since fentanyl is the most used opioid, the health care personnel might not have experience with the others, which might lead to dosage error. Also, sufentanil, remifentanil, alfentanil show more limitations when compared to fentanyl, since they have a shorter half-life.

2.3. Opioids in Brazil: availability, and dependence

When managing COVID-19 patients, few drugs presented proved efficacy to modulate the outcome mainly regarding more severely affected individuals that required intensive care treatment and IMV. Among these drugs, dexamethasone and remdesivir reduced mortality risk and hospital care time, respectively (Beigel et al., 2020; RECOVERY Collaborative Group et al., 2021). However, other drugs such as opioids gained relevance in the COVID-19 pandemic for providing patients with greater comfort during treatment. Another fact to be taken into consideration is that since the start of the pandemic, Brazil has supported the acquisition of several drugs without scientific evidence for the COVID-19 treatment such as hydroxychloroquine, chloroquine and oseltamivir (Boschiero et al., 2021; MS-SUS COVID-19 Medications) spending around BRL 90 million to purchase such drugs (MS-SUS COVID-19 Medications). Curiously, the amount spent could have been used in the acquisition of other medicines, including opioids, which were missing in many healthcare centers in several parts of the country at certain times during the pandemic. As a result of the magnitude of the COVID-19 pandemic in Brazil, with approximately 22 million confirmed cases and over 600 thousand deaths (WHO Coronavirus (COVID-19) Dashboard) a variety of medicines, mainly opioids, were used to manage patients in ICU and under IMV.

In Brazil, around 80% of the population is assisted by the National Unified Health System (SUS, the Brazilian public health system), while the remaining population use private health care. Curiously, SUS is responsible for only 45% of the total expenditure with health in the country, while the private system accounts for 55%, this fact disagrees with the volume of assistance provided in each health sector (public and private) (SUS - 20 years, 2021). Unfortunately, according to the Relação Nacional de Medicamentos Essenciais - Rename (Essential Medication National List), when it comes to opioids, only morphine and fentanyl are available for routine use at the SUS, and the small variety of drugs available can be explained, at least partly, by the low investment in this service (Rename, 2020). Therefore, the fact that the SUS that assists most of the population does not have enough resources to assist suitably those that requires this service is a matter of concern, mainly in a public health emergency situation such as that provoked by the COVID-19 pandemic.

As a consequence of the high use of opioids during the COVID-19 pandemic and public resource bad management, mainly by the federal government, there were reports of lack of opioids, as well as shortage of other medicines and inputs needed to perform intubation in Brazilian patients (Boschiero et al., 2021; Folha de São Paulo, 2021); and there were several reports of collapse in the health service. For example, according to the Associação Nacional de Hospitais Privados – ANAHP (Private Hospital National Association), on 18th March 2021, the institutions that are members of that association reported having a stock of fentanyl that would last only 20 days (ANAHP, 2021). Also, according to a survey carried out up to 13th April 2021 by the Federação das Santas Casas e Hospitais Beneficentes do Estado de São Paulo – Fehosp (Federation of Santa Casas and other charitable hospitals of São Paulo), around 160 hospitals had stocks of anesthetics and other medication needed for intubation that would only last from 3 to 5 days, with certain municipalities such as Guarujá and Rio Preto reporting even lower stocks that would probably end in 2 or 3 days (Fehosp – News). Such supply crisis affected and might still affect the combat to the pandemic in Brazil, preventing the treatment of patients that require intubation and potentially increasing dosage errors by the medical team, for not being acquainted with the use of the alternative medication available (Adams et al., 2020) or even, impairing the analgesia of those patients, preventing measures to alleviate their respiratory distress.

Unfortunately, the medication supply crisis in Brazil goes beyond opioids, several means of communication informed and are still informing that hospitals have low stocks of the “intubation kit”, that is, medication and necessary supplements to carry out orotracheal intubation (CNM, 2021; Folha de São Paulo, 2021). This fact might have contributed, at least partly, to the high mortality rate of patients in ICU throughout the country. In fact, the mortality rate among Brazilian patients with the COVID-19 disease in ICUs (~55%), was higher than those of many other countries such as China (37.7%), Italy (25.6%), Spain (29.2%), United States of America (23.6%), Denmark (41.2%), Germany (24.3%), and the United Kingdom (8.0%) (Quah et al., 2020; Ranzani et al., 2021). The figures in Brazil were distributed differently among the states and regions of the country, with the highest death index, 79%, being observed in the Northern region of the country.

Interestingly, up to October 20, 2021, Brazil used a total of 5,273,598 opioids in its five regions, with only three different types of opioids available in the SUS, and out of those morphine, fentanyl and remifentanil, accounted for, respectively, 559,270 (10.6%), 4,624,328 (87.6%) and, 90,000 (1.8%) units of opioids used. In our analysis, we also observed that many Brazilian regions with high number of confirmed cases of COVID-19 had few units of opioids available, as the Southeast region, with a 0.23 units of opioids per confirmed COVID-19 case, and the South region, with 0.05 units. Furthermore, taking into account the number of deaths due to COVID-19 and total opioids, these 2 Brazilian regions also presented the lowest index in the country, in which the Southeast had 6.90 opioids units per death due to COVID-19, and the South region accounted for 2.30 (**Table 2**). These two regions were the most affected by the COVID-19, presenting the highest numbers of cases and deaths, thus their opioid supply should have been increased in order to better manage the COVID-19 cases.

A Brazilian study on hospital analgesic consumption trends carried out from 2011 to 2015 showed that although a noticeable reduction in the public expenditure with analgesia occurred, the costs are still high, so that in the last year analyzed, the total cost of analgesics was 326.515€, and out of this total, 84.545€ were spent with analgesic opioids, which represents approximately 26% of the total cost (Monje et al., 2019).

It seems relevant to observe that Brazil has a lower prevalence of opioid use when compared to the United States of America or the rest of the world. One report from 2004 surveyed more than 15,000 individuals in the 1st and 2nd grade of high schools and the prevalence of opioid use, at least once in lifetime, was 0.7% (ranging from 0.2% in Rio de Janeiro to 1.4% in Salvador) (Baltieri et al., 2004). Another report interviewed 8,589 Brazilians citizens aged between 12 and 65 years old, and the prevalence of opioid use was only 1.4% (Galduróz and Cebrid, 2003). Finally, the latest report on opioid use in Brazil observed an increased prevalence when compared to previous years, nearly 2.9% of the individuals surveyed stated that they had used opioids at least once in their lives (Krawczyk et al., 2020).

Regarding positive points, the federal government could distribute opioids to all Brazilian states, even with a logistic issue related to great distances and difficult access to some cities in the North. Also, Brazil seems to have a lower prevalence of opioid use disorder. On the negative side, we observed that the federal government distributed a low number of opioids to the Brazilian states, which might have predisposed some regions to shortage of opioids. Also, Brazil did not distribute the opioids taking the COVID-19 cases and deaths into account, which might have had an impact in the outcome of the public health policy of the states.

2.4. A growing issue: the dependence of opioid worldwide

Although the management of sedation in critical patients in IMV is difficult, it is required during the therapeutical intervention. In high doses or for long periods, its use might result in undesirable effects such as the occurrence of delirium or acute cerebral disfunction, which are considered serious problems for the medical team and the patients' families. European and American guidelines recommend that, in mechanically ventilated patients, sedation is dosed so that the patient can be awaken easily and at the same time has a competent analgesia, since this might reduce delirium incidence (Page, 2021; Pun et al., 2021). However, chronic and indiscriminate use of opioids might cause dependence as reported in the literature (Kosten and George, 2002). Nevertheless, their use in the COVID-19 pandemic is justifiable for the reasons listed above. Delirium incidence is highly prevalent and prolonged in COVID-19 patients and the use of benzodiazepines along with the absence of the family were modifiable risk factors identified in a multicenter study (Pun et al., 2021).

Patients with opioid dependence might be one of the most affected groups in the pandemic, since they are considered a risk population that is marginalized and require more personalized and constant care (Alexander et al., 2020). Several factors can be associated to the greater impact of the pandemic on this group, for example, a study in the South Africa reported that long periods of lockdown might increase the risk of overdose, since a reduction in the addicted individual's tolerance occurs. In addition, those individuals might use other substances that are also nervous system depressants such as alcohol and benzodiazepines (Stowe et al., 2020; Thylstrup et al., 2020). Another relevant factor affecting this group is the shortage of methadone and buprenorphine, medicines used to treat opioid use disorder, since the delivery of this medication in the pandemic context might be harmed, which might have led to treatment discontinuation and a return to the use of illegal opioids (Magura and Rosenblum, 2001; Elliott et al., 2017; Sordo et al., 2017; Degenhardt et al., 2019; Gisev et al., 2019).

The United States of America and Europe perhaps are the regions that were most affected by opioid use disorders worldwide, and the COVID-19 might have played an important role in this health issue, as described below.

2.4.1. United States of America

The United States of America (US) faces a growing epidemic of opioid use, in fact, since 2007 statistical data has shown increased death rates related to opioid consumption, with the death of nearly 91 American individuals every day and over 100 million individuals treated in emergency rooms for opioid use (Rudd, 2016; Dayer et al., 2019; Understanding the Epidemic | CDC's Response to the Opioid Overdose Epidemic | CDC, 2021; CDC WONDER). Also, from 1999 to 2018, the US estimated about 450,000 deaths related to opioid use disorder (Wilson et al., 2020; Seyler et al., 2021). This particular country has a greater variety of opioids than Brazil; therefore, fentanyl and morphine, heroin, oxycodone (OxyContin), methadone, and hydrocodone (Vicodin) are widely used and responsible for the opioid use disorder (Opioid Basics | CDC's Response to the Opioid Overdose Epidemic | CDC, 2021).

Since 2018, deaths related to drug overdose, including opioid overdose, seem stable, with nearly 70,000 reported deaths per month, however in the early 2020, the number of reported deaths began to rise, reaching nearly 96,000 deaths per month in 2021, in part due to the difficulties the pandemic brought to all American citizens (Products - Vital Statistics Rapid Release - Provisional Drug Overdose Data, 2021). In the literature, a recent report observed that during the COVID-19 pandemic, fewer drug tests were performed, and unfortunately, the percentage of individuals using opioids (fentanyl, heroin and other opioids) increased significantly when compared to the period prior to the pandemic. For instance, about 4.3 % of the individuals tested positive for fentanyl before the pandemic, whereas during the pandemic, this number reached 5.8% of individuals (Niles et al., 2021).

Perhaps, many factors related to the COVID-19 pandemic led to this increased opioid overdose death rate. For instance, there are many barriers related to regulations of essential drugs to treat the opioid use disorder such as methadone and buprenorphine. Also, one way to decrease the SARS-CoV-2 spread was isolation; however, physical and social contact are of utmost importance in the treatment of this disorder (Green et al., 2020). Even before the World Health Organization declared the COVID-19 as a pandemic, several healthcare personnel advocated for the removal of barriers related to the treatment of substance disorder (Samet et al., 2018; Davis and Carr, 2019; Fiscella et al., 2019; Green et al., 2020; Summary of H.R. 2482 (116th): Mainstreaming Addiction Treatment Act of 2019). Unfortunately, a recent study observed that more than 10% of the methadone clinics in the United States of America and Canada were not accepting new patients due to the COVID-19 pandemic (Joudrey et al., 2021). Several tools can be used to attenuate the impact of the pandemic, as the use of telehealth, the greater flexibility to take the drugs to treat this disorder, and home and online group meetings (Green et al., 2020; National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Examination of the Integration of Opioid and Infectious Disease Prevention Efforts in Select Programs, 2020; Mehtani et al., 2021). In fact, telehealth was particularly effective when used as a complement of in-person treatment of selected patients (Cales et al., 2021).

The United States of America faces a growing problem related to drug abuse and the COVID-19 might have hampered the access to opioid use disorder treatment. Also, individuals with opioid use disorder are at increased risk of COVID-19. However, some tolls were implemented in order to attenuate the impact of the pandemic in this particular group, as the use of telehealth to help in the opioid use disorder treatment.

2.4.1 Europe

Although the literature for opioid dependence in Europe is scarce, the findings reported are similar to those found in the United States of America. For example, in 2019, 1.0 million individuals were high-risk opioid users, and 76% of drug fatal overdoses were due to opioids. Also, 26% of the requests for drug treatment were for opioid users (Statistical Bulletin 2021 — prevalence of drug use | www.emcdda.europa.eu). Even though it is clear that Europe also faces a growing problem of opioid use disorder, many factors found in the United States of America such as over prescription and use of opioids to manage pain, availability and the cheap cost of opioids, and the lack of accessibility to treatment, are not found in Europe (Volkow et al., 2019; Torrens and Fonseca, 2021). This might have contributed to the fact that dependence levels are not the same in Europe. Although heroin consumption appears to be declining in Europe, maybe due to aging of the population, new synthetic opioids seem to be emerging, as fentanyl and analogues, which constitutes a problem in the COVID-19, since they could be adulterated, falsified, or substituted, thus enhancing their toxic effects (Torrens and Fonseca, 2021).

Few studies evaluated the impact of the COVID-19 in the pattern of drug use in Europe, one Italian study with only 30 subjects observed the levels of heroin use appeared to have decreased during the lockdown period, and right after the end of the lockdown they went back to pre-lockdown levels, this might be explained by the fact that the lockdown provided fewer social interactions in which these individuals were able to use drugs (Gili et al., 2021; EMCDDA Trendspotter briefing: impact of COVID-19 on patterns of drug use and drug-related harms in Europe | www.emcdda.europa.eu). Another study in Finland observed increased use of buprenorphine, amphetamine and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol in 2020, after a short drop in May 2020. Unfortunately, this study did not evaluate opioid use (Mariottini et al., 2021). European individuals with opioid use disorder were more affected by the COVID-19 pandemic, and perhaps, similar measures as those taken in the United States of America could be implemented to attenuate their burden.

Europe also faces a growing opioid addiction problem, and the COVID-19 might have made the access to opioid use disorder treatment more difficult. In that continent, individuals with opioid use disorder are also at increased risk of COVID-19. However, some tools were implemented in order to attenuate the impact of the pandemic in this particular group such as the use of telehealth to help in the opioid use disorder treatment.

2.5 Use of opioids in COVID-19 patients and their adverse effects

COVID-19 patients with pulmonary impairment also presented other symptoms such as dyspnea, which is a frequent clinical manifestation with repercussions at the physical and psychological levels causing suffering to the patient. Dyspnea mechanisms include: (i) increase in the afferent signals of chemoreceptors and mechanoreceptors of the upper airways, lung, chest wall, and muscles of breathing; (ii) increase in the respiratory effort sensation, and (iii) dissociation between the ventilatory needs and the ventilation capacity (Burki and Lee, 2010)

One of the opioids main mechanisms of action in intubation is the reduction in the metabolic rate and ventilatory needs, decrease in the bulbar reflex to hypercapnia and hypoxia, respiratory center neurotransmission alteration, respiratory sensitization suppression, reduction in the respiratory drive, vasodilation, and anxiety reduction effects (Helms et al., 2020; Kapp et al., 2020; Pun et al., 2021). However, in COVID-19 patients, the strategies to prevent cough and dyspnea with the use of opioids might, many times, postpone the orotracheal intubation procedure and generate severe pulmonary consequences. In addition, the continuous use of opioids was associated with greater risk of patients in intensive care developing delirium, probably due to the fact that higher doses are prescribed, of both sedatives and analgesics, to COVID-19 patients, when compared to patients that did not have this disease (Helms et al., 2020; Kapp et al., 2020; Pun et al., 2021).

A quite trendy term these days is analgosedation, which consists in reaching sedation through the use of opioids before considering sedation through non-analgesic medication (Devlin et al., 2018; Adams et al., 2020). Throughout the pandemic, the use of analgesia and analgosedation was advisable in usual care (Riker et al., 2009; Adams et al., 2020). In the H1N1 virus pandemic, the use of fentanyl was higher in patients with pneumonia caused by the H1N1 virus or with acute respiratory distress syndrome associated with bacterial pneumonia (Olafson et al., 2012), showing that in the context of respiratory virus pandemics such as the current one, opioids are even more demanded. As exemplified, opioids play a relevant role in orotracheal intubation due to several factors. More specifically, fentanyl acts reducing the sympathetic nervous system, mainly reducing arterial pressure and causing respiratory depression (Allen et al., 2021).

However, opioids also present side effects such as diarrhea, hyperalgesia, dysphoria, tolerance and dependence processes, their prolonged use might be associated to immunological system suppression, and high doses of opioids might lead to respiratory depression, exacerbating the poor respiratory condition of those patients (Boom et al., 2012; Franchi et al., 2019; Cismaru et al., 2021). Patients with high doses of opioids might experience hypercapnia and hypoxia, due to the previously mentioned mechanisms, thus contributing to more severe respiratory symptoms (LeGrand et al., 2003; Ataei et al., 2020; Velavan and Meyer, 2020). Chronic use of opioids might lead to the induction of immune cell apoptosis, thymus and splint hypotrophy, and suppression of the proliferation of lymphocytes B and T, in addition to the leukocyte activity (Nabati et al., 2013; Ataei et al., 2020). Unfortunately, the lack of clinical studies on patients infected by the SARS-CoV-2 prevents a thorough evaluation of the possible side effects of the use of opioids during the pandemic (Drożdżal et al., 2020), and an analysis of the impact of the use of these drugs might only be possible after further observational studies are carried out.

Regarding the positive points of opioids in this topic, we could observe that opioids can be used in IMV in order to decrease patients' pain and the anxiety in respiratory depression. They can also prevent asynchronous breath and reduce the respiratory drive, which is harmful to the patient, and optimize ventilation. However, some negative points were also observed, since the use of opioids might be also associated with increased chest wall rigidity, which can increase the respiratory depression of these patients. Some adverse effects of their use such as diarrhea, hyperalgesia, dysphoria, tolerance and dependence processes were also found, and their prolonged used might be associated with immune system impairment.

3. Perspectives

There are several opioids that are important in the COVID-19 management, consequently, the demand for this medication increased exponentially during the pandemic. However, several doubts still remain to be clarified only when further studies are developed, as for example, whether the use of short action opioids can result in greater benefit for COVID-19 patients. Unfortunately, in Brazil, only remifetanil is available and in small amounts, which hampers its implementation, even if it has shown more efficacy in intubation. Additionally, Brazil is going against the pandemic combat, a fact that was observed in different news sources that showed shortage of the ‘intubation kit’ in several hospitals of the country. Even with the efforts of the Health Ministry to buy and distribute this medication and supplements, they were still scarce. On top of that, the investment in drugs without proved efficacy and the dissemination of information related to the ‘COVID kit’, which was proved inefficient against the virus, created costs that could have been better used in the purchase of greater quantities of opioids. It is still uncertain whether the purchase of opioids could or not have had some relevant impact on the number of COVID-19 patients’ deaths. However, if stocks were not so low, those patients could have been assisted with greater comfort.

It is also necessary to evaluate the possible side effects of the use of high doses of opioids in COVID-19 patients. As previously exemplified, opioid continuous use was appointed as an independent risk factor to delirium COVID-19 patients in the ICU. Their indiscriminate use and in high doses in patients in need of mechanical ventilation might result in several side effects that still require further observational studies. For this reason, their use must always be based on the most solid scientific evidence. In addition, high doses of sedation and analgesia in COVID-19 patients are probably related to age and, initially, the affection of a single target organ – lung – which makes sedoanalgesia more difficult. Therefore, it is necessary to manage the combination of several agents (for example, propofol, ketamine, hydromorphone, dexmedetomidine, midazolam, fentanyl, morphine, and remifentanil), increasing the potential risk of side effects such as the increased QT effect, hypertriglyceridemia, hypotension, and delirium, requiring the surveillance of a multi-professional team.

Finally, we must address one of the most important issues is the patients’ addiction to opioid use. Individuals with disorders caused by the use of substances, mainly opioid-related disorders, are at greater risk in the COVID-19 pandemic due to a possible immunological suppression. Opioid users represent a population at high risk of developing critical diseases, either due to complications of underlying conditions that led them to use opioids, or complications caused by the opioids. In addition to overdosing, the use of opioids has been associated to a series of complications that might affect adversely the prognosis of critically ill patients, including myocardial infarction, cerebrovascular accident, and infection. It has become evident that the pandemic had greater impact on marginalized individuals such as drug addicts, mainly those addicted to opioids, since the search for medication and psychological support to treat the addiction was affected by the social isolation measures. Further studies must make a clear distinction whether opioid dependence increased during the pandemic as a result of their more frequent use in hospitals that could lead to addiction, or whether the tools used to fight addiction were affected by the social isolation and restrictive measures, which would lead addicted individuals to a relapse, since both hypotheses are possible.

An informative summary regarding the pros and cons of the opioid use is presented in **Figure 3**.

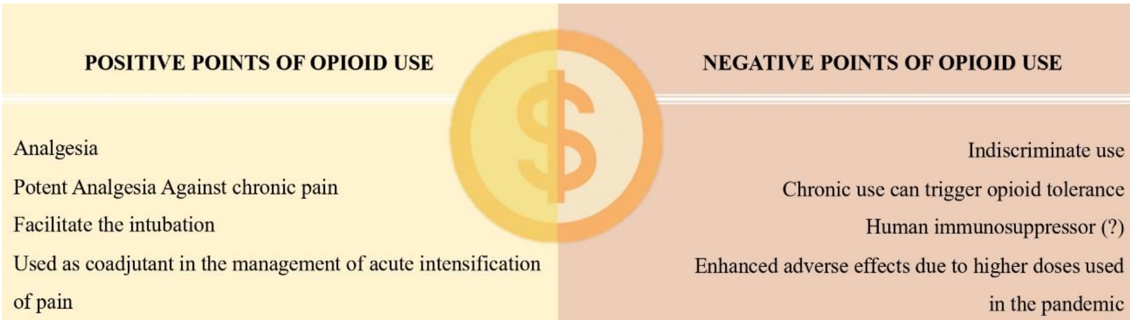

FIGURE 3. Main risks and benefits associated with the use of opioids.

4. Limitations

The study was carried out based on information made available by the government after a survey on the PubMed-Medline database, which might blur the understanding of the real scenery of opioid use in Brazil, since no hospital was directly evaluated. Governmental data bases as the one used in this study might not be updated or even have lost data, which might hamper the analysis carried out in this study. Despite its importance, the literature for opioids use is still scarce and it is difficult to achieve the highest degree of scientific evidence up to this date regarding all-pros and cons of opioid use during the COVID-19 pandemic. Also, there is discrepancy related to the availability of each drug in different countries, which makes the interpretation of our findings in a broad scenery more difficult.

5. Conclusions

In the COVID-19 pandemic scenario, the positive points related to opioids were mainly the occurrence of analgesia, to facilitate the intubation and their use as coadjutant drugs in the management of acute intensification of pain, whereas the negative points included indiscriminate use, the presence of human immunosuppressor response and the enhanced adverse effects due to higher doses of the drug. Also, the importance of rational and individualized use of analgesic hypnotic and sedative anesthetic medication must be considered at all times, mainly in situations of high demand such as the COVID-19 pandemic. Even though necessary, the opioids might be used carefully, since one of their adverse effects is respiratory depression, which can worsen the respiratory symptoms in COVID-19 patients. Finally, the pandemic might have affected not only critically ill patients who needed intubation, but also those with opioid use disorder, who faced a major problem posed by the pandemic isolation measures, thus decreasing their adherence to the drug disorder treatment.

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TABLE 1. Characteristics of the main opioids used in patients affected by the coronavirus disease (COVID-19). Adapted from Ammar et al. 2020

Medication	**Mechanism of action**	**Pharmacokinetics**	**IC50**	**EC50**	**Potency***	**Adverse events**	**Place in therapy**	**Patients care considerations**	**Available at SUS**
Fentanyl	Mu-opioid receptor agonist	(i) Onset: immediate (ii) Duration 3-60 min (iii) T1/2 >100 min (iv) Elimination t1/2: 2-4 h	<20 nM	1.58 ± 0.04 nM	80-100x	Chest wall rigidity with rapid infusion	First-line therapy	(i) Prolonged and unpredictable clearance can be extended beyond infusion discontinuation (ii) Risk of hypotension lower than morphine (iii) Accumulation in hepatic dysfunction (iv) Fentanyl patch is an alternative, but consider absorption (delayed onset and offset) and effect issues	Yes
Morphine	Mu-opioid receptor agonist	(i) Onset: 5-10 min (ii) Duration: 3-5 h (iii) Elimination T1/2: 3-4 h	193 nM	50-100 nM	1x	Hypotension and bradycardia	First-line therapy	(i) Metabolite can accumulate in kidney dysfunction (ii) Accumulation of morphine-6-glucorinide and morphine-3-glucorinide can cause neurotoxicity (iii) Enteral morphine is an alternative during shortage	Yes

Hydromorphone	Mu-opioid receptor agonist	(i) Onset: 15-30 min (ii) Duration: 3-4 h (iii) Metabolized into hydromorphone-3-glucorinide (iv) Elimination T1/2: 2-3 h	>50 µM	>0.41 nM	0.9 to 1.2 mg is equivalent to 10mg morphine	Hypotension	First-line therapy	(i) 5-7 times more potent than morphine (ii) Accumulation of hydromorphone-3-glucoronide in kidney dysfunction can cause neurotoxicity	No
Remifentanil	Mu-opioid receptor agonist	(i) Onset: 1-3 min (ii) Duration: 3-10 min (iii) Offset: 5-10 min (iv) Terminal T1/2: 10-20 min (v) Metabolized by blood and esterase	0.19 nM	30 nM	100-200x	Hypotension and chest wall rigidity	Alternative therapy	(i) Monitor for opiate withdrawal symptoms for 24h after discontinuation (ii) No accumulation in hepatic/renal failure (iii) Can cause serotonin syndrome with concomitant use with serotonergic agents	Yes
Sufentanil	Mu-opioid receptor agonist	(i) Onset: 1-3 (IV) and 30 min (sublingual) (ii) Duration: 2 h (IV) and 3 h (sublingual) (iii) T1/2: >100 min (IV) and 3 h (sublingual)	5.5 nM	1.8 ± 0.8 nM	500-1000x	Bradyarrhythmia and hypotension	Alternative therapy	(i) Can cause serotonin syndrome with concomitant use with serotonergic agents (ii) 5-10 times more potent than fentanyl	No

Alfentanil	Mu-opioid receptor agonist	(i) Onset: 5 min (ii) Duration: 30-60 min (iii) T1/2: 1.5-2 h	2.5 nM	1,248 ± 391 nM	8-20x	Hypotension	Alternative therapy	(i) 5 times more potent than fentanyl (ii) Can cause serotonin syndrome with concomitant use with serotonergic agents	No
Methadone	Mu-opioid receptor agonist and NMDA receptor agonist	(i) Onset: 0.5-1h (PO) and 10-20 min (IV) (ii) Duration: 12-48 h (iii) T1/2: 8-59 h (iv) Reaching steady state in 3-5 days	NI	NI	150x	QTc prolongation	Opioid conservation and adjuvant therapy	(i) Long half-life (ii) Prolonged effect with hepatic and renal dysfunction (iii) Elimination half-life does not match short duration of analgesic effect (iv) Caution with administration of other drug which can enhance QTc prolongation	No

IV, intravenous; PO, per oral; NMDA, N-methyl-D-aspartate receptor; QTc, Corrected QT Interval; IC50, half the maximum inhibitory concentration; EC50, concentration of a drug that gives half-maximal response; NI, not informed.

*Potency is compared to morphine

Adapted from (Ammar et al., 2021)

References: (Mahler and Forrest, 1975; Villiger et al., 1983; Yu and Sadée, 1988; Martin et al., 1991; Chiu et al., 1993; Lambert et al., 1993; Gozzani, 1994, 1994; Fantoni et al., 1999; Lötsch, 2005; Vieweg et al., 2005; Hannam et al., 2016, 2; Jeleazcov et al., 2016; Li et al., 2017; Palladone capsules 1.3 mg - Summary of Product Characteristics (SmPC) - (emc)).

TABLE 2. Epidemiological characteristics of COVID-19 cases, death, and distribution of opioids in the Brazilian states and Federal District.

Brazilian Regions and states	Type of opioid - N (%)*			
	Fentanyl	Morphine	Remifentanil	Total
Southeast	**1,878,032**	**87,880**	**16,985**	**1,982,897**
Espírito santo	24,016	840	40	24,896
Minas Gerais	186,260	11,520	3,815	201,595
Rio de Janeiro	582,956	21,070	NI	604,026
São Paulo	1,084,800	54,450	13,130	1,152,380
Northeast	**1,358,149**	**230,970**	**39,515**	**1,628,634**
Alagoas	189,200	5,020	NI	194,220
Bahia	279,125	21,420	17,305	317,850
Ceará	312,740	134,500	2,250	449,490
Maranhão	132,950	8,000	45	140,995
Paraíba	99,824	27,370	2,000	129,194
Pernambuco	22,585	7,210	NI	29,795
Piauí	70,800	10,560	NI	81,360
Rio Grande do Norte	160,260	12,200	5,415	177,875
Sergipe	90,665	4,690	12,500	107,855
Midwest	**458,637**	**95,740**	**2,125**	**556,502**
Federal District	81,534	28,770	NI	110,304
Goiás	100,734	1,070	880	102,684
Mato Grosso do Sul	168,105	58,990	1,245	228,340
Mato Grosso	108,264	6,910	NI	115,174

North	**794,861**	**84,550**	**7,485**	**886,896**
Acre	93,355	32,300	NI	125,655
Amazonas	67,557	46,410	5,415	119,382
Amapá	117,410	NI	NI	117,410
Pará	173,971	NI	280	174,251
Rondônia	144,089	2,020	1,500	147,609
Roraima	138,089	1,350	290	139,729
Tocantins	60,390	2,470	NI	62,860
South	**134,649**	**60,130**	**23,890**	**218,669**
Paraná	58,024	14,310	20,560	92,894
Rio Grande do Sul	44,885	45,820	NI	90,705
Santa Catarina	31,740	NI	3,330	35,070

* Data last updated on 20/10/2021; ** Data last updated on 21/10/2021

NI, not informed

This data was collected up to 21 October 2021 from the Brazilian Ministry of Health website (Coronavírus Brasil; Localiza SUS). NI, not informed.

(Contiue) Table 2. Epidemiological characteristics of COVID-19 cases, death, and distribution of opioids in the Brazilian states and Federal District.

Brazilian Regions and states	**COVID-19 confirmed cases****	**Number of deaths due to COVID-19****	**Incidence per 100,000 inhabitants** **	**Mortality per 100.000 inhabitants** **	**Total opioids per confirmed COVID-19 cases****	**Total opioids per deaths due to COVID-19****
Southeast	**8,475,071**	**287,071**	**9,590**	**324**	**0.23**	**6.90**
Espírito santo	600,914	12,796	14,953	318	0.04	1.94
Minas Gerais	2,172,199	55,281	10,261	261	0.09	3.64
Rio de Janeiro	1,308,908	67,697	7,581	392	0.46	8.92
São Paulo	4,393,050	151,297	9,566	329	0.26	7.61
Northeast	**4,826,500**	**117,631**	**8,457**	**206**	**0.34**	**13.84**
Alagoas	239,499	6,268	7,176	187	0.81	30.98
Bahia	1,241,122	26,992	8,345	181	0.26	11.77
Ceará	942,351	24,393	10,319	267	0.48	18.42
Maranhão	359,227	10,219	5,077	144	0.39	13.79
Paraíba	444,184	9,380	11,054	233	0.29	13.77
Pernambuco	627,188	19,914	6,562,	208	0.05	1.49
Piauí	323,274	7,073	9,876	216	0.25	11.50
Rio Grande do Norte	371,278	7,368	10,587	210	0.48	24.14

Sergipe	278,377	6,024	12,110	262	0.39	17.90
Midwest	**2,318,879**	**58,012**	**14,229**	**356**	**0.24**	**9.59**
Federal District	512,089	10,745	16,983	356	0.22	10.26
Goiás	890,310	23,987	12,685	342	0.12	4.28
Mato Grosso do Sul	375,571	9,626	13,515	346	0.61	23.72
Mato Grosso	540,909	13,654	15,523	392	0.21	8.43
North	**1,857,010**	**46,729**	**10,075**	**253**	**0.48**	**18.97**
Acre	88,019	1,842	9,980	208	1.43	68.21
Amazonas	427,304	13,761	10,309	332	0.28	8.67
Amapá	123,342	1,989	14,584	235	0.95	59.02
Pará	595,995	16,713	6,928	194	0.29	10.42
Rondônia	268,187	6,559	15,090	369	0.55	22.50
Roraima	127,010	2,019	20,967	333	1.10	69.20
Tocantins	227,153	3,846	14,442	244	0.28	16.34
South	**4,203,028**	**94,785**	**14,021**	**316**	**0.05**	**2.30**
Paraná	1,539,756	40,002	13,466	350	0.06	2.32
Rio Grande do Sul	1,454,824	35,252	12,787	310	0.06	2.57
Santa Catarina	1,208,448	19,531	16,866	350	0.03	1.79

* Data last updated on 20/10/2021; ** Data last updated on 21/10/2021

NI, not informed

This data was collected up to 21 October 2021 from the Brazilian Ministry of Health website (Coronavírus Brasil; Localiza SUS). NI, not informed.

4. Conclusão

A literatura descreve valores da PEEP ideal como ainda controversos, talvez isso se deva ao fato de os estudos apontarem que a melhor estratégia para a escolha dela seria a titulação guiada pela melhor complacência, o que indica que a mecânica ventilatória é de fundamental importância nos ajustes dos parâmetros do ventilador mecânico. Outra forte evidência acerca da importância do conhecimento da mecânica ventilatória é o fato da *driving pressure* mostrar influência significativa no desfecho clínico no paciente sob VMI. Assim, infere-se que os diferentes valores da PEEP se devem ao fato da individualidade da mecânica ventilatória em cada paciente, assumindo ainda, que ela sofre influência de acordo com a fisiologia associada a cada doença.

Nosso estudo epidemiológico apontou taxa de mortalidade de 39,5% e dentre os preditores foram considerados o sexo (feminino), a idade (idosos), o diagnóstico admissional de sepse e o acidente vascular cerebral, a hipoxemia e o emprego da PEEP acima de 8 cmH_2O. Apesar de haver fatores preditores que não podem ser alterados, há aqueles que o manejo pode mudar reduzindo sua influência no desfecho; por sua vez, a PEEP mostrou ser uma ferramenta beira leito que pode ser titulada a fim de melhorar o desfecho clínico. Evitar a ocorrência de hipoxemia pela correta oferta de oxigênio e PEEP também pode reduzir a taxa de mortalidade; sendo que a PEEP deve ser titulada e personalizada ao paciente. Campanhas e acesso à serviço preventivo de saúde à população pode reduzir a incidência de acidente vascular cerebral e infecções, além de controlar a prevalência de outros fatores, tais como diabetes mellitus e a hipertensão arterial sistêmica, que foram frequentes em nossa casuística.

Em indivíduos sob VMI sem pneumopatias o incremento na PEEP não foi associado a alterações na hemodinâmica, na hematose e na driving pressure; podendo, estes valores, serem utilizados com segurança á beira leito. Ainda nesses termos podemos sugerir o uso de níveis de PEEP mais baixos, no intuito de otimizar uma ventilação protetora nos pacientes sob VMI.

A importância do uso racional e individualizado de medicamentos hipnóticos analgésicos e anestésicos sedativos deve ser considerada em todos os momentos, principalmente em situações de elevada demanda como a pandemia da COVID-19. Nesse contexto, é evidente que a presença de uma equipe multidisciplinar treinada e experiente, educação continuada frequente e boa administração, principalmente, no setor público de saúde são fatores que contribuem no manejo destas drogas. Diante de uma doença nova (COVID-19) e que cursa com longos períodos de internação e VMI, a titulação criteriosa e individualizada de opioides se mostra ainda mais evidente, principalmente, devido a dois fatores, escassez da droga e decorrente dos efeitos que seu uso prolongado pode acarretar o paciente.

5. Referência

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Anexos: Aprovação do CAAE

UNIVERSIDADE SÃO FRANCISCO-SP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Impacto da pressão positiva expiratória final no índice de oxigenação em participantes sem doença pulmonar prévia: um estudo de intervenção, clínico, não randomizado e controlado

Pesquisador: Fernando Augusto de Lima Marson

Área Temática:

Versão: 2

CAAE: 29718820.9.0000.5514

Instituição Proponente: Universidade São Francisco-SP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.988.122

Apresentação do Projeto:

Impacto da pressão positiva expiratória final no índice de oxigenação em participantes sem doença pulmonar prévia: um estudo de intervenção, clínico, não randomizado e controlado. Grande Área 4. Ciências da Saúde. Estudo Clínico. Condições de saúde ou problemas: Trauma. Ventilação mecânica invasiva. Descritores Gerais para as Condições de Saúde Código CID Descrição CID CID1-10: Classificação Internacional de Doenças - J44 - Outras doenças pulmonares obstrutivas crônicas. Descritores da Intervenção - Índice de oxigenação positive end-expiratory pressure. Será realizado um estudo de intervenção, clínico, não randomizado, controlado, com o intuito de quantificar, em porcentagem, o incremento na PaO2 utilizando diferentes níveis de positive end-expiratory pressure (PEEP) (seis ou oito ou 10 cmH2O) no mesmo participante sob VMI. A PaO2 será avaliada pela gasometria arterial (que, se na presença de acesso arterial periférico, a mesma será coletada por ele), que é realizada na rotina de atendimento dos pacientes submetidos à ventilação mecânica invasiva (VMI). Número Total de participantes: 150. Contemplará um grupo de pesquisa: Pacientes sob ventilação mecânica invasiva - Avaliação da PaO2 de acordo com o implemento do PEEP.

Objetivo da Pesquisa:

Objetivo Primário: Avaliar a resposta da PaO2 e do índice de oxigenação perante a aplicação de diferentes níveis (seis ou oito ou 10 cmH2O) de PEEP em participantes submetidos à VMI. Objetivo

Avaliação dos Riscos e Benefícios:

Riscos: No estudo não haverá riscos adicionais ao participante em relação a prática da rotina. Além disso, o PEEP a ser avaliado como intervenção será realizado dentro da variabilidade padrão aceita internacionalmente e praticada na rotina hospitalar. Benefícios: O impacto do estudo será promover o conhecimento quanto ao incremento da PaO2 e, consequentemente, do índice de oxigenação, de maneira mais específica do que é conhecido atualmente, visando otimizar o manejo da ventilação mecânica invasiva (VMI) que é um recurso indispensável na unidade de terapia intensiva. Adicionalmente, será avaliada a hemodinâmica dos pacientes submetidos à VMI fornecendo numerosos marcadores a serem comparados entre os diferentes valores do PEEP.

Comentários e Considerações sobre a Pesquisa:

Trata-se da versão 2, o TCLE foi ajustado conforme necessidades apontadas pela relatoria deste CEP.

Considerações sobre os Termos de apresentação obrigatória:

Foram todos apresentados e estão de acordo.

Recomendações:

Não se aplica neste caso.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado, não foram encontrados óbices éticos.

Considerações Finais a critério do CEP:

APÓS DISCUSSÃO EM REUNIÃO DO DIA 23/04/2020, O COLEGIADO DELIBEROU PELA APROVAÇÃO DO PROJETO DE PESQUISAS. APÓS A CONCLUSÃO DO PROJETO É OBRIGATÓRIO O ENVIO DO RELATÓRIO FINAL PARA ENCERRAMENTO DO PROJETO.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1515459.pdf	30/03/2020 16:02:19		Aceito
Outros	CartaRespostaCamila.pdf	30/03/2020 15:43:32	Fernando Augusto de Lima Marson	Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_CEP_3939784.pdf	30/03/2020 15:42:19	Fernando Augusto de Lima Marson	Aceito
Projeto Detalhado / Brochura	ProjetoMestradoCamilaVersao2.pdf	30/03/2020 15:41:57	Fernando Augusto de Lima Marson	Aceito

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Secundário: (i) avaliar o valor da PaO2 nos diferentes níveis de PEEP (seis ou oito ou 10 cmH2O) em participantes submetidos à VMI; (ii) avaliar a repercussão hemodinâmica [SpO2, frequência cardíaca (batimentos por minuto), pressão arterial diastólica (mmHg), pressão arterial sistólica (mmHg) e pressão arterial média (mmHg)] associada aos diferentes níveis de PEEP (seis ou oito ou 10 cmH2O) em participantes submetidos à VMI; (iii) quantificar, em porcentagem, o incremento da PaO2 nos diferentes níveis de PEEP (seis ou oito ou 10 cmH2O) em participantes submetidos à VMI; (iv) avaliar a influência dos níveis de PEEP (seis ou oito ou 10 cmH2O) na relação PaO2/FiO2 (denominado de índice de oxigenação) em participantes submetidos à VMI; (v) avaliar a influência da PEEP (seis ou oito ou 10 cmH2O) na pressão arterial de CO2 (PaCO2) (mmHg) em participantes submetidos à VMI;(vi) avaliar a influência da PEEP (seis ou oito ou 10 cmH2O) na SpO2, frequência cardíaca, pressão arterial diastólica, pressão arterial sistólica e pressão arterial média antes e após cada nível de PEEP; (vii) avaliar o número de eventos fora do padrão de normalidade denominados de hipoxemia e hiperóxia, pela presença de PaO2, respectivamente, abaixo e acima do valor de referência decorrente dos diferentes níveis de PEEP (seis ou oito ou 10 cmH2O) em participantes submetidos à VMI; (viii) realizar um estudo epidemiológico dos participantes submetidos à VMI na unidade de terapia intensiva do hospital universitário São Francisco de Assis nos últimos cinco anos de seguimento (2016 a 2020) com a descrição dos seguintes marcadores demográficos, clínicos e laboratoriais: sexo (masculino ou feminino), idade (anos), índice de massa corpórea (IMC, Kg/m2), PaO2 (mmHg), diagnóstico ou hipótese diagnóstica (p. ex. traumatismo crânio encefálico, politraumas, sepse, cirurgias eletivas, infarto agudo do miocárdio, acidente vascular encefálico, hemorragia subaracnóide, patologias neuromusculares, antecedentes pessoais de tabagismo, dislipidemia, diabetes tipos 1 e 2, obesidade, alergias, doenças neurológicas e psiquiátricas, cardiopatias, demência, sequelas motoras) e antecedentes pessoais (diabetes mellitus, hipertensão arterial sistêmica, tabagismo, etilismo, uso de drogas, dislipidemia, cardiopatia e pneumopatia). Os marcadores serão coletados pela análise dos prontuários eletrônicos, após aprovação do comitê de ética em pesquisa da Universidade São Francisco. A coleta de dados irá ser realizado no sistema Philips Tasy (Philips Healthcare®, Barueri, São Paulo, Brasil) de gestão hospitalar, no qual constam diagnósticos, avaliações, evoluções, monitorizações e exames complementares de todos os pacientes internados nestes períodos. Os dados dos marcadores poderão ser complementados, se necessário, pela pesquisa em prontuários físicos da instituição, sejam manuscritos ou impressos; (ix) realizar uma revisão sistemática da literatura considerando a influência dos diferentes níveis de PEEP no uso VMI (considerando os seguintes descritores: PEEP, adulto, SARS, PaO2 e índice de oxigenação) e associar os achados com os diferentes desfechos do paciente após a VMI.

UNIVERSIDADE SÃO FRANCISCO-SP

Continuação do Parecer: 3.988.122

Investigador	ProjetoMestradoCamilaVersao2.pdf	30/03/2020 15:41:57	Fernando Augusto de Lima Marson	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoMestradoCamilaVersao1.pdf	30/03/2020 15:41:47	Fernando Augusto de Lima Marson	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TermoConsentimentoVersao1.pdf	30/03/2020 15:41:28	Fernando Augusto de Lima Marson	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TermoConsentimentoVersao2.pdf	30/03/2020 15:39:42	Fernando Augusto de Lima Marson	Aceito
Cronograma	CronogramaCamila.pdf	04/03/2020 14:40:22	Fernando Augusto de Lima Marson	Aceito
Declaração de Instituição e Infraestrutura	ConcordanciaInstitucionalCamila.PDF	04/03/2020 14:39:13	Fernando Augusto de Lima Marson	Aceito
Folha de Rosto	CapaCamila.pdf	04/03/2020 14:38:09	Fernando Augusto de Lima Marson	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BRAGANCA PAULISTA, 24 de Abril de 2020

Assinado por:
CARLOS EDUARDO PULZ ARAUJO
(Coordenador(a))

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