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## Predictors of mortality in mechanically ventilated patients: an integrative review

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### ABSTRACT

**Aim:** To identify, by means of scientific evidence, the predictive factors of mortality in patients using Invasive Mechanical Ventilation. **Method:** Integrative literature review. The search was performed in Pubmed, Cochrane and Web of Science databases, using the descriptors: "humans", "respiration", "artificial", "mechanical ventilation", "ventilator weaning", "mechanical ventilator weaning", "Mortality" and "hospital mortality", mediated by the Boolean operators AND and OR. **Results:** Twenty-six articles were selected. The analysis of these articles allowed a discussion directed to the identification of predictors of mortality, classified in clinical and ventilatory predictors; and the main changes in ventilation during the years. Of the 26 articles found, 96% were published in English, 92% were observational studies, 4% were meta-analyzes and 4% were clinical trials. **Conclusion:** Prolonged weaning, extubation failure and reintubation were the main predictors identified by the studies analyzed.

**Descriptors:** Respiration, Artificial; Mortality; Respiratory Insufficiency, Intensive Care Units.

## INTRODUCTION

Critically ill patients have physiological, psychosocial, and spiritual needs that require differentiated and specialized health care. These precautions are intended to overcome the compromised physiological functions and to guarantee the possibility of restoring them partially or totally, such as the use of invasive mechanical ventilation (IMV)<sup>(1,2)</sup>. The emergence of critical care units, technological advances and progressive scientific knowledge have made possible the survival and physiological re-establishment of patients with acute critical illness<sup>(3)</sup>.

In Brazil, it is estimated that approximately 40% of patients admitted to the Intensive Care Units (ICUs) require surgical support<sup>(4)</sup>. However, variations in the prevalence of IMV use can be explained by the specific population characteristics of each region, the availability of life support devices, as well as by the regional culture regarding the provision of health services<sup>(5)</sup>.

Invasive supportive therapies used in intensive care units or in critically ill patients are paramount in restoring vital organ function. However, these can cause deleterious effects to the clinical condition of the patients in a serious condition and, in the long term, can cause damage to their quality of life, since after surviving an episode of acute critical illness, full recovery and patient autonomy become late because of the dependence generated by intensive care<sup>(3,6,7)</sup>.

Sometimes the need for ventilatory therapy is prolonged, increasing the individual's exposure to complications and, consequently, the deleterious effects associated with their use<sup>(3,6,7)</sup>. The incidence of complications may be related to mechanical ventilation-associated pneumonia (VAP), as well as to non-infectious causes. In 39.8% of the cases, they are characterized by organic dysfunctions resulting from cardiovascular, metabolic, digestive, neurological and

neuromuscular impairment related to clinical worsening<sup>(3,4)</sup>. These complications have an impact on the length of hospital stay, considerably increasing mortality rates<sup>(3,4)</sup>.

The use of VMI alone is a predictor of mortality. As the period of IMV treatment increases, there is a transition from the acute phase of the critical illness to the chronic phase (defined as a period of ventilatory support equal to or greater than 21 days), which increases the risk of repeated episodes of infection and complications and, consequently, an increase in death rates<sup>(3,6,7)</sup>. These complications can be avoided through measures of care management, supported through evidence-based practice<sup>(2)</sup>.

Promoting quality in care is the responsibility of the interdisciplinary team that provides care. Critical patient care aims to offer the most appropriate treatment that integrates a faster recovery and an increase in the quality of life, associated to the reduction of mortality rates and hospital costs<sup>(8)</sup>. The use of evidence-based practice has been important in this quality process, since it guides the conduct of the best clinical practice<sup>(2)</sup>.

Thus, the present study aimed to identify, through scientific evidence, which the predictors of mortality are in mechanically ventilated patients.

## METHODS

It is an integrative literature review based on the following guiding question: "What are the predictors of mortality evidenced by the literature in the critically ill patients ventilated mechanically?". For the elaboration of the guiding question, the PICO strategy was used, characterized by the acronym Patient, Intervention, Comparison and Outcomes<sup>(9)</sup>; following the steps of an integrative review<sup>(10)</sup>.

The search was performed on March 15, 2016 in the Pubmed, Cochrane and Web of Science databases, using the following Medical Subject Headings (MESH terms) terms: “humans”, “respiration, artificial”, “mechanical ventilation”, “Ventilator weaning”, “mechanical ventilator weaning”, “mortality” and “hospital mortality”, mediated by the Boolean operators AND for crossing different descriptors and OR for similar descriptors. After the search, the manual and electronic exclusion of duplicate references was carried out.

The inclusion criteria were the scientific articles published in English, Spanish and Portuguese, freely available in full, published in the period between 2005 and 2015, encompassing studies conducted with adult individuals, addressing as the central theme the outcome of mortality related to the use of IMV in critical patients. Articles that were not freely available in electronic form in full text form and those that did not address information related to the present research or that were in the form of case reports, editorial and expert reports were excluded. The references found in the cited databases according to established selection criteria, after the removal of the duplicate references, were submitted to the reading of the title and abstract, thus sorting them for full reading.

The articles selected for the composition of the final sample were evaluated in paired form by two independent reviewers, and the differences were discussed and solved. After the articles were read in full, they were organized and synthesized using a specific instrument that addressed the following criteria: name of the article, authors, type of study, research objective, analyzed sample, results, main recommendations and predictors of mortality evidenced in each study. The studies were categorized according

to the type of intervention proposed and level of evidence<sup>(11)</sup>, according to Table I.

**Table I.** Levels of evidence proposed by Fineout-Overholt, Melnyk, Schultz<sup>(11)</sup>

Level of Evidence	Type of Study
I	Systematic reviews or meta-analysis of relevant clinical trials
II	Evidence from at least one well-delineated randomized controlled clinical trial
III	Well-delineated clinical trials without randomization
IV	Well-designed cohort and case-control studies
V	Systematic review of descriptive and qualitative studies
VI	Evidence derived from a single descriptive or qualitative study
VII	Authorities' opinion or expert committees report

Source: Fineout-Overholt, Melnyk, Schultz<sup>(11)</sup>

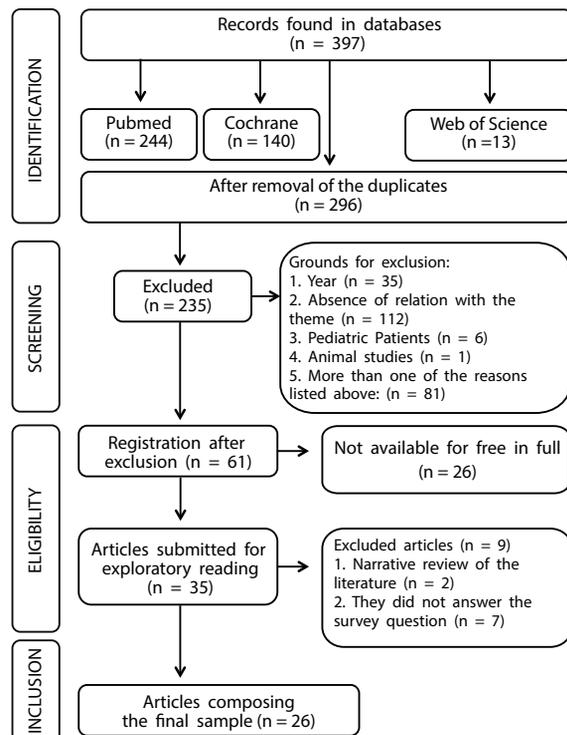
## RESULTS

26 studies responding to the research question, reporting predicting mortality factors, were included, as shown in figure I. Of these, English was the predominant language present in 96% (25) of the studies. Regarding the place of studies, only 8% (2) were performed in Brazilian ICUs, located in the state of São Paulo. The other studies were performed in international units, with 31% (8) in the Asian continent. Of the 26 studies analyzed, 92% were observational (levels of evidence IV and VI), 4% clinical trial (level II) and 4% meta-analysis (level I), as described in Table II.

The studies analyzed in this review evidenced some predictors of mortality associated with the use of IMV, which can be divided into predictors related to mechanical ventilation (ven-

tilatory predictors) and clinical characteristics presented by the patients (clinical predictors). Among the ventilatory predictors are: prolonged mechanical ventilation, prolonged and inadequate ventilatory weaning, failure of the extubation process, need for reintubation, late tracheostomy, and low PaO<sub>2</sub>/FiO<sub>2</sub> ratio, characterizing a worsening of respiratory dysfunction. In relation to the clinical predictors, there was the presence of COPD, advanced age, presence of diverse comorbidities (isolated or in association), increase of clinical severity and need of support therapies for maintenance of vital functions.

**Figure I.** Flowchart according to study selection criteria. Brasília, DF, Brazil, 2016.



Source: Data related to the complication of searching databases

## DISCUSSION

VMI corresponds to the most used therapy in ICUs and its application must consider the

demographic and clinical peculiarities of each individual<sup>(12)</sup>. Scientific research has reiterated the benefits of certain ventilatory practices already instituted, as well as identified possible conducts and variables that negatively influence the recovery of the critical patient using IMV, generating potentially preventable complications and increased mortality rate<sup>(12-16)</sup>.

Among the studies of this review, PMV and prolonged weaning were the main predictors of mortality<sup>(13,17,18,20-22,29,32)</sup>. The occurrence of PMV can be influenced by pre-existing chronic comorbidities at admission, among which chronic kidney disease, diabetes mellitus, cerebrovascular disease and pulmonary disease are prominent<sup>(13,17,18)</sup>. An observational study<sup>(19)</sup>, with 7848 patients using IMV, identified that infectious causes, such as pneumonia and septic shock, also determine ventilator dependence. These factors have a higher rate of readmissions, longer hospitalization<sup>(17,19)</sup>, prolonged weaning and extubation<sup>(20-22)</sup>, since recovery is slower in patients with chronic and/or infectious chronic diseases<sup>(13)</sup>.

The ventilatory changes that occurred in the last 10 years point to the management of care as the main modulator in the prevention of infections and/or additional complications related to chronic diseases, capable of preventing the need for PMV, as well as prolonged weaning<sup>(19,23,24)</sup>. These include early tracheostomy, independently of the technique used (percutaneous or surgical)<sup>(23,24)</sup> and the use of ventilatory modalities that allow alternation between assisted and spontaneous breathing cycles<sup>(12)</sup>.

Early tracheostomy prevents VAP and sepsis, since orotracheal intubation makes it difficult to eliminate mucus due to the depression of the cough reflex caused by the use of sedatives, which contributes to the proliferation of bacteria in the upper and lower respiratory tract<sup>(23,24)</sup>. In conscious and tracheostomized patients who

**Table II.** Characterization of the studies according to author, year of publication, country of origin, method, level of evidence, sample characterization and predictors of mortality. Brasília, DF, Brazil, 2016.

Article and year of publication	Country of origin	Method	Level of Evidence	Characterization of the sample	Predictors of Mortality
2013 <sup>12</sup>	Multicentric in 40 countries	Cohort	IV	18,302 patients from 927 ICUs	Clinical complications, sepsis, cardiovascular failure, low PEEP and high CV
2013 <sup>13</sup>	Taiwan	Retrospective Cohort	IV	119 patients with PMV undergoing extubation	Extubation failure and reintubation, ineffective cough. VMP. Chronic Comorbidities
2015 <sup>14</sup>	Taiwan	Retrospective Cohort	IV	213,945 patients submitted to IMV for more than 96h	Age, male, high Charlson score, comorbidities
2014 <sup>15</sup>	United States	Retrospective	V	1,885 patients with neurological damage and using IMV	There was no predictor of mortality
2011 <sup>16</sup>	Brazil	Cohort	IV	317 patients undergoing intracranial surgery and using IMV	Extubation failure and level of consciousness
2010 <sup>17</sup>	Taiwan	Retrospective Cohort	IV	243 patients in PMV, who underwent weaning	Neoplastic diseases, neurological diseases and IMV dependence
2010 <sup>18</sup>	Iran	Retrospective	VI	1,056 patients who underwent myocardial revascularization surgery and required IMV	PMV as a cause of renal failure, intra-aortic balloon use and stroke
2011 <sup>19</sup>	United Kingdom	Retrospective Cohort	IV	7848 patients using IMV (prolonged and not prolonged)	PMV associated with increased age and disease severity. Hemodynamic instability
2009 <sup>20</sup>	Austria	Cohort	IV	257 patients who started the weaning process	Prolonged weaning and age
2011 <sup>21</sup>	Multicentric in 23 countries	Cohort	IV	2714 patients using IMV in 23 countries	Prolonged weaning
2011 <sup>22</sup>	France	Retrospective	VI	115 patients who received IMV for more than 48 hours and who were weaned	Prolonged weaning
2011 <sup>23</sup>	Germany	Retrospective Cohort	IV	296 patients requiring tracheostomy due to extubation and/or weaning failure	Late tracheostomy
2005 <sup>24</sup>	Taiwan	Retrospective	VI	163 tracheostomized patients	Late tracheostomy
2009 <sup>25</sup>	Spain	Cohort	IV	118 tracheostomized patients	Presence of tracheostomy after discharge from the ICU, BMI > 30 and abundant expectoration
2008 <sup>26</sup>	Chile	Cohort	IV	156 adult patients using IMV for more than 12 hours	Plateau pressure > 30 cm, SAPS II > 60 and low PaO <sub>2</sub> /FiO <sub>2</sub> ratio
2005 <sup>27</sup>	Israel	Cohort	IV	69 patients in IMV for more than 10 days	Weaning failure
2011 <sup>28</sup>	Multicentric in 7 countries	Retrospective Cohort	IV	1,152 patients in 36 ICUs from 7 countries	Reintubation after extubation failure

2015 <sup>29</sup>	South Korea	Cohort	IV	680 patients undergoing weaning	Difficulty in weaning, low PaO <sub>2</sub> /FiO <sub>2</sub> ratio and respiratory acidosis
2005 <sup>30</sup>	United States	Case-control	IV	300 extubated patients, 100 in the case group: unplanned extubation and 200 in the control group: planned extubation	Age and reintubation
2012 <sup>31</sup>	Brazil	Retrospective	VI	252 patients submitted to IMV for more than 24h	Reintubations
2013 <sup>32</sup>	Austria	Prospective Cohort	IV	194,453 patients, 16,774 of whom had COPD	COPD, high SAPS II, PMV and prolonged weaning
2013 <sup>33</sup>	United States	Retrospective	VI	803 patients submitted to weaning protocol	There was no predictor of mortality
2013 <sup>34</sup>	Taiwan	Retrospective Cohort	IV	100 patients with severe acute respiratory failure	High score SOFA and low PaO <sub>2</sub> /FiO <sub>2</sub> ratio
2009 <sup>35</sup>	—————	Meta-analysis	I	2,447 patients in a total of 5 randomized controlled trials	Low level of PEEP
2008 <sup>36</sup>	France	Randomized Clinical Trial	II	767 patients undergoing different levels of PEEP	There was no predictor
2010 <sup>37</sup>	United States	Cohort	IV	336 patients submitted to weaning	Depressive Disorders and Charlson Comorbidity Index

Source: data referring to the complication of the selected articles. IMV: Invasive Mechanical Ventilation; PMV: Prolonged Mechanical Ventilation; ICU's: Intensive Care Units; COPD: Chronic Obstructive Pulmonary Disease; CV: Current Volume; Stroke: Cerebral Vascular Accident; SAPS II: Simplified Acute Physiology Score; BMI: Body Mass Index; SOFA: Sepsis-related Organ Failure Assessment.

are discharged from the ICU, these benefits are impaired due to the potential complications that may occur in the infirmary related to infectious processes, especially in patients with abundant expectoration<sup>(25)</sup>. The studies use different classifications for early tracheostomy; however, in general terms, this can be defined when its use occurs within 21 days after orotracheal intubation, that is, during the period in which the patient is in the state of acute critical illness. Two observational studies considered late tracheostomy as a predictor of mortality<sup>(23,24)</sup>.

Regarding ventilatory modalities, the assisted-controlled modality remains the most used at the beginning of IMV therapy. There is a tendency to replace it with supportive ventilation and synchronized intermittent mandatory ventilation, which seem to bring less patient dependence on the ventilator<sup>(12,26)</sup>.

Other identified mortality predictors refer to weaning failure and extubation failure, with

the consequent need for reintubation<sup>(13,16,27-31)</sup>. Prolonged weaning most often influences extubation failure and increases reintubation rates, as it may cause hypoxemia, associated respiratory acidosis and decreased level of consciousness, as well as its association with chronic and infectious diseases. The period between failure of extubation and reintubation leads to greater clinical worsening in critically ill patients. In addition, reintubation directly determines the development of complications such as cardiovascular failure, renal and hepatic failure, VAP and sepsis<sup>(13, 16, 27-31)</sup>.

Prolonged weaning is a recurrent factor in patients who had COPD as the cause of acute respiratory failure<sup>(32)</sup>. In an observational study with 803 patients, no association of weaning with extubation failure and mortality was identified<sup>(33)</sup>. However, the other evidences found in this review suggest that the success of weaning can be achieved through the use of the weaning

process guided by clinical protocols, based on scientific evidence to replace the weaning process guided by medical opinion<sup>(20-22,26,29,31,33)</sup>.

Several studies explored in this review<sup>(17-19,26)</sup> tested the efficacy of the new weaning classification from the International Consensus Conference on weaning from MV (2005), which selects patients ready for extubation, generating the classification of weaning (simple, difficult and prolonged) and predicting the prognosis for patients in IMV. The results of these studies confirm the clinical relevance of this new weaning classification<sup>(20-22,29)</sup>.

Significant statistical association between age and mortality were identified<sup>(14,30)</sup>. Such association is justified by the greater number of comorbidities found in these patients, as well as by their own characteristics that interfere in the adaptation to the hemodynamic changes characteristic of the ventilatory support therapy and to the physiological adaptations after extubation.

Another determining factor in mortality among critically ventilated critical patients is the low PaO<sub>2</sub>/FiO<sub>2</sub> ratio, identifying and characterizing patients with Acute Respiratory Distress Syndrome (ARDS). As these patients have severe acute respiratory failure, they develop associated metabolic disorders, which lead to a higher mortality rate<sup>(26,29,34)</sup>. In this sense, the positive effects of protective pulmonary ventilation for these patients are highlighted, since it uses low current volume (CV) and high end expiratory pressure (PEEP)<sup>(12,26,35)</sup>.

In a cohort (12), the mortality rate was estimated in patients using IMV, compared in three different periods (1998, 2004 and 2010). The authors concluded that, although the clinical severity of these patients increased, mortality rates decreased over time, suggesting that this can be attributed to changes in institutional practices and use of protective pulmonary ventilation.

In a randomized clinical trial<sup>(36)</sup>, when assessing the benefits of a high PEEP vs low PEEP value associated with the use of CV of 6 ml/kg body weight, there was no statistical significance in mortality rates between the two groups. On the other hand, in a meta-analysis<sup>(35)</sup>, which consisted of 5 randomized clinical trials, the high value of PEEP with low CV significantly reduced hospital mortality and mortality at 28 days, especially in more severe patients with higher APACHE II scores.

The heterogeneity of results found among the studies selected in this review can be justified by the clinical differences of the samples, suggesting that high levels of PEEP associated with low CV bring benefits to more critically ill individuals with ARDS; however, their use should be limited and careful, since individuals with mild acute respiratory insufficiency appear to respond differently to this strategy<sup>(26,35,36)</sup>.

Regarding psychological disorders, a cohort of 336 patients in the weaning process pointed out that depressive disorders are strongly associated with mortality in critically ill patients and that Delirium may not have the same association with this outcome<sup>(37)</sup>. Finally, it was verified that the creation of specialized weaning units contributes to the success of weaning and to the reduction of associated complications<sup>(19,26)</sup>.

## CONCLUSION

The main predictors of mortality in these studies refer to prolonged mechanical ventilation and/or prolonged weaning, with extubation failures associated with the need for reintubation, in addition to late tracheostomy, advanced age and low PaO<sub>2</sub>/FiO<sub>2</sub> ratio. Some studies have established protective care routines that avoid or minimize the occurrence of these predictors, demonstrating that evidence-based practice is

the main tool for improving the prognosis of critically ill and at risk patients.

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