Factors associated with non-invasive ventilation failure and mortality in oncologic patients outside the intensive care unit

Fatores associados a falha da ventilação não invasiva e mortalidade em pacientes oncológicos fora da unidade de terapia intensiva

Factores asociados com el fracasso de la ventilación no invasiva y la mortalidad en pacientes oncológicos fuera de la unidad de cuidados intensivos

Received: 08/20/2021 | Reviewed: 08/25/2021 | Accept: 08/26/2021 | Published: 08/29/2021

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Abstract

Introduction: New treatments have been introduced with the objective to increase the survival rate of oncologic patients. As a result of these approaches, there was an increase in the number of cases of toxicity and complications, which can lead to acute respiratory failure (ARF). One of the most frequent ways to treat ARF is non-invasive ventilation (NIV). Despite the proven benefits in several clinical conditions, NIV results in cancer patients are controversial. Objective: To evaluate risk factors associated with NIV failure and hospital mortality in oncologic patients. Methods: Retrospective cohort study including patients with solid tumors and hematological neoplasms admitted for hospitalization at National Cancer Institute between January 1, 2017 and December 31, 2019, who underwent NIV. The association between the variables of exposure and the outcome was performed by gross and adjusted logistic regression. The Kaplan-Meier method was used to analyze the length of hospital stay. Results: Sixty-three patients who underwent NIV in hospitalization were evaluated, and 26 failed NIV. The patients had a mean age of 58.5 years (±15.6), most were male (57.1%), under 60 years old (58.7%) and had comorbidities (55.5%). The patients with pulmonary infection (OR 6.53; 95% CI 1.21-35.12; p=0.02) had a higher risk of failure in NIV. In relation to hospital mortality, patients older than 60 years (OR 6.90; 95% CI, 2.12-22.45; p=0.001) had a higher risk. Conclusion: Patients who presented pulmonary infection were more likely to fail in NIV. Higher hospital mortality was observed among elderly patients.

Keywords: Noninvasive ventilation; Cancer; Mortality.

Resumo

Introdução: Novos tratamentos têm sido introduzidos visando o aumento da sobrevida dos pacientes oncológicos. Com isso, existe um aumento do número de casos de complicações e toxidades que podem levar a insuficiência respiratória aguda (IRA). Um dos caminhos mais frequentes para tratamento da IRA é a ventilação não invasiva (VNI). Apesar dos benefícios em diversas condições clínicas, o uso da VNI em pacientes oncológicos é controverso. Objetivo: Avaliar os fatores associados a
In Brazil, cancer is the second largest cause of death, and is estimated for the 2020-2022 three-year period the occurrence of 625,000 new cancer cases for each of these years, with the highest incidence being observed in non-melanoma skin cancer, followed by breast cancer, prostate, colon, rectum and lung (BRASIL, 2017). In each year 18.1 million new cases appear worldwide, and the most common are prostate, breast, lung and colon cancer (Bray et al. 2018).

An increase in the survival rate of cancer patients in recent decades has been associated with advances in antineoplastic treatment and early diagnosis (Azoulay et al. 2010; Azoulay et al. 2011; Avgencel et al. 2014). However, these survival gains also have increased the number of cases of toxicity and complications, resulting in a higher number of cancer patients admitted to intensive care units (ICU) (Azoulay et al. 2004; Soares et al. 2010).

Among the complications that lead to deterioration of the clinical status of cancer patients, acute respiratory failure (ARF) is the main cause of hospitalization of cancer patients in the ICU, occurring in 30% of cases (Soares et al. 2010; Azevedo et al. 2014). ARF has a high mortality rate in cancer patients of up to 50% and even higher in patients who need invasive ventilation (Azoulay et al. 2004; Azevedo et al. 2014; Yeo et al. 2012; Soubani et al. 2014).

Noninvasive ventilation (NIV) is increasingly used to treat ARF of various etiologies, like bacterial pneumonia and opportunistic pulmonary infections, and it is demonstrating a remarkable reduction of intubation and mortality for specific populations (Schnell et al. 2013; Keenan et al. 2011). Most patients diagnosed with ARF are treated with NIV and about 20% start this type of treatment in the ward (Ozsancak et al. 2015).

Despite all benefits presented regarding the efficacy of ARF treatment of several etiologies, there are still few studies that contemplate the several oncological clinics and even rarer in patients who perform NIV outside the ICU. Therefore, the...
objective of the study was to describe the factors associated with NIV failure and hospital mortality in oncological patients hospitalized outside the ICU.

2. Methods

This study was approved by the Research Ethics Committee of the National Cancer Institute (protocol CAAE: 94932318000005274, number 2842917/2018); due to its retrospective cohort study, no informed consent from patients was required.

A cohort study was conducted in patients with solid tumors and hematologic neoplasms admitted at the wards of Brazilian National Cancer Institute (INCA) between January 1, 2017 and December 31, 2019. Patients older than 18 years who underwent NIV and who had at least 3 physiological and clinical indicators that result in ARF were included in the study. The following indicators were considered: severe dyspnea or respiratory frequency higher than 30 breaths per minute and signs of the effort of the respiratory muscles, oxygen saturation under 90% or PaO$_2$ lower than 60mmHg in ambient air (Azoulay et al. 2010). Protocol for NIV was based on internationally recommended guides (Keenan et al. 2011).

This study started with 111 patients who underwent NIV in the wards, but 48 patients were excluded because they did not meet the established criteria for ARF. The cases were identified in the Physiotherapy System of the institution. The patients were submitted to NIV with portable devices (VPAP ST-A iVAPS, ResMed, Australia), using two positive pressure levels, inspiratory positive airway pressure – IPAP and expiratory positive airway pressure – EPAP with orofacial masks attached with a head fixator to ensure the comfort of the patient and minimum leak, plus oxygen supply in liters/min close to the system circuit.

Clinical and demographic data were extracted from physical and electronic medical records (Intranet) from hospital admission until December 2020. The exposure variables evaluated were: gender, age, marital status, education, baseline disease, motive of hospitalization, comorbidities, motive of the NIV.

Early failure of NIV and hospital mortality were the main outcomes of interest. Early immediate of NIV was defined as the occurrence of endotracheal intubation and invasive mechanical ventilation until 24 hours after the first session of NIV. The decision to conduct endotracheal intubation after NIV was based on the clinical judgment of the assistant physician and clinical and gasometry signs of the patients (Ferreira et al. 2015). The secondary outcome was the length of hospital stay.

The descriptive analysis of the variables was performed, utilizing mean ± standard deviation (SD) for continuous variables and percent (%) for categorical variables. Chi-square test or Fisher exact test were used to identify differences among groups. The association between the variables of exposure and outcomes (failure of NIV and mortality) was done by logistic regression and presented through the raw odds ratio (OR). The analysis of survival rate was made with the Kaplan-Meier method, considering the time between hospitalization and the date of hospital discharge. Differences between survival curves was estimated by the log-rank test. For all the analyzes, the values of p<0.05 were considered statistically significant. Analyses were performed using SPSS software (Statistical Package for the Social Sciences of Windows, São Paulo, Brazil) version 21.0.

3. Results

It was included 63 patients with an average age of 58.5 years (±15.6) and an average time of hospitalization was 25.5 days (±21.7). Most of the patients were male (57.1%) and presented solid tumors (50.8%). The clinical hospitalization was the main motive (82.5%), most of the patients had comorbidities (55.6%), leukocytosis (55.5%), were married (52.4%) and 30 (47.6%) patients had a pulmonary infection (Table 1). The most common neoplasms were: leukemia (25.4%), colon and rectal (17.5%), lymphoma (14.3%), genitourinary system (11.1%) and multiple myeloma (7.9%).
Table 1. Sociodemographic and clinic characteristics (n=63)

| Characteristics                  | n (%)     |
|----------------------------------|-----------|
| **Age**                          |           |
| ≤ 60 years old                   | 37 (58.7) |
| > 60 years old                   | 26 (41.3) |
| **Gender**                       |           |
| Male                             | 36 (57.1) |
| Female                           | 27 (42.9) |
| **Marital status**               |           |
| Married                          | 33 (52.4) |
| Separated                        | 5 (7.9)   |
| Widowed                          | 4 (6.3)   |
| Single                           | 13 (20.6) |
| Missing                          | 8 (12.7)  |
| **Education**                    |           |
| Illiterate                       | 1 (1.6)   |
| 1º incomplete degree             | 14 (22.2) |
| 1º complete degree               | 16 (25.4) |
| 2º incomplete degree             | 1 (1.6)   |
| 2º complete degree               | 16 (25.4) |
| Incomplete higher                | 2 (3.2)   |
| Complete higher                  | 4 (6.3)   |
| Missing                          | 9 (14.3)  |
| **Baseline Disease**             |           |
| Solid tumors                      | 32 (50.8) |
| Hematologic                      | 31 (49.2) |
| **Motive of hospitalization**    |           |
| Clinic                           | 52 (82.5) |
| Surgical                         | 11 (17.5) |
| **Comorbidities**                |           |
| Yes                              | 35 (55.6) |
| No                               | 28 (44.4) |
| **Motive of the NIV**            |           |
| Pulmonary infection               | 30 (47.6) |
| Acute pulmonary edema            | 12 (19.0) |
| Others                           | 21 (33.3) |

NIV= non-invasive ventilation
Source: Authors.

The total time of NIV on average was 133.8 minutes (±117.9), the mean time of the first session was 74.7 minutes (±59.9), and on average, the patients underwent 2.1 (±1.8) NIV sessions. The frequency of failure in NIV was 49.2% and 31 (49.2%) of the patients were transferred to the ICU.
The possible factors associated with failure in NIV were presented in Table 2. Patients with pulmonary infection had a 6.53 times higher risk of failure in NIV compared to patients with acute pulmonary edema (OR 6.53; 95% CI 1.21-35.12; p=0.02).

Table 2. Factors associated to failure of non-invasive ventilation (Univariate Analysis).

| Characteristics               | Failure in the NIV (N=26) | Success in the NIV (N=37) | OR (CI 95%) | P value |
|-----------------------------|---------------------------|---------------------------|-------------|---------|
| **Gender**                  |                           |                           |             |         |
| Female                      | 9 (34.6)                  | 18 (48.6)                 | Reference   | 0.27    |
| Male                        | 17 (65.4)                 | 19 (51.4)                 | 1.78 (0.63-5.03) |         |
| **Age**                     |                           |                           |             |         |
| > 60 years old              | 10 (38.5)                 | 16 (43.2)                 | Reference   | 0.70    |
| ≤ 60 years old              | 16 (61.5)                 | 21 (56.8)                 | 1.21 (0.43-3.39) |         |
| **Marital status**          |                           |                           |             |         |
| Living without partner      | 8 (34.8)                  | 14 (43.8)                 | Reference   | 0.50    |
| Living with partner         | 15 (65.2)                 | 18 (56.8)                 | 1.45 (0.48-4.40) |         |
| **Education**               |                           |                           |             |         |
| > 8 years of study          | 13 (56.5)                 | 19 (61.3)                 | Reference   | 0.72    |
| ≤ 8 years of study          | 10 (43.5)                 | 12 (38.7)                 | 1.21 (0.40-3.64) |         |
| **Motive of the NIV**       |                           |                           |             |         |
| Acute pulmonary edema       | 2 (7.7)                   | 10 (27.0)                 | Reference   |         |
| Pulmonary infection         | 17 (65.4)                 | 13 (35.1)                 | 6.53 (1.21-35.12) | 0.02    |
| Others                      | 7 (26.9)                  | 14 (37.8)                 | 2.50 (0.42-14.65) | 0.31    |
| **Baseline Disease**        |                           |                           |             |         |
| Solid tumors                | 12 (46.2)                 | 20 (54.1)                 | Reference   | 0.53    |
| Hematologic                 | 14 (53.8)                 | 17 (45.9)                 | 1.37 (0.50-3.75) |         |
| **Motive of hospitalization** |                         |                           |             |         |
| Surgical                    | 2 (7.7)                   | 9 (24.3)                  | Reference   | 0.10    |
| Clinic                      | 24 (92.3)                 | 28 (75.7)                 | 3.85 (0.73-19.61) |         |
| **Ethnicity**               |                           |                           |             |         |
| Others                      | 11 (50.0)                 | 16 (50.0)                 | Reference   | 1.00    |
| White                       | 11 (50.0)                 | 16 (50.0)                 | 1.00 (0.33-2.96) |         |
| **Comorbidities**           |                           |                           |             |         |
| No                          | 11 (42.3)                 | 17 (45.9)                 | Reference   | 0.77    |
| Yes                         | 15 (57.7)                 | 20 (54.1)                 | 1.15 (0.42-3.18) |         |

NIV= non-invasive ventilation; OR=odds ratio; CI = confidence interval. In bold, the selected variables for the model of multiple regression.

Source: Authors.
The median hospitalization time of patients who failed in the NIV was 8 days and those who were successful were 27 days, and this difference was statistically significant (p=0.04) (Figure 1).

**Figure 1.** Median hospitalization time among patients with success and failure of non-invasive ventilation.

Hospital mortality of patients who failed in the NIV was 48.6%. The possible factors associated with hospital mortality were presented in Table 3. The patients older than 60 years had an 8.69 times higher risk of death in hospitalization compared to patients younger than 60 years (OR 6.90; 95% CI, 2.12-22.45; p=0.001).
Table 3. Factors associated to hospital mortality (Univariate Analysis).

| Characteristics                  | Yes (N= 35) | No (N= 28) | OR (CI 95%) | P value |
|----------------------------------|-------------|------------|-------------|---------|
| **Gender**                       |             |            |             |         |
| Female                           | 14 (40.0)   | 13 (46.4)  | Reference   | 0.60    |
| Male                             | 21 (60.0)   | 15 (53.6)  | 1.30 (0.47-3.55) |         |
| **Age**                          |             |            |             |         |
| ≤ 60 years old                   | 14 (40.0)   | 23 (82.1)  | Reference   | 0.001   |
| > 60 years old                   | 21 (60.0)   | 5 (17.9)   | 6.90 (2.12-22.45) |         |
| **Marital status**               |             |            |             |         |
| Living without partner           | 11 (35.5)   | 11 (45.8)  | Reference   | 0.43    |
| Living with partner              | 20 (64.5)   | 13 (54.2)  | 1.53 (0.51-4.57) |         |
| **Education**                    |             |            |             |         |
| ≤ 8 years of study               | 12 (40.0)   | 10 (41.7)  | Reference   | 0.90    |
| > 8 years of study               | 18 (60.0)   | 14 (58.3)  | 1.53 (0.36-3.19) |         |
| **Motive of the NIV**            |             |            |             |         |
| Acute pulmonary edema            | 4 (11.4)    | 8 (28.6)   | Reference   |         |
| Pulmonary infection              | 18 (51.4)   | 12 (42.9)  | 3.00 (0.73-12.22) | 0.12    |
| Others                           | 13 (37.1)   | 8 (28.6)   | 3.25 (0.73-14.40) | 0.12    |
| **Baseline Disease**             |             |            |             |         |
| Hematologic                      | 19 (54.3)   | 12 (42.9)  | Reference   | 0.36    |
| Solid tumors                     | 16 (45.7)   | 16 (57.1)  | 1.58 (0.58-4.30) |         |
| **Motive of hospitalization**    |             |            |             |         |
| Surgical                         | 6 (17.1)    | 5 (17.9)   | Reference   | 0.94    |
| Clinic                           | 29 (82.9)   | 23 (82.1)  | 1.05 (0.28-3.88) |         |
| **Ethnicity**                    |             |            |             |         |
| Others                           | 12 (41.4)   | 15 (60.0)  | Reference   | 0.17    |
| White                            | 17 (58.6)   | 10 (40.0)  | 2.12 (0.71-6.31) |         |
| **Comorbidities**                |             |            |             |         |
| Yes                              | 19 (54.3)   | 16 (57.1)  | Reference   | 0.82    |
| No                               | 16 (45.7)   | 12 (42.9)  | 1.12 (0.41-3.05) |         |

NIV= non-invasive ventilation; OR=odds ratio; CI = confidence interval. In bold, the selected variables for the model of multiple regression.
Source: Authors.
The 6-month survival rates were 19.2% for the patients who failed in the NIV and 35.6% for patients who did not fail in the NIV. The 12-month survival rates were 11.5% for the patients who failed in the NIV and 25.4% for patients who did not fail in the NIV.

4. Discussion

In this retrospective cohort of patients diagnosed with hematological neoplasms and solid tumors with ARF admitted to wards, it was observed/that NIV was not effective for reversing ARF in 49% of patients for any cause. The risk factors associated with NIV failure was pulmonary infection as the cause of ARF, while the risk factor associated with mortality was age.

The NIV has been a technique used and linked to the improved survival rates of cancer patients in recent years, as it is a less invasive alternative for the treatment of ARF in patients who have already undergone such aggressive treatments (Azoulay et al. 2004; Saillard et al. 2014). There is still much concern about the failure of NIV because it is associated with worse clinical results (Czeszynska et al. 2020; walkey et al. 2013), in studies with cancer patients, NIV failure rates range from 25% to 70% (Azoulay et al. 2004; Azevedo et al. 2014; Gristina et al. 2011; Adda et al. 2008; Azevedo et al. 2013)

When comparing the frequency of use of NIV for ARF treatment, this feature is most often used in the wards when compared to the emergency and ICU sectors (Ozsancak et al. 2015). In wards, we need to distinguish which patients have a risk of failing NIV and which may benefit from the technique. In order to be more successful in the use of NIV, a careful evaluation of patients is necessary. Therefore, it is important to identify which factors may be associated with NIV failure to better guide the clinical decision of ARF patients. Only a few previous studies have evaluated the risk factors associated with NIV failure in ICU cancer patients, as far as known, this study is the first to exclusively address cancer patients outside the ICU with ARF.

Azevedo et al. (2014) prospectively analyzed 85 cancer patients with ARF who used NIV, reporting that 53% of the patients failed NIV. They observed that the risk factors associated with NIV failure were septic shock and high respiratory rate on the first day of NIV. However, Ferreira et al. (2015) argue that a high respiratory rate may be better described as an indicator that NIV is not effective, and not a risk factor itself.

A Brazilian study that analyzed 114 cancer patients in the ICU showed that predictors factors of NIV failure were pulmonary infection (OR=3.55) and male gender (OR=2.42) (Ferreira et al. 2015). Another retrospective study evaluated cancer patients who performed NIV outside the ICU without ARF and demonstrated that pulmonary infection was associated with NIV failure (OR=4.71) (Araújo et al. 2019).

In the present study, a similar result was demonstrated, patients with ARF caused by pulmonary infection were 6.53 times more likely to fail in NIV. This result demonstrate that cancer patients hospitalized in wards with ARF caused by pulmonary infection, NIV should be used with caution, with rigorous monitoring and intubation performed if there are no signs of improvement in the first hours after NIV. Other studies have demonstrated predictive factors for NIV failure in variables that were not found or analyzed in our study (Briones et al. 2017 ; Rath et al. 2017; Al-Rajhi et al. 2018). Rath et al. (2017) analyzed 1.614 cancer patients with hypoxemic respiratory failure who underwent NIV in the ICU, demonstrating that the factors associated with NIV failure were race (OR=1.60), age (OR=0.98) and disease category (hematologic vs solid) (OR=1.87). Briones et al. (2017) conducted a prospective study that analyzed patients who used NIV outside the ICU, where they demonstrated an association with NIV failure in age, respiratory rate, number of quadrants affected at radiography, and IPAP level, PaCO\textsubscript{2}, PaO\textsubscript{2}. 

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A cohort study in a single center demonstrated that NIV failure is associated with an increase in patients referred to ICU, longer hospitalization time, and an increased risk of hospital mortality (Corrêa et al. 2011). Studies have shown that a long time in NIV increases the risk of failure. The same authors argued that late failure in NIV (intubation after 48 hours or more) is associated with high mortality rates, in the multiple analyses of these studies, failure of NIV was independently associated with increased mortality (Azoulay et al. 2004; Rathi et al. 2017; Neuschwander et al. 2017).

In the present study, the hospital mortality rate was 84.6% for patients who failed in NIV and 64.9% for those who were successful. Hospital mortality was associated with age, demonstrating that patients with more than 60 years had almost nine times higher risk of progressing to death during hospitalization when compared to patients with less than 60 years. In a study with non-cancer patients with ARF who underwent NIV, it also was observed a higher risk related to age, as each decade increased, the patients had a higher risk of progressing to death (OR=1.51) (Hayek et al. 2020). Rathi et al. (2017) conducted a study with cancer patients in the ICU and related hospital mortality to the disease category (hematologic vs solid tumors) (OR=2.69). Neuschwander et al. (2017) associated hospital mortality with NIV failure (OR=2.63), but in ICU patients. Rathi et al. (2017) demonstrated a hospital mortality rate of 79.5% for patients who failed in NIV and 47.3% for those who were successful, and this difference was statistically significant. Some studies have associated hospital mortality with NIV failure (Ferreira et al. 2015; Rathi et al. 2017; Neuschwander et al. 2017). The non-identification of positive association with some variables in our study can be attributed to the small number of participants.

An American study has shown that the length of hospital stay for patients who start NIV in the ICU is higher than for patients who start in the ward (Ozsancak et al. 2015). This can be explained because when were compared patients with ARF who perform NIV in the ward and in the ICU it was observed that patients in the ward have lower respiratory and heart rate, milder blood pressure levels and are less acidotic and hyperpneic (Ozsancak et al. 2015). Rathi et al. (2017) demonstrated that patients who failed in NIV had a mean hospitalization time of 21 days and patients with success in NIV had 14 days. In this present study, the patients who presented NIV failure were hospitalized 24 days on average and the patients who had success 26 days. These results can be explained by the high hospital mortality rate of patients who fail in NIV. A Canadian study with pneumonia patients submitted to NIV showed a median hospitalization time of 22.5 days for patients who failed in NIV and 10 days for those who were successful, and this difference was statistically significant (p<0.001) (Al-Rajhi et al. 2018). A Brazilian study with cancer patients submitted to NIV showed a median hospital stay prior to admission to the ICU of 4 days for patients who failed in the NIV and 3 days for those who were successful, and this difference was not statistically significant (p=0.364) (Ferreira et al. 2015).

The present study presented some limitations. The type II error may have been induced by the small number of patients included in the study. Because it was a retrospective study based on reviews of medical records, the bias in patient selection is inevitable. In addition, access to complete information on some relevant factors were more difficult to obtain/ such as ventilatory parameters (arterial blood gas, peripheral oxygen saturation and respiratory rate). Both physical and electronic medical records were used, in order to limit the possibility of the absence of information, in an attempt to obtain quality data for a vigorous analysis of the results.

5. Conclusion

This retrospective cohort study with cancer patients suggests that in patients with ARF caused by pulmonary infection, NIV should be used with caution, because these factors are associated with NIV failure. Besides that, age is an independent factor associated with hospital mortality, so if patient’s age is over 60 years, they have a higher risk of death during hospitalization.

New research needs to be carried out focusing on clinical variables that can impact these outcomes.
Soubani A O, Shehada E, Chen W, Smith D (2014). The outcome of cancer patients with acute respiratory distress syndrome. *J Crit Care* 29:183.e7–183.e12. http://dx.doi.org/10.1016/j.jcrc.2013.10.011.

Walkey A J, & Wiener R S (2013). Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: a population-based study. *Ann Am Thorac Soc* 10:10–7. http://dx.doi.org/10.1513/AnnalsATS.201206-034OC.

Yeo C D, Kim J W, Kim S C, Kim Y K, Kim K H, Kim H J, et al (2012). Prognostic factors in critically ill patients with hematologic malignancies admitted to the intensive careunit. *J Crit Care* 27:739.e1–6. http://dx.doi.org/10.1016/j.jcrc.2012.07.014.