Predictive Factors for Failure of Non-Invasive Ventilation in Hospitalized Patients with Cancer

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Fatores Preditores para a Falha da Ventilação não Invasiva em Pacientes Hospitalizados com Câncer

Factores Predictores para la Falla de la Ventilación no Invasiva en Pacientes Hospitalizados con Cáncer

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Abstract

Introduction: The non-invasive ventilation (NIV) presents confirmed benefits in various clinical conditions, however, the results in patients with cancer are controversial. Objectives: To analyze the predicting factors for failure of the NIV in cancer patients; To describe hospital mortality and overall survival after admission. Method: Study of retrospective cohort including patients with solid tumors and hematological neoplasm who have been admitted to the hospital stay at Hospital of Cancer I of the National Cancer Institute José Alencar Gomes da Silva (HCI/INCA) between Jan 1st and Dec 31 2017 and were submitted to NIV. The association between the exposure (clinical and socio-demographic variables) and the outcome (NIV failure) was performed by gross and adjusted logistic regression. The Kaplan-Meier method was used to analyze the overall survival. Results: Sixty-six patients with mean age of 62.3 years (± 15.0 years) were included. The average lasting time of the first session was 49.8 min (±30.9), the average number of sessions was 2.1 (±1.4). The patients who showed failure had longer time hospital stay (11.8 days vs 6.0 days) and higher hospital mortality (90.9 vs 43.6%). The patients with lung infection showed a higher risk of 4.71 times of failure in NIV related to those patients who showed succeeding (OR 4.71; IC 95%, 1.14-19.47; p=0.032). Conclusion: Patients who showed lung infection were more likely to fail in NIV. Was observed a worst overall survival between those patients who failed in NIV.

Key words: Survival Analysis; Noninvasive Ventilation; Neoplasm.

Resumo

Introdução: A ventilação não invasiva (VNI) apresenta benefícios comprovados em diversas condições clínicas, entretanto, os resultados em pacientes com câncer são controversos. Objetivos: Analisar os fatores preditores para falha da VNI em pacientes oncológicos; descrever a mortalidade hospitalar e a sobrevida global após internação. Método: Estudo de coorte retrospectiva incluindo pacientes com tumores sólidos e neoplasias hematológicas, admitidos para internação hospitalar no Hospital do Câncer I do Instituto Nacional de Câncer José Alencar Gomes da Silva (HCII/INCA), entre 1º de janeiro e 31 de dezembro de 2017, e que foram submetidos à VNI. A associação entre as variáveis de exposição (variáveis clínicas e sociodemográficas) e os desfechos (falla na VNI) foi realizada pela regresseog logística bruta e ajustada. Foi utilizado o método de Kaplan-Meier para análise da sobrevida global. Resultados: Foram incluídos 66 pacientes com média de idade de 62,3 anos (±15,0). O tempo médio de VNI na primeira sessão foi de 49,8 minutos (±30,9); o número médio de sessões foi de 2,1 (±1,4). Os pacientes que apresentaram falha tiveram maior tempo de internação hospitalar (11,8 dias vs 6,0 dias) e maior mortalidade hospitalar (90,9 vs 43,6%). Os pacientes com infecção pulmonar tiveram um risco de 4,71 vezes maior de falharem na VNI, em relação àqueles pacientes que apresentaram sucesso (OR 4,71; IC 95%, 1,14-19,47; p=0,032). Conclusão: Pacientes que apresentaram infecção pulmonar tiveram maior probabilidade de falhar na VNI. Foi observada pior sobrevida global entre aqueles pacientes que falharam na VNI.

Palavras-chave: Análise de Sobrevida; Ventilação não Invasiva; Neoplasias.

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INTRODUCTION

Cancer is a disease with 18.1 million new cases per year in the world and the higher incidence is observed in lung, breast, prostate and colon cancer. In Brazil, it is estimated 600 thousand new cases of cancer for 2018 and 2019.

New treatments have been introduced with the objective of extending the survival of the patients with cancer, including chemotherapy, radiotherapy, stem-cells transplantation and molecular targets-driven therapies. As a consequence of these approaches, the global survival of patients have increased substantially, nonetheless, the cases of toxicity and complications have augmented as well.

Some of these complications lead to the deterioration of the clinical condition of these patients and to the necessity of hospitalization with frequent episodes of severe events as acute respiratory failure (ARF), which occurs in up to 30% of the hospitalized patients and presents a high mortality (of until 50%), being higher yet in patients requiring mechanic ventilation.

The majority of the patients with ARF is treated initially with noninvasive ventilation (NIV) and around 20% initiate this kind of treatment in the ward. NIV is a ventilatory support with positive pressure connecting the ventilator and the patient through an interface. In hospitalized patients, the most used interfaces are the orofacial, nasal or full face model. The success of NIV, in addition to eligibility criteria, is contingent upon the accurate adaptation of the interface, the comfort, acceptance and optimization of the patient.

In the last years, the use of NIV has been growing in the oncologic scenario. Despite NIV is an effective treatment for ARF of various specific etiologies, scarce are the studies that address the various oncologic clinics and the results are still uncertain in relation to the final outcome, either in the reduction of the incidence of orotracheal intubation or in the failure of the method adopted and in hospital mortality. By virtue of the benefits that can be achieved with NIV and for being a noninvasive method, new studies are necessary to determine the risk factors for NIV failure in the population with cancer.

That been said, the objectives of this study were: analyze the predictive factors for NIV failure in oncologic patients, describe the hospital mortality and global survival after hospitalization.

METHOD

It was conducted a cohort retrospective study that included patients with solid tumors and hematologic neoplasms admitted at the wards of “Hospital do Câncer I” of “Instituto Nacional de Câncer José Alencar Gomes da Silva (HCI/INCA)” between January 1 and December 31, 2017. The patients submitted to NIV who presented physiologic and clinical indicators that might result in ARF were enrolled and considered the following indicators: oxygen saturation under 90% or PaO2 lower than 60 mmHg in ambient air, serious dyspnea or respiratory frequency higher than 30 breaths per minute and signs of effort of the respiratory muscle. The protocol for NIV was based in internationally recommended guides utilized.
The analysis of survival was made through the method of Kaplan-Meier, considering the time between hospitalization and date of death. It were also considered the date of the last contact (for patients with loss to follow-up) or final of the follow up period. In order to identify differences of curves of whom progressed to death or not, it was calculated the test of Log-Rank. For all the analyzes, the values of p < 0.05 were considered statistically significant. The data were analyzed with the software SPSS (Statistical Package for Social Science for Windows, São Paulo, Brazil), version 23.0.

The Institutional Review Board of INCA approved this work, report number 2842917/2018, protocol CAAE: 9493231800000574.

RESULTS

It were included 66 patients with average age of 62.3 years (±15.0) and average time of hospitalization of 6.9 days (±8.3). Most of the patients were females (56.1%), eutrophic (50.0%) and with diagnosis of solid tumors (54.5%). The main comorbidities were diabetes (21.2%) and cardiovascular diseases (21.2%); clinical hospitalization was the main motive (80.3%), more than half (56.1%) of the patients presented leukocytosis and 22 (33.3%) pulmonary infection (Table 1).

The average time of the first session was 49.8 minutes (±30.9), the average number of sessions of NIV was 2.1 (±1.4) and the total average time for NIV was 110.2 minutes (±96.5). The frequency of failure in NIV was 16.7%. In comparison with the patients who had success in NIV, the patients with failure in NIV were hospitalized for more time (11.8 days vs 6.0 days) and higher hospital mortality (90.9 vs 43.6 p=0.004). In total, 24 (36.3%) of the patients were transferred to the Intensive Care Unit (ICU).

The possible factors associated to failure in NIV that presented level of significance of p < 0.20 in the raw analysis, were tested in the multiple analysis (Table 2). The patients with pulmonary infection had a risk 4.71 greater of failing in NIV than those who had success in NIV (OR 4.71; CI 95%, 1.14-19.47; p=0.032).

The global median survival time after hospitalization was of 25 days (CI 95%; 0.00-71.12) for those patients who failed in NIV and 77 days (CI 95%; 0.00 - 185.94) for those who succeeded in NIV and this difference was statistically significant (p=0.011) (Figure 1).

DISCUSSION

The present study, which enrolled patients with diagnosis of solid tumors or hematologic neoplasms provides overwhelming information and similar to previous studies, but in a setting out of the Intensive Care Unit (ICU) and of the emergency room. Therefore, the results obtained show that the outcomes are not contingent upon the scenario where the patient with cancer actually is, but of his clinical condition and its complications.
Table 2. Factors associated to failure of non-invasive ventilation (univariate analysis)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Failure in the non-invasive ventilation (N=11)</th>
<th>Success in the non-invasive ventilation (N=55)</th>
<th>Odds ratio (CI 95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ± standard deviation)</td>
<td>61.3±15.4</td>
<td>62.5±15.1</td>
<td>0.81 (0.94-1.04)</td>
<td>0.818</td>
</tr>
<tr>
<td>Time of hospitalization (days, mean ± standard deviation)</td>
<td>11.8±15.5</td>
<td>6.0±5.8</td>
<td>1.06 (0.99-1.13)</td>
<td><strong>0.080</strong></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (54.5)</td>
<td>23 (41.8)</td>
<td>1.67 (0.45-6.13)</td>
<td>0.440</td>
</tr>
<tr>
<td>Female</td>
<td>5 (45.5)</td>
<td>32 (58.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>With spouse</td>
<td>7 (70)</td>
<td>23 (51.1)</td>
<td>2.23 (0.51-9.74)</td>
<td>0.286</td>
</tr>
<tr>
<td>Without spouse</td>
<td>3 (30)</td>
<td>22 (48.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 8 years of study</td>
<td>7 (70)</td>
<td>30 (68.2)</td>
<td>1.08 (0.24-4.85)</td>
<td>0.911</td>
</tr>
<tr>
<td>≤ 8 years of study</td>
<td>3 (30)</td>
<td>14 (31.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (54.5)</td>
<td>27 (49.1)</td>
<td>1.24 (0.33-4.56)</td>
<td>0.741</td>
</tr>
<tr>
<td>Eutrophic</td>
<td>5 (45.5)</td>
<td>28 (50.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline disease</td>
<td></td>
<td></td>
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<tr>
<td>Hematologic</td>
<td>6 (54.5)</td>
<td>24 (43.6)</td>
<td>1.55 (0.42-5.69)</td>
<td>0.509</td>
</tr>
<tr>
<td>Solid tumors</td>
<td>5 (45.5)</td>
<td>31 (56.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motive of the hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>2 (18.2)</td>
<td>9 (16.4)</td>
<td>1.13 (0.20-6.15)</td>
<td>0.883</td>
</tr>
<tr>
<td>Clinical</td>
<td>9 (81.8)</td>
<td>46 (83.6)</td>
<td></td>
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<td>Comorbidities</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>3 (27.3)</td>
<td>23 (41.8)</td>
<td>1.91 (0.45-8.01)</td>
<td>0.373</td>
</tr>
<tr>
<td>No</td>
<td>8 (72.7)</td>
<td>32 (58.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motive of the non-invasive ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>7 (63.6)</td>
<td>15 (27.3)</td>
<td>4.66 (1.19-18.26)</td>
<td><strong>0.027</strong></td>
</tr>
<tr>
<td>Others</td>
<td>4 (36.4)</td>
<td>40 (72.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (63.6)</td>
<td>30 (54.5)</td>
<td>1.45 (0.38-5.56)</td>
<td>0.581</td>
</tr>
<tr>
<td>No</td>
<td>4 (36.4)</td>
<td>25 (45.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Caption: CI = confidence interval.
Note: In bold, the selected variables for the model of multiple regression.

The interest in using NIV in the ICU, wards and emergency rooms settings has greatly increased in the last years\(^6,8,15,20,21\). As long as there are no counter indications, NIV can be a first line treatment for patients with cancer that present ARF. One of the advantages of using NIV is the reduction or even the elimination of the necessity of intubation, consequently lessening the associated complications to this invasive method (trauma in the airways, nosocomial infections, and necessity of sedation) and reduction of hospital costs\(^22\).

The utilization of NIV for ARF treatment is higher in the ward when compared to closed areas of emergency and ICU\(^15\). In the wards, safety and success of NIV are contingent upon a meticulous evaluation of the patients to separate those who could benefit or had risks of failure. For that reason, it is essential to identify variables that may
be associated to ARF for management of patients with ARF. To the best of our knowledge, this is the first study in Brazil which addresses the NIV failure predictive factors in patients with cancer out of the ICU. In the present study, it was observed that the patients submitted to NIV, because of pulmonary infection, had nearly five-fold more odds of failing NIV. Previous studies in patients with cancer in the ICU showed similar results in the multiple analysis.\textsuperscript{9,20} A retrospective study where 114 patients were submitted to NIV demonstrated that predictive factors to NIV failure were pulmonary infection (OR=3.55) and male gender (OR=2.42).\textsuperscript{20} An European multicenter study, where 387 patients received NIV demonstrated that pulmonary infection (OR=1.77), severe ARF (OR=2.08) and fungal infection (OR=1.90) were associated to NIV failure.\textsuperscript{4} Still, other studies encountered predictive factors for NIV failure in variables that were not found or addressed in our study.\textsuperscript{4,7,19} In a retrospective study, 1,614 patients with cancer and hypoxemic respiratory distress were submitted to NIV in ICU and the predictive factors for failure of NIV were age (OR=0.98), race (OR=1.60) and category of the disease (hematologic vs solid) (OR=1.87).\textsuperscript{17} In the study of Al-Rajhi et al.,\textsuperscript{18} it was evidenced that, the bigger the number of quadrants affected in the radiography, higher was the risk of failure of NIV (OR=2.47 to 11.25), as well as some ventilatory parameters prior to NIV also influenced the failure of NIV, among them RF (respiratory frequency) >35 (OR=1.64) and pH ≤ 7.2 (OR=4.96). At last, a prospective study that approached patients submitted to NIV out of the ICU demonstrated that age, respiratory frequency, level of IPAP, PaCO\textsubscript{2}, PaO\textsubscript{2} and number of quadrants affected were associated to failure in NIV.\textsuperscript{4} The non-identification of positive association with some variables, in our study, may be attributed to the small number of participants.

In the present study, in 80.3% of the patients, the motive for hospitalization was clinical and in 16.7%, was surgical. The patients who failed NIV were hospitalized 11 days in average, and those who succeeded remained six days hospitalized in average. The tendency of more hospitalization time among patients who failed NIV was observed in former retrospective studies.\textsuperscript{7-20} An American study demonstrated that the time of hospitalization was of 14 days in patients who succeeded in NIV and 21 days for those who failed NIV (p<0.0001).\textsuperscript{7} Recently, a Canadian study that approached 163 patients with pneumonia submitted to NIV demonstrated that the median time of hospitalization was of ten days in patients who succeeded in NIV and 22.5 days for patients who failed NIV (p<0.0001).\textsuperscript{18} A Brazilian study, on its turn, demonstrated that the median time of hospitalization prior to the admission to ICU was of three days in successful NIV patients and four days for patients failing NIV, but this difference was not statistically significant (p=0.364).\textsuperscript{20} According to Ozsancak Ugurlu et al.,\textsuperscript{15} the time of hospitalization of patients who commence NIV in the ICU are higher in comparison to patients who commence NIV at the ward. The patients with ARF in the ward present lower respiratory and cardiac frequency, milder pressure levels and are less acidotic and hypercapnic when compared to patients with ARF in ICU.

Recent researches addressed the fact that patients who initiated the NIV and failed, needing invasive mechanic ventilation have higher hospital mortality rates.\textsuperscript{9,18,20} Rath et al.\textsuperscript{2} demonstrated hospital mortality of 47.3% in patients who had success in NIV and 79.5% in patients who failed NIV (p<0.0001). A retrospective study, which did not address patients with cancer, demonstrated a hospital mortality of 16% of the patients with success of NIV and 41% of the patients who failed NIV (p<0.0001). Ferreira et al.\textsuperscript{20} reported that the mortality in the ICU was 15% in patients who had success in NIV and 74% of the patients who failed NIV (p<0.0001). Our results converge towards these reports. The hospital mortality was considerably higher in patients with failure of NIV (90.9%), compared with 43.6% when NIV had success and the difference was statistically significant (p=0.004). The patients who failed NIV have 2.63 more chances of dying.\textsuperscript{9} The high rate of hospital mortality may be related with the delay of the intubation in patients who failed NIV.\textsuperscript{10,16} For Azoulay et al.,\textsuperscript{12} the late failure of NIV, (intubation after 48 hours or more) is directly associated to high rates of mortality.

The limitations of this study must be mentioned. A small number of patients enrolled in the study may have induced to error type II. As a medical chart record-based review retrospective study, it is inevitable a bias in the selection of the patients. In addition, it was more difficult to obtain complete information about important factors such as ventilatory parameters (arterial gasometry, oxygen peripheral saturation and respiratory frequency). It was attempted to restrain the possibility of lack of information through the utilization of electronic charts in order to obtain qualified data for a potent analysis of the results.

CONCLUSION

As a conclusion, the present study suggests that patients with cancer and that later present pulmonary infection are more prone to failure of NIV. It was observed worse global survival among those patients that failed NIV. New studies need to be carried out to improve the basis for more thorough justification of NIV in hospital settings.
CONTRIBUTIONS

Gustavo Telles da Silva, Bianca Paraíso de Araujo and Eduarda Martins de Faria participated of the conception and planning of the study, analysis and/or interpretation of data as well as wording and/or critical review and final approval of the published version. Larissy Machado da Silva and Luciana Velasco Bizzo participated of the analysis and/or interpretation of the data as well as of the wording and/or critical review and final approval of the published version. Luiz Claudio Santos Thuler, Mônica Maria Pena Quintão and Anke Bergmann participated of the wording and/or critical review and final approval of the published version.

DECLARATION OF CONFLICT OF INTERESTS

The author Anke Bergmann states potential conflict of interests because she is the scientific editor of the Brazilian Journal of Cancerology of INCA. The other authors have no conflict of interests.

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REFERENCES


