Determinants of Mortality for Cancer Patients With Unscheduled Admission to the ICU: A Prospective Multicenter Study

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Not unfrequently, oncological patients need admission to the ICU. A retrospective multicenter Dutch study showed that 6.4% of cancer patients required ICU admission, revealing that the majority of these admissions took place after surgical procedures [1]. In another retrospective study, 5.2% of the patients required ICU admission within the first 2 years of cancer diagnosis[2].

The majority of the oncological patients are admitted for immediate postoperative care and commonly present a low mortality rate[3]. Moreover, in the last decade, the unscheduled admissions to the ICU by acute medical conditions related to the cancer have risen considerably worldwide. Improvements in short-term and long terms survival rates of these cancer patients have been documented explaining this generalized reality[4]. The advent of new targeted therapies and the enhancement of supportive care justify this increment of ICU admission even in patients with advanced diseases.

Despite these progresses, death rates of oncology patients in the ICU remain substantially high. It is essential the identification of prognostic factors in critically ill cancer patients. The knowledge of factors associated with poor outcome in this high-risk population may assist physicians, patients, and their relatives in deciding treatment options and their intensity. In the ICU, patients with a hematologic malignancy have higher mortality rates than solid cancer patients[5]. However, literature is equivocal whether risk factors for mortality differ in patients with solid or hematological malignancies.

Neutropenia has been considered to be associated with a dismal prognosis in cancer and many clinicians are reluctant to admit patients with severe neutropenia in the ICU. However, this is an ongoing debate if neutropenia influences the outcomes of cancer patients in the ICU and whether this influence differs between solid and hematology malignancies[6,7,8].

The aims of this study are to identify risk factors for mortality of those admitted to the ICU analyzing the entire cohort as well as a specific analysis for patients with solid cancer and for hematological malignancy in order to determine if factors associated with mortality are different in these two populations.

Methods

Prospective observational study carried out in Spanish ICUs using the ENVIN registry. The ENVIN registry is an observational, prospective and multicenter (national) project that was started in 1994 by the Study Group of Infectious Diseases and Sepsis

(GTEIS) of SEMICYUC. It is performed yearly since April 1st to June 30th. Its objectives have been described in detail elsewhere[9]. Data entry is done through a webpage (http://hws.vhebron.net/envin-helics/). The ENVIN registry has been approved by several local and regional Clinical Research Ethics Committees (CEIC). The specific authorization of patients is not required for the use of their data as it is recognized as a Registry of national Interest for the National Health System (year 2014).

In 2018, an extension of cancer patient data was carried out associating a new database called "ONCOENVIN database". Adult patients (≥18 years) admitted to any of the participating ICUs for more than 24 hours during the three months of the ENVIN registry of 2018 were registered in this study. We included only patients with a clinically confirmed hematologic or solid malignancy who were admitted to the ICU for any reason. In the present manuscript, we report the results of all patients with an unplanned admission due to an acute medical or surgical condition related to the cancer. We exclude patients who were admitted to the ICU for acute conditions not related to their oncological disease and patients admitted for elective surgery.

Variables collected at ICU admission were age, gender, severity of illness assessed by APACHE II score in the first 24 hours in the ICU, underlying comorbidities, history of surgery within 30 days prior to admission, use of antibiotics in the previous 48 hours, type of cancer, year of diagnosis, hospital size (less than 200 beds, 200-500, and more than 500 beds), cancer treatment (no treatment, neoadjuvant chemotherapy, adjuvant chemotherapy, first-line and second-line chemotherapy, symptomatic treatment, chemotherapy for hematological malignancy, allogeneic bone marrow transplantation, and autologous bone marrow transplantation), and length of hospital stay before ICU admission. Solid cancers were grouped into nine categories (see footnotes in Table 3 for details). Hematologic malignancies were categorized as: acute leukemia, chronic leukemia, lymphoma, multiple myeloma, and others. Based on their primary reason for admission to the ICU, patients were categorized in the following groups: sepsis/septic shock, acute respiratory failure, acute renal failure, coma, hemorrhagic shock, severe metabolic disturbances, or other.

During the ICU stay, details regarding the need for invasive mechanical ventilation, renal replacement therapy (RRT), occurrence of neutropenia (neutrophils < 500/mm^3), development of ICU-acquired infection (catheter-related bloodstream infection, ventilator-associated pneumonia, pulmonary aspergillosis), administration of chemotherapy in the ICU, tumor lysis syndrome[10], and limitation of life-sustaining treatment (LTST) were collected daily. Diagnosis of pulmonary aspergillosis required compatible signs and symptoms and isolation of *Aspergillu*s spp. in respiratory culture or Galactomannan antigen detection in serum or bronchoalveolar lavage with significative optical density index[11]. All patients were followed up until death or ICU discharge.

Statistical Analysis

Descriptive analysis was conducted. Categorical variables were summarized with frequencies and percentages, while quantitative variables were described with mean and standard deviation or median (P25-P75) as appropriate. To compare the survivors vs non-survivors the three groups (Total cohort, patients with solid malignancy, and patients with hematological malignancy and) a bivariate analysis was performed. Chi-Square test or Fisher exact test was used according to application

conditions for the categorical variables and Mann-Whitney U test was used for quantitative variables. For every group, the significant and marginally significant variables ($p<0.1$) obtained in the bivariate analysis and the variables considered clinically relevant, were introduced in a multivariate binary logistic regression analysis in order to assess the factors related to death in the ICU. Variables without statistical significance in the model were subsequently manually removed in a backward step-by-step procedure, until the best possible model was obtained, showing adjusted odds ratio with their 95% confidence interval and p-values for each of the final variables. Calibration and discrimination power of the model were assessed with Hosmer-Lemeshow test and area under the curve (AUC) respectively. In all analyses, p-values less than 0.05 were considered as statistically significant.

Results

During the study period, 2,557 cancer patients were admitted to the participating ICU. Of them, 1,506 were scheduled post-operative care, 567 required ICU admission for acute conditions not related to their oncological disease, and 484 patients had an unplanned ICU admission for an acute medical or surgical illness related to a solid or a hematological malignancy. Two of these 484 patients were excluded from the analysis for incomplete data. Therefore, 482 patients comprise the study group of this research. The diagnosis of cancer had occurred in 2018 or 2019 (January to June) in 407 patients (84.4%). Invasive mechanical ventilation was used in 215 patients (44.6%).

Table 1 depicts the comparison of those patients who were discharged alive from the ICU and those who died in the Unit (29.2%). Of note, age was not statistically different in those who died in comparison to those who were discharged alive from the ICU. The most common indications for ICU admission are sepsis (n=180) and respiratory insufficiency (n=179). Length of hospital stay before ICU admission was significantly shorter in patients who survived. Hospital bed size did not affect mortality in the total cohort or in the other two subgroups. Overall, 215 patients (44.6%) required invasive mechanical ventilation, 156 in the first 24 hours in the ICU. By multivariate logistic regression analysis, factors independently associated with mortality were APACHE II, medical admission, lung cancer, and delay of initiation of mechanical ventilation (Table 2). Figure 1 shows the number of deaths for the different subgroups of patients depending on the day of invasive mechanical ventilation onset.

To better understand whether these risk factors differ between patients with solid cancer (n=311) and hematological malignancies (n=171), we analyzed these two cohorts separately. Patients with hematological cancer were younger [61 years (51-70) vs 64 years (55-71); p=0.046] and with higher APACHE II score [20 (15-25) vs 17 (12-23); p=0.007] than those with solid cancer. Mortality was not statistically different in these two groups of patients: 51.8% vs 36.4% (p=0.072). The rate of patients requiring invasive mechanical ventilation was similar in these two groups: 45.6% vs 44%. Conversely, neutropenia at admission to the ICU was significantly more common in hematological patients than in solid tumors (36.8% vs 9.9%; $p<0.0001$). Chemotherapy was more frequently administered in the ICU in hematological than in solid tumor patients (15.8% vs 2.25 %; $p < 0.001$). the rate of LSTL was similar in both groups (16.3% in solid neoplasms and 17.5% in hematological cancers).

Table 3 shows the comparison between survivors and non-survivors in patients with solid cancer. The commonest solid malignancy was lung cancer (25.7 %) followed

by colon (14.8%) and urologic (13.8%) cancers. Mortality was significantly higher in patients with lung cancer than in patients with other solid malignancies (40% vs 22%; p=0.0017). Urological and gynecological cancers presented the lowest mortality rate (16.6 and 18.7%, respectively). Only 7 patients received chemotherapy in the ICU (4 survived). The multivariate logistic regression analysis identified five factors as independently associated with mortality (Table 2).

Lymphoma was the commonest hematological malignant disease in our series and the great majority of hematological patients had a medical cause of ICU admission (Table 4). Twenty-seven patients received chemotherapy in the ICU (mortality rate 33%). As expected, allogenic HSCT had the highest mortality rate (58.3%). In the multivariate analysis, only APACHE II and delay of initiation of mechanical ventilation were independently associated with mortality (Table 2). As in the previous analyses, neutropenia was not included in the final model.

Discussion

This prospective and multicenter study has identified several risk factors associated with mortality in cancer patients admitted to the ICU. It must be highlighted that in those who required invasive mechanical ventilation, its initiation after 24 hours in the ICU was independently associated with mortality. This factor has been identified in the total cohort as well as in solid cancers and in hematological patients. The poor prognosis of lung cancer needing ICU admission has been confirmed in this study.

The identification of factors associated with mortality will aide physicians to identify cancer patients who are likely to benefit from ICU care, the use of supportive treatments and the time of initiation. The majority of the information on the prognosis of patients with cancer patients who are admitted to the ICU derives from retrospective analyses of large databases or from studies carried out in specialist cancer ICUs.

Approximately, two-thirds of our patients presented a solid cancer and the remaining had a malignant hematological disease. This proportion of hematological patients is higher than the reported by others[4,12], probably reflecting the improvement of the prognosis of these patients. In agreement with previous investigations, either in solid cancer and in hematological malignancies, respiratory failure and sepsis were the most common indications for admission.

In our series, medical cancer patients have 3.5 times higher risk of ICU mortality compared to surgical admissions. In a systematic review[13], medical cancer patients had an increased risk of ICU mortality between two- and fourfold compared to surgical admissions. Of note, medical admission was not a variable associated with mortality in hematological patients. This can be explained by the fact that less than 5% of these patients had a surgical reason for ICU admission. As expected, severity of illness measured by APACHE II score is associated with greater risks of mortality as generally occurs in previous studies[13]. In our data, each point of increment rises 10% the risk of death.

Lung cancer is the commonest tumor type admitted to the ICU and the one with the poorest outcome[13]. Lung cancer patients may benefit less from ICU admission than other location of cancers. Importantly, a recent manuscript has demonstrated that from 2011 to 2019 adjusted mortality in cancer patients requiring ICU admission decreased by 9.2% but lung cancer patients had the lowest reduction in mortality[14].

The impact of cancer stage on mortality has been long debated with conflicting results. Diverse studies suggest that advanced or metastatic cancer was associated with higher ICU or hospital mortality. However, very scarce information is available about the impact on the outcome depending on the type of chemotherapy that is administered before ICU admission. Notably, in our data, the type of chemotherapy received, including, second line chemotherapy did not influence ICU mortality rate. In addition, administration of chemotherapy in the ICU does not impact on ICU mortality although the long-term prognosis is dismal[15]. In comparison to hematological patients, chemotherapy was unfrequently administered to patients with solid tumors[16].

We found that neither neutropenia at admission to the ICU nor the development during the ICU stay increases mortality. It is important to point out that we considered cases of severe neutropenia defined by neutrophil count below 500/mm^3. A recent meta-analysis on individual data that considered neutropenia as neutrophil count below 1,000/mm^3 concluded that neutropenia was independently associated with mortality[8].

Mechanical ventilation has been identified as an independent predictor of mortality by previous studies[6,17,18]. However, very few information is available about the impact on prognosis of delayed intubation. Inconsistent data have been published regarding the harm or benefit from noninvasive mechanical ventilation (NIV) in these patients. Others have documented that the use of NIV is associated with increased mortality because it delays endotracheal intubation and mechanical ventilation[19]. A recent multicenter study concluded that the need of invasive mechanical ventilation immunocompromised patients (85% of them with cancer) was associated with mortality with higher likelihoods of mortality in case of NIV or HFNC failure[20]. Conversely, cancer patients undergoing initial invasive MV had an increased ICU and hospital mortality[21]. This discrepancy may in part be explained by differences in the case mix, admission criteria, and treatment protocols.

Our data demonstrate that intubation after the first day in the ICU is an independent risk factor for mortality. In other words, the use of prolonged periods to avoid intubation cannot be considered the standard of care since this delay is associated with an increased probability of death. We cannot rule out that in some cases, delayed intubation may have been explained by the poor prognosis of these patients since mechanical ventilation it is recognized as an independent predictor of mortality.

We acknowledge several limitations of this study. First, hospital or long-term mortalities were not recorded in our database admitting their importance in cancer patients. Second, since the use of NIV or the reason for intubation were not recorded we cannot explore whether the use of these ventilatory support methods may be associated with a higher mortality. Third, failure of organs was not monitored throughout the length of ICU stay. Finally, as this is an observational study, management of patients was not standardized and different treatment protocols were used in the participating Units.

Some strengths of our research should also be highlighted. This is a prospective, multicenter study with a relatively large number of enrolled, in polyvalent ICUs across Spain and therefore reflecting the real-life situation. All the clinical predictors identified as independently associated with mortality are easily available

and may help to identify patients who may not benefit from intensive care or the use of aggressive therapies.

In summary, identifying the determinants of outcomes in critically ill patients with cancer is crucial to improve the use of ICU avoiding unnecessary advanced life support. The long-held belief about the worse prognosis of cancer patients with neutropenia in the ICU is not supported by our data. Similarly, the type of chemotherapy that the patient is receiving does not influence the short-term outcome. Although the intubation of a critically ill cancer patient is frequently a stressful decision, our data suggest that it should not be delayed because it worsens the patient chance of survival. The prognosis of lung cancer requiring ICU admission is worse than in any other type of cancer including hematological malignancy . All this information may be of aid for clinicians involved in critically ill cancer patient management but larger studies with a longer follow-up are warranted to more precisely define the patient who will benefit from ICU admission optimizing the use of ICU resources.

Kingah P, Alzubaidi N, Yafawi JZD, Shehada E, Alshabani K, Soubani AO. Factors Associated with Mortality in Patients with a Solid Malignancy Admitted to the Intensive Care Unit - A Prospective Observational Study. J Crit care Med (Universitatea Med si Farm din Targu-Mures) [Internet]. octubre de 2018 [citado 31 de agosto de 2020];4(4):137-42

Figure 1. ICU mortality for the different subgroups of patients with cancer depending on the day of invasive mechanical ventilation initiation.

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