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Research Article

Impact of factors at admittance predicting intensive care unit mortality in critically ill cancer patients

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ABSTRACT

Background: The aim of this study is to evaluate the prognostic factors at medical ICU admittance predicting intensive care unit (ICU) mortality in cancer patients.
Methods: Retrospectively data of adult patients admitted to medical ICU of a 1200-bed university hospital during January 2012-December 2013 interval were analysed. The patients were divided into three groups; patients with solid tumor, patients with hematologic malignancy and patients without cancer. The study end point was ICU mortality.
Results: 512 patients were identified; 374 patients without cancer, 89 patients with solid tumor and 49 patients with hematologic malignancy. Overall mortality rate in intensive care unit was 46% (n=236). The ICU mortality rate of patients with hematologic malignancy was significantly higher than patients with solid tumors (68.6% vs 53%; p<0.001) and patients without cancer (68.6% vs 39.8%; p<0.001). Logistic regression analysis showed high APACHE II score and the requirement for invasive mechanical ventilation (odds ratio [OR], 5.52; 95% confidence interval [CI], 2.10-14.53; p<0.001) at the time of intensive care unit admittance as independent risk factors for increased mortality. In addition, the requirement of renal replacement therapy(OR, 2.34; [CI: 1.44-3.80]; p<0.002) and vasopressors(OR, 1.67; [CI: 1.10-2.54]; p<0.02) at the time of intensive care unit admittance were detected as independent risk factors for increased mortality in cancer free group.
Conclusions: In critically ill cancer patients; high APACHE II score and the requirement of invasive mechanical ventilation should be evaluated at the time of intensive care unit admittance, for these are strong predictors of increased mortality.

Keywords: Malignancy, Cancer, Critical care, Critically ill, Mortality

INTRODUCTION

In the head of the eighties a diagnosis of cancer was accepted to be a contraindication for ICU admittance.[1] The invention of new and potent chemotherapeutic agents and stem cell transplantation gave rise to severe myelosuppression and multiple organ failures. These complications during the treatment of cancer patients brought by the need for ICU care.[2] The improvements in cancer management increased the survival rates of these patients and towards 1990 new protocols for admittance of cancer patients to ICU were considered.[3,4] Successful treatment in ICUs increased survival rates of patients with malignancy.[5] 6-month survival of cancer patients being 2-14% before 1996 ameliorated thereafter to 33-66%.[6,7]

The most common hematologic malignancies admitted to ICU are lymphoma and leukemia whereas the most common solid tumour is lung cancer. Approximately 40% of allogenic bone marrow transplantation patients face complications that require intensive care once or

more.[8] The indications for ICU hospitalization may be due to the cancer itself, the side effects of chemotherapeutics or the comorbid diseases accompanying. The most common indication for ICU admittance is acute organ failure of the most commons being acute respiratory failure requiring mechanical ventilation support, cardiovascular failure requiring vasopressor treatment and renal failure requiring renal replacement therapy.[9-11]

The mortality rate of cancer patients in ICU was as high as 44-98% before 1996 but, currently decreased to 21-57%.[12-16] The common negative prognostic factors for all patients are multiple organ failure, the requirement for mechanical ventilation, vasopressors, renal replacement therapy, advanced age and high disease severity scores at admittance.[17-21] Other factors that may be responsible of mortality are the etiology and severity of respiratory failure, duration of invasive mechanical ventilation, the source of infection, presence of sepsis and neutropenia, the timing of ICU admittance and the procedures applied for diagnosis and treatment.[22-26]

In this study, we aimed to evaluate the factors at admittance affecting the ICU mortality of cancer patients and meanwhile guide practitioners in admittance and monitorization of cancer patients and cost effective management of ICU resources.

METHODS

This study has been conducted as retrospective, observational evaluation of patients' data who were admitted to 12-bed medical intensive care unit of a 1200-bed university hospital. Every adult patient (≥18 years old) who required ICU admission was evaluated between January 1, 2012, and December 31, 2013. Only the first admission was recorded in patients with multiple ICU admissions and patients who were hospitalized in ICU for less than 24 hours were excluded. This study was approved by the institutional review board.

The data analysed for the study were achieved from registration and follow-up forms of ICU and hospital digital registration system. These documents briefly included all laboratory results, vital signs, treatment orders , Acute Physiology and Chronic Health Evaluation (APACHE) II scores, any mechanical ventilation support if required (mode and settings), any renal replacement therapy (RRT) if required (mode and settings) and medical records of whole hospitalization period.

The patients were divided into three groups as the ones free of cancer (CF), the ones with solid tumour (ST) and the ones with hematologic malignancy (HM). The age, gender, presence of infection, any organ failure, any accompanying disease and the severity of critical disease were recorded at ICU admittance for all patients. The state of remission, history of stem cell transplantation, any chemotherapy applied any time after diagnosis and state of neutropenia of the patients with solid or hematologic malignancy were also recorded at ICU admittance.

The presence of respiratory, cardiovascular or renal failure at the time of ICU admittance was recorded. The requirement of invasive or noninvasive mechanical ventilation support was accepted as respiratory failure, the requirement of vasopressors to resume a mean arterial pressure above 65 mmHg was accepted as cardivascular failure and the requirement for RRT was accepted as renal failure. The state of accompanying diseases was evaluated by Charlson Comorbidity Index (CCI) and the severity of critical illness was evaluated by APACHE II scores. The presence of infection at admittance was evaluated by analysing the vital signs, laboratory and imaging results and medical records of the patients. The state of remission and history of hematopoietic stem cell transplantation was evaluated by previous medical history and hospital records. The study endpoint was ICU mortality.

Continuous variables were expressed as mean ± standard deviation and discrete variables were expressed as median (25-75%). Continuous variables were analysed by Kolmogorov-Smirnov test for normal distribution. Continuous variables in normal distribution were evaluated by t-test whereas continuous variables in not normal distribution were evaluated by Mann-Whitney U test. The differences among cathegorical variables were evaluated by ki-square test and Fisher for sure ki-square test. The logistic regression analysis was used to identify independent risk factors affecting mortality. $p<0.05$ was accepted as statistically significant. All statistical analysis was done by SPSS 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

RESULTS

Five hundred and twelve patients were identified fulfilling the inclusion criteria. Among these 512 patients 89 had a ST, 49 had a HM and 374 patients were CF.

In total 215 (41.9%) patients were female and 297 (58.1%) were male. 24 (26.9%) of the patients with ST were female and 65 (73.1%) were male. 16 (32.6%) of the patients with HM were female and 33 (67.4%) male. The CF group included 175 (46.8%) female and 199 (53.2%) male patients. The age of the patients varied between 18 and 92. The average age of the patients was 68 ± 11.6, 59.8 ± 17.4 and 69.6 ± 16.1 in ST group, HM group and CF group respectively. The average age in ST group was significantly higher than HM group ($p<0.006$) but there was no statistical difference when compared to CF group. Besides HM patients were younger when compared to CF group ($p<0.001$) (Table 1).

In ST group 56 (62.0%), in HM group 22 (44.8%) and in CF group 188 (50.2%) patients were on invasive mechanical ventilation (IMV) support at ICU admittance.

The number of patients who were on non-invasive mechanical ventilation (NIMV) support was 15 (16.8%), 16 (32.6%) and 67 (17.9%) for ST, HM and CF groups respectively. The requirement for IMV in ST patients was significantly higher than HM and CF groups ($p<0.05$ and $p<0.04$ respectively) but there was no significant difference between HM and CF groups. The application of NIMV in HM group was significantly higher than ST and CF groups ($p<0.04$ and $p<0.02$ respectively) but there was no difference between the two latter groups. 44 (49.4%) patients in ST group,23(46.9%) patients in HM group and 160 (42.7%) patients in CF group required vasopressor support .The number of patients requiring RRT at admittance in ST group, HM group and CF group were 24 (26.9%), 9 (18.3%) and 88 (23.5%) respectively. There was no statistical difference among groups for vasopressor and RRT requirements (Table 1).

Table 1: Characteristics of patients.

	ST n=89	HM n=49	CF n=374	P
Age	68.0± 11.6	59.8± 17.4	69.6± 16.1	<0.001
Gender (M/F)	65/24	33/16	199/175	>0.05
CCI	8 (7-10)	5 (3-6.5)	5 (4-6)	<0.001
APACHE II	23.1± 7.1	20.6± 7.6	20.5± 8.5	<0.03
IMV requirement (%)	56 (62.0)	22 (44.8)	188 (50.2)	>0.05
NIMV requirement (%)	15 (16.8)	16 (32.6)	67 (17.9)	<0.05
Vasopressor requirement (%)	44 (49.4)	23 (46.9)	160 (42.7)	>0.05
RRT requirement (%)	24 (26.9)	9 (18.3)	88 (23.5)	>0.05
Remission (%)	5 (5.6)	4 (8.1)		>0.05
Neutropenia (%)	2 (2.2)	16 (32.6)		<0.05
Chemotherapy (%)	46 (48.3)	39 (79.5)		<0.005
Evidence of infection (%)	79 (88.8)	45 (91.8)	310 (82.9)	>0.05
Immunsupressive treatment in last month (%)	18 (20.2)	30 (61.2)	39 (10.4)	<0.001
Mortality rate (%)	61 (68.6)	26 (53)	149 (39.8)	<0.001

M: male, F: female, CCI: Charlson Comorbidity Index, APACHE: Acute Physiology and Chronic Health Evaluation, IMV: invasive mechanical ventilation, NIMV: noninvasive mechanical ventilation, RRT: renal replacement therapy

The median of CCI score in ST group was calculated as 8 whereas it was 5 for the other groups. The CCI score of ST group was significantly higher than the other groups ($p<0.001$) but there was no difference between the other groups. The average of APACHE II scores of ST, HM and CF groups was 23.1 ± 7.1, 20.6± 7.6 and 20.5 ± 8.5 respectively. APACHE II scores of ST group was significantly higher than the other groups ($p<0.03$) but there was no statistical difference between HM and CF groups (Table 1).

There was clinical evidence of infection in 79 (88.7%) patients in ST group, 45 (91.8%) patients in HM group and 310 (82.8%) patients in CF group. There was no statistical difference among groups. Eighteen (20.2%) patients in ST group, 30 (61.2%) patients in HM group and 39 (10.4%) patients in CF group were treated with immune suppressive agents in the last month before ICU admittance. Immune suppressive treatment in CF group constituted of corticosteroids for chronic obstructive pulmonary disease and rheumatological diseases. The rate of immune suppressive treatment was extremely high in HM group compared to ST and CF groups ($p<0.001$). This rate was also high in ST group compared to CF group ($p<0.02$) (Table 1).

Five (5.6%) patients in ST group and 4 (8.1%) patients in HM group were in remission. 2 (2.2%) patients in ST group and 16 (32.6%) patients in HM group were neutropenic at time of ICU admittance. These rates were statistically significant ($p<0.05$). 43 (48.3%) patients in ST group and 39 (79.5%) patients had received chemotherapy any time before ICU hospitalization. The rate of chemotherapy was significantly higher in HM group ($p<0.005$) (Table 1). While there were no hematopoietic stem cell transplantations applied in ST group, 10 (20.4%) patients in HM group had undergone stem cell transplantation.

236 patients died during ICU hospitalization. The distribution of this total number was 61 (68.6%), 26 (53%) and 149 (39.8%) in ST, HM and CF groups respectively. The mortality rate in ST group was significantly higher than CF group ($p<0.001$). There was no statistical difference in mortality between ST versus HM and HM versus CF groups (Table 1).

To evaluate the effect of gender, ICU data and scores on mortality prediction, odds ratios were calculated. In logistic regression analysis; high APACHE II scores and requirement for IMV (odds ratio [OR], 5.52; 95% confidence interval [CI], 2.10-14.53; $p<0.001$) at ICU admittance were detected as independent risk factors associated with increased mortality in all groups. Requirement for RRT (OR, 2.34; 95% CI, 1.44-3.80; $P<0.002$) and vasopressors (OR, 1.67; [CI: 1.10-2.54]; $p<0.02$) at admittance were also independent risk factors associated with increased mortality in CF group (Table 2).

Table 2: Factors effecting mortality at ICU admission.

	Solid tumour			Hematologic malignancy			Cancer free		
	OR	**CI**	**p**	**OR**	**CI**	**p**	**OR**	**CI**	**p**
Gender	1.45	0.54-3.89	>0.05	1.20	0.36-3.97	>0.05	1.29	0.85-1.96	>0.05
IMV requirement	5.52	2.10-14.53	<0.001	4.53	1.34-15.37	<0.02	3.51	2.26-5.44	<0.001
NIMV requirement	0.32	0.10-1.01	>0.05	0.26	0.07-0.93	<0.04	0.49	0.28-0.89	<0.02
Vasopressor requirement	1.82	0.73-4.53	>0.05	1.30	0.42-4.01	>0.05	1.67	1.10-2.54	<0.02
RRT requirement	2.08	0.69-6.31	>0.05	1.13	0.26-4.84	>0.05	2.34	1.44-3.80	<0.002
Evidence of infection	1.53	0.40-5.91	>0.05	1.14	0.15-8.84	>0.05	1.57	0.88-2.79	>0.05
Immunsupressive treatment in last month	0.90	0.30-2.70	>0.05	0.35	0.11-1.18	>0.05	1.05	0.54-2.07	>0.05
Remission	1,18	0,34-4,14	>0,05	0,88	0,11-6,77	>0,05			
Chemotherapy	0,59	0,24-1,46	>0,05	0,41	0,09-1,81	>0,05			
Neutropenia				0,83	0,25-2,76	>0,05			

IMV: invasive mechanical ventilation, NIMV: noninvasive mechanical ventilation, RRT: renal replacement therapy

DISCUSSION

In our study, the rate of cancer patients admitted to ICU was 26.9% (n=138) of all-cause hospitalization. This rate was significantly high according to the literature. The distribution of cancer patients admitted was solid tumours 64.4% (n=89) and hematologic malignancies 35.6% (n=49). A multi-center international survey by Taccone et al cancer patients constituted 15% of all ICU patients; 85% solid tumors and 15% hematologic malignancies and ICU mortality of ST, HM and CF patients was observed as 20%, 42% and 18% respectively.[27] Puxty et al in a research of ST patients in 35 centers reported ICU mortality of ST varying between 4% and 85% (average:31.2%).[15] In a survey from Turkey, Aygencel et al. reported ICU mortality of ST and HM patients as 53.8% and 57% respectively.[21] The results of our study though being high compared to the rest of the world are compatible with our national data. The mortality rates of HM patients in both our country and whole world was detected higher than ST patients but our study results displayed vice versa. But while interpreting these results one must consider that those results reflect a mixed ICU patient profile whereas patients in our study were medical ICU patients and the number of HM patients was less than ST patients.

At admittance to ICU the ST group had a statistically significant increased requirement for IMV. This may be attributable to advanced stage of lung cancer, being elder than the other groups, intolerance of NIMV due to dementia and therefore requirement of early intubation. The requirement of IMV at admittance was associated with increased ICU mortality in all groups. This finding is compatible with most of the other researches.[28,29] Namendys et al reported IMV not to be associated with increased ICU mortality in ST patients but this study included postoperative patients.[26]

NIMV is a way of reducing the requirement for IMV. Due to various complications of IMV, especially in the immune-compromised patient population NIMV application is increasing. In our study HM group had significantly increased NIMV application which may be attributable to younger age, better tolerance of the procedure and avoiding invasive procedures as much as possible due to the high incidence of cytopenia in these patients. Although NIMV in HM and CF groups in our study seems to be associated with increased survival, logistic regression analysis displayed no association with increased mortality in neither of the groups. In a study by Azoulay et al in-hospital mortality was detected as 46.2% in NIMV applied group and 60.5% in the group ventilated by IMV.[10] These results are also compatible with our study where we detected mortality rates of 30.6% and 61.7% in NIMV and IMV applied groups respectively.

The requirement for RRT at ICU admittance in HM and ST groups was not associated with mortality. This finding is compatible with another study from our country but conflicts with other researches. Aygencel et al reported that the need of RRT of cancer patients during ICU hospitalization had no effect on ICU mortality.[22] Jin Heo et al and Zuber et al reported that the requirement for RRT in cancer patients is associated with increased ICU mortality.[25,30] Uchino et al reported increased mortality rates in a multicenter and multinational study on CF patients requiring RRT.[31] The requirement for RRT in CF patients in our study was associated with increased mortality similar to the literature.

The requirement for vasopressors was associated with a worse prognosis in CF group but statistically it was not associated with increased mortality in overall patients. Although there are conflicting results in literature, studies based on ICU mortality mostly report no association.[32,33]

This conflict seems to result from the heterogenity of study groups.

The clinical evidence of infection was shown to increase mortality in critically ill cancer patients.[34] In our study there was a contradictory as we detected that clinical evidence of infection at ICU admittance was not associated with increased mortality. This conflicting result may be due to few number of patients included. The similar rates of clinical evidence of infection in both malignancy groups although significantly lower rates of immune suppressive treatment in ST group, supports the idea that immune suppressive treatment is not solely responsible of the increased rates of infection in cancer patients. In the current study, immune suppressive treatment in the last month before ICU was not found to be associated with increased mortality. Though the number of patients limits the validity of this result we may suggest that recent immune suppressive treatment should not be regarded as a contraindication for ICU admission.

The use of scoring systems in ICUs for objective evaluation of the severity of the illness, mortality and morbidity rates is of gold standart. The most common used scoring system is 'Acute Physiology and Chronic Health Evaluation (APACHE) II' which was developed by Knaus et al in 1985.[35] The APACHE II scores of ST group were significantly high. A high APACHE II score was detected to be an independent risk factor for increased mortality in all groups. There are conflicting results about the relation of APACHE II scores and mortality. Afessa et al suggested that this scoring system underestimated mortality and had no correlation with the duration of stay in ICU or hospital, but Paz et al reported it to be significant in predicting mortality.[36,37] The fact that the state of accompanying diseases may influence morbidity and mortality led us to calculate their Charlson Comorbidity Score which was developped by Charlson et al in 1987.[38] According to this scoring system patients with 3 points or more have a predicted mortality of more than 50% in a year whereas 85% are predicted to die if calculated a score of 8 points or more. The significantly high scores of ST group may be due to advanced age and metastasis. We could not detect a relationship between Charlson scores and ICU mortality.

No association was detected between remission and mortality. The few number of patients who were on remission period for malignancy limited the evaluation of its effect on outcome. No association between blood marrow transplantation and mortality could be identified.

The number of patients that received chemotherapy any time before ICU hospitalization was significantly less in ST group (48.3%) than HM group (79.5%) but no association was detected between a history of chemotherapy and mortality. Although neutropenia was regarded as a factor increasing mortality in cancer patients for long years, recent studies suggest that it does not affect mortality. While Darmon et al reported that neutropenia is associated with increased mortality in cancer patients, Soares et al and Aygencel et al reported contradictary results.[9,18,21] Mokart et al. reported neutropenia to increase mortality in coexistance of other factors like mechanical ventilation.[39] In our study the rate of neutropenia in ST patients was far less (2.2%) to analyse but in HM patients the rate was 32.6% and analysis of the data revealed no association with mortality which was compatible with recent studies. In the current study we detected that disease related factors do not influence mortality in cancer patients.

CONCLUSIONS

APACHE II score and requirement for IMV at ICU admittance were independent risk factors for increased mortality in all patients. Additionally, requirement for RRT and vasopressors were detected to be risk factors for increased mortality in CF group. Overall ICU mortality was detected to be 46% and mortality rates of ST, HM and CF groups were 68.5%, 53.0% and 39.8% respectively. The mortality rates of cancer patients especially the ST group was high. In the light of these results we may anticipate the factors predicting survival and mortality rates of cancer patients at ICU admittance. But there are many studies to predict factors influencing ICU mortality in cancer patients with controversial results which may be due to heterogenity of patient profiles. There is still need for more homogenous, multicentered and randomized studies including more patient data.

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