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Outcome and Prognostic Factors of Lung Cancer Patients Admitted to the Medical ICU

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ABSTRACT

Objective: To assess the outcome of lung cancer patients who were admitted to a medical ICU (MICU), and to identify the measurable predictors of their MICU outcome.

Design: Retrospective study.

Setting: MICUs of a university affiliated medical center

Patients: Adult lung cancer patients admitted to the MICU between January 1998 and October 2005.

Measurements and main results: 139 lung cancer patients included during the study period. The mean age (+/-SD) at MICU admission was 64.2 +/- 10.2years (men 48%, women 52%). 96 patients (69%) had non-small cell lung cancer, 18 patients (13%) had small cell lung cancer, and one patient had mesothelioma. The MICU mortality was 22% (31 patients), while the in-hospital mortality was 40% (56 patietns). Sixty eight patients (49%) required mechanical ventilation (MV), with MICU mortality of 38% and in-hospital mortality of 53%. The independent predictors of poor MICU outcome were the need for MV, APACHE III and SAPS III scores, the use of vasopressors, positive blood cultures, high serum lactate, two or more organ system failure, the need for ACLS. On multivariate analysis only the need for vasopressors and the presence of two or more organ systems failure predicted poor MICU outcome.

Conclusion: The study shows that the MICU outcome of lung cancer patients is better than previously reported. Intensive care and MV should not be considered futile care in this patient population. While there were no absolute predictors of mortality, the need for vasopressors and the presence of two or more organ systems failure predicted poor MICU.

Abbreviations: ACLS = Adult Cardiac Life Support; APACHE = Acute Physiology And Chronic Health Evaluation; LOS = Length Of Stay; MICU = Medical Intensive Care Unit; MOSF = Multiorgan System Failure; MV = Mechanical Ventilation; SAPS = Simplified Acute Physiology Score.

Lung cancer is the third most common malignancy, but remains the leading cause of cancer mortality in both men and women in the United States and throughout the world. The 1-year relative survival for lung cancer has increased from 37% in 1975 to 42% in 1999-2001, largely due to improvement in surgical technique and combined therapies; however, the 5-year survival rate for all stages combined is only 15%.[1-5] Despite this poor prognosis, lung cancer patients are often admitted to the medical ICU (MICU) for critical illness either related to their underlying malignancy or comorbid illnesses, regardless of their cancer cell type or disease stage.[11-23]

Previous studies on cancer patients who were admitted to the MICU,[11-26] and specifically the few studies on lung cancer patients,[6-10] have shown that the outcome of lung cancer patients who were admitted to MICU; especially those requiring mechanical ventilation (MV), is extremely poor. This study was conducted to assess the outcome of a recent cohort of lung cancer patients admitted to the MICU, including those who required MV and to identify the measurable predictors of adverse MICU outcomes.

MATERIALS AND METHODS

This study was conducted at Wayne State University affiliated medical center in Detroit, Michigan. The medical center consists of tertiary-care teaching hospitals and a comprehensive cancer center. The criteria for admission to and discharge from the MICU follow the guidelines set by the American College of Critical Care Medicine and Society

of Critical Care Medicine.[27] The MICU is managed by full-time faculty members of the Pulmonary and Critical Care Division. Medical oncologists also conducted daily rounds on oncology patients in the MICU.

After obtaining approval from the institutional review board (IRB), a retrospective analysis of the medical records of lung cancer patients who were admitted to the MICU between January 1998 and October 20005 was performed. The criteria for including patients in this study were histologically proven diagnosis of lung cancer made within the last 2 years prior to their admission to the MICU. Patients who stayed in the MICU for less than 24 hrs and those admitted for routine postoperative care were excluded from the study. For those patients who were admitted more than once to the MICU during the same hospitalization, only the first MICU admission was analyzed.

Demographic, physiologic, and clinical data including age, gender, race, smoking history, comorbidities, type and stage of lung cancer on admission to the MICU were collected. Attempts were made to determine the indication for admission to the MICU based on clinical and laboratory parameters. In addition, laboratory data obtained within 24 h of admission to the MICU were collected. If the laboratory values were not available within 24 h of MICU admission, the values obtained up to 72 h prior to MICU admission were used. These laboratory data included the following: hemoglobin; WBC count; platelet count; coagulation profile; BUN level, creatinine level; electrolytes levels, liver functions tests, arterial blood gas measurements; serum lactate level; and blood cultures. Radiological findings were also recorded.

APACHE (Acute Physiology And Chronic Health Evaluation) III score and SAPS (Simplified Acute Physiology Score) III were collected retrospectively for each patient based on data collected within the first 24 h after their admission to the MICU.[28] The authors made every attempt to determine the number and type of organ system failure during each patient's MICU stay.

Organ-system failure was recorded if the patient had one or more of the following conditions occur during their MICU stay: respiratory failure (i.e., the presence of hypoxemia or hypercapnia, or the need for intubation and MV); cardiovascular failure (i.e., the presence of congestive heart failure, the occurrence of ventricular tachycardia or fibrillation, or the need for I.V. infusion of dobutamine, norepinephrine, vasopressin, or epinephrine at any dose, or for dopamine at >5ug/kg/min for at least 4 h); renal failure (i.e., serum creatinine level ≥ 3.4mg/dL, or the need for hemodialysis); neurologic failure (i.e., Glasgow coma scale ≤ 6 when available, or subjective criteria such as the presence of confusion, decreased responsiveness, or coma in the absence of sedation); and hepatic failure (total bilirubin level ≥ 4mg/dL). Sepsis was defined according the criteria developed by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference [24, 29]

MICU data including indication and duration of MV; Noninvasive mechanical ventilation (NIPPV); and vasopressors use were also reviewed. If the patient died, the mode of death,

such as withdrawal of life- sustaining support or failure to recover spontaneous circulation after adult cardiac life support (ACLS) protocol was documented.

All patients were evaluated longitudinally to determine their MICU and hospital outcomes. In addition, the 6-month survival rate was also recorded when data were available. Values were reported as the median and/or the mean ± SD. All percentages were approximated to round numbers. Parametric interval data were initially analyzed using a two-tailed Student t test. These data are listed as the mean ± SD. Nominal data were analyzed by X^2 analysis with Yates continuity correction or by Fisher exact test when appropriate.

Multiple logistic regression analysis was used to identify the variables that were independently associated with death. Each variable that was found to be significant at $p<0.05$ by univariate analysis was introduced into back ward, stepwise, logistic regression model. A p value of <0.05 was used to indicate statistical significance.

RESULTS

During the study period, there were 139 lung cancer patients admitted to the MICU. The total number of patients with lung cancer admitted to the hospital during the study period was not available. While we did not have data on the number of lung cancer patients who may have had critical illness and the patients, family or treating physicians decided not to transfer them to the MICU, it is the general policy and practice at our institution to

transfer oncology patients, including lung cancer patients, to the MICU when they develop critical illness. The baseline clinical characteristics of patients on admission to the MICU are summarized in Table 1. Their mean age (± SD) was 64.2 ± 10.2 years. Forty eight percent of the patients were males and 52% were females. Ninety fine (68%) patients were African-American, which probably reflects the local population demographics. Smoking history was documented in 129 (93%) of patients.

Ninety-six (69%) patients had nonsmall cell lung cancer, 18 (13%) patients had small cell lung cancer, one patient had mesothelioma, and the type of lung cancer could not be determined –based on the available medical records- in the remaining 24 (17%) patients. In patients with nonsmall cell lung cancer 56 patients had stage 4, 28 patients had stage 3, one patient had stage 2, and 5 patients had stage 1. In patients with small cell lung cancer 7 patients had limited disease and 8 patients had extensive disease. In 34 (24%) patients the stage of lung cancer was not available. The type and stage of lung cancer was unknown in some patients, either because they were diagnosed in other hospitals prior to transfer to our MICU, or the staging was not completed upon their admission to the MICU.

There were no significant differences in the baseline clinical characteristics between survivors and nonsurvivors during the MICU admission, with the exception of the African-American race, history of smoking, and nonsmall cell type that were associated with favorable outcome (Table 1).

The main indications for admission to the MICU are summarized in Table 2. Pneumonia was the most common respiratory indication for MICU admission (26 patients), other respiratory conditions included COPD exacerbation, pulmonary edema, hemoptysis, post bronchoscopy procedures, advanced lung cancer and malignant pleural effusions. The main cardiac indications were arrhythmias (13 patients), cardiac arrest prior to MICU admission, myocardial infarction, congestive heart failure, and pericardial effusion. Seizure disorder and mental status changes were equally the most common neurologic indications (3 patients each), while one patient had stroke. Hyponatremia was the most common metabolic/electrolytes indication (4 patients) for MICU admission.

A total of 68 patients (49%) required intubation and mechanical ventilation during their stay in the MICU. Table 3 describes the clinical features of the patients who received MV. Forty two of those mechanically ventilated (62%) survived their MICU stay, and 32 patients (47%) were discharged alive from the hospital. This was in contrast to the outcome of patients who did not require MV (71 patients), of whom 66 patients (93%) were discharged alive from the MICU, and 51 patients (72%) were discharged alive from the hospital. There was no significant difference in the duration of MV between the survivors and non survivors groups (p=0.18). The most common indications for MV were pulmonary/airway problems in 46 patients (68%), cardiovascular problems in 12 patients (18%); and sepsis in 7 patients (10%). Pulmonary indications for MV were associated with favorable MICU outcome (p= 0.04), while those with sepsis as the main indication for MV had poor MICU outcome (p=0.001). Those mechanically ventilated patients with

high APACHE III and SAPS III scores on admission to the MICU and those with high serum lactate had unfavorable outcome.

The median LOS in the MICU was 2 days (range 1-31 days), and this was similar in survivors and nonsurvivors. Thirty one patients (22%) died during their MICU stay, and 56 patients (40%) died during their hospitalization. During their MICU stay, the decision was made to forego life-sustaining care in 44 patients (32%). Twenty one of these patients died in the MICU. ACLS was performed on 10 patients, and only one patient survived the MICU stay, but subsequently died in the hospital.

Acuity scores, MICU data and main laboratory variables on admission to the MICU were recorded and compared between survivors and nonsurvivors as shown in Table 4. The initial APACHE III score and SAPS III, demonstrated significant differences between survivors and nonsurvivors (mean APACHE III: survivors, 54.3 ± 21.4; non survivors, 85.8 ± 28.5 [$p<0.0001$]; mean SAPS III: survivors, 37.4 ± 19; nonsurvivors, 66.8 ± 27.1 [$p<0.0001$]). There were significant differences between the two groups regarding the need for vasopressors ($P<0.0001$) and MV ($p< 0.0001$). Other MICU admission laboratory data that were significantly different between the two groups were serum lactate levels, serum calcium levels, and positive blood culture results. The serum lactate levels on admission to the MICU were significantly higher in patients who eventually died in the MICU (survivors, 1.4 ± 1.8 mMol/L, nonsurvivors, 3.7 ± 4.4 mMol/L, $p=0.008$). Sixteen patients (12%) had positive blood culture results either during the 24 h immediately prior to MICU admission, or within the first 48 h after MICU admission.

The most common isolates were gram-positive cocci in 14 patients, and gram-negative bacilli in 3 patients. One patient had 2 organisms isolated from blood culture. Patients with positive blood cultures had a poor outcome (p=0.001). No differences in outcome were observed based on the type of organism isolated. There was no significant difference between survivors and nonsurvivors regarding the type of lung cancer treatment whether it was surgery (p=0.25), chemotherapy (p=0.18), radiation therapy (p=0.08), or combination therapy (p=0.14).

One hundred-fifteen patients (83%) had one or more organ systems failure, according to the criteria described in the "Materials and Methods" section. Mortality increased with the number of organ systems that failed beyond one organ system failure, and this trend was seen with all types of organ system failure.

To determine the predictors of MICU outcomes, statistically significant MICU data, physiologic and laboratory variables on MICU (Table 4), as well as the need for MV, the use of vasopressors, and the presence of mutliorgan system failure (MOSF), were entered into a stepwise backward elimination regression analysis model. Race and smoking history were not included in the regression analysis. Only the need for vasopressors and the presence of two or more MOSFs during their MICU stay predicted poor MICU outcome (Table 5).) The final model showed good discrimination and calibration.

DISCUSSION

The aim of this study was to assess the outcome of lung cancer patients who had been admitted to our MICU, and to identify the predictors of MICU adverse outcome for this group. The data showed that the MICU mortality rate was 22%, while the in-hospital mortality was 40%. The predicted MICU mortality for these patients based on the APACHE III score was 29%. For those who required MV (49% of the patients), the MICU mortality was 38% and the in-hospital mortality was 53%. The independent predictors of adverse MICU outcome in this patient population were hemodynamic instability requiring vasopressors use and the presence of MOSF.

This study shows that the outcome of lung cancer patients admitted to the MICU has improved significantly compared to historical studies, and confirms the findings of a recent study on a similar group of patients from Brazil and France (Table 6) [6-10,30] Furthermore, this study shows that the mortality rate for those lung cancer patients who require MV is higher than that for the group as a whole; however the MICU outcome of these patients showed similar favorable trend compared to previous studies. In the study by Lin YC et al,[8] on the outcome of lung cancer patients with acute respiratory failure requiring MV, the MICU mortality was 73%, and the in-hospital mortality was 85%. Another study by Emer et al,[9] reported the in-hospital mortality as high as 91%, and a 6 months mortality of 98%. In the recent study by Soares et al [30], the MICU mortality rate for lung cancer patients who required MV was 56% and the in-hospital mortality was 69%.

The improved outcome of lung cancer patients admitted to the MICU reported in this study and by Soares et al may be related to improved MV strategies that minimize further lung injury; better management of sepsis, multidisciplinary approach to the management of these cases; and the improvement in the therapeutic options for patients with lung cancer. This study was not designed to test these theories. It is also possible that there is selection bias that resulted in admitting patients who are thought to benefit from ICU care. It is difficult to measure the role of the latter possibility on the improved outcome of lung cancer patients admitted to the MICU. Prospective studies and more strict inclusion criteria are necessary to confirm and address the reasons of the improved survival noticed in these recent studies.

Several studies tried to identify the clinical variables that are associated with poor MICU outcome. The outcome predictors reported by Reichner et al,[6] were the need for MV, advanced lung cancer stage, and higher SOFA score. In the study by Boussat et al,[7] acute pulmonary disease and Karnofsky performance status <70 were associated with higher mortality. In the recent study by Soares [30] the predictors of poor MICU outcome were the severity of comorbid illnesses, the number of organ system failure, cancer recurrence or progression, and airway infiltration or obstruction by cancer. In our study we were able to identify several predictors of poor MICU outcome that included high admission APACHE III and SAPS III scores, the need for MV, the use of vasopressors, positive blood cultures, high serum lactate, the presence of two or more organ system failure, and the need for ACLS protocol for cardiopulmonary arrest. However on multivariate logistic regression only the use of vasopressors and the presence of two or more MOSF predicted

poor MICU outcome, with odds ratio 8.7 and 40.8 respectively (Table 5). The stage of lung cancer, the presence of metastasis, or the type of cancer therapy did not correlate with poor MICU outcome. This was similar to the findings in the study by Boussat et al,[7] but in contrast to the findings of Reichner et al [6] and Soares et al [30]. We also observed that patients with nonsmall cell lung cancer had a favorable MICU outcome (p=0.027), which is in contrary to the findings of other studies.[6-7]

In our study only one patient underwent ACLS protocol and survived his MICU stay, but subsequently died in the hospital. Although the number is small, this observation suggests that, while aggressive therapy is appropriate for this patient population, subjecting them to the ACLS protocol appears to be futile, and such an intervention probably should be avoided. This goal could be achieved by addressing the code status and initiating end-of-life discussion early during the course of their illness probably before the patients' condition deteriorates.

This study has important limitations including the retrospective nature of the analysis that may have resulted in selection bias, and the lack of assessment of potentially significant predictors of outcome such as the role of progression of lung cancer, airway infiltration, the severity of co-morbid illnesses, complications of cancer therapy, or performance status in predicting the MICU outcome of lung cancer patients. Prospective, multicenter trials are necessary to address these issues

In conclusion, our data have shown that the MICU outcome of lung cancer patients is improving, and is comparable to other critically ill patient population. Intensive care and MV should not be regarded as futile care. While there were no absolute predictors of mortality, hemodynamic instability requiring vasopressors use, and the development of two or more organ system failures are less likely to survive their MICU care.

Table 1-Baseline Clinical Characteristics of All Lung Cancer Patients, Survivors, and Nonsurvivors Admitted to the MICU

Variables	All Patients (n = 139)	Survivors (n = 108)	Nonsurvivors (n = 31)	P Value
Age, years	64.2 ± 10.2	63.6 ± 10.4	66.5 ± 9.4	0.15
Gender				
Male	67 (48%)	53 (49%)	14 (45%)	0.15
Female	72 (52%)	55 (51%)	17 (55%)	0.15
Race				
White	41	30	11	0.12
African-American	95	78	17	0.03
Other	3	0	3	0.01
Smoking history	129 (93%)	103 (95%)	26 (84%)	0.04
Type of lung cancer				
Nonsmall cell	96 (69%)	79 (73%)	17 (55%)	0.03
Small	18 (13%)	13 (12%)	5 (16%)	0.19
Other	1	0	1 (3%)	0.22
Unknown	24 (17%)	16 (15%)	8 (26%)	0.08
Stage of lung cancer				
1	5 (4%)	4 (4%)	1 (3%)	0.41
2	1 (<1%)	1 (1%)	0	0.77
3	28 (20%)	23 (21%)	5 (16%)	0.17
4	56 (40%)	44 (41%)	12 (39%)	0.16
limited disease	7 (5%)	5 (5%)	2 (6%)	0.30
Extensive disease	8 (6%)	7 (6%)	1 (3%)	0.30
Unknown	34 (24%)	24 (22%)	10 (32%)	0.09
Treatment received				
Chemotherapy	8 (6%)	5 (5%)	3 (10%)	0.18
Radiation therapy	26 (19%)	23 (22%)	3 (10%)	0.08
Surgery	11 (8%)	8 (7%)	3 (10%)	0.25
Combination	47 (34%)	35 (32%)	12 (38%)	0.14
None	43 (31%)	35 (32%)	8 (26%)	0.14
Unknown	4 (3%)	2 (2%)	2 (6%)	0.18

Table2-Main Indication by Organ System for MICU Admission for All Lung Cancer Patients, Survivors, and Nonsurvivors

Indication	All patients (n = 139)	Survivors (n = 108)	Nonsurvivors (n = 31)	P Value
Respiratory	68 (49%)	50 (46%)	18 (58%)	0.08
Cardiovascular	34 (25%)	29 (27%)	5 (16%)	0.09
Sepsis	11 (8%)	5 (5%)	6 (20%)	0.01
Neurologic	7 (5%)	7 (6%)	0	0.16
Renal	2 (1%)	1 (1%)	1 (3%)	0.35
Metabolic	9 (7%)	8 (7%)	1 (3%)	0.27
Bleeding	2 (1%)	2 (2%)	0	0.60
Others	6 (4%)	6 (6%)	0	0.21

Table 3-Clinical Characteristics of Lung Cancer Patients Requiring Mechanical Ventilation*

variables	All patients (n = 68)	Survivors (n = 42)	Nonsurvivors (n = 26)	P value
Age, yr	65.3 ± 9.9	65 ± 10.1	65.8 ± 9.6	0.74
Type of lung cancer				
Nonsmall cell	42 (62%)	29 (69%)	13 (50%)	0.06
Small	9 (13%)	4 (10%)	5 (19%)	0.15
Other	1 (1%)	0	1 (4%)	0.38
Unknown	16 (24%)	9 (21%)	7 (27%)	0.20
Stage of lung cancer				
1	4	3	1	0.37
2	0	0	0	
3	13	8	5	0.25
4	24	15	9	0.21
limited disease	6	4	2	0.33
Extensive disease	1	0	1	0.38
Unknown	20	12	8	0.21
Indication for MV				
Pulmonary/Airway	46 (68%)	32 (76%)	14 (54%)	0.04
Cardiovascular	12 (18%)	7 (17%)	5 (19%)	0.24
Sepsis	7 (10%)	1 (2%)	6 (23%)	0.001
others	3 (4%)	2 (5%)	1 (4%)	0.45
SAPS III	52 ± 26.6	42 ± 20.4	67.1 ± 29	0.0006
APACHE III score	69.4 ± 28.3	59.6 ± 22.2	85 ± 30.3	0.0006
Lactate level mmmol/L	2.86 ± 3.4	2 ± 1.97	4.2 ± 4.6	0.03
MV duration >24 hours	47 (69%)	30 (71%)	17 (65%)	0.18

* P value <0.05 is considered significant.

Table 4-Acuity Scores, Vasopressors, MV, and Main Laboratory Variables on MICU Admission for Survivors and Nonsurvivors*

Variables	Survivors (n = 108)	Nonsurvivors (n = 31)	P value
SAPSIII	37.4 ± 19	66.8 ± 27.1	<0.0001
APACHEIII Score	54.3 ± 21.4	85.8 ± 28.5	<0.0001
Vasopressors use, No.	12	23	<0.0001
Mechanical Ventilation	42	26	<0.0001
Lactate, mMol/L	1.4 ± 1.8	3.7 ± 4.4	0.008
Albumin, gm/dL	1.7 ± 1.4	1.3 ± 1.2	0.12
Calcium, mg/dL	8.7 ± 1.8	7.4 ± 2.2	0.005
Sodium, mMol/L	137.2 ± 8.2	134.6 ± 27	0.60
Creatinine, mg/dL	1.6 ± 1.9	1.4 ± 0.9	0.41
T. Bilirubin, mg/dL	0.4 ± 0.5	0.4 ± 0.8	0.99
Hematocrit %	33.2 ± 6.7	31.2 ± 5.4	0.09
Platelets, k/cumm	289.4 ± 130	259.8 ± 139.8	0.29
Positive blood Culture, No.	7	9	0.001

* P value <0.05 is considered significant. Values indicate mean +/-SD except where No. is indicated

Table 5-Predictors of MICU Mortality on Stepwise Backward Elimination Regression Analysis

Variables	Odds ratio	Confidence interval	P Value
Vasopressors use	8.7	2.8-27	<0.0001
MOSF ≥ 2	40.8	5.1-328.3	<0.0001

*Variables from Table 4 with a $p<0.05$ were entered into the regressional analysis

Table 6-Mortality of Lung Cancer Patients admitted to the MICU and Literature Review*

Study/Year	Patients, No.	MV Patients, %	MICU Mortality, %	Hospital Mortality, %	Long-term Mortality, %†	Predictors of Outcome
Ewer et al[9] / 1986	46	100%	85%	91%	98%	MV duration
Boussat et al[7]/ 2000	57	91%	67%	75%	NR	Acute pulmonary disease, Karnofsky performance status<70
Jennens et al[10] / 2002	20	45%	NR	NR	85%	Extensive disease, elevated adjusted Manchester score
Lin et al[8] / 2003	81	100%	73%	85%	NR	Albumin level, APACHE III score, highest fractional inspired O2, highest positive end-expiratory pressure, organ failure, ability to shift to partial ventilatory support, MV duration
Reichner et al[6] / 2006	47	49%	43%	60%	NR	MV, advanced lung cancer stage, higher SOFA score
Soares et al[29] / 2007	143	70%	44%	60%	67%	Airway infiltration or obstruction by cancer, number of organ failures, cancer recurrence or progression, severity of comorbidities
Current study	139	49%	22%	40%	48%	Hemodynamic instability requiring vasopressors, 2 or more organ failures

*NR = not reported. MV = Mechanical ventilation.
†Long-term survival signifies survival > 6 months after MICU admission

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