CHEST

Original Research

CRITICAL CARE

Use of Intensive Care in Patients With Nonresectable Lung Cancer

Anne-Claire Toffart, MD; Clémence Minet, MD; Bruno Raynard, MD; Carole Schwebel, MD, PhD; Rebecca Hamidfar-Roy, MD; Samia Diab, MD; Sébastien Quetant, MD; Denis Moro-Sibilot, MD, PhD; Elie Azoulay, MD, PhD; and Jean-François Timsit, MD, PhD

Background: **Admission of patients with lung cancer to the ICU has been criticized. We evaluated whether ICU admission improved 3-month survival in patients with nonresectable lung cancer. Factors associated with survival were identified.**

Methods: **A retrospective study was conducted in consecutive nonsurgical patients with lung cancer admitted to three ICUs in France between 2000 and 2007, 2005 and 2007, and 2005 and 2006.**

Results: **We included 103 patients with a median (interquartile range) Simplified Acute Physiology Score II of 33 (25-46) and logistic organ dysfunction (LOD) score of 3 (1-4). Invasive mechanical ventilation was required in 41 (40%) patients. Sixty-three (61%) patients had metastasis and 26 (25%) an Eastern Cooperative Oncology Group performance status (ECOG-PS) > 2. The reason for ICU admission was acute respiratory failure in 58 (56%) patients. Three-month survival rate was 37% (95% CI, 28%-46%). By multivariate analysis, variables associated with mortality were ECOG-PS > 2 (hazard ratio [HR], 2.65; 95% CI, 1.43-4.88), metastasis at admission (HR, 1.90; 95% CI, 1.08-3.33), and worse LOD score (HR, 1.19; 95% CI, 1.08-1.32). An LOD score decrease over the first 72 h was associated with survival.**

Conclusions: **Survival in nonsurgical patients with lung cancer requiring ICU admission was 37% after 90 days. Our results provide additional evidence that ICU management may be appropriate in patients with nonresectable lung cancer and organ failure.** ***CHEST 2011; 139(1):101–108***

Abbreviations: AIC = Akaike Information Criterion; CCI = Charlson Comorbidity Index; ECOG-PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IQR = interquartile range; LOD = logistic organ dysfunction; MV = mechanical ventilation; SAPS II = Simplified Acute Physiology Score II

In 2009, the number of new lung cancer cases in the United States was estimated at 219,440, representing 15% of all new cases of cancer. The same year, lung cancer was responsible for 159,390 deaths (28% of all cancer deaths) and was the most common cause of death from cancer.[1]

Recent therapeutic advances have improved survival in patients with lung cancer, including those who are not eligible for surgical treatment.[2,3] Complications related to the cancer itself or to the treatment may result in acute life-threatening events. ICU admission of patients with nonresectable lung cancer has been criticized based on the high mortality rate in this population.[4] The overall 5-year survival rate in patients who are not treated surgically is only 16%.[1] However, advances in pharmacologic treatments[2] for lung cancer may have made ICU admission legitimate in situations where life-supporting treatment was previously considered futile.[5] Furthermore,

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Affiliations: From the Clinique de Pneumologie (Drs Toffart, Diab, Quetant, and Moro-Sibilot) and Clinique de Réanimation (Drs Minet, Schwebel, Hamidfar-Roy, and Timsit), Pôle Médecine Aiguë Communautaire, Centre Hospitalier Universitaire de Grenoble, Grenoble; Réanimation Médico-Chirurgicale (Dr Raynard), Institut Gustave Roussy, Villejuif; Inserm U823 (Drs Moro-Sibilot, Azoulay, and Timsit), Université Joseph Fourier, Grenoble; and Réanimation (Dr Azoulay), Centre Hospitalier Universitaire Saint-Louis, Paris, France.

Correspondence to: Jean-François Timsit, MD, PhD, Medical Polyvalent ICU, University Hospital, 38000 Grenoble, France; e-mail: JFTimsit@chu-grenoble.fr

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outcomes in patients with cancer admitted to the ICU have improved in recent years[6] as a result of early admission strategies and new noninvasive diagnostic and therapeutic tools.

ICU management is burdensome, costly, and associated with risks to the patient.[7] ICU admission decisions should be based on short-term and long-term survival data and on patient wishes and expected post-ICU quality of life.

The objective of this study was to assess ICU, hospital, 90-day, and 1-year survival in patients with lung cancer admitted to the ICU. We also sought to identify the effect of logistic organ dysfunction (LOD) score changes over the first 72 h in the ICU.

Materials and Methods

Study Design

We conducted a retrospective review of the medical charts of patients with lung cancer admitted to three tertiary-level hospital ICUs in France that manage large numbers of patients with cancer. In these three ICUs, patients with cancer are admitted only if they are eligible for potentially lifespan-extending anticancer treatment. The study was approved by the appropriate ethics committee (Comité d'éthique des Centres d'Investigation Clinique de l'inter-région Rhône-Alpes-Auvergne), which waived the need for informed consent. The study was retrospective and, therefore, had no impact on patient management.

Study Subjects

Cases were identified through the hospital databases. The case-ascertainment periods in the three ICUs were 2000 to 2007, 2005 to 2007, and 2005 to 2006. During each period, all ICU patients with a past or present history of lung cancer were included. We did not include patients admitted for postoperative management. We reviewed the medical chart of each included patient.

The data in Tables 1 and 2 were abstracted from the medical records. We used the Charlson Comorbidity Index (CCI) without the malignant solid tumor item. We recorded the histologic type of cancer, cancer status (remission, newly diagnosed, or progression/recurrence), cancer spread (TNM classification[8]), anticancer treatment, and performance status (Eastern Cooperative Oncology Group performance status [ECOG-PS][9]). We also recorded the treatments used in the ICU (vasoactive drugs, endotracheal and noninvasive mechanical ventilation [MV], and renal replacement therapy) and the acute organ failures that developed within the first 48 h in the ICU. The Simplified Acute Physiology Score II (SAPS II)[10] severity score and the LOD[11] score were calculated on the first ICU day. Individual organ failure was defined as an LOD score ≥ 1 for the relevant organ system. The LOD score and number of organ failures after 48 h in the ICU were recorded. In August 2008, vital status was assessed based on death registry data. At this time point, 11 patients were lost to follow-up after a mean of 143 days since hospital discharge.

Statistical Analysis

Continuous variables are reported as median (25%-75% interquartile range [IQR]) and categorical variables as number (percentage). The SAPS II and the LOD score are expressed in points. Survival curves were obtained using the Kaplan-Meier method and compared using the log-rank test. Data for patients who were lost to follow-up were considered censored. Cut-off points for severity scores were decided prior to the analysis based on clinical discussion and previous work. Univariate and multivariate analyses were used to identify factors associated with 90-day survival. Only variables available on the day of ICU admission were entered into a forward multivariate Cox model stratified by center. At the first step of variable selection, either the SAPS II or the LOD score was entered. The accuracy of the two nonnested models was compared using the Akaike Information Criterion (AIC).[12] The best model was defined as that with the lower AIC value. Results were expressed as hazard ratios (HRs) with their 95% CIs and *P* values. For continuous variables (SAPS II), the assumption of linearity was checked using a categorization approach, and the HR was indexed to an increment of 1 unit. Categorical variables were recorded as absent or present.

Results

Patient Characteristics

We included 105 patients; only two patients were excluded because of missing data. Table 1 reports the main characteristics of the remaining 103 patients. Median follow-up in survivors was 109 days (IQR, 33-227 days). At 3 months, 7 (7%) patients were lost to follow-up.

At referral for ICU admission, 32 (31%) patients were from the ED, eight (8%) were transported to the hospital from home by an emergency mobile unit, and 63 (61%) were from the hospital wards. Most of the patients had squamous cell carcinoma or adenocarcinoma that was not resectable. In general, the patients had few comorbidities (median modified CCI, 1; IQR, 0-2) and a good performance status (ECOG-PS ≤ 2 in 75% of patients). The main reasons for ICU admission are shown in Table 2.

ICU mortality was 31%, and in-hospital mortality was 48%. The Kaplan-Meier estimates of 90-day and 1-year survival rates were 37% (95% CI, 28%-46%) and 12% (95% CI, 6%-18%), respectively, with no differences among the three centers. Among the 71 (69%) patients discharged alive from the ICU, median survival after ICU discharge was 104 days (IQR, 18-227 days), estimated 90-day survival was 54% (95% CI, 48%-60%), and estimated 1-year survival was 18% (95% CI, 13%-23%).

The univariate analysis results are reported in Table 3. Mortality after 90 days was not associated with center, age, CCI, time since cancer diagnosis, reason for ICU admission, use of noninvasive MV, or ICU length of stay. Variables where values differed significantly between patients alive and dead after 90 days were ECOG-PS > 2, metastatic disease at ICU admission, need for invasive ventilation or vasoactive drugs within 72 h after ICU admission, and worse severity score (LOD score or SAPS II). Three-month survival was similar in patients who required noninvasive MV (40%) and in those who required no ventilatory assistance

Table 1—*Main Patient Characteristics*

Characteristic	All Patients (N = 103)	Alive at 90 d (n = 35)	Died Within 90 d (n = 61)	Lost to Follow-up[a] (n = 7)
Demographics				
Male sex	79 (77)	29 (37[b])	45 (57)	5 (6)
Age, y	61 (54-68)	60 (52-67)	61 (54-69)	67 (55-72)
ECOG-PS[c]				
0-2	76 (75)	30 (39)	41 (54)	5 (7)
3-4	26 (25)	5 (19)	20 (77)	1 (4)
Modified CCI	1 (0-2)	1 (0-3)	1 (0-2)	2 (1-3)
Cancer history				
Type of cancer				
Squamous cell carcinoma	33 (32)	11 (33)	18 (55)	4 (12)
Adenocarcinoma	26 (25)	7 (27)	18 (69)	1 (4)
Small cell lung cancer	21 (20)	9 (43)	11 (52)	1 (5)
Large cell lung cancer	11 (11)	4 (36)	6 (55)	1 (9)
Other	12 (12)	4 (33)	8 (67)	0 (0)
Extensive disease[c]				
No (I-IIIa)	26 (25)	11 (42)	13 (50)	2 (8)
Yes (IIIb-IV)	76 (75)	24 (32)	47 (62)	5 (6)
Metastasis at ICU admission	63 (61)	15 (24)	42 (67)	6 (9)
Cancer status				
Not yet treated	23 (22)	8 (35)	14 (61)	1 (4)
First-line treatment ongoing	31 (30)	13 (42)	16 (52)	2 (6)
Controlled	11 (11)	5 (46)	4 (36)	2 (18)
Recurrence/progression	20 (19)	6 (30)	14 (70)	0 (0)
Diagnosed in the ICU	18 (18)	3 (17)	13 (72)	2 (1)
Previous anticancer treatments				
Chemotherapy	59 (57)	23 (39)	32 (54)	4 (7)
Radiation therapy	16 (16)	9 (56)	7 (44)	0 (0)
Surgery	17 (1)	8 (47)	7 (41)	2 (12)
No previous anticancer treatment	41 (49)	11 (27)	27 (66)	3 (7)
Time since cancer diagnosis, d	95 (25-251)	152 (40-276)	86 (24-182)	150 (1-1,010)

Data are presented as median (interquartile range) for quantitative data and No. (%) for qualitative data. CCI = Charlson Comorbidity Index; ECOG-PS = Eastern Cooperative Oncology Group performance status.

[a]Seven patients were censored after < 3 mo of follow-up.

[b]Percentage of the overall population for this characteristic.

[c]Data are missing for one patient.

(47%; $P = .71$) but was significantly lower in patients who required endotracheal MV (22%; $P = .02$). The multivariate analysis also is reported in Table 3. With SAPS II in the model, higher SAPS II and ECOG-PS > 2 were associated with 90-day mortality. With the LOD score in the model, higher LOD score, presence of metastatic disease, and ECOG-PS > 2 were associated with 90-day mortality. This last model had a lower AIC value and was therefore selected (Table 3). Kaplan-Meier survival curves comparing low and high ECOG-PS and LOD score values are shown in Figure 1.

During the study period, the Kaplan-Meier estimates of 90-day and 1-year survival rates in all patients with lung cancer managed at the Albert Michallon Teaching Hospital (admitted and not admitted in the ICU) were 90% (95% CI, 87%-92%) and 68% (95% CI, 63%-72%), respectively. In patients with stage I to IIIa lung cancer, these proportions were 96% (95% CI, 93%-98%) and 85% (95% CI, 79%-89%), respectively. In patients with extensive disease, they were 82% (95% CI, 76%-87%) and 44% (95% CI, 37%-52%), respectively. Thus, the occurrence of a critical illness leading to ICU admission was associated with a considerable decrease in survival.

Impact of Organ Dysfunctions at 72 h

Of the 21 (20%) patients with LOD scores > 6 after 72 h, 18 (86%) died in the ICU (Fig 2). The remaining three (14%) had septic or cardiogenic shock that required renal replacement therapy (5 points in the LOD score). Of the 12 (12%) patients whose LOD score decreased during the first 72 h, only one (8%) died in the ICU. Of the 58 (57%) patients whose LOD score remained unchanged during the first 72 h, 17 (29%) died. Of the 31 (31%) patients whose LOD score increased during the first 72 h, 14 (45%) died ($P = .06$).

Impact of Treatment Limitation Decisions

All but seven (7%) patients were admitted to the ICU for unrestricted management. A decision to withhold or withdraw life-sustaining treatment was

Table 2—*Characteristics of the Critical Illnesses*

Characteristic	All Patients (N = 103)	Alive at 90 d (n = 35)	Died Within 90 d (n = 61)	Lost to Follow-up[a] (n = 7)
Reason for ICU admission				
Acute respiratory failure	58 (56)	21 (36[b])	34 (59)	3 (5)
Infection	18 (31)	3 (17)	14 (78)	1 (5)
Airway obstruction	9 (16)	3 (33)	4 (45)	2 (22)
Obstruction by the tumor	7 (78)	2 (29)	4 (57)	1 (14)
Superior vena cava syndrome	2 (3)	0 (0)	2 (100)	0 (0)
Pneumothorax	7 (12)	5 (71)	2 (29)	0 (0)
Pulmonary embolism	4 (7)	1 (25)	3 (75)	0 (0)
Pleural effusion	4 (7)	1 (25)	3 (75)	0 (0)
Hemoptysis	4 (7)	1 (25)	3 (75)	0 (0)
Acute pulmonary edema	4 (7)	4 (100)	0 (0)	0 (0)
Other	6 (10)	3 (50)	3 (50)	0 (0)
Shock	27 (26)	7 (26)	17 (63)	3 (11)
Septic	11 (41)	1 (9)	9 (82)	1 (9)
Cardiogenic	6 (22)	2 (33)	3 (50)	1 (17)
Other	10 (37)	4 (40)	5 (50)	1 (10)
Neurologic complications	7 (7)	3 (43)	3 (43)	1 (14)
Other	11 (11)	4 (36)	7 (64)	0 (0)
LOD score	3 (1-4)	1(0-4)	3 (1-4)	3 (1-5)
Number of organ failures	1 (1-2)	1 (0-1)	2 (1-2)	1 (1-3)
SAPS II	33 (25-46)	26 (22-35)	36 (30-52)	33 (26-46)
Treatments during the first 48 h				
Noninvasive ventilation	20 (19)	8 (40)	11 (55)	1 (5)
Invasive ventilation	41 (40)	9 (22)	30 (73)	2 (5)
Vasoactive drugs	33 (32)	7 (21)	25 (76)	1 (3)
Renal replacement therapy	5 (5)	2 (40)	3 (60)	0 (0)
LOD score on day 3	2 (0-5)	1 (0-4)	3 (1-10)	2 (1-5)
Number of organ failures on day 3	1 (0-3)	1 (0-1)	2 (1-2)	1 (1-2)
ICU length of stay, d	3 (2-7)	4 (2-7)	3 (1-7)	3 (2-6)
Hospital length of stay, d	9 (2-20)	12 (6-22)	6 (2-19)	9 (15-23)

Data are presented as median (interquartile range) for quantitative data and No. (%) for qualitative data. LOD = logistic organ dysfunction; SAPS II = Simplified Acute Physiology Score II.

[a]Seven patients were censored after < 3 mo of follow-up.

[b]Percentage of the overall population for this characteristic.

implemented in 13 (13%) additional patients on day 3. These 13 patients died before hospital discharge. In all these patients, the LOD score increased over the first 72 h.

Effect on Life After ICU Discharge

Fifty-four (52%) patients were discharged alive from the hospital and followed for a median time of 177 days (IQR, 57-384 days). Among them, six (11%) never returned home, 40 (74%) spent > 50% of the follow-up time at home, 33 (61%) spent > 75% of the follow-up time at home, and 15 (28%) were not readmitted during follow-up except for scheduled treatments.

Discussion

Although our patients with nonresectable lung cancer had acceptable rates of ICU and in-hospital survival (69% and 52%, respectively), survival rates were substantially lower after 90 days and 1 year (37% and 12%, respectively). Patients with lung cancer who had a poor ECOG-PS at baseline or who developed multiorgan failure early after ICU admission had significantly higher mortality rates.

Nevertheless, our data suggest that ICU admission may produce meaningful benefits in some patients. Although we did not measure their quality of life, the patients who were discharged alive from the hospital spent most of their time at home. Previous studies of patients with lung cancer conducted in recent years (2006-2008) showed ICU mortality rates of 22% to 44%.[13-15] Over the past decade, advances in both oncology and intensive care have improved survival in critically ill patients with cancer. Before 2004, ICU mortality rates ranged from 73% to 85%.[16,17] The survival gains are probably ascribable to improvements in the ICU management of critically ill patients with cancer and in their selection for ICU admission.[6,18]

Strengths of our study consist of the relatively large size of the cohort recruited at three centers, exclusion of postoperative patients, and 1-year follow-up data available for nearly all patients. Because patients with lung cancer often are considered too sick to

Table 3—*Univariate and Multivariate Analyses of Factors Associated With 90-d Mortality*

Factor	Univariate Analysis[a]		Multivariate Analysis[a] (Model With SAPS II)		Multivariate Analysis (Model With LOD)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Demographic feature						
Age > 61 y	1.00 (0.60-1.67)	.98	…	…	…	…
Male sex	0.74 (0.41-1.32)	.31	…	…	…	…
Performance status > 2	1.91 (1.10-3.33)	.02	1.96 (1.11-3.46)	.02	2.65 (1.43-4.88)	$<10^{-2}$
Modified CCI	0.61 (0.31-1.16)	.14	…	…	…	…
Cancer history						
Cancer status						
Not yet treated	1.15 (0.63-2.13)	.64	…	…	…	…
First-line treatment ongoing	0.87 (0.48-1.56)	.64	…	…	…	…
Controlled	1.01 (0.61-1.67)	.98	…	…	…	…
Recurrence/progression	1.17 (0.62-2.22)	.63	…	…	…	…
Diagnosed in the ICU	1.09 (0.58-2.03)	.79	…	…	…	…
Metastasis at ICU admission	2.00 (1.14-3.49)	.01	…	…	1.90 (1.08-3.33)	$<10^{-2}$
Cancer diagnosis for > 90 d	0.94 (0.56-1.59)	.82	…	…	…	…
Cancer excision surgery	0.68 (0.32-1.45)	.32	…	…	…	…
Reasons for ICU admission						
Acute respiratory failure[b]	0.90 (0.55-1.5)	.70	…	…	…	…
Shock	1.40 (0.79-2.50)	.25	…	…	…	…
Treatment in the first 72 h						
Invasive ventilation	1.90 (1.13-3.19)	.02	…	…	…	…
Noninvasive ventilation	0.83 (0.45-1.53)	.54	…	…	…	…
Vasoactive drugs	2.27 (1.33-3.87)	$<10^{-2}$	…	…	…	…
Scores at ICU admission			…	…	…	…
LOD, per point	1.17 (1.05-1.29)	$<10^{-2}$	…	…	1.19 (1.08-1.32)	$<10^{-3}$
LOD > 3	1.99 (1.18-3.38)	.01	…	…	…	…
SAPS II, per point	1.03 (1.02-1.05)	$<10^{-4}$	1.03 (1.02-1.05)	10^{-4}	…	…

The Akaike Information Criterion of the model was 376.1 with SAPS II and 366.9 with the LOD score. HR = hazard ratio. See Tables 1 and 2 for expansion of other abbreviations.

[a]Analysis stratified by center.

[b]Refers to the category in Table 2.

benefit from ICU management and therefore are referred for ICU admission infrequently (except for immediate postoperative care), 103 patients constitute a good-sized cohort. Although other studies have evaluated patients with lung cancer admitted to the ICU,[6,14,15,19] this study is the first to provide data on LOD score changes over time.

The retrospective design of the present study is a weakness. Although the study involved several centers, two specialize in treating patients with cancer, and the third is a university hospital. The management of patients with lung cancer in these centers may not accurately reflect usual care. Furthermore, we included only patients who were admitted to the ICU. This select population of patients is expected to benefit from ICU admission and to have a better prognosis than the overall population of patients with nonresectable lung cancer. In addition, the decision to admit patients to the ICU may be subject to the biases of individual physicians. We do not know the extent to which mortality was influenced by the decision to admit patients to the ICU as opposed to the natural history of the disease. A prospective study is needed to evaluate triage policies and prognosis in all patients with lung cancer and organ failure.

The challenge, therefore, is to identify those patients with lung cancer who are likely to benefit from ICU admission. Performance status and severity of the acute critical illness (SAPS II or LOD score) were the main prognostic factors in our study.[20-22] By multivariate analysis with the LOD score in the model, we found that 90-day mortality was affected by the ECOG-PS, presence of metastatic disease,[13] and an LOD score > 3 at ICU admission.[13,20] In a retrospective study of patients with cancer admitted to the ICU between 2001 and 2005, the only variable independently associated with 30-day mortality was an ECOG-PS of 3 to 4.[23] It is also interesting to note the parallel with the eligibility for chemotherapy when ECOG-PS is < 3.[24,25] Cancer spread had a smaller impact,[14,26] although the presence of metastatic disease was independently associated with mortality. Interestingly, adequate tumor control as evaluated by the oncologists was not associated with mortality. Tumor-related factors had a considerably smaller impact on the prognosis of critically ill patients with

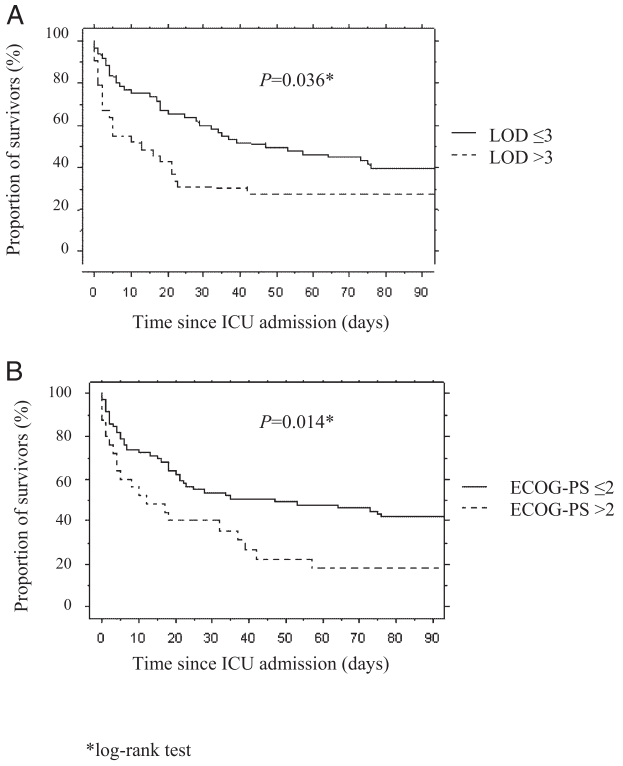

FIGURE 1. A, Probability of survival at 90 days according to the LOD score. B, Probability of survival at 90 days according to the ECOG-PS. Kaplan-Meier curve of survival in patients with nonresectable lung cancer admitted to the ICU according to acute illness severity at ICU admission (LOD score) and ECOG-PS. *Log-rank test. ECOG-PS = Eastern Cooperative Oncology Group performance status; LOD = logistic organ dysfunction.

advanced cancer than factors related to the acute disease.[27,28] Severity scores (SAPS II and APACHE II [acute physiology and chronic health evaluation]) at ICU admission have been studied extensively and found often to be associated with mortality. Nevertheless, these scores perform poorly for making ICU admission or other treatment decisions in individual patients.[29] In a prospective study, only 20% of physicians' predictions about the survival of terminally ill patients were accurate, with 63% of the predictions being overly optimistic and 17% overly pessimistic.[30] Interestingly, among patients on MV, noninvasive ventilation was associated with a lower mortality rate.[31] A study of 23 patients with cancer receiving palliative care and experiencing severe acute respiratory failure showed that noninvasive ventilation was successful in ensuring resolution of the acute episode, provided the cause of the respiratory failure was reversible.[32] Survival results from a database study of critically ill patients with cancer indicated that the use of MV generally should not be restricted.[33] However, the study population chiefly comprised surgical patients, and the encouraging results may not apply to other patients with cancer.

In patients with cancer but without factors indicating that ICU management would be futile, a reasonable strategy consists of ICU admission with unrestricted care for a limited period of time. The patient's situation is reappraised if the patient and family are willing.[33,34] After 48 to 72 h, the treatment strategy should be reevaluated based on the response to unrestricted management, but this recommendation is subject to further study. In our study, an LOD score > 6 after 48 h was associated with death, except in three patients whose organ dysfunctions were stabilized but who still required dialysis on day 3. Thus, an LOD score > 6 suggests that life-supporting treatment may not be beneficial. In addition to the absolute LOD score value, the change over time is of interest. A decrease in the LOD score over the first 48 h was associated with ICU survival in 92% of patients compared with only 55% of patients whose LOD score increased.

CONCLUSIONS

In a select population of patients with nonresectable lung cancer, ICU admission was followed by a 37%

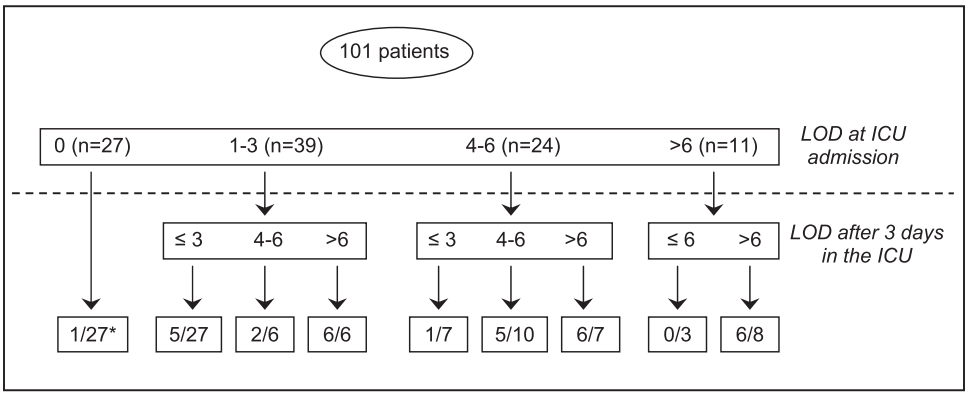

FIGURE 2. ICU mortality according to LOD score evolution (data missing for two patients). Description of the characteristics of the LOD scores at ICU admission and after 3 days in the ICU. *Number of patients who died/total number of patients. See Figure 1 legend for expansion of abbreviation.

90-day survival rate. This survival rate is similar to that reported in ICU patients with any type of malignant disease. Factors associated with survival were an ECOG-PS >2, nonmetastatic disease, and an admission LOD score ≤ 3. ECOG-PS was the main prognostic factor, except when the acute disease was very severe. This study provides the first data on the course of organ dysfunction over the first 3 ICU days in patients with nonresectable lung cancer. Further LOD score deterioration over the first 3 days suggests a need for considering treatment limitation.

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