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European Journal of Cancer 39 (2003) 783–792

European Journal of Cancer

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Outcome analysis of 189 consecutive cancer patients referred to the intensive care unit as emergencies during a 2-year period☆

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Received 11 November 2002; accepted 13 November 2002

Abstract

The referral of critically ill cancer patients to an intensive care unit (ICU) is a matter of controversial debate. This study was conducted by an interdisciplinary clinical group to evaluate the outcome of ICU treatment in cancer patients according to their characteristics at the time of referral. A retrospective analysis was used to identify relevant subgroups among 189 consecutive cancer patients referred as emergencies to one of four ICUs during a 2-year period. Reasons for ICU referral were pneumonia (29.6%), sepsis (27.0%), fungal infection (11.1%), another infection (9.5%), gastrointestinal emergency (16.9%), treatment-related organ toxicity (6.9%), or other, non-infectious complications (43.9%). Vasopressor support was required in 50.3%, mechanical ventilation in 49.7%, and haemodialysis/-filtration in 26.5% of the patients. Overall, 41.3% died during ICU treatment, 12.2% died after transfer from ICU to a non-ICU ward, and 35.4% were discharged alive. Sepsis, mechanical ventilation, vasopressor support, renal replacement therapy and neutropenia were independent risk factors for fatal outcome, but no single risk factor unequivocally predicted death. All patients with fungal infection who required vasopressor support and either had sepsis ($n=13$) or needed mechanical ventilation ($n=14$) died during ICU treatment, while all non-septic patients. who did not require mechanical ventilation, were younger than 74 years of age and had a non-infectious underlying complication ($n=29$), survived. This analysis may help to early identify relevant subgroups of cancer patients with different prognoses under ICU treatment. A prospective study to confirm the predictive usefulness of this approach is needed. Cancer patients should not be excluded from referral to the intensive care unit in an emergency solely due to their underlying malignant disease or a single unfavourable prognostic factor.

Keywords: Intensive care; Risk factors; Fungal infection; Sepsis; Neutropenia; Decision-tree analysis; Prognosis

1. Introduction

Patients with malignancies who are referred to an intensive care unit (ICU) in an emergency are considered to have an extremely poor prognosis with respect to survival of ICU treatment and intermediate-term survival after transfer to non-ICU wards. Studies

☆ This paper was given as an oral presentation at the European Conference on Cancer and Clinical Oncology, ECCO-XI, Lisbon, 21–27 October 2001.

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doi:10.1016/S0959-8049(03)00004-2

published during the past two decades have reported fatality rates of up to 98% in defined subgroups of patients (Table 1), particularly in those requiring mechanical ventilation after allogeneic bone marrow or peripheral blood stem cell transplantation [1–5], those with failure of more than two organ systems [6,7], those with acute renal failure due to sepsis [8,9] or those with a very poor Acute Physiology and Chronic Health Evaluation (APACHE-II) score [10–13].

As a consequence, institution of ICU treatment procedures in cancer patients has been subject to much debate [8,14–17] or explicitly discouraged for distinct subgroups of cancer patients [1,3,18–20]. In contrast, it has been argued that patients with malignant diseases treated with curative intention should be admitted to an ICU with a higher priority than patients with incurable chronic degenerative diseases [21]. At the same time, it has been shown that the anticipated poor prognosis of cancer patients may result in a negative bias among those involved and thereby may have an adverse impact on the success rates in pts. requiring cardiopulmonary resuscitation [22,23].

Since haematologists and oncologists who have been previously treating the patients rarely manage critical care units, there may also arise an additional bias among ICU personnel, resulting in considerable disagreement on treatment requirements. This disagreement is likely to result in considerable stress being placed on the patients affected, their families, nursing staff and physicians.

Information given to patients who are to be enrolled in antineoplastic treatment or haematopoietic stem cell transplant procedures as well as the informed consent obtained from those patients do not necessarily contain explicit information regarding eventual emergencies. Not least, decisions made by physicians regarding the institution and limitation of critical care treatment procedures may be markedly influenced by legal considerations, in particular the risk of prosecution in cases of intentional treatment terminations.

In an attempt to facilitate an interdisciplinary approach to treating cancer patients requiring ICU support in our hospitals, we retrospectively analysed the outcome of patients referred to the ICU as an emergency during a 2-year period.

Table 1
Fatality rates reported for cancer patients requiring ICU treatment

Authors	*n*	Setting	Fatality rate (%)
Bonfirm and colleagues [1]	90	MV post-SCT	98
Groeger and colleagues [14]	782	MV in cancer	76
Price and colleagues [15]	115	ICU post-SCT	54
Tremblay and colleagues [11]	32	MV in AML	97
Faber-Langendoen and colleagues [3]	191	MV post-BMT	90
Paz and colleagues [4]	36	ICU post-BMT	67
Afessa and colleagues [6]	35	ICU post-BMT	77

ICU, intensive care unit; MV, mechanical ventilation; SCT, haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; BMT, bone marrow transplantation.

2. Patients and methods

The Charité University Hospital is a 2500-bed Medical School of the Humboldt University of Berlin with three separate sites including three adult haematology/oncology departments, three adult marrow/blood stem cell transplant units and four ICUs involved in the treatment of patients with malignancies. The ICUs are operated by cardiologists (ICU #1), internal intensive care specialists (ICU #2), anaesthesiologists (ICU #3) and both surgical oncologists and anaesthesiologists (ICU #4). All patients with haematological or oncological diseases who were admitted to one of these four intensive care units were identified by evaluation of the consecutive admission files during 1998 and 1999. Patients electively admitted for postoperative care and other non-emergency indications were excluded from the analysis. Parameters evaluated were: age, gender, underlying malignant disorder, most recent anticancer treatment, presence of neutropenia (defined as granulocyte count below 1000 per cubic millimetre), duration of ICU stay, duration of hospitalisation, reason for ICU admission, requirement of vasopressor support (i.e. administration of dopamine, epinephrine or norepinephrine), haemodialysis or haemofiltration, and the need for mechanical ventilation. In addition, patient records were checked for written instructions given by the patients defining the limitation of their medical treatment. Outcome was analysed with respect to death during ICU treatment, death in hospital after transfer from ICU to a non-ICU ward, and discharge alive from hospital.

Sepsis was defined according to Bone and colleagues [24]. A possible, probable or proven fungal infection was defined according to the criteria proposed by the consensus paper of the Invasive Fungal Infection Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group of the National Institutes of Allergy and Infectious Diseases [25].

The indication for intubation and mechanical ventilation was based upon the appraisal of the ICU professionals.

2.1. Statistical methods

Risk factors for death during ICU treatment were calculated by univariate as well as by multivariate analysis using a logistic regression. For each analysis within the logistic regression model, the total number of cases, selected cases, and valid cases were calculated. The

decision tree learning method for approximating discrete-valued functions was applied according to Ripley [26]. The root of a tree was the top node, and parameters were passed down the tree, with decisions being made at each node until a terminal node or leaf was reached. Each non-terminal node contained one question on which a split was based. Each leaf contained the label of a classification. Since each parameter was being classified by the label of the leaf it reaches with a distinct probability, the classification tree partitioned the space of possible observations (i.e. patient data sets) into subregions corresponding to the leaves.

The entropy based decision tree learning methods search a completely expressive hypothesis space and thus avoid the difficulties of restricted hypothesis spaces. The inductive bias is a preference for small trees over large trees. Additional techniques for improving the predictive accuracy were 'boosting' and 'cost functions'. The accuracy is measured in connection with n-fold cross-validation. The cases in the data file were divided into n blocks of roughly the same size and class distribution (here, $n=10$). For each block in turn, a classifier was constructed from the cases in the remaining blocks and tested on the cases in the hold-out block. In this way, each case was used just once as a test case. The error rate of a classifier produced from all the cases was estimated as the ratio of the total number of errors on the hold-out cases to the total number of cases [26]. Cost function was used to calculate decision trees for which the total cost of misclassification was minimised. A boosting procedure [27] was applied to achieve a higher predictive accuracy at the expense of increased classifier construction time. For this purpose, a single decision tree or rule-set was constructed as described above. Since this classifier will usually make mistakes on some cases in the data and the first decision tree possibly gives the wrong class for some cases, a second classifier is constructed giving more attention to these cases. The third classifier focused upon errors to be expected on some cases due to the second classifier. This process was continued for a predetermined number of iterations.

Decision trees were generated by entropy based methods and cross-checked by various statistical tests (calculation of P values). A F test was used for continuous variables. For nominal variables, the Pearson Chi-squared test or the likelihood-ratio tests was used. An association model and the likelihood-ratio test were applied for ordinal target variables.

The results of the analysis were not used for individual therapeutic decisions.

3. Results

From a total of 189 patients evaluable, 103 (54.5%) had a solid tumour, 32 (16.9%) malignant lymphoma, 23 (12.2%) acute myeloid leukaemia, 8 (4.2%) multiple myeloma, 5 (2.6%) acute lymphoblastic leukaemia, and 18 (9.5%) another malignancy such as chronic myeloid leukaemia or myelodysplastic syndrome. Median age was 62 years (range 18–96 years), 102 patients (54.0%) were male. 60 patients (31.7% of the total) had undergone conventional chemotherapy, 51 (27.0%) surgery, 27 (14.3%) high-dose therapy followed by stem cell transplantation, and 17 (9.0%) radiotherapy as their most recent therapeutic procedure, whereas 34 patients (18.0%) had not received specific anticancer treatment before ICU admission. 53 patients (28.0% of the total) were neutropenic at the time of their ICU admission. The reason for ICU referral was pneumonia in 56 (29.6%), sepsis in 51 (27.0%), fungal infection in 21 (11.1%), another infection in 18 (9.5%), gastrointestinal emergency in 32 (16.9%), treatment-related organ toxicity in 13 (6.9%), and another, non-infectious complication in 83 (43.9%) patients. Vasopressor support was required in 95 (50.3%), mechanical ventilation in 94 (49.7%), and haemodialysis or haemofiltration in 50 (26.5%) patients.

Of 189 patients, 78 (41.3%) died during ICU treatment, 23 (12.2%) died after transfer from ICU to a non-ICU ward, and 67 (35.4%) could be discharged alive from hospital (Table 2). For 21 patients (11.1%), no information about their outcome was available after their transfer from the ICU to another ward. Autopsy was performed in 33 patients, i.e. 32.7% of the 101 patients who died in hospital. Among 51 patients who had undergone surgery as their most recent therapeutic intervention, ICU mortality was 27.4% compared with 46.4% among non-surgical patients ($P=0.029$). The overall results broken down for different patient characteristics are depicted in Table 3.

Sepsis, mechanical ventilation, vasopressor support, renal replacement therapy and neutropenia were significantly correlated with an increased risk of death during ICU treatment, whereas the presence of organ toxicity from preceding cancer treatment was significantly predictive for survival. In a logistic regression analysis, vasopressor support and mechanical ventilation ($P<0.0001$, each) were identified as independent risk factors most strongly predicting fatal outcome during ICU treatment, whereas treatment-related organ

Table 2
Overall results

	n	(%)
Death in ICU	78	(41.3)
Death in hospital after discharge from ICU	23	(12.2)
Discharged alive from ICU, lost to follow-up	21	(11.1)
Discharged alive from hospital	67	(35.4)
Total	189	(100.0)

ICU, intensive care unit.

toxicity and pretreatment by surgical oncology significantly predicted a favourable outcome ($P = 0.0495$ and 0.029, respectively) (Table 4). The median duration of mechanical ventilation was 9.4 days in patients who died in the ICU compared with 9.8 days in patients who survived the ICU treatment period ($P = 0.87$). The underlying disease was not an independent prognostic factor with regard to the outcome of ICU treatment.

Entering different prognostic factors into a prediction model for the outcome of ICU treatment, requirement of vasopressor support predicted ICU outcome with an accuracy of 79.0% (sensitivity, 74.0%, specificity, 86.1%). This predictive power could only be increased to 83.5% (sensitivity, 84.6%, specificity, 81.9%) by sequential

Table 3
Treatment results related to patient characteristics

	n	Death in ICU (%)	Documented hospital mortality (%)
Fungal infection	21	71.4	76.2
Sepsis	51	62.7	72.5
Pneumonia	56	55.4	67.9
Abdominal infection	6	66.7	66.7
Other infection	12	33.3	50.0
Gastrointestinal complication	32	21.9	40.6
Other, non-infectious complication	83	34.9	45.8
Treatment-related organ toxicity	13	15.4	30.8
Neutropenia	53	54.7	67.9
Vasopressor support	95	69.5	72.6
Mechanical ventilation	94	68.1	72.3
Haemodialysis or haemofiltration	50	60.0	66.0

Table 4
Death in ICU: adverse prognostic factors

Factor	*n*	Fatal outcome (%)	*P* Value
Sepsis	51	62.8 versus 33.3	0.0003
Vasopressor support	95	69.5 versus 12.1	<0.0001
Mechanical ventilation	94	68.1 versus 13.8	<0.0001
Neutropenia	53	54.7 versus 35.8	0.0180
Treatment-related organ toxicity	13	15.4 versus 43.2	0.0495
Surgical treatment	51	27.4 versus 46.4	0.029
Haemodialysis/haemofiltration	50	60.0 versus 34.6	0.0018
Total	189	41.3	

Fatal outcome was analysed by comparing mortality rates in patients with versus without the presence of the respective prognostic factor.

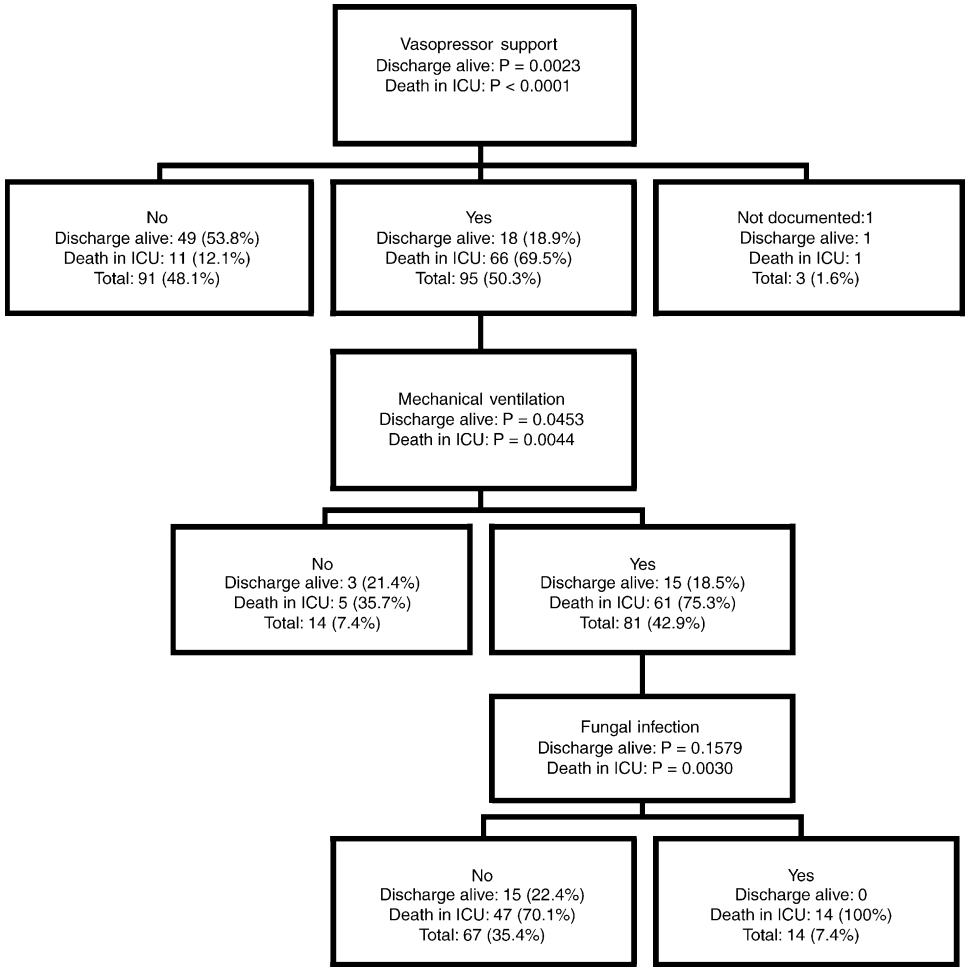

Fig. 1. Decision-tree analysis of ICU survival in patients requiring vasopressor support.

supplementation of other prognostic parameters such as mechanical ventilation, treatment-related organ toxicity, gender and haemodialysis or haemofiltration.

Using a decision tree analysis, subgroups of patients were identified who had particularly poor or markedly favourable outcomes depending on their individual patterns of risk factors, type of complication or intensive care procedure applied. Requirement of vasopressor support was the most significant single factor predicting ICU mortality (69.5 versus 12.1% ICU mortality, $P<0.0001$). Of the 95 patients who required vasopressor support (Fig. 1), 81 were on mechanical ventilation, whereas 14 were not. The ICU mortality rate showed a significant difference in favour of the non-ventilated patients (ICU mortality rate, 75.3 versus 35.7%, $P=0.0044$). Of the 81 patients with vasopressor support and mechanical ventilation, the underlying complication was fungal infection in 14. These 14 patients had a mortality rate of 100% compared with 70.1% in the 67 patients with an underlying complication other than fungal infection ($P=0.003$) (Fig. 1).

Neutropenia was present in 53 of 189 (28.0%) patients (Fig. 2), and was identified as significant factor predicting for ICU mortality (death rate, 54.7 versus 35.8%, $P<0.018$). In neutropenic patients who required mechanical ventilation ($n=36$), ICU mortality rate in these patients was significantly higher compared with the 17 neutropenic patients not being ventilated (ICU mortality rate, 72.2 versus 17.6%, $P=0.0001$). The underlying complication among neutropenic, ventilated patients was fungal infection in 11 patients, of whom only 1 survived (Fig. 2).

Of 134 non-neutropenic patients, 21 (11.1%) had sepsis (Fig. 3). Their ICU mortality rate (66.7%) was significantly higher compared with the 113 non-neutropenic patients without sepsis (mortality rate, 30.1%, $P=0.0017$). However, the subgroup of non-neutropenic patients with sepsis who did not require mechanical ventilation ($n=6$) had a significantly lower ICU mortality compared with those who underwent mechanical ventilation ($n=15$) (ICU mortality rates, 16.7 versus 86.7%, $P=0.002$) (Fig. 3).

Sepsis with or without its sequelae was diagnosed in 51 patients (Fig. 4) Their ICU mortality was 62.7% compared with 33.3% in patients without sepsis ($P<0.0003$). In patients with sepsis, the need for vasopressor support was significantly correlated with fatal outcome ($P<0.0001$). In 13 patients with invasive fungal infection as their reason for sepsis and vasopressor support, mortality rate was 100%, compared with other reasons (mortality rate, 65.5%, $P=0.003$). There was no significant difference in the ICU mortality rates of sepsis

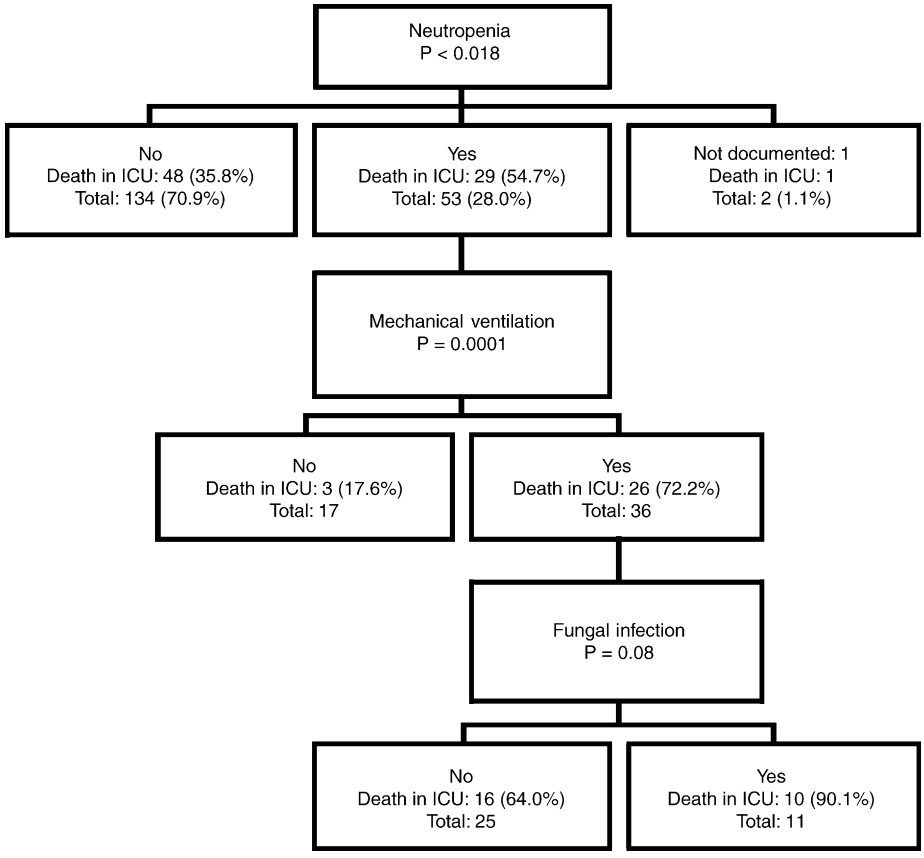

Fig. 2. Decision-tree analysis of ICU survival related to presence or absence of neutropenia (part 1).

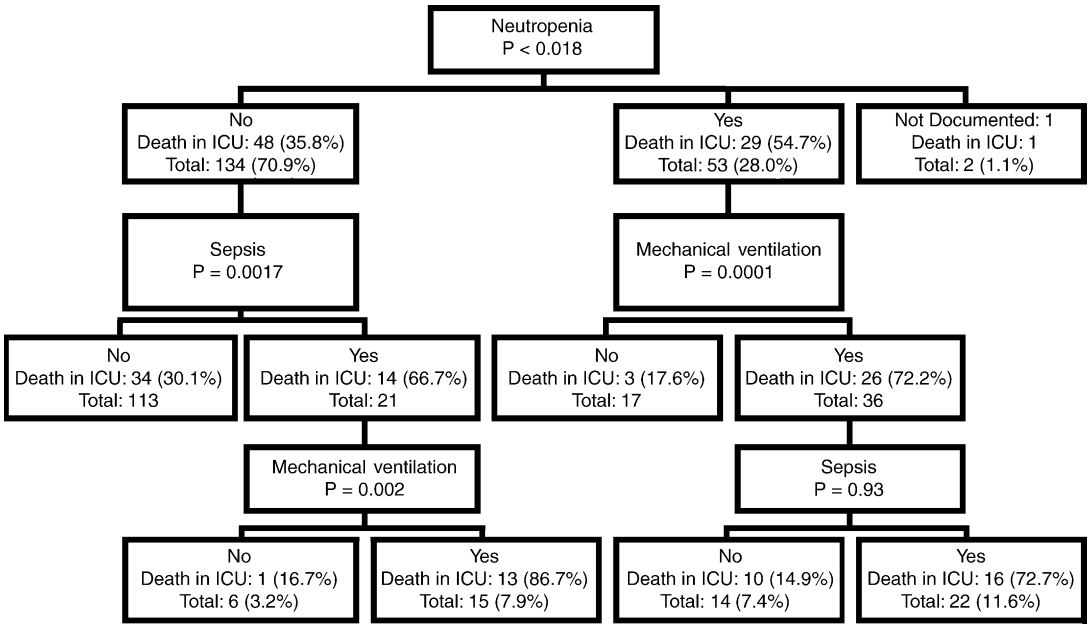

Fig. 3. Decision-tree analysis of ICU survival related to presence or absence of neutropenia (part 2).

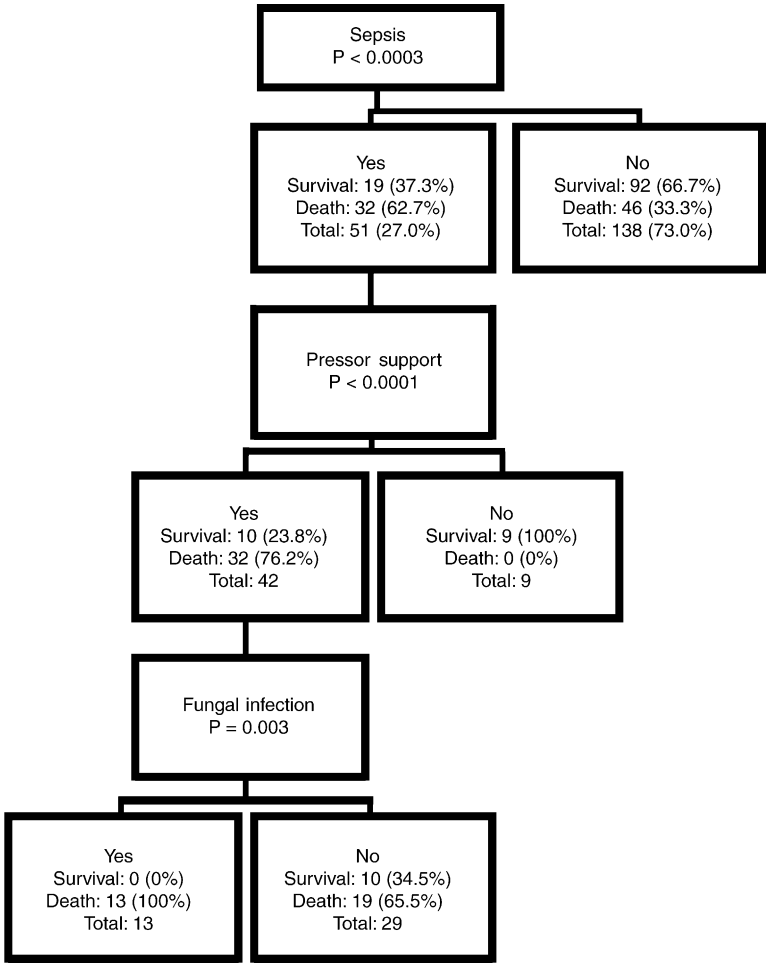

Fig. 4. Decision-tree analysis of ICU survival in patients with sepsis.

patients with neutropenia ($n=30$) compared with non-neutropenic patients ($n=21$, mortality rates, 60.0 versus 66.7%, $P=0.63$) (Fig. 4).

Patients without sepsis ($n=138$) had an ICU survival rate of 66.7% (Fig. 5). Those who did not require mechanical ventilation ($n=80$), had an ICU survival rate of 87.5%, compared with non-septic, mechanically ventilated patients ($n=57$) who had an ICU survival rate of 38.6% ($P<0.0001$). Among the non-septic, non-ventilated patients, 61 were younger than 74 years of age. The ICU survival rate in this subgroup was 93.4%. If this group was further analysed for the type of underlying complication, a 100% survival rate among 29 patients with a non-infectious complication was found (Fig. 5).

A prognostic model optimised for the prediction of death during ICU treatment was derived from these data by a boosting procedure based upon 10 entropy-based, inductive learning procedures. Of 78 patients who died during ICU treatment, death was predicted by this model in 74 (94.9%). The 4 patients who died, but for whom survival would have been predicted by this model, were re-evaluated for their individual ICU course. In all 4 patients, no vasopressor support and no

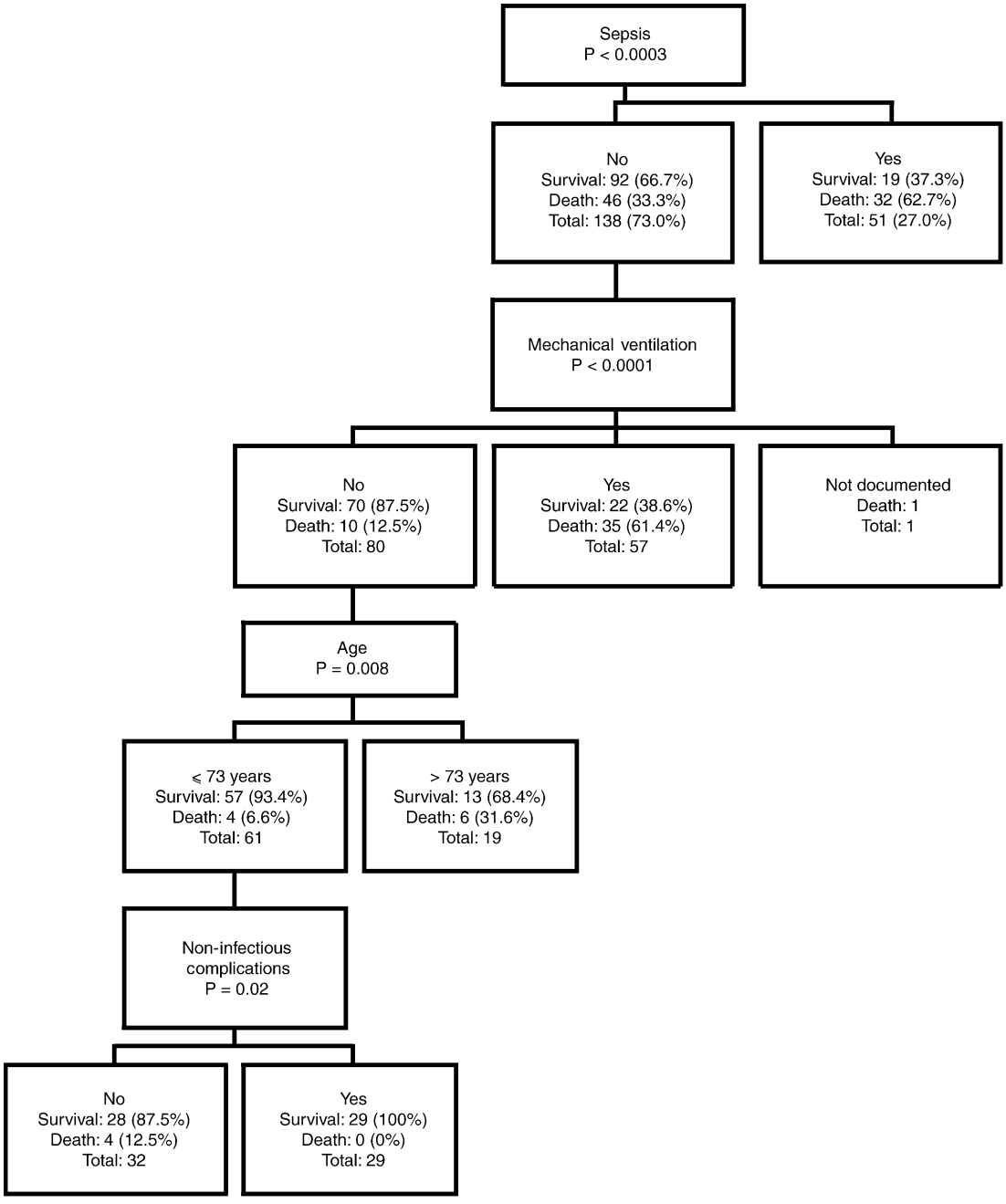

Fig. 5. Decision-tree analysis of ICU survival in patients without sepsis.

mechanical ventilation was performed due to their older age (69, 78, 81 and 96 years, respectively) and/or their poor short-term prognosis due to their underlying malignancy.

A written instruction given by patients specifying their will concerning the extent and duration of intensive care procedures in case of a life-threatening emergency was found in the records of 6 of 189 patients (3.2%).

4. Discussion

In accordance with other reports [4,14,15], the results of our analysis indicate that the presence of an underlying malignancy in itself does not inevitably predict unfavourable outcome of intensive care procedures and therefore does not justify the exclusion of critically ill cancer patients from these procedures. This study might also help to reduce/avoid any adverse bias with regard to the effectiveness of the efforts of critical care personnel. It should be interesting to compare the outcome observed in cancer patients to that of patients with non-malignant diseases undergoing ICU treatment in ICU wards during the same time period evaluated, and match the results with the prognosis of their underlying diseases [23]. Analysing patient subgroups by a mathematical decision-tree technique, we could not identify a single factor that was unequivocally correlated with a fatal outcome so, from our perspective, no patient included in this retrospective analysis should not have been referred to an ICU for a single, specific factor. We did not, however, evaluate how many cancer patients during this 2-year period have never been referred to the ICU because of their poor prognosis or their explicit refusal to undergo critical care management.

The negative prognostic impact of haemodialysis or haemofiltration, which was associated with a 60% mortality rate in our study, has also been observed by Lanore and colleagues [9] who described a 72% overall mortality rate in 43 patients with haematological malignancies undergoing haemodialysis. In their multivariate analysis of prognostic factors, they underlined that among these patients, only the presence of sepsis, the need for mechanical ventilation, and an unfavourable performance score predicted for poor outcome. These findings match well our observations and indicate that the need for renal replacement therapy in itself is not an independent risk factor with respect to mortality in patients with haematological malignancies.

Our study confirms that the necessity of mechanical ventilation is a significant prognostic parameter predicting poor outcome of ICU treatment. In our cohort, 64 (68.1%) of 94 patients undergoing mechanical ventilation died during their ICU treatment, and another 5 patients (5.3%) died after extubation and discharge from the ICU. This is in accordance with the results reported by Groeger and colleagues [6] on a larger number of mechanically ventilated cancer patients ($n = 782$), who had a 76% hospital mortality rate. The availability of non-invasive mask ventilation (NIMV) in many institutions with critical care patients has allowed intubation and mechanical ventilation to be avoided in some cases. In our hospital, only patients undergoing allogeneic bone marrow or peripheral blood stem cell transplantation were offered prophylactic training of the use of NIMV. As a consequence of favourable results reported in the literature [28], our group has encouraged activities to establish NIMV in order to prevent progressive respiratory failure and intubation in cancer patients at high risk of respiratory failure, e.g. from invasive pulmonary fungal infections.

As reported by other authors, vasopressor support has been the most significant single parameter predicting unfavourable outcome in our study. However, here, as well as in other reports, vasopressor support was not further specified with respect to indication, dose, time and substances administered. Thus, it cannot be excluded that in individual cases the administration of vasopressors has reflected imminent death rather than indicating the risk of fatal outcome. This important differentiation will therefore be specified in our future documentation system.

Because of the retrospective approach, dynamic parameters such as the duration of mechanical ventilation have not been considered here. Prolonged mechanical ventilation has been reported to be associated with a particularly poor outcome [20]. However, other investigators have not confirmed this parameter as an independent, adverse prognostic factor [5,8]. For clinical decision-making, the response over time to mechanical ventilation among patients with respiratory failure is likely to be a useful criterion to help decide whether treatment should be escalated or limited. Therefore, our prospective documentation system will precisely record these data in the future.

Although we did not investigate the prognostic impact of the number of organ systems affected by dysfunction, it can be assumed that the requirement of mechanical ventilation and vasopressor support is a surrogate for multi-organ dysfunction. Therefore, we believe that our findings confirm the prognostic impact of multi-organ dysfunction reported by others [6,7].

Prognostic scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE-II) [13] or Simplified Acute Physiology score (SAPS-II) [29] have been found to be of predictive value in cancer patients undergoing ICU treatment [9,10,30]. Since the four ICUs participating in this retrospective analysis did not utilise the same documentation procedures, we have not included those scores in our retrospective data analysis in order to avoid entering arbitrary data into the

database. For future documentation, the SAPS-II [29,31] and the Sepsis-related Organ Failure Assessment (SOFA) score [32,33] will be recorded daily to enable comparability of data from different institutions. It must be considered, however, that these scoring systems may not precisely reflect the prognostic status of patients with malignancies, but will more likely underestimate their fatality rate [15].

Invasive fungal infection (IFI) was diagnosed in 21 patients in our cohort and was associated with a 71.4% rate of ICU mortality, indicating that IFI necessitating ICU treatment is not inevitably fatal. As in the study by Janssen and colleagues [34], who reported a 92% mortality rate in patients with invasive aspergillosis, a small number of patients with this high-risk condition may be salvaged by ICU procedures. It might be argued that invasive fungal infections are not definitely proven in our study. However, in clinical practice it is usual that the diagnosis of an IFI is not clearly proven at the time a decision on initiating critical care treatment is made. Treatment decisions in these patients are based upon clinical evidence, eventually supplemented by imaging techniques [35] and non-culture based procedures [36–38] which at present are validated in clinical studies with respect to their accuracy in confirming the diagnosis of IFI.

Written instructions regarding the extent and limitation of critical care procedures in cases of a life-threatening emergency have been obtained from a small number of cancer patients included in our analysis. Those instructions may facilitate therapeutic decisions, particularly for physicians not involved in the previous treatment of an individual patient [39]. However, they do not necessarily reflect the present state of mind of the affected patients, who may exhibit marked fluctuations in their will to live [40]. This must be carefully taken into consideration. Moreover, in our study, we did not analyse the number of patients with very advanced malignancies who were not referred to the ICU because of their explicit decision not to undergo critical care procedures.

We conclude from these data that cancer patients, provided that they have not recently given their explicit statement to refuse ICU treatment, should be considered for referral to the intensive care unit in an emergency. It may be justified, however, to decide against ICU treatment in patients with invasive fungal infections requiring vasopressor support and mechanical ventilation. Before our retrospective data analysis will be considered for individual therapeutic decisions, a prospective validation of a documentation system based upon the most significant prognostic parameters is essential.

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