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Outcome of Hemato-oncologic Patients with and without Stem Cell Transplantation in a Medical ICU

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Abstract

Objective: To assess the outcome of a mixed population of critical ill patients with haematological malignancies with special focus on the comparison of patients who underwent stem cell transplantation with non-transplanted patients.

Methods: Retrospective, unicentric analysis of 94 critical ill cancer patients in a tertiary care centre in a period of two years time.

Results: We analysed different variables at admission as well as different treatment modalities during the ICU stay. We compared the outcome by using chi-square test by Pearson for categorical variables and Kaplan-Meier as well as Cox-Regression for survival analysis. The general patients characteristics did not significantly differ between transplanted and non-transplanted patients. The overall ICU and hospital mortality were 43% and 54%. Considering just patients with mechanical ventilation we found ICU and hospital mortalities of 65% and 82% in the stem cell transplantation group vs. 67% and 74% in the non-transplanted group, respectively. As risk factors for overall mortality in multivariate analysis only the Simplified Acute Physiology Scale II and the need of ventilation remained significant. Between the underlying diseases mortality did not show significant differences at all.

Conclusions: The outcome and prognosis of critical ill cancer patients has generally slightly improved over the last years. Our data show no statistically significant differences regarding outcome and prognosis between stem cell transplanted and non-transplanted patients receiving ICU treatment. A stem cell transplantation should not be considered a strong contraindication for ICU treatment or artificial ventilation.

Key words: Hematologic malignancy, stem cell transplantation, critical care, intensive care unit, outcome, mortality.

Introduction

The prognosis and outcome in patients with hemato-oncologic malignancies has substantially improved over the last years. Better treatment modalities including intensified treatment protocols as well as advanced supportive therapies have led to an improved survival. Bone marrow or peripheral stem cell transplantation (SCT) has become an established part of many treatment regimes. The use of more aggressive therapies has led to an increase of disease- or therapy-related complications with the need of consecutive intensive care treatment [1].

The prognosis and outcome of cancer patients admitted to the intensive care unit (ICU) is still considered to be poor [2-25]. Respiratory failure with mechanical ventilation or multi-organ-failure are associated with high mortality rates over 80% [9, 11, 12, 14, 21, 25]. Stem cell transplantation itself is regarded as a negative prognostic factor with high mortality rates [4, 7, 8, 10, 13, 16, 17, 20, 22, 23, 24]. In several retrospective analyses further risk factors for high mortality were identified, i.e. high age [11], unresponsive malignancy [11, 14, 15] or hepatic failure [26]. The mortality rates of recent studies are lower in comparison to older studies.

Several scoring systems have been analysed to predict the outcome of hematologic patients in the ICU. Common ICU scores like the Acute Physiology and Chronic Health Evaluation (APACHE) II, III or the Simplified Acute Physiology Scale (SAPS) II have been used to predict the outcome of critical ill cancer patients in several studies [17, 27, 28-30]. However, having been developed for general ICU populations they have not been validated especially for cancer patients. Some data show that the Apache III Score is significantly associated to the survival of patients receiving allogeneic SCT [31]. Specific scores for critical ill cancer patients have been developed but did not find general acceptance because of their complexity [32].

Few studies on the outcome of critical ill cancer patients identified predictive factors or prognostic indicators at all [8, 22, 34-37].

The aim of our study was to asses the outcome including ICU- and hospital-mortality in a mixed group of hemato-oncologic patients, who were admitted to the ICU. Special focus was the comparison between patients who received a SCT and non-transplanted cancer patients regarding the outcome as well as the reasons of admission to the ICU, different treatment modalities and further factors.

Methods and Statistics

Patients: We performed a retrospective analysis at a medical intensive care unit in a university hospital. We screened all charts from patients with a hemato-oncologic malignancy, who where admitted from the H/O

department to the ICU from January 1, 2002, until December 31, 2003. All patients were treated by the intensive care staff members in cooperation with the attending hematologists. In this period we collected data of 94 patients from their flow charts as well as from the hospital computer data base. Complete laboratory values were available in 82 out of 94 patients, in patients with lab values missing for the calculation of the scores, scores were censored left sided.

Regarding the hemato-oncologic diagnosis we included patients with acute leukaemia, myeloproliferative syndrome, lymphoma, myeloma and patients with solid tumors, who received high dose chemotherapy. We included patients after allogeneic (n = 18) as well as autologous transplantation (n = 10) without further differentiation to avoid small group sizes. Stem cell transplantation (SCT) was performed with standardized protocols for routine indications as well as in clinical trials. Therefore four patients with solid tumors where included in our study as well. We analysed hereby a quite heterogenous patient group regarding diagnoses, which was however well comparable regarding treatment modalities. Besides that mortality in our patient group differed only one percent when comparing it to mortality of all patients excluding those four with solid tumors. For stem cell source peripheral blood stem cells were used in all cases. Patients with autologous SCT received high dose chemotherapy for conditioning in all cases. Patients with allogeneic SCT received standard conditioning including total body irridation plus high dose cyclophosphamide in 50% (n = 9) or a reduced intensity protocol with fludarabin, BCNU and melphalan in also 50% (n = 9). Immunosuppression was performed with cyclosporin and methotrexate or mycophenolatmofetil.

Table 1. Patients characteristics at the time of transfer to the medical intensive care unit with comparison of stem cell transplanted - patients and non - stem cell transplanted - patients.

	All patients (n = 94)	**SCT-patients (n = 28)**	**Non-SCT-patients (n = 66)**	**P value**
Demographics				
Age, yr, median (range)	61.0 (22 – 88)	47.0 (22 – 63)	67.5 (29-88)	0.032
Sex, female	41	11	30	0.581
Time of intensive care treatment				
Days, median (range)	4.5 (1-60)	3.0 (1-56)	5.0 (1-60)	0.582
Scores				
APACHE II, median (range)	19.0 (5 – 46)	17.5 (5 – 38)	20.5 (8 – 46)	0.100
SAPS II, median (range)	47.5 (15-107)	40.0 (15 –102)	51.5 (16 – 107)	0.228
Type of hemato-oncologic malignancy				0.289
Acute leukemia	32	8	24	
Myeloproliferative syndromes	14	6	8	
Lymphoma	30	6	24	
Myeloma	14	5	9	
Solid tumors	4	3	1	
Blood cell count				
WBC (1000/nl), median (range)	4.73 (0.03-291.00)	4.03 (0.03-79.38)	5.05 (0.03-291.00)	0.341
WBC < 1000/nl	26	4	22	
WBC 1000-4000/nl	13	7	6	
WBC 4000-12000/nl	18	7	11	
WBC > 12000/nl	25	4	21	
RBC (g/dl), median (range)	9.1 (2.8-16.4)	8.9 (5.1-16.4)	9.2 (2.8-13.8)	0.744
Hemoglobin 0-6 g/dl	5	2	3	
Hemoglobin 6-12 g/dl	70	19	51	
Hemoglobin > 12 g/dl	7	1	6	
Causes of admission				0.357
Cardiopulmonary resuscitation	7	2	5	
Sepsis	17	1	16	
Respiratory failure	21	8	13	
Neurologic disorders	13	5	8	
Metabolic impairment	8	3	5	
Hemodynamic instability	16	6	10	
Intensive care monitoring	12	3	9	

SCT, Stem Cell Transplantation; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Scale; WBC, white blood cell count; RBC, red blood cell count.

Table 2. Comparison of different treatment modalities between stem cell transplanted and non - stem cell transplanted - patients.

Need of	All patients (n = 94) (%)	SCT-patients (n = 28) (%)	Non-SCT-patients (n = 66) (%)	P value
Ventilation	56 (59.6	17 (60.7)	39 (59.1)	0.883
No need of ventilation	38 (40.4)	11 (39.3)	27 (40.1)	
Non invasive ventilation	2 (2.1)	1 (3.6)	1 (1.5)	
Non invasive ventlilation + Invasive ventilation	10 (10.6)	5 (17.9)	5 (7.6)	
Invasive ventilation	54 (57.4)	16 (57,1)	38 (57.6)	
Renal replacement	18 (19.1)	4 (14.3)	14 (21.2)	0.435
CVVH	9 (9.69	3 (10.7)	6 (9.1)	
CVVHD	6 (6.4)	1 (3.6)	5 (7.6)	
Dialysis	3 (2.3)	-	3 (4.5)	
Plasma exchange therapy	4 (4.3)	2 (7.1)	2 (3.0)	0.366
Surgery	21 (22.3)	7 (25.0)	14 (21.2)	0.687
Visceral surgery	13 (13.8)	3 (10.7)	10 (15.2)	
Thoracic surgery	2 (2.1)	-	2 (3.0)	
Neuro surgery	5 (5.3)	3 (10.7)	2 (3.0)	
ENT	1 (1.1)	-	1 (1.5)	

CVVH, chronic veno-venous hemofiltration; CVVHD, chronic veno-venous hemodialysation.

Further parameters included the time in the ICU, white blood cell count and the Acute Physiology and Chronic Health Evaluation (APACHE) II Score as well as the Simplified Acute Physiology Scale (SAPS) II Score [29, 30] at time of admission. Variables collected during the ICU stay included the need of non-invasive and invasive ventilation, the length of ventilation, renal replacement therapy, the use of antimicrobial agents, plasma exchange therapy and operations. ICU mortality and hospital mortality were noted. From patients surviving the hospital stay we evaluated whether they were alive at 100 days after admission, if information could not be collected, the last contact to our hospital was used for survival analysis.

Statistical Analysis: The statistical analysis was made with the SPSS 12.0 statistical software (SPSS inc., Chicago, IL) and Microsoft Excel. Values are shown as total numbers, median with range or as percentages where necessary. The major outcome variables were the ICU and hospital mortalities compared between the SCT and non-SCT patient groups. To compare the differences in baseline characteristics between the two groups we used a chi-square test by Pearson for categorical variables. For the analysis of survival (ICU mortality, overall mortality) Kaplan-Meier analysis was used. All patients were observed until day 100 or censored at the last day of observation. Risk factors for mortality were analysed in a Cox proportional hazard model for overall mortality first in a univariate model. Variables with a significant influence on the hazard ratio were then included in a multivariate model. Patients were stratified due to their status of having received stem cell transplantation or not. A p-value <0.05 was considered statistically significant.

RESULTS

Patient Population: The characteristics from all 94 patients are shown in Table 1. Gender, time of ICU stay, APACHE II and SAPS II scores, as well as degree of neutropenia and anemia did not differ statistically between SCT and non SCT patients. Patients in the SCT group were significantly younger than non SCT patients.

Treatment modalities: We focused our studies on special treatment modalities such as mechanical ventilation, renal replacement therapy, plasma exchange therapy, antibiotic treatment as well as the need of surgery. The complete data is shown in Table 2. Regarding ventilation support we classified whether patients needed non-invasive, invasive or both types of respiratory therapies. A renal replacement therapy was used in 18 patients (19%). A plasma exchange therapy was needed in 4 patients (4%). We had 21 patients (22%) who underwent surgery during their ICU stay. There were no differences between SCT and non SCT patients.

Outcome: Survival analysis by Kaplan Meier comparing stem cell transplanted and non - stem cell transplanted patients is shown in Figure 1. Figure 2 presents survival function according to different hemato-oncologic malignancies with cox regression analysis. Regarding the overall outcome 54 patients from 94 survived the ICU stay, another 13 patients died after transfer back to their oncologic ward in the hospital. This results in an ICU mortality of 43% with a hospital mortality of 56%. 41 patients (44%) survived the entire hospital stay. Comparing SCT- and non-SCT patients there was no significant difference in ICU- and hospital-mortali-

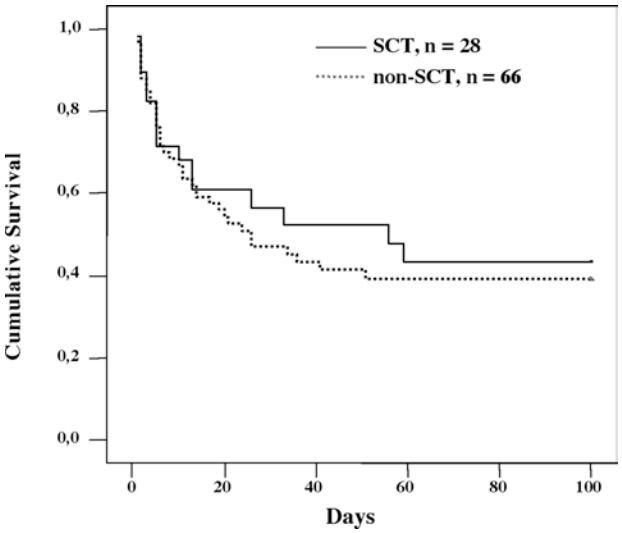

Fig. 1. Survival analysis by Kaplan Meier comparing stem cell transplanted and non - stem cell transplanted patients (p = 0.6536).

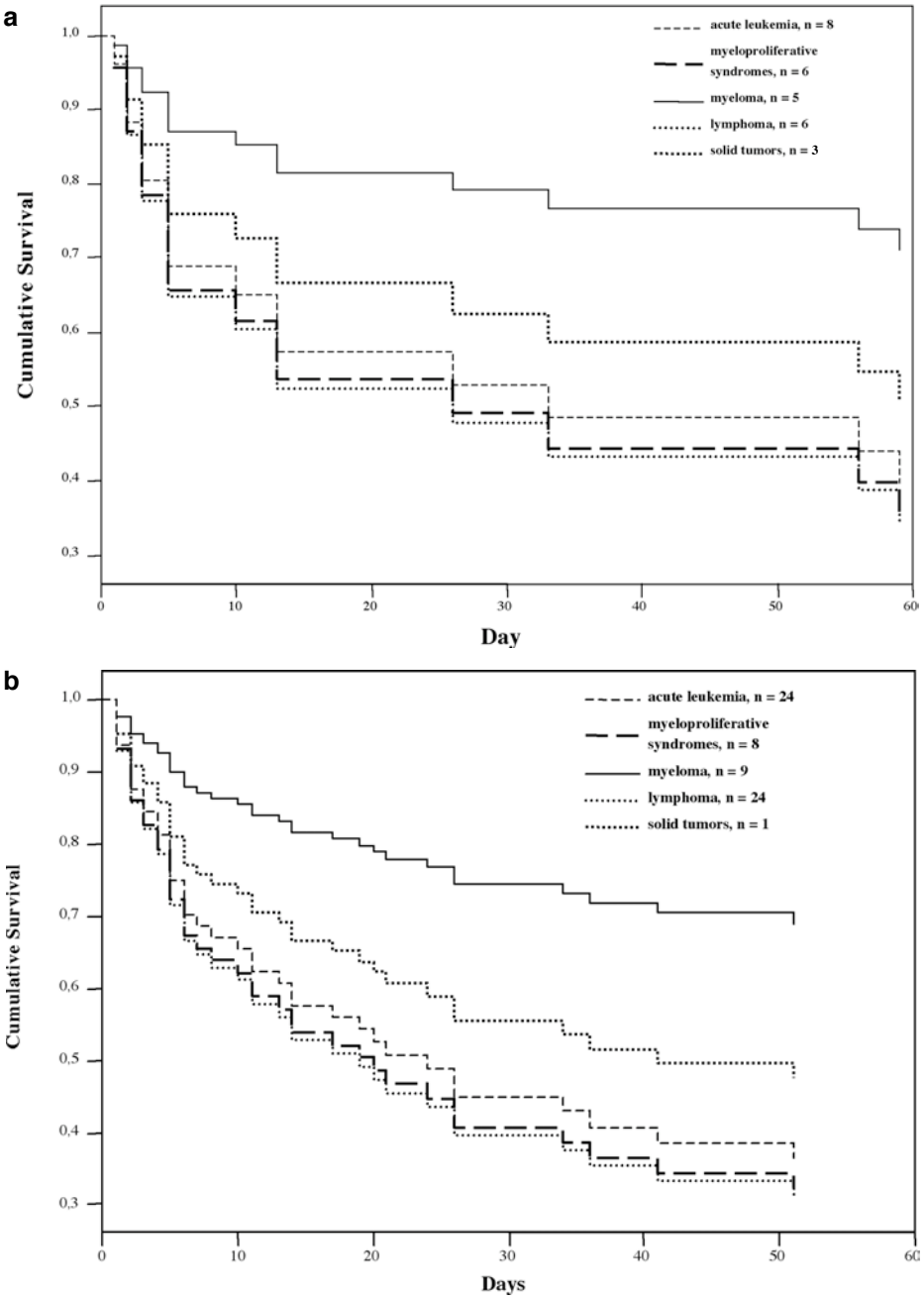

Fig. 2. Survival function of stem cell transplanted patients (a) and non - stem cell transplanted patients (b) due to different hemato-oncologic malignancies with cox regression analysis.

Table 3. Different treatment modalities between stem cell transplanted and non stem cell transplanted - patients and relationship to the outcome.

Mortality	ICU mortality (%)			Hospital mortality (%)			P value
	All (%)	SCT (%)	Non-SCT (%)	All (%)	SCT (%)	Non-SCT (%)	
Ventilation							0.8325
Non invasive ventilation (n=2)	0	0	0	0	0	0	
Non invasive ventlilation + Invasive ventilation (n=10)	100	100	100	100	100	100	
Invasive ventilation (n=54)	69	69	68	80	88	76	
Total ventilation (n=56)	66	65	67	77	82	74	
Renal replacement							0.3769
CVVH (n=9)	89	67	100	89	67	100	
CVVHD (n=6)	100	100	100	100	100	100	
Dialysis (n=3)	0	-	0	0	-	0	
Total (n=18)	78	75	79	78	75	79	
Plasma exchange therapy (n=4)	100	100	100	100	100	100	0.3898
Surgery							0.9276
Visceral surgery (n=13)	38	67	30	69	100	60	
Thoracic surgery (n=2)	50	-	50	50	-	50	
Neuro surgery (n=5)	20	0	50	40	33	50	
ENT (n=1)	0	0	-	100	100	-	
Total (n=21)	33	29	36	62	71	57	

CVVH, chronic veno-venous hemofiltration; CVVHD, chronic veno-venous hemodialysation.

Table 4. Cox proportional hazard model for overall mortality using uni- and multivariate analysis.

Variable	Mono- HR	CI	Multi- HR	CI	p
Age	1.04	1.013-1.073	1.037	1.0-1.08	0.052
Sex	0.79	0.463-1.363	-		
Cause of admission			n.s.		
Intensive care monitoring	1 (Reference)				
Cardiopulmonary Resuscitation	17.2	3.5-85.0			
Sepsis	4.0	0.9-18.5			
Respiratory failure	5.9	1.3- 26.8			
Metabolic impairment	4.8	0.9-26.5			
Neurologic disorders	7.4	1.6-35.5			
Hemodynamic instabilities due to bleeding	5.4	1.2-24.6			
Type of hemato-oncologic malignancy AML vs. others	n.s.		-		
Apache II Score	1.07	1.04-1.10	0.95	0.83-1.01	n.s.
SAPS II Score	1.04	1.03-1.05	1.04	1.02-1.09	0.001
Treatment modalities					
Ventilation	4.52	2.26-9.06	2.87	1.38-5.95	0.005
Surgery	1.07	0.57-2.01	-	-	-
Renal replacement therapy	1.72	0.93-3.18	-	-	-

Mono-HR, monovariate hazard ratio; multi-HR, multivariate hazard ratio; CI, confidence interval; n.s., not significant; AML, acute myelogenous leukaemia; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Scale.

ty of 39% and 54% vs. 44% and 58%. As already mentioned no differentiation between allogeneic and autologous transplanted patients (18 and 10 patients) was made to avoid even smaller group sizes. Regarding just the 10 patients after autologous transplantation the hospital mortality rates are tending to be better than regarding patients after allogeneic transplantation (40% vs. 61%), but there was no significant difference in Kaplan Meier survival analysis ($p = 0.41$).

Treatment related outcome: Regarding ventilation, renal replacement therapy, plasma exchange therapy as well as the need of surgery, there was no difference between the SCT population and the non SCT group (Table 3). With differentiating in the SCT group between allogeneic and autologous transplantation we noticed no significant difference in survival analysis among intubated SCT patients ($p = 0.68$). With patients after autologous transplantation showing just a slight trend for a better outcome in our study we decided to summarize both patients in one group.

Prognostic indicators: For the analysis of prognostic risk factors we performed uni- and multivariate Cox-Regression-analysis. Hazard ratios, 95% confidence intervals and p-values are given in Table 4. Significant risk factors for overall mortality in univariate analysis were age, the cause of admission, the APACHE II score at admission, the SAPS II score at admission, and the need for ventilation support. Although patients with myeloma seem to have a better outcome, mortality did not differ significantly between the different underlying diseases. In multivariate analysis older age did only show a trend towards higher mortality, the SAPS score remained significant with a hazard ratio of 1.04 (an increased risk of 4% for each score point more) and the need for ventilation support with a hazard ratio of 2.87.

Discussion

The aim of our study was to assess the outcome of an unselected group of critical ill patients with hematologic malignancies with special focus on a subpopulation of patients receiving stem cell transplantation. The entire population in our medical ICU showed a mortality of 14% in this period of time (data not shown). The ICU mortality of all 94 cancer patients was 43%, the overall hospital mortality was 56%. This result is comparable to recent published case series [26, 31, 32, 36] and underlines a positive trend towards a better prognosis of cancer patients with the necessity of intensive care treatment. The reasons for this effect may be better treatment of infections, optimised ventilation modalities and patient selection [26, 38].

As severity of illness scoring systems we analysed the APACHE II and the SAPS II scores. Being validated in different patient populations, they may underestimate the mortality risk in critical ill cancer patients [4, 16]. Comparing our patient group with other case series we found lower median values for APACHE II and SAPS II than i.e. Massion et al. [35] or Benoit et al. [36], but comparable or somewhat higher values as well, i.e. compared to Silvast et al. [39]. The median duration at ICU of 4,5 days, the prevalence of ventilation (56%) or renal replacement therapy (18%) is similar compared to other series [34, 35]. The relatively good outcome in our patients may be influenced by the selection of patients before transfer to ICU.

Focussing on patients' characteristics and underlying diseases we had a mixed group with hematologic malignancies as well as solid tumors. The decision to include 4 patients with solid tumors was based on the fact, that treatment regimens of both populations were comparable. Excluding them, results would not change significantly. The causes for admission to the ICU differed from life threatening complications to situations with the need of (postoperative) monitoring. Regarding these facts, we should be cautious comparing our data to other studies with a more selected patient group.

The subpopulation of our SCT group showed an overall ICU survival of 61% and of 35% in ventilated SCT patients, respectively. We found an overall hospital mortality of 46% in transplanted patients and of 82% in transplanted and ventilated patients, compared to a survival of 19% among intubated patients published 7 years ago by Price at al. [22]. In 1993 Paz et all found a mortality of over 90% in ventilated SCT patients [20]. Rubenfeld et al. could demonstrate in the period between 1988 to 1992 an improvement of survival from 5% to 16% of ventilated patients after allogeneic bone marrow transplantation [23]. In consequence the analysis of several studies in different time periods leads to the conclusion that the outcome even in mechanical ventilated cancer patients is improving. Some authors suggest that an increased focus on non-invasive ventilation may trigger these effects [38, 40].

Renal replacement therapy as a risk factor for mortality in critical ill cancer patients has been analysed in several studies before [33-36]. In uni- and multivariate analyses it was shown that its use as an early prognostic indicator generally was not justified whereas in combination with acute liver failure or within multi-organ failure the role as a predictor of death is established.

A mortality of 100% was found in the 7 patients, who received intensive care treatment after primary successful cardio-pulmonary resuscitation. Recently published and our data contradict unjustified reluctance to admit cancer patients with and without SCT to the ICU. However resuscitation may be seen with reservation.

Our study has three major limitations. The retrospective and unicentric design limits its applicability to general cancer patient populations. Furthermore the SCT group with only 28 patients has a small size, limiting the analysis of more risk factors. In addition the differentiation of allogeneic and autologous patients were not meaningful for having very small group sizes.

In conclusion the outcome and prognosis of critical ill cancer patients in general shows an improvement over the last years. The decision to transfer a cancer patient to an ICU should be discussed with all participating colleagues including intensivists, hematologists and if possible the patient and his family. Independent risk factors for cancer patients, which were characterized in several studies before, should be mentioned,

but the aspect of life quality should be integrated into the decision. Intensive care conditions do undergo permanent changes and improvements, which optimises treatment modalities of critical ill cancer patients and therefore requires regular re-evaluations of the policy regarding ICU treatment [41]. In our setting the risk factor of stem cell transplantation, which has been analysed in several studies before, should not be overestimated. Our data does not show statistically significant differences regarding outcome and prognosis between autologous or allogeneic transplanted and non-transplanted patients receiving ICU treatment. Further investigations in prospective multicentric studies with larger SCT patient groups and accurate analysis of different factors are necessary.

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