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Original Article

Survival of Critically Ill Older Patients with Haematological Malignancies

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SUMMARY

Background: For a significant majority of cancers age is a major risk factor. The aim of our study was to investigate survival of older patients admitted to an intensive care unit (ICU) with underlying haematological malignancy and compare them to younger patients.
Matherials and methods: A prospective observational study was carried out in Vilnius University Hospital Santaros Klinikos from 2017 to 2019. Patients were categorized into two groups: younger (< 65 years) and older (≥ 65 years), depending on age on admission to ICU.
Results: 114 patients were included in the study. There were 61 (53.51%) patients in the younger patient group and 53 (46.49%) patients in the older patient group. The older patient group had more chronic heart failure (34.0% vs. 11.5%), vascular disease (67.9% vs. 21.3%), poor physical performance status (39.6% vs. 13.1%) and higher APACHE II scores (23.34 vs. 20.31). Younger patients more often received intensive chemotherapy (57.4% vs. 39.6%). The proportion of patients for whom SOFA score increased over the first 48 hours in ICU also qSOFA and SOFA scores did not differ between the groups. Both groups received the same amount of organ support therapies such as vasopressors, invasive mechanical ventilation, and renal replacement therapy. We found that age did not influence survival of the patients as there was no difference in ICU, 30 days and overall mortality between the groups.
Conclusion: Age group does not influence survival of critically ill oncohaematological patients, and it shouldn't be the criteria for eligibility to the ICU.

1. Introduction

It is expected that the share of Europeans over 65 will increase to just below one-third of the total population by 2060, with those aged over 80 comprising 11.5%.[1] As such, the burden on health care will continue to mount due to the increased health issues of the older population and the challenges in management they bring.

For a significant majority of cancers, such as both non-Hodgkin and Hodgkin lymphomas and chronic myeloid leukemias, age is a major risk factor.[2] Moreover, in the UK, the median age of patients with haematological cancer is 70 years.[3] Similar trends can be observed in the USA, where the median age of patients with acute myeloid leukemia and acute leukemias of ambiguous lineage is 66 and 73 years, respectively.[4]

Over the last three decades, a notable increase in survival among patients diagnosed with haemato-oncological disease has been reported.[5–7] These improvements have been seen among all age groups, albeit to a lesser degree in the elderly.[8] The resulting increase in survival, combined with toxic treatment complications and a general increase of cases due to the aging population, means that these patients will be more often referred to intensivists.

While there has been a surge of investigations on assessing geriatric patients with underlying haematological malignancies, none of these put emphasis on critically unwell patients.[9–11] Historically, many of these patients have been denied treatment on the grounds of advanced age and poor prognosis secondary to underlying oncological illness. Yet, given the changes in treatment options and resulting overall survival, this might not be the case anymore.

The aim of our study was to investigate the outcomes and trends in older patients admitted to an intensive care unit (ICU) with underlying haematological malignancy and compare them to younger patients.

2. Materials and methods

A prospective observational study was carried out in Vilnius University Hospital Santaros Klinikos from 2017 to 2019. Vilnius Regional Biomedical Research Ethics Committee approval was received with inclusion criteria: transfer to the ICU; confirmed haematological malignancy (codes C80–C96 and D45–D47 of International Statistical Classification of Diseases and Related Health Problems 10th Revision WHO Version for 2016); age > 18 years on the day of admission to the ICU; central line or arterial line inserted or planned to be inserted within three hours after transfer to the ICU; signed informed consent form. All study participants signed informed consent form. If patients were unable to sign the consent form, their next-of-kin were

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approached. Transfers to the ICU were initiated by a haematologist, and the patients were accepted by the ICU doctor on call. The study did not influence the acceptance of a patient to the ICU. The chemotherapy regimen was classified as intensive, depending on possible myelosuppression and pharmacological toxicity. Previous medical history and follow-up were recorded from the patients' electronic medical notes. Charlson's comorbidity index, qSOFA, and SOFA scores were calculated on the patients' first day in the ICU, and the SOFA score calculation was repeated on each of the subsequent four days in the ICU. Invasive mechanical ventilation, use of vasopressors, and renal replacement therapy were initiated by the ICU doctor in charge according to standard practice. Patients were categorized into two groups: younger (< 65 years) and older (≥ 65 years), depending on age on admission to ICU.

2.1. Statistics

The normality of the distribution was assessed with the Kolmogorov-Smirnov test. We used a Student's *t*-test to evaluate the differences between the two independent normally distributed variables and Mann-Whitney U test for non-normally distributed variables. The difference between two independent qualitative data groups was evaluated with the Chi-squared test. Fisher's exact test was used to evaluate the differences between the small-size independent categorical data groups. Survival was analysed using the Kaplan-Meier method. A two-tailed p-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using the Statistical Analysis System (SAS Institute, Cary, North Carolina, USA) package version 9.2.

3. Results

There were 227 admissions to the ICU during the study period, with 183 original patients, of which 114 (62.30%) were included in the study. Reasons for exclusion are provided in supplemental Table 1. There were 61 (53.51%) patients in the younger patient group and 53 (46.49%) patients in the older patient group. Patient characteristics are provided in Table 1. The older patient group had a higher proportion of women (54.7% vs. 32.8%), more patients with chronic heart failure (34.0% vs. 11.5%), vascular disease (67.9% vs. 13 21.3%), and poor physical performance status (39.6% vs. 13.1%); they also had higher APACHE II scores (23.34 vs. 20.31). Younger patients more often received intensive chemotherapy (57.4% vs. 39.6%) and bone marrow transplantation (45.9 vs. 20.8%). The majority of patients were admitted to ICU from haematological wards. The proportion of patients for whom SOFA score increased over the first 48 hours in ICU also the results of qSOFA and SOFA scores did not differ between the groups (Table 2). Both groups received the same amount of organ support therapies such as vasopressors, invasive mechanical ventilation, and renal replacement therapy. We found that age did not influence survival of critically ill oncohaematological patients as there was no difference in ICU, 30 days and overall mortality between the groups (Figure 1).

4. Discussion

We evaluated the association between age groups and survival of critically ill oncohaematological patients. Our findings showed that age group did not influence neither short nor long-term survival which encourages to extend usage of ICU resources for older patients with blood cancer.

It is known that large proportion of patients with haematological malignancies are older, but strict eligibility criteria make it very difficult for these patients to participate in clinical trials,[12] which slows down the progress of cancer treatment in this population. New drugs[13] and new treatment regimens[14–16] have been developed for older patients with acute myeloid leukemia (AML) as an alternative to aggressive chemotherapy. It is known that under-treatment is

Table 1
Demographic characteristics.

	< 65 years (n = 61, 53.51%)	≥ 65 years (n = 53, 46.49%)	p value
Female	20 (32.8)	29 (54.7)	0.023
Disease			
AL	31 (50.8)	23 (43.4)	0.208
NHL	17 (27.9)	11 (20.8)	
MM	6 (9.8)	7 (13.2)	
CL	2 (3.3)	9 (17.0)	
HL	2 (3.3)	2 (3.8)	
AA	1 (1.6)	0	
Other	2 (3.3)	1 (1.9)	
High risk malignancy	45 (73.8)	34 (64.2)	0.312
Treatment naïve	6 (9.8)	5 (9.4)	1.000
Intensive chemotherapy	35 (57.4)	21 (39.6)	0.050
Conditioning chemotherapy	20 (32.78)	3 (5.66)	0.002
BMT	28 (45.9)	11 (20.8)	0.006
Allo-BMT	20 (32.8)	5 (9.4)	0.007
Chronic health (according to Charlsons)			
Heart	7 (11.5)	18 (34.0)	0.006
Vascular	13 (21.3)	36 (67.9)	< 0.001
Respiratory	1 (1.6)	0	1.000
Endocrine	6 (9.8)	12 (22.6)	0.075
Renal	3 (4.9)	7 (13.2)	0.184
Movement	6 (9.8)	4 (7.5)	0.749
ECOG 0–2	53 (86.9)	32 (60.4)	0.002
ECOG ≥ 3	8 (13.1)	21 (39.6)	

AA, aplastic anaemia; AL, acute leukemia; Allo-BMT, allogeneic bone marrow transplant; BMT, bone marrow transplant; CCI, Charlson Comorbidity Index Groups; CL, chronic leukemias; ECOG, Eastern Cooperative Oncology Group Performance Status; HL, Hodgkin's lymphoma; MM, multiple myeloma; NHL, Non-Hodgkin's lymphoma.

Table 2
Characteristics in ICU.

	< 65 years (n = 61, 53.51%)	≥ 65 years (n = 53, 46.49%)	p value
Source of admission to ICU			
Haematological wards	42 (68.9)	35 (66.0)	0.882
General haematology	27 (44.26)	29 (54.72)	
Bone marrow transplant	15 (24.59)	4 (7.55)	
Emergency department	8 (13.1)	8 (15.1)	
Department of internal medicine	4 (6.56)	5 (9.43)	
Department of immunocompromised patients	7 (11.48)	5 (9.43)	
Reason for ICU admission			
Acute respiratory failure	24 (39.34)	24 (45.28)	0.521
Shock	13 (21.31)	10 (18.87)	0.7457
Neurological dysfunction	7 (11.48)	7 (13.21)	0.7838
Sepsis	3 (4.92)	4 (7.55)	0.7029
Multiple organ failure	3 (4.92)	3 (5.66)	1.000
Observation after surgery	3 (4.92)	2 (3.77)	1.000
Other	8 (13.11)	3 (5.66)	0.2166
Length of stay before ICU	24.31 ± 29.18	16.43 ± 39.81	0.237
Length of stay in ICU	6.16 ± 4.78	7.32 ± 6.17	0.271
APACHE II (mean ± SD)	20.31 ± 5.68	23.34 ± 5.29	0.004
SAPS 3 (mean ± SD)	73.25 ± 12.65	77.04 ± 13.79	0.131
qSOFA score 0	10 (16.4)	6 (11.3)	0.790
qSOFA score 1	28 (45.9)	26 (49.1)	
qSOFA score 2	13 (21.3)	14 (26.4)	
qSOFA score 3	10 (16.4)	7 (13.2)	
SOFA score day 1 (mean)	6.56	6.56	
SOFA score day 1 in ICU 0–4	14 (23.0)	17 (32.1)	0.367
SOFA score day 1 in ICU 5–9	37 (60.7)	25 (47.2)	
SOFA score day 1 in ICU 10–20	10 (16.4)	11 (20.8)	
SOFA score increased over first 48 hours in ICU	34 (55.7)	32 (60.4)	0.796
Absolute neutrophil count < 0.5×10^9/l	25 (41.0)	19 (35.8)	0.698
Absolute platelet count < 50×10^9/l	23 (37.7)	16 (30.2)	0.434
Invasive mechanical ventilation	36 (59.0)	27 (50.9)	0.452
Vasopressors	47 (77.0)	39 (73.6)	0.828
Renal replacement therapy	18 (29.5)	14 (26.4)	0.835
Number of organ dysfunction			
0	2	2	0.184
1	5	9	
2	21	8	
3	17	14	
4	3	6	
5	1	0	
n/d	12	14	
Organ support			
0	9 (14.75)	11 (20.75)	0.871
1	16 (26.23)	13 (24.53)	
2	24 (39.34)	19 (35.85)	
3	12 (19.67)	10 (18.87)	
ICU mortality	31 (50.82)	20 (37.74)	0.191
30-day mortality	37 (60.66)	26 (49.06)	
90-day mortality	43 (70.49)	31 (58.49)	
180-day mortality	46 (75.41)	34 (64.15)	
Overall mortality	48 (78.69)	37 (69.81)	

APACHE II, The Acute Physiology and Chronic Health Evaluation severity score 2nd edition; ICU, intensive care unit; qSOFA, quick Sepsis Related Organ Failure Assessment; SAPS 3, The Simplified Acute Physiology Score 3rd edition; SOFA, Sequential Organ Failure Assessment score.

still common in geriatric oncology.[17] Survival of patients with AML older than 60 years is worse compared with younger patients.[4] A large study of patients with ovarian cancer found that older women had more residual disease after surgery, and they received fewer cycles of chemotherapy.[18] Our study showed that younger patients more often received intensive chemotherapy and bone marrow transplants compared with older patients who also had more comorbidities and worse performance status, which prevented them from being candidates for intensive chemotherapy. For older adults with newly diagnosed AML, the American Society of Hematology recommends offering antileukemic therapy over best supportive care.[19] The eligibility for ICU of older patients even without cancer varies from 5.6% to 38.8%, depending on the ICU team which reviews the patient.[20] Some countries have a consensus for acceptance of older patients with cancer depending on the prognosis for the long-term survival with the underlying malignancy.[21] It was also found that older critically ill oncological patients had similar mortality rates compared to those without cancer.[22] We want to emphasize that haematological patients not only have higher chances of oncological emergencies such as tumor lysis syndrome, but also the nature of haematological malignancies makes them different compared with solid tumours. Early intensive treatment is of prime im-

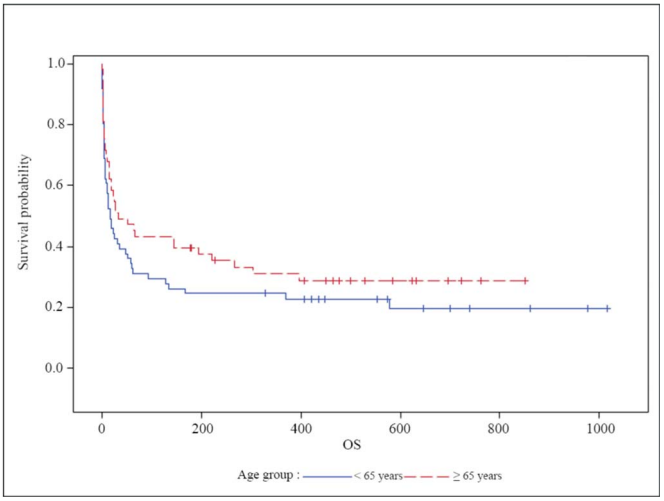

Figure 1. Overall survival of patients according to the age groups. Kaplan-Meier curves for overall survival (days) of patients according to age groups. OS, overall survival.

portance and even preemtive treatment in ICU is beneficial in cases of aggressive leukemias and hyperleukocytosis. Studies showed that direct admission to the ICU of patients with high-risk AML with physiological disturbances but no organ dysfunction was associated with improved outcomes.[23,24] In our study, the oldest patient was 85 years old, and 16.67% of patients were older than 75 years. None of the patients were refused treatment in ICU solely because of age. The proportion of older and younger patients was the same. There were no treatment withdrawals or limitations. None of these patients had a "do not resuscitate" status.

Our study found that neither chronic health conditions nor the main haematological diagnosis influenced the outcome of critically ill oncohaematological patients. We observed more patients with chronic heart and vascular disease in the older patient group. Almost 40% of patients in the older patient group were ECOG $\geq$ 3. The APACHE II score was found to be higher in the older patient group in our study. This is explained by the fact that age is one of the components in the APACHE II scoring system. The difference in APACHE II scores between the groups was 3 points, reflecting the difference in scores given for the age groups. There was no difference between the groups in SOFA scores and increase in SOFA scores over the first 48 hours in ICU. This shows that patients in both groups had the same level of organ dysfunction, which resulted in no differences in survival. There is little data in the literature regarding the extent of treatment intensity in ICU for older patients. We didn't find a difference in treatment intensity between the groups: vasopressors, invasive mechanical ventilation, and renal replacement therapy were used for 73.6%, 50.9%, and 26.4% of older patients, respectively. In two recent studies, the use of vasopressors ranged from 12.9% to 56.4%, and the use of invasive mechanical ventilation ranged from 33.4% to 71.9%.[25,26]

Survival of critically ill older patients varies widely, from 21.8% to 58.5%.[25,27] The large French study in which 10% of all participants had active cancer found that mortality rates increased progressively with age and more sharply in those 80 years and older. However, compared with the general population matched by age and sex, excess long-term mortality was high in young surviving patients but not in older patients. Older patients who survived to hospital discharge had a life expectancy much closer to that of the age-matched general population.[28] It is very difficult to compare ICU mortality of critically ill older oncohaematological patients among different countries because there are huge differences in eligibility and acceptance criteria together with varied treatment courses in ICU. There are also differences in definition of age groups and study methodologies. We did not find any studies which solely analyse the survival of older critically ill oncohaematological patients. Apart from that, there is extremely limited data on survival of critically ill older patients, even those with any sort of cancer. Data differ even within countries. In one study of critically ill older patients with cancer done in Brazil, ICU mortality was 53.8%,[22] while another large study in 94 ICUs in Brazil of patients aged 80 years or older with active cancer observed hospital mortality of 39.2%.[29] The French study which analysed older patients with solid tumors admitted to ICU over the 10-year period observed lower ICU mortality of 22.2% and one-year mortality of 41.3%.[26] Our study found that age did not influence ICU survival. There was a trend of better survival in older patient group. The reasons for that might be that younger patients more often received aggressive chemotherapy regimens and bone marrow transplantations. When we analyzed chemotherapies further, we found that conditioning regiments used for allogeneic bone marrow transplantation made 57.14% of intensive chemotherapies in younger patient group compared with only 14.29% in older patient group. These treatment modalities result not only in profound immunosuppression but also have higher toxicity and complications associated with it. Another reason is graft versus host disease (GVHD). There were only two patients (3.77%) older than 65 years who had GVHD both of which were controlled and both patients were discharged alive from ICU. Whereas GVHD was diagnosed in 23% of younger patients and in nine cases (14.8%) it was uncontrolled or refractory to treatment what makes prognosis of these patients very poor. Unfortunately, seven of them died in ICU.

The weakness of our study is that our patient cohort had only eight participants who were more than 80 years old when they were admitted to ICU; thus, we lack survival data for very old patients. On the other hand, our study provides a single-centre experience. Every year approximately 100 patients with haematological malignancies are admitted to ICU, and conducting a high-volume single-centre study is very difficult.

The strength of our study is that we did not need to factor in treatment limitations or withdrawal of treatment in ICU. We were able to observe the pathway of the patients with the use of maximum therapy. Another strength is that our study was prospective and had a long median follow-up of 553 days.

We hope that the results of our study will change the perception of older oncohaematological patient eligibility to ICU, providing more hope for older patients and increasing chances of their acceptance to ICU.

5. Conclusions

Age group does not influence survival of critically ill oncohaematological patients, and it shouldn't be the criteria for eligibility to the ICU. We need to look closely at haematological prognosis, thorough discussion of treatment choices in ICU, and, most importantly, wishes of patients and their families.

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Declaration of potential financial and non-financial conflicts of interest

All authors confirm that they don't have any competing financial and non-financial conflicts of interest.

Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=21.

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