The Charlson Comorbidity Index Predicts Poor Prognosis in Elderly AML Patients

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ABSTRACT

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults and patients older than 65 years have a poor prognosis. Patient-related factors, such as comorbid conditions that affect performance status, and insufficient organ functions, explain why elderly patients have a worse prognosis. The Charlson Comorbidity Index (CCI), is used to predict prognosis according to comorbidities. This retrospective study was conducted on patients diagnosed with AML between 2010 and 2019. Patients >60 years were included. Demographic information, comorbidities, CCI, ECOG (Eastern Cooperative Oncology Group) score, cytogenetic characteristics, treatment regimens, treatment response, follow-up periods were recorded for all patients. Evaluation was made of a total of 82 patients with a mean age of 71.18 ± 7.67. The median follow-up was 6.7 months. The median number of comorbidities was 1 [0.0-4.0] with the median CCI score of 3 [2.0-6.0]. Median overall survival (OS) was 7.0 months [3.1-10.8] and PFS was 6.8 months [3.6-10.0]. As the median CCI score was 3, patients were divided into two groups as CCI > 3 and CCI ≤ 3. Age, gender, ECOG, cytogenetic risk profile, first-line treatment and CR1 achievement status were all similar in both groups ($p > 0.05$). Patients with CCI > 3 had significantly shorter OS than patients with CCI ≤ 3 (3.6 months [0.3-29.3] vs 8.6 months [0.2-60.2], $p= 0.049$). The results of the current study demonstrated that CCI, can be used as a prognostic index in elderly patients with AML independently of other patient and disease-related characteristics.

Keywords: AML, Elderly, Comorbidity, Charlson, Prognosis

INTRODUCTION

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with an estimated incidence of >20,000 new cases diagnosed per year, of which >10,000 do not survive.[1,2] The pathogenesis can be defined as abnormal proliferation and differentiation of the clonal population of myeloid stem cells. Chromosomal aberrations and molecular changes have been identified in the development of AML.[3] It is a common disease in patients older than 65 years, and has a poor prognosis in this population.[4-7] One of the strongest disease-specific risk factors is chromosomal aberrations, whereas age is the most substantial patient-specific risk factor.[8] Patient-related factors, such as comorbid conditions that affect performance status, and abnormal organ functions, explain why elderly patients have a worse prognosis.[9-12]

The Charlson Comorbidity Index (CCI) is used to predict prognosis according to comorbid conditions of the patients.[13] It is one of the most widely-used and studied comorbidity indexes. The widespread use of this index can be explained by the fact that it is not intended for patients with a particular disease.

The CCI is also a practical way to register data in administrative databases.[14-20] Performance status (PS) of a patient, which is an independent prognostic indicator, evaluates capability of self-care and functions that play a key role in treatment decisions for malignant patients. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status (KPS) scores are commonly used for assessing PS in patients in both clinical trials and real-life cancer treatments.[21,22]

The aim of this study was to determine the prognostic value of comorbidity and performance status for elderly patients with AML admitted to our hematology department.

PATIENTS AND METHODS

This retrospective study was conducted on patients diagnosed with AML in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital between 2010 and 2019. The diagnosis of AML was made according to the World Health Organization criteria including bone marrow (BM) and flow cytometry findings. Patients >60 years were included and patients who were diagnosed with acute promyelocytic leukemia were excluded from the current study due to different management and treatment strategies. Demographic information, specific diagnosis, date of diagnosis, comorbidities, CCI, ECOG score, cytogenetic characteristics, treatment regimens, treatment response and follow-up periods were recorded for patients. At the time of diagnosis, complete blood count (CBC) and hematological parameters including hemoglobin (Hb) level, hematocrit (Hct) level, platelet count, white blood cell count (WBC), albumin, lactate deyhydrogenase (LDH) levels, ferritin and B_{12} vitamin levels were examined. Using these data, demographic and clinical characteristics, response assesments and survival rates were analyzed. The impact of the parameters on survival was analyzed.

Statistical Analysis

SPSS Statistics 20 software (IBM, Armonk, NY, USA) was used for statistical analysis. The Independent Samples t-test was used to compare two independent groups with normal distribution with the measured values (t-table value) and the Mann-Whitney U-test (Z-table value) was applied to data with non-normal distribution. χ^2-cross tables were used to examine the relationships between two qualitative variables. A value of $p< 0.05$ was considered statistically significant. The Kaplan-Meier method was used for survival analysis. Overall survival (OS) was measured from the time of diagnosis to death or until the final visit. Progression-free survival (PFS) was measured from diagnosis to death, disease progression or relapse, whichever was earlier, or until the final visit. The Log-Rank test was applied in the comparisons between groups.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. As a standard of care/action of Ankara Diskapi Yildirim Beyazit Research and Training Hospital, the patient records confirmed that all the study patients gave informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care

Ethical approval was obtain from Ankara Diskapi Yildirim Beyazit Research and Training Hospital Clinical Research Ethical Comitee (06.04.2020; No: 85/08).

RESULTS

Evaluation was made of a total of 82 patients, comprising 49 (59.8%) females and 33 (40.2%) males with a mean age of 71.18 ± 7.67 years. The median number of comorbidities was 1 [0.0-4.0] with the median CCI score of 3 [2.0-6.0] and median ECOG score of 1 [0.0-3.0]. Intermediate risk was determined in 16 (72.7%) of 21 patients who were applied with cytogenetic analysis. The median follow-up was 6.7 months [0.2-60.2] and 75 (91.5%) patients were non-survivors at the end of the follow-up period. The demographic data and disease characteristics of the patients are given in Table 1. The distribution of biochemical parameters is given in Table 2.

Table 1. Demographic and disease characteristics of patients > 60 years **(n= 82)**

		Results	
		n	**%**
Age (median, year) [X ± S.S. (year)]	71.18±7.67		
Gender			
Female		33	40.2
Male		49	59.8
Comorbidity [Median (Min-Max)]	1.0 [0.0-4.0]		
CCI [Median (Min-Max)]	3.0 [2.0-6.0]		
ECOG score [Median (Min-Max)]	1.0 [0.0-3.0]		
Cytorisk			
Unfavorable		5	27.3
Intermediate		16	72.7
First treatment			
Supportive treatment		26	31.7
Hypometylating agents		34	41.5
Intensive treatment		22	26.8
Follow up (month) [Median (Min-Max)]	6.7 [0.2-60.2]		
Final status			
Exitus		75	91.5
Survivor		7	8.5

CCI: Charlson comobidity Index ECOG: Eastern Cooperative Oncology Group

Intensive treatment was administered to 22 (26.8%) patients and 34 patients (41.5%) were given hypometylating agents as induction regimen. Complete remission (CR1) was achieved in 20 (24.4%) patients after induction treatment. It was determined that 62 patients (75.6%) were refractory. CR2 was achieved in only 1 patient and 14 patients (20.6%) were refractory to salvage therapy. At the final follow-up, 9 (11%) patients were in still CR. Allogeneic bone marrow transplantation was performed in 2 (2.9%) patients. The treatments and response assessments of the patients are given in Table 3.

According to survival analysis, median OS was 7.0 [3.1-10.8] months and PFS was 6.8 [3.6-10.0] months. As the median CCI score was 3, patients were classified into two groups as CCI > 3 and CCI ≤ 3. Age, gender, ECOG, cytogenetic risk profile, first-line treatment and CR1 achievement status were all similar in both groups (p > 0.05). Patients with CCI > 3 had significantly shorter OS than patients with CCI ≤ 3 (3.6 months [0.3-29.3] vs 8.6 months [0.2-60.2], p= 0.049) (Table 4).

Table 2. Distribution of biochemical parameters for patients aged > 60

(n= 82)	$\overline{X}$ **±"S.S."**	**Results** **Median [Min-Max]**
Hb (gr/dL) [mean±SD]	9.34±2.01	9.2 [5.3-15.3]
Wbc (x10³/L) [mean±SD]	24276.83±36325.25	6600.0 [200.0-188000.0]
Plt (x10³/L) [mean±SD]	69841.38±74592.77	49000.0 [93.0-484000.0]
Albumin (mg/dl) [mean±SD]	3.62±0.66	3.7 [2.1-4.7]
LDH (U/L) [mean±SD]	536.80±448.26	393.0 [107.0-2235.0]

Hb: Hemoglobin, Plt: Platelet, WBC: White blood cell count, LDH: Lactate dehydrogenase

Table 3. Distribution of treatment characteristics for patients 60 years and older

(n= 82)	Results	
	n	%
First treatment		
Supportive treatment	26	31.7
Hypometylating agents	34	41.5
Intensive treatment	22	26.8
Induction response		
CR1	20	24.4
Refractory	62	75.6
Salve1 response		
CR2	1	1.5
Refractory	14	20.6
No	53	77.9
Salve2 response		
CR2	1	1.4
Refrakter	2	2.9
No	66	95.7
Allogeneic SCT		
Yes	2	2.9
No	68	97.1
Final response		
Refractory	73	89.0
Remission	9	11.0

CR: Complete Response Salve: Salvage

DISCUSSION

AML is a malignant disease which is mostly diagnosed in patients with a median age of 65-74 years.[23] Elderly patients with AML have both poor survival and higher morbidity, which may be explained by aggressive tumor biology and age-related patient characteristics.[6,24-26] Moreover, AML is a heterogeneous disease with gene mutations, which interact with cell proliferation, maturation and differentiation. Elderly patients may have specific gene mutations and an accumulation of these gene mutations may affect the treatment outcomes.[3,27,28]

After significantly evaluating the risks and benefits, such as gene mutations, patient characteristics and tumor biology, the only hope for long-term survival is accepted to be intensive chemotherapy. However, toxicity and poor outcomes are major limitations. Therefore, other treatments such as hypomethylating agents and palliative approaches may be considered.[29-33] With the current knowledge, it is impossible to predict which older patients will benefit from which therapy using available clinical and biological factors. Nevertheless, assessment of comorbidities may be helpful in this respect, especially for older AML patients.[34-36,37]

Kantarjian, et al. reported that multiple factors are associated with a low CR rate, short survival, and a high mortality rate, especially in elderly patients. Cytogenetics, LDH, serum creatinine, and leukocytosis have been shown to have prognostic significance.[38] Comorbidities have been previously assessed and demonstrated to have an independent prognostic impact in patients including cancer patients.[39] In fact, most studies have shown an association between comorbidities and the effect on overall survival, remission, and early mortality 36. The CCI is the most commonly used comorbidity index, which is intended to evaluate the role of comorbidities on mortality risks, and has been assessed in studies of many diseases, such as breast cancer.[13], postoperative problems[15], elderly cancer patients[39-41], and hematopoietic stem cell transplantation.[42]

Baudard, et al. performed a retrospective analysis of 235 AML patients. In multivariate analysis, with good performance status there was a correlation with long survival and one of the reasons for treatment failure in patients aged > 60 years was poor performance status. The same study also showed that in the observation of patients aged > 70 years, performance status was found to be a significant prognostic factor.[43]

In the current study, prognostic markers and comorbidities in elderly AML patients were investigated and it was demonstrated that CCI is an independent factor which significantly affects OS in elderly AML patients. Similar to the current study, Etienne et al. retrospectively evaluated 133 AML patients aged ≥ 70 years who were treated intensively, and found a relationship between higher CCI scores and lower remission rates.[44] Unlike that study, in the current study CCI was determined to be an independent prognostic index for all elderly AML patients irrespective of the type of induction regimen including intensive, hypomethylating agents and supportive care.

There were some limitations to this current study. We had patients' data from only two centres that

Table 4. Comparison of parameters according to CCI

Variable	CCI		p
	≤ 3 (n= 73)	> 3 (n= 39)	
Age (year)	69.0 [60.0-87.0]	73.0 [60.0-85.0]	Z=–1.845 p= 0.065
Gender			
Female	24 (%39.3)	9 (%42.9)	$\chi 2$= 0.001
Male	37 (%60.7)	12 (%57.1)	p= 0.980
ECOG	1.0 [0.0-3.0]	1.0 [0.0-3.0]	Z= –0.326 p= 0.745
Cytorisk			
Unfavorable	5 (%25.0)	1 (%50.0)	$\chi 2$= 0.000
Intermediate	15 (%75.0)	1 (%50.0)	p= 1.000
First treatment			
Supportive treatment	16 (%26.2)	10 (%47.6)	$\chi 2$= 5.418
Hypometylating agents	25 (%41.0)	9 (%42.9)	p= 0.067
Intensive treatment	20 (%32.8)	2 (%9.5)	
CR1 status			
CR1 (+)	18 (%29.5)	2 (%9.5)	$\chi 2$= 3.383
CR1 (-)	43 (%70.5)	19 (%90.5)	p= 0.066
OS (month)	8.6 [0.2-60.2]	3.6 [0.3-29.3]	Z= –1.965 p= 0.049

OS: overall survival

may limit the generalizability of the results to overall disease population. The retrospective design can be considered other limitations.

Conclusion

Elderly patients with AML have poor survival and higher morbidity with aggressive tumor biology and age-related patient characteristics. Several factors including disease and patient-related characteristics have been previously shown to have significant impact on survival. The results of the current study demonstrated that CCI can be used as a prognostic index in elderly patients with AML independently of all other patient and disease-related characteristics. Therapeutic strategies may be able to be improved by considering easily available initial prognostic markers such as CCI.

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