MARMARA
MEDICAL JOURNAL

Original Article

https://dergipark.org.tr/tr/pub/marumj

The predictive value of HCT-CI and CCI comorbidity indices in predicting survival and mortality before allogeneic stem cell transplantation in acute leukemia patients: A single-centre experience

Ozlem CANDAN[1], Ali YENIGUN[2], Derya DEMIRTAS[1], Ahmet Mert YANIK[1], Meral ULUKOYLU MENGUC[1], Ceren UZUNOGLU GUREN[1], Secil SALIM[1], Fatma ARIKAN[1], Asu Fergun YILMAZ[1], Isik ATAGUNDUZ[1], Ayse Tulin TUGLULAR[1], Tayfur TOPTAS[1]

[1] Division of Hematology, Department of Internal Medicine, School of Medicine, Marmara University, Pendik Training and Research Hospital, Istanbul, Turkey
[2] Department of Internal Medicine, School of Medicine, Marmara University, Pendik Training and Research Hospital, Istanbul, Turkey

Corresponding Author: Ozlem CANDAN
E-mail: ozlemego@gmail.com

Submitted: 22.03.2024 **Accepted:** 10.06.2024

ABSTRACT

Objective: Acute leukemia often involves comorbidities, impacting treatment decisions and patient outcomes. Clinicians commonly use the Charlson Comorbidity Index (CCI) and the Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) to assess their influence. However, their effectiveness in predicting survival and non-relapse mortality (NRM) in acute leukemia patients under 65 undergoing allogeneic stem cell transplantation remains unclear.

Patients and Methods: We conducted a retrospective single-center analysis on adults diagnosed with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL). The study included 35 patients, comprising 16 AML and 19 ALL cases. Patients were categorized based on age-adjusted HCT-CI and CCI scores.

Results: The 2-year NRM rate was determined to be 51.4%. Statistical analysis found no significant associations between age-adjusted CCI (p=0.217) and age-adjusted HCT-CI (p=0.102) with NRM. However, median overall survival significantly varied based on risk levels (p=0.003), HCT-CI groups (p=0.009), and CCI groups (p=0.011).

Conclusion: Using age-adjusted HCT-CI and CCI for comorbidity scoring in initial assessment of acute leukemia patients and those under 65 shows promise. However, these indices were ineffective in predicting NRM, emphasizing the importance of considering other significant pre-transplant factors like genetic risk, conditioning regimens, and donor type.

Keywords: HCT-CI, CCI, Score, Allogeneic stem cell transplantation, Age adjusted, Acute leukemia

1. INTRODUCTION

Conditions that occur concurrently with acute leukemia significantly impact treatment planning and outcomes. Various indices are employed to assess how different comorbidities affect the primary disease and guide treatment strategies. The Charlson Comorbidity Index (CCI) and Hematopoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) are commonly utilized for this purpose. When evaluated before allogeneic hematopoietic stem cell transplantation (Allo-HSCT), these indices not only determine the patient's suitability for Allo-HSCT but also aid in predicting post-transplant survival [1, 2].

The CCI, a standardized score calculated as just a simple weighted sum of comorbidity item scores, was developed in 1987 by Mary E. Charlson, and has been considered the gold-standard tool in clinical research as a prognostic index to predict mortality. The original version of the CCI was based on 19 items corresponding to different clinical comorbidities [3, 4]. These 19 selected conditions are weighted and totalled to an index on a scale of 0–37 points [5, 6] (Table I). Subsequently, different versions of the CCI have been developed based on different sources of data, including the age-adjusted CCI, ICD-9 code based CCI and ICD-10 code based CCI [7, 8].

The HCT-CI was initially designed using clinical data from 1055 consecutive patients treated with allogeneic HCT from 1997 to 2004 at the Seattle Cancer Care Alliance (SCCA)/ Fred Hutchinson Cancer Research Center (FHCRC) [9]. The index was validated among patients who underwent transplantation at the SCCA/FHCRC, [10] as well as other transplant institutions world-wide [11, 12]. The HCT-CI includes 17 pre-transplant comorbidities assigned a weighted semi-quantitative impact on outcomes based on the predictive hazard ratio (HR) for non-relapse mortality (NRM). The HCT-CI has been recently developed to help estimate the

How to cite this article: Candan O, Yenigun A, Demirtas D, et al. The predictive value of HCT-CI and CCI comorbidity indices in predicting survival and mortality before allogeneic stem cell transplantation in acute leukemia patients: A single-centre experience. Marmara Med J 2024;37(3): doi: 10.5472/marumj.1571254

ISSN: 1309-9469

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

risk of NRM in two years after transplantation, based on pre-transplant comorbid diagnoses and objective evidence of organ dysfunction [9]. The HCT-CI is assessed on a scale of 0 to 29 [13] (Table II). In retrospective studies, the HCT-CI appears useful in non-myeloablative and myeloablative transplant recipients [14], in patients with acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) [15], lymphoma [12], or chronic lymphocytic leukemia [16], and in patients from more than one institution [10].

The CCI was initially designed to predict survival following different treatments in cancer patients and those with severe chronic conditions, but it was not originally intended for HSCT recipients. Moreover, the HCT-CI is an adapted iteration of the original CCI developed to assess how patients' comorbidities affect their post-transplant outcomes. There is no study in the literature that evaluates the performance of these indices in predicting survival and NRM in patients diagnosed with acute leukemia, under the age of 65, and undergoing allogeneic hematopoietic stem cell transplantation. The aim of this study was to assess the predictive performance of age-adjusted CCI and age-adjusted HCT-CI in these patients.

Table I. *Age-adjusted Charlson Comorbidity Index*

Comorbid condition	Weight
Age	<50 years **0** 50–59 years **1** 60–69 years **2** 70–79 years **3** ≥80 years **4**
Myocardial infarction (MI) History of definite or probable MI (EKG changes and/or enzyme changes)	**1**
Congestive heart failure Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents	**1**
Peripheral vascular disease	**1**
Cerebrovascular accident or transient ischemic attack History of a cerebrovascular accident with minor or no residua and transient ischemic attacks	**1**
Dementia	**1**
Chronic obstructive pulmonary disease	**1**
Rheumatologic disease	**1**
Peptic ulcer Any history of treatment for ulcer disease or history of ulcer bleeding	**1**
Hemiplegia/ paraplegia	**2**
Diabetes mellitus	*Uncomplicated* ***1*** *End-organ damage* ***2***
Liver disease Mild: Chronic hepatitis (or cirrhosis without portal hypertension), moderate = cirrhosis and portal hypertension but no variceal, bleeding history, severe = cirrhosis and portal hypertension with variceal bleeding History	Mild **1** Moderate to severe **3**
Moderate/severe renal disease Moderate = creatinine >3 mg/dL (0.27 mmol/L), Severe = on dialysis, status post kidney transplant, uremia	**2**
Any tumor	Localized **2** Metastatic **6**
Leukemia	**2**
Lymphoma	**2**
AIDS	**6**

EKG: Electrocardiogram, AIDS: Acquired Immunodeficiency Syndrome

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

Table II. *Age-adjusted Hematopoietic Stem Cell Transplantation Comorbidity Index*

Comorbid condition	Weight
History of arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias 1
Cardiac disease CAD = ≥1 vessel coronary stenosis requiring medical treatment, stent, or CABG	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤50% 1 Valvular disease (except mitral prolapse) 3
Inflammatory bowel disease	Crohn disease or ulcerative colitis 1
Diabetes mellitus	Treated with insulin or oral hypoglycemics 1
Cerebrovascular accident or transient ischemic attack	1
Psychiatric disturbance Depression or anxiety requiring psychiatric consultation or treatment	2
Hepatic dysfunction	Chronic hepatitis, bilirubin >ULN to 1.5 × ULN, or AST/ALT >ULN to 2.5 × ULN 1 Cirrhosis or fibrosis or bilirubin >1.5 × ULN or AST/ALT >2.5 × ULN 3
Obesity (body mass index ≥35 kg/m^2)	1
Infection Requiring continuation of antibiotics after day 0	1
Rheumatologic disease	2
Peptic ulcer	2
Renal dysfunction Serum Cr >2 mg/dL (177 µmol/L), on dialysis, or prior renal transplant	2
Pulmonary dysfunction	Dyspnea on slight activity or DLCO and/or FEV1 66 to 80% 2 Dyspnea at rest or requires oxygen or DLCO and/or FEV1 ≤65% 3
Prior solid tumor Treated at any point in the patient's history	3
Type of transplant Allo-HCT = allogeneic hematopoietic cell transplant, ASCT = autologous stem cell transplant	Allo-HCT 2 ASCT 2
Age **For age-adjusted HCT-CI (allo-HCT only)**	<40 years **0** ≥40 years **1**

CAD: Coronary Artery Disease, CABG: Coronary Artery Bypass Surgery, EF: Ejection Fraction, ULN: Upper Limit of Normal, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, DLCO: The Carbon Monoxide Diffusing Capacity Test, FEV: Forced Expiratory Volume, HCT: Hematopoietic Cell Transplantation, HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index

2. PATIENTS and METHODS

This retrospective single-centre analysis was conducted to determine the relationship between comorbidities assessed using existing indices, and survival in adults (age ≥18 years) diagnosed with AML or Acute lymphoblastic leukemia (ALL). The study included 35 patients as 16 cases diagnosed with AML and 19 cases with ALL between 2016 and 2023. Non-relapse mortality (NRM) is more significantly influenced by pretransplant comorbidities than deaths resulting from disease progression or relapse. Therefore, patients who died due to relapse or treatment resistance were excluded. Pre-primary treatment comorbidities were assessed using the age-adjusted HCT-CI and age-adjusted CCI. The age-adjusted CCI is evaluated on a scale of 0 to 37, considering the patient's age and certain comorbidities, while the age-adjusted HCT-CI is assessed on a scale of 0 to 29 [13]. Patients were classified into low-intermediate risk (age-adjusted HCT-CI = 0, 1-2) and high risk (age-adjusted HCT-CI ≥3) groups according to the age-adjusted HCT-CI [9]. Age-adjusted CCI attributes two points for "leukemia"; therefore, patients are classified into two groups based on the age adjusted CCI scores as 0-2 and ≥3. In this study, comorbidity data were obtained from a central electronic database where each patient's diagnoses were officially coded and recorded. In addition, all medical notes in the hospital records of the patients were reviewed to attribute comprehensive information.

The study was approved by the Marmara University, Shool of Medicine Clinical Research Ethics Committee (date: 03.11.2023, approval number: 09.2023.1455). All participants provided informed consent, and the study was conducted in accordance with good clinical practice standards and in compliance with the Helsinki Declaration.

Statistical Analysis

Statistical analyses were conducted using "IBM SPSS Statistics for Windows, Version 25.0 software (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)." Descriptive statistics were presented as number (n) and percentage (%) for categorical variables and mean±standard deviation (SD) values

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

for continuous variables. ROC curve analysis was utilized to analyze the predictive value of CCI and HCT-CI parameters for mortality. The Kaplan-Meier method was used to assess overall survival (OS) of the patients. A value of $p<0.05$ was considered statistically significant.

3. RESULTS

The baseline characteristics of the patients are summarized in Table III. The median age of the patients was 34 years (range, 20-65 years), and 65.7% of the patients were males. Patients diagnosed with ALL constituted 45.7% of the total, while those diagnosed with AML comprised 54.3%. In terms of genetic features, 51.4% of the patients were classified as standard risk, while 48.6% were considered high risk (Table III).

Table III. *Patient and disease characteristics*

Characteristics	n	%
Age		
Mean±SD	35.89±12.44	
Median (min-max)	34 (20-65)	
≤34	18	51.4
>34	17	48.6
Gender		
Female	12	34.3
Male	23	65.7
HCT-CI		
Low-intermediate risk	27	77.1
High risk	8	22.9
CCI		
0-2	25	71.4
≥3	10	28.6
GVHD story		
Absent	9	25.7
Present	26	74.3
Cytogenetic features		
Standart risk	18	51.4
High risk	17	48.6
Diagnosis		
ALL	16	45.7
AML	19	54.3
Progression		
Absent	17	48.6
Present	18	51.4
Mortality		
Alive	17	48.8
Dead	18	51.4
Cause of Death		
Covid-19	1	5.5
GVHD	2	11.1
Sepsis	15	83.4
Mean follow-up duration	19.80±4.94	

HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index, CCI: Charlson Comorbidity Index, GVHD: Graft-versus-host-disease, ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia

The 2-year NRM rate was determined to be 51.4% (Figure 1). The estimated statistics for the parameters of the age-adjusted CCI (p=0.217) and age-adjusted HCT-CI (p=0.102) were not found to be statistically significant in distinguishing the presence of NRM (Table IV, Figure 2). As seen in Table V, the overall median OS (months) could not be reached. There was no significant difference in the 2-year OS among the diagnosis groups (p=0.243) (Figure 3). The 2-year OS of patients with standard-risk genetic features was significantly higher compared to patients with high-risk genetic features (p=0.003) (Figure 4). Statistically significant differences were found in median OS (months) according to HCT-CI groups (p=0.009), and CCI groups (p=0.011) (Figures 5,6).

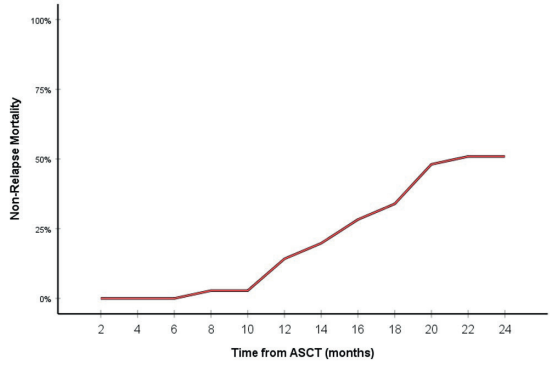

Figure 1: *The 2-year NRM rate was determined to be 51.4%.*

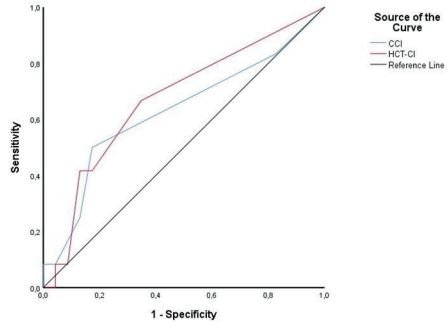

Figure 2: *ROC curves.*

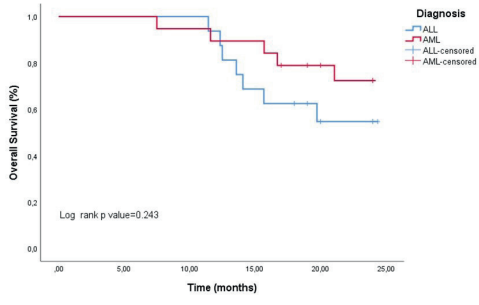

Figure 3: *There was no significant difference in the 2-year OS among the diagnosis groups (p=0.243).*

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

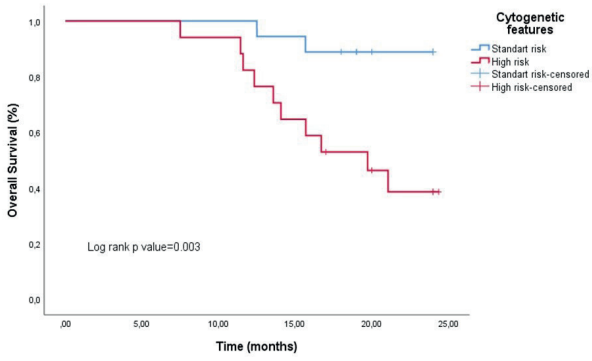

Figure 4: *The 2-year OS of patients with standard-risk genetic features was significantly higher compared to patients with high-risk genetic features (p=0.003).*

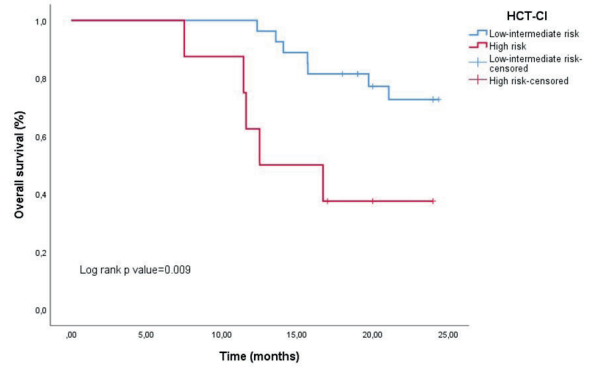

Figure 5: *Statistically significant differences were found in median OS (months) according to HCT-CI groups (p=0.009).*

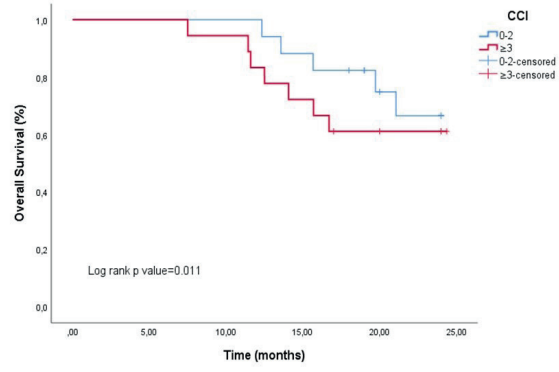

Figure 6: *Statistically significant differences were found in median OS (months) according to CCI groups (p=0.011).*

Table IV. *Analysis of the predictive values of HCT-CI and CCI values in distinguishing non-relapse mortality*

Variables	AUC	%95 CI	Cut-off	Sensitivity (%)	Specificity (%)	P
CCI	0.629	0.420-0.838	≥2.50	50.0	82.6	0.217
HCT-CI	0.670	0.477-0.864	≥0.50	66.7	65.2	0.102

AUC, Area Under the Curve; %95 CI, Confidence Interval

Table V. *Comparisons of overall survival among the patients*

Variables	2-year OS (%)	Median OS (%95 CI)	P
General	64.2	NR	
Gender			
Female	83.3	NR	0.121
Male	55.2	NR	
Age			
≤34	76.2	NR	0.067
>34	52.9	NR	
Diagnosis			
ALL	54.7	NR	0.243
AML	72.4	NR	
Cytogenetic features			
Standard	88.9	NR	**0.003**
High	38.6	19.73 (13.34-26.11)	
HCT-CI			
Düşük-orta risk	72.7	NR	**0.009**
Yüksek risk	37.5	12.50 (5.43-19.56)	
CCI			
0-2	74.4	NR	**0.011**
≥3	40.0	14.07 (7.56-20.57)	
GVHD			
Absent	66.7	NR	0.864
Present	63.6	NR	

OS: Overall Survival, HCT-CI: Hematopoietic Stem Cell Transplantation Comorbidity Index, CCI: Charlson Comorbidity Index, GVHD: Graft-versus-host-disease, ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia, %95 CI: Confidence Interval,
The Kaplan-Meier curve, Log-rank test, p<0.05 were statistically significant

4. DISCUSSION

The results of this study demonstrated statistically significant differences in median OS (months) according to risk levels (p=0.003), HCT-CI groups (p=0.009), and CCI groups (p=0.011). However, no relationship was found between age-adjusted HCT-CI or age-adjusted CCI scores and NRM. Allogeneic hematopoietic stem cell transplantation is the preferred treatment for numerous hematological conditions, both malignant and benign. Nonetheless, it carries a notable risk of NRM, primarily attributable to graft-versus-host disease and infections. The declining trend in NRM risk and the concurrent improvement in long-term survival in recent years are likely due to more adaptable conditioning regimens, enhanced donor

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

selection, and improved supportive care. However, NRM continues to pose a significant challenge. Therefore, accurate prediction of OS and NRM is crucial for evaluating the risk-benefit ratio of Allo-HSCT and providing better counseling to patients.

Since, the mortality associated with Allo-HSCT is significantly high, it is necessary to assess the potential risks for patients before undergoing this procedure. Sorror et al., identified the most common medical conditions in HSCT patients to establish a scoring system for assessing the risk and survival probability after allogeneic HSCT [13]. NRM, which is often affected by pre-allogeneic HSCT comorbidities, was used instead of survival. The original report of the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) [1] is currently the most popular index for associating post-HSCT comorbidities with outcomes and included 1055 patients. This report indicated that 38% of patients scored 0 points, 34% scored 1-2 points, and 28% scored ≥3 points. The authors also concluded that the previously used CCI had a higher overall predictive value, with nearly 90% concentration in the low score [17].

The CCI has been applied across various cancer types and leukemias, such as AML, breast cancer, colorectal cancer, esophageal cancer, and non-Hodgkin's lymphomas. It has been observed that this score can also be employed for predicting OS in patients with acute leukemia [15]. Although, the HCT-CI scores demonstrated high efficacy in predicting patient outcomes post-HCT, it is essential to acknowledge that other significant pre-transplant factors also play pivotal roles. Factors such as age and disease stage of a specific hematological malignancy should be taken into consideration when assessing HCT risks [18, 19].

In our study, we observed that the age-adjusted HCT-CI and the age-adjusted CCI were effective in predicting overall survival, but it was seen that they did not effectively predict NRM. There could be several reasons for this discrepancy. One possibility is that these indices may have primarily focused on factors related to the primary disease and its impact on overall survival, but they may not have fully captured specific risk factors associated with nonrelapse mortality, such as graft-versus-host disease and infections. In addition, the development and progression of NRM may be influenced by a variety of factors beyond those assessed by these indices, including patient-specific factors, transplant-related complications, and variations in treatment protocols. Further research may be needed to identify additional predictive factors specifically related to NRM in the context of hematopoietic stem cell transplantation, or to refine these indices.

The ALFA-9803 trial evaluated the impact of pre-treatment comorbidities on survival in a large cohort of 416 AML patients aged ≥65 years treated with intensive therapy. The multivariate analysis model results showed that age ≥75 years, performance status (PS) ≥2, infection, HCT-CI, white blood cell (WBC) >50×109/L, and high-risk cytogenetics were independent adverse risk factors for survival. The HCT-CI score, high-risk cytogenetics, and infection at baseline predicted 4 and 12-month OS as initially predefined. However, neither HCT-CI nor infections reached the 10% predefined prevalence level. It should be noted that only 5% of patients in this cohort had HCT-CI ≥3 due to the exclusion criteria. Age, PS, and WBC count needed to be associated to achieve a high specificity. High-risk cytogenetics was the only independent strong risk factor. A risk score was developed, including high-risk cytogenetics and/or at least two of the following parameters (age ≥75 years, PS ≥2, and WBC >50×109/L). Patients received intensive therapy if they had no risk factors, and the others were offered alternative therapies. This two-class decisional index identified 24% of patients with a lower 1-year survival rate of 19% [20].

Although, several studies have shown that waiting for cytogenetics does not have an impact on induction treatment outcome, many hematologists feel compelled to start treatment before cytogenetics data are available [21, 22]. Scarce material quality or an incomplete metaphase quantity may also be reasons for the unavailability of cytogenetic information at the initiation of treatment. The CCI and HCT-CI can be determined without cytogenetic or molecular data.

Allogeneic hematopoietic cell transplantation (allo-HCT) holds potential as a curative treatment for specific patients with hematological diseases. Various factors influence the outcomes, and clinical judgment often guides patient selection [23]. However, allo-HCT comes with a notable risk of NRM, especially in the presence of comorbidities and among older patients [24]. NRM is commonly associated with graft-versus-host disease, organ toxicity, and infectious complications. Patient age, comorbidities, donor type, remission status, and the conditioning regimen used are among the parameters that can significantly impact outcomes [9, 25, 26]. Therefore, it is essential that a thorough pre-transplant assessment must be conducted to assess the risks and benefits associated with allo-HCT.

Limitations

There were several limitations to this study. First, the retrospective nature of the data collection, as reliance on data recorded in medical charts might have resulted in the omission of potentially important information, which could then have been excluded from this analysis. However, the introduction of laboratory and functional data, most of which were stored in the database, reduced the likelihood of missing comorbidities. New protocols should include prospective scoring of enrolled patients to be able to better address this issue.

Another limitation of the study was the heterogeneity of both preparative regimens and disease types. The retrospective nature of the analysis was a potential source of bias, although, age-adjusted HCT-CI scores and age-adjusted CCI scores were collected prospectively. Nevertheless, the importance of assessing single-centre data to be able to realistically predict post-transplant outcomes within that centre has been emphasised in this study. New research approaches may need to be developed for pre-transplant risk calculation that can be applicable to patients from various centres characterized by heterogeneous practices.

http://doi.org/10.5472/marumj.1571254
Marmara Med J 2024;37(3): 274-281

Conclusion

It is encouraging to include formal comorbidity scoring, using age-adjusted HCT-CI and age-adjusted CCI in the initial assessment of patients with acute leukemia and those under 65 years old. It seems reasonable to classify patients for current treatment or protocol entry based on their age-adjusted HCT-CI and age-adjusted CCI scores. However, it was noted that these indices were not effective in predicting NRM. When predicting NRM, it is important to acknowledge the critical roles played by other significant pre-transplant factors. Factors such as the genetic risk of the disease, conditioning regimens, and donor type should be carefully considered.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University, Shool of Medicine Clinical Research Ethics Committee (date: 03.11.2023, approval number: 09.2023.1455). All participants provided informed consent, and the study was conducted in accordance with good clinical practice standards and in compliance with the Helsinki Declaration.

Financial support: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

Author contributions: OC, AY, DD, AMY, MUM, CUG, SS, FA, AFY, IA, ATT and TT: Concept, OC: Design and Writing, OC, AY, TT: Data Collection or Processing, OC, AY, DD, AMY, MUM, CUG, SS, FA, AFY, IA, ATT and TT: Analysis or Interpretation, OC and TT: Literature Search. All authors read and approved the final manuscript.

REFERENCES

[1] Sorror ML, Maris MB, Storer B, et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood 2004;104:961-8. doi: 10.1182/blood-2004-02-0545.

[2] Armand P, Gibson CJ, Cutler C, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood 2012;120:905-13. doi: 10.1182/blood-2012-03-418202.

[3] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83. doi: 10.1016/0021-9681(87)90171-8

[4] Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom 2022;91:8-35. doi: 10.1159/000521288

[5] Hall SF, Groome PA, Streiner DL, Rochon PA. Interrater reliability of measurements of comorbid illness should be reported. J Clin Epidemiol 2006;59:926-33. doi: 10.1016/j.jclinepi.2006.02.006

[6] De Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. J Clin Epidemiol 2003;56:221-9. doi: 10.1016/s0895-4356(02)00585-1

[7] Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson comorbidity index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits 2019;12:188-97.

[8] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005:1130-9. doi: 10.1097/01.mlr.000.018.2534.19832.83

[9] Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912-9. doi: 10.1182/blood-2005-05-2004

[10] Sorror ML, Giralt S, Sandmaier BM, et al. Hematopoietic cell transplantation–specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. Blood 2007;110:4606-13. doi: 10.1182/blood-2007-06-096966.

[11] Maruyama D, Fukuda T, Kato R, et al. Comparable antileukemia/lymphoma effects in nonremission patients undergoing allogeneic hematopoietic cell transplantation with a conventional cytoreductive or reduced-intensity regimen. Biol Blood Marrow Transplant 2007;13:932-41. doi: 10.1016/j.bbmt.2007.04.004

[12] Farina L, Bruno B, Patriarca F, et al. The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. Leukemia 2009;23:1131-8. doi: 10.1038/leu.2009.1

[13] Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 2010;363:2091-101. doi: 10.1056/NEJMoa1004383

[14] Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer 2008;112:1992-2001. doi: 10.1002/cncr.23375

[15] Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status–based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 2007;25:4246-54. doi: 10.1200/JCO.2006.09.7865

[16] Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. Blood 2008;111:446-52. doi: 10.1182/blood-2007-07-098483.

[17] Horan JT, Logan BR, Agovi-Johnson M-A, et al. Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress

has been made? J Clin Oncol 2011;29:805. doi: 10.1200/JCO.2010.32.5001

[18] Cahn J, Labopin M, Schattenberg A, Reiffers J, Willemze R, Zittoun R, et al. Allogeneic bone marrow transplantation for acute leukemia in patients over the age of 40 years. Leukemia 1997;11:416-9. doi: 10.1038/sj.leu.2400573.

[19] Gomez-Nunez M, Martino R, Caballero M, et al. Elderly age and prior autologous transplantation have a deleterious effect on survival following allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results from the Spanish multicenter prospective trial. Bone Marrow Transplant 2004;33:477-82. doi: 10.1038/sj.bmt.1704379

[20] Malfuson J-V, Etienne A, Turlure P, et al. Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. Haematologica 2008;93:1806-13. doi: 10.3324/haematol.13309

[21] Bertoli S, Bérard E, Huguet F, et al. Time from diagnosis to intensive chemotherapy initiation does not adversely impact the outcome of patients with acute myeloid leukemia. Blood 2013;121:2618-26. doi: 10.1182/blood-2012-09-454553

[22] Röllig C, Kramer M, Schliemann C, et al. Does time from diagnosis to treatment affect the prognosis of patients with newly diagnosed acute myeloid leukemia? Blood 2020;136:823-30. doi: 10.1182/blood.201.900.4583.

[23] Hamadani M, Craig M, Awan F, Devine S. How we approach patient evaluation for hematopoietic stem cell transplantation. Bone Marrow Transplant 2010;45:1259-68. doi: 10.1038/bmt.2010.94

[24] Farag SS, Maharry K, Zhang M-J, et al. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. Biol Blood Marrow Transplant 2011;17:1796-803. doi: 10.1016/j.bbmt.2011.06.005. .

[25] Stone RM. Acute myeloid leukemia in first remission: to choose transplantation or not? J Clin Oncol 2013;31:1262-6. doi: 10.1200/JCO.2012.43.4258

[26] Magenau J, Couriel DR. Hematopoietic stem cell transplantation for acute myeloid leukemia: to whom, when, and how. Curr Oncol Rep 2013;15:436-44. doi: 10.1155/2022/1828223.