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An Assessment of the Three Popular Prognostic Scoring Systems for Chronic Myelomonocytic Leukemia (CMML) in an Indian Context

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Abstract

Introduction: Chronic myelomonocytic leukemia (CMML) is a rare clonal hematopoietic neoplasm with a prevalence of 1.05 to 1.94 cases per 1,00,000 population. There are multiple prognostic scoring system used in practice for CMML, which include both cytogenetic and next-generation sequencing based.

Objective This study assesses the clinicohematological profile of CMML patients, along with comparison of three widely used prognostic scoring systems for CMML (CMML-specific prognostic scoring system, MD Anderson prognostic score, Mayo prognostic model).

Materials and Methods: This study is an 8-year retrospective study. All relevant data had been retrieved and reviewed by the authors. Inclusion and exclusion criteria: All the cases that were diagnosed before 2016 as per 2008 criteria were reclassified, (2) all the cases that were positive for the mutations associated with myeloproliferative neoplasms were excluded, and (3) cases with more than or equal to 20% blast/blast equivalents were excluded. A univariate analysis was done followed by a multivariate analysis for all the parameters constituting each scoring system. Lastly, a receiver operating characteristic curve was plotted for all the three scoring systems.

Result: There were total 23 patients, with a median age of 63 years and a male to female ratio of 2.3:1. Cytogenetic aberration and genetic mutation were observed in 6 and 3 cases, respectively. The median overall survival (OS) was 48 months and the median leukemia-free survival was 12 months. Post-multivariate analysis, the parameters with significant impact on OS were absolute monocyte count more than $10 \times 10\text{^}9/L$, myeloid precursors in peripheral blood, hemoglobin less than 10g/dL, platelet less than $100 \times 10\text{^}9/L$, hemoglobin less than 12g/dL, and absolute lymphocyte count more than $2.5 \times 10\text{^}9/L$.

Conclusion: To summarize, we discovered CPSS to be a better prognostic tool for a setup like ours, since molecular investigations are not always readily available for each case. More such researches are needed in the near future so that we can design better prognostic tools and see for their usefulness in real life.

Keywords
- CMML
- prognostic tools
- cytogenetics
- overall survival
- leukemia-free survival.

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Introduction

Chronic myelomonocytic leukemia (CMML) is a rare clonal hematopoietic neoplasm with a prevalence of 1.05 to 1.94 cases per 1,00,000 population. The diagnostic criteria for CMML now include both the absolute monocyte count (AMC) and the relative monocyte percentage as part of the criteria.[1]

They can be further subcategorized based on the blast percentage in peripheral blood (PB) and bone marrow (BM) into CMML-0, CMML-1, and CMML-2, as well as based on white blood cell (WBC) count into dysplastic($<13 \times 10^9$/L) and proliferative($>13 \times 10^9$/L) types. The proliferative subtype is more commonly seen to be associated with splenomegaly, constitutional symptoms, and JAK2 and RAS mutations, whereas the dysplastic ones are commonly associated with hematopoietic insufficiency symptoms (fatigue, infections, or bleeding).[1,2]

There are multiple prognostic scoring system used in practice for CMML, such as CMML-specific prognostic scoring system (CPSS), CPSS-molecular (CPSS-Mol), MD Anderson Prognostic Score (MDAPS), Mayo prognostic scoring model, Mayo-molecular model, and Groupe Francophones des Myelodysplasies (GFM). These scoring methods aid in classifying patients into high- and low-risk groups so that a treatment plan may be determined.[3–6]

This study discusses the clinicopathological profile of CMML patients experienced at our center. We also did a comparison between the three commonly used prognostic scoring systems based on cytogenetics (CPSS, MDAPS, Mayo prognostic model) for CMML patients.

Materials and Methods

This study is an 8-year (72 months) retrospective analysis from January 2013 to December 2021. This study had been conducted in Gujarat Cancer Research Institute, Ahmedabad. All necessary data such as demographics, clinics, laboratory parameters, marrow studies, radiology, cytogenetics, and/or mutation studies, and follow-up had been retrieved from the medical records. Old histopathology and hematology slides were collected and reviewed by the authors. Inclusion and exclusion criteria: (1) all the cases that were diagnosed before 2016 as per 2008 World Health Organization (WHO) classification were reclassified, rest were excluded, (2) all the cases which were positive for the various mutations associated with myeloproliferative neoplasm (MPN) were excluded, and (3) cases with more than 20% blast/blast equivalents were excluded.

Karyotyping and fluorescence in situ hybridization studies were done using phase contrast microscopy. Karyotyping was done using a short-term culture technique and at least 20 metaphases were studied. The cytogenetic risk stratification was done as per the Spanish study by Such et al.[4]

Next-generation sequencing (NGS) data was available in only selected cases (not done in present institute) and it was done primarily on PB. The NGS panel included 40 key DNA targets and 29 driver genes that are known to be associated with major myeloid disorder (including juvenile myelomonocytic leukemia (JMML)).

All the cases were subcategorized according to the WBC counts (dysplastic [$<13 \times 10^9$/L] and proliferative [$>13 \times 10^9$/L]) and blast count (CMML-0,1,2). The CPSS score, MDAPS score, and Mayo prognostic score were calculated for each case. The transfusion requirements were in accordance with the WHO based prognostic scoring system.[7]

Statistical analysis was performed using Statistical Package for the Social Sciences software version 25.0 (SPSS Inc., Chicago, Illinois, United States). A univariate analysis was done using Kaplan–Meier method for the interval from the date of diagnosis till last contact/death (overall survival [OS]) or progression to acute myeloid leukemia (leukemia-free survival [LFS]), to determine a two-tailed *p*-value for each of the individual parameters of each scoring system. The *p*-value was considered significant only if less than 0.05. Categorical values were represented as counts and relative frequencies, whereas continuous variables are represented as medians and range. For those parameters with significant *p*-value on univariate analysis, a multivariate analysis was performed using Cox regression hazard model to assess their independent impact. And lastly a receiver operating characteristic (ROC) curves was plotted for each of the scoring system and the area under the curve was calculated to compare the specificity and sensitivity for each system individually.

Ethics: All the approvals had been taken from the institutional review board. Ethical approval was waived by the local ethics committee of institute in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. All the necessary permission had been taken priorly for collection and analysis of materials and data from the concerned authorities.

Results

Out of the 9,000 cases of hematological malignancies that came to our facility over the past 8 years, we received a total of 23 cases of CMML, with a median age of 63 years (29–76 years) and a predominance of male patients (male to female ratio: 2.3:1). The three scoring systems and all patient characteristics are summarized in ►**Table 1** along with the risk classification of every case. On marrow examination, we had minimal to nil dysplasia in four cases, while rest had dysplasia in at least one lineage (►**Fig. 1**). The cases with minimal to nil dysplasia, however, had a history of persistent monocytosis for more than 3 months or some associated clonal abnormality. Splenomegaly was seen in 10 cases (10/19, 53%), hepatomegaly in 5 (5/19, 27%), and lymphadenopathy in 4 (4/20, 20%). Lactate dehydrogenase (LDH) was elevated in 13/15 (87%) (median LDH: 429/µL). Hepatomegaly, splenomegaly, lymphadenopathy, and LDH levels were not significantly associated with OS or LFS (p-value > 0.05). Cytogenetic aberrations were seen in 6/23 cases (5q deletion with t(4,12)(1), 7q deletion(1), trisomy 8(1), inversion 12(1), inversion Y(1) and complex karyotype(1)). In 3/5 cases, molecular abnormality was seen, one case each of ASXL1, RUNX1, and IDH2 along with NRAS mutation. The case with IDH2 and NRAS mutation also had inversion Y. Among the

Table 1 Patient characteristics and scores of various scoring systems

Characteristics		Median (range)	Total cases ($n = 23$)
Age (years)		63 (29–76)	
Gender	Male		16 (70%)
	Female		7 (30%)
WHO subtype based on blast%	CMML-0		6 (26%)
	CMML-1		7 (30%)
	CMML-2		10 (43%)
FAB subtype based on total leukocyte count	Dysplastic ($<13 \times 10^9$/L)	25.7 (4.8–203)	5 (22%)
	Proliferative ($\geq 13 \times 10^9$/L)		18 (78%)
Hb (g/dL)	<10g/dL	8.5 (4.5–11.8)	18 (78%)
	≥10g/dL		5 (22%)
	<12g/dL		23 (100%)
	≥12g/dL		0
Platelets (x10^9/L)	$<100 \times 10^9$/L	90 (7–491)	13 (57%)
	$\geq 100 \times 10^9$/L		10 (43%)
ALC (x10^9/L)	$>2.5 \times 10^9$/L	3.5 (0.54–16.1)	14 (61%)
	$\leq 2.5 \times 10^9$/L		9 (39%)
AMC (x10^9/L)	$>10 \times 10^9$/L	5.47 (1.008–81.2)	6 (26%)
	$\leq 10 \times 10^9$/L		17 (74%)
Presence of immature myeloid precursors	Present		17 (74%)
	Absent		6 (26%)
Bone marrow blast %	≥5%	8 (2–17)	17 (74%)
	<5%		6 (26%)
	≥10%		9 (39%)
	<10%		14 (61%)
RBC transfusion dependency	Present		19 (83%)
	Absent		4 (17%)
Spanish cytogenetic risk stratification	Low risk		15 (66%)
	Intermediate risk		4 (17%)
	High risk		4 (17%)
CPSS score	Low		1 (4%)
	Intermediate 1		4 (17%)
	Intermediate 2		14 (61%)
	High		4 (17%)
MDAPS score	Low		3 (13%)
	Intermediate 1		5 (22%)
	Intermediate 2		10 (43%)
	High		5 (22%)
Mayo clinic score	Low		2 (9%)
	Intermediate		3 (13%)
	High		18 (78%)
AML transformation			4(17%)
Expired			10 (43%)

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; CMML, chronic myelomonocytic leukemia; CPSS, CMML-specific prognostic scoring system; FAB, French American British (FAB); Hb, hemoglobin; MDAPS, MD Anderson prognostic score; RBC, red blood cell; WHO, World Health Organization.

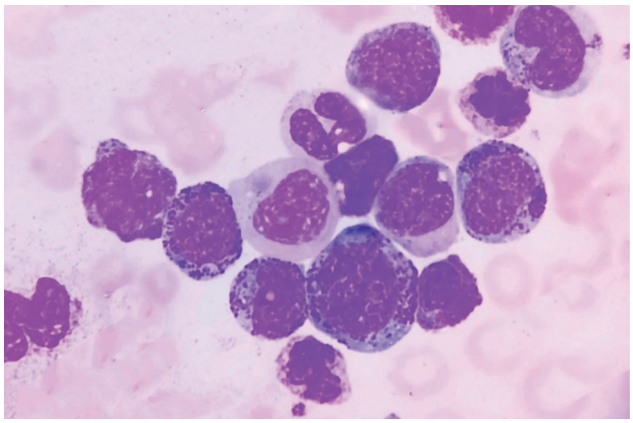

Fig. 1 Peripheral smear of chronic myelomonocytic leukemia, showing proliferation of myeloid and monocytic precursors (1000x oil immersion, Leishman stain).

three cases with molecular abnormality, two had leukemic transformation (ASXL1 and IDH2 with NRAS mutation). In one case out of 23, we also encountered cerebrospinal fluid infiltration.

The median OS and LFS were 48 and 12 months, respectively. ►**Table 2** represents the univariate analysis for all the parameters, while ►**Table 3** illustrates the multivariate analysis. Post-multivariate analysis, the parameters with significant association with OS were AMC more than 10 × 10^9/L, Immature myeloid cell (IMC) in PB, hemoglobin (Hb) less than 10g/dL, platelet less than 100 × 10^9/L, Hb less than 12g/dL, and absolute lymphocyte count more than 2.5 × 10^9/L. While the prognostic parameters with significant impact on LFS were BM blast more than or equal to 5% and IMC in PB. Lastly on ROC curve analysis, we found CPSS with maximum area under the curve followed by MDAPS and Mayo clinic (►**Fig. 2**).

Discussion

Similar to other studies, a predominance of elderly patients was noted.[7–9] Herein, we found hepatosplenomegaly mostly in association with proliferative type CMML, although we did not find any significant association of the same with OS, similar to Hoversan et al.[10] In contrast to the literature, we found a predominance of proliferative type CMML.[9,10] On subcategorizing based on blast percentage, we got maximum cases of CMML-2, while Azeez et al and Hoverstan et al got a predominance of CMML-1 and CMML-0, respectively.[10,11] We did not find any significant association of raised LDH with OS and LFS that was concordant to the literature[10]

We experienced a higher median OS compared to previous studies, although the median LFS was lower.[9,12] In the study by Calvo et al, the parameters with significant impact on OS were BM blast more than or equal to 5%, WBC more than or equal to 13 × 10^9/L, red blood cell transfusion dependency, cytogenetic risk stratification, and platelet less than 100 × 10^9/L. While for LFS, the parameters with significant impact were BM blast more than or equal to 5%, WBC more than or equal to 13 × 10^9/L, AMC more than or equal to 10 × 10^9/L, and platelet less than 100 × 10^9/L. Based on their findings they even proposed a new prognostic

Table 2 Kaplan–Meier estimate for OS and LFS

Characteristics	Total (*n*)	OS		LFS	
		Median (months)	Log rank (*p*-value)	Median (months)	Log rank (*p*-value)
Overall	23	48(4)	–	12	–
CPSS score					
BM blast (≥5%)	17	36(4)	0.009	12(4)	0.027
WBC≥13 × 10^9/L	18	36(4)	0.020	12	0.030
RBC transfusion dependency	19	36(4)	0.224	12	0.156
Cytogenetic score	8	36(4)	0.830	12(2)	0.931
Mayo clinic score					
AMC >10 × 10^9/L	6	24(4)	0.011	–	0.507
IMC in PB	17	36(3)	0.012	12(1)	0.014
Hb(<10g/dL)	17	36(3)	0.009	12(1)	0.095
Platelet (<100 × 10^9/L)	13	48(3)	0.008	12(1)	0.049
MDAPS score					
Hb(<12g/dL)	23	24(4)	0.042	12	0.075
ALC(>2.5 × 10^9/L)	14	48(3)	0.008	12(1)	0.095
IMC in PB	17	36(3)	0.012	12(1)	0.014
BM blast (≥10%)	9	36(2)	0.064	12(2)	0.262

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; BM, bone marrow; CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; Hb, hemoglobin; LFS, leukemia-free survival; MDAPS, MD Anderson prognostic score; OS, overall survival; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell.

Table 3 Cox regression hazard analysis

Characteristics	*n* (%)	OS		LFS	
		Hazard ratio	Cox regression (*p*-value)	Hazard ratio	Cox regression (*p*-value))
CPSS score					
BM blast (≥5%)	17	2.64	0.056	2.43	0.017
WBC≥13 × 10^9/L	18	1.811	0.071	2.81	0.061
RBC transfusion dependency	19	–	–	–	–
Cytogenetic score	8	–	–	–	–
Mayo clinic score					
AMC >10 × 10^9/L	6	0.266	0.012	–	–
IMC in PB	17	0.592	0.033	1.735	0.047
Hb(<10g/dL)	17	0.572	0.031	–	–
Platelet (<100 × 10^9/L)	13	1.782	0.047	2.711	0.083
MDAPS score					
Hb(<12g/dL)	23	0.987	0.009	–	–
ALC(>2.5 × 10^9/L)	14	0.521	0.028	–	–
IMC in PB	17	0.339	0.059	1.735	0.475
BM blast (≥10%)	9	–	–	–	–

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; BM, bone marrow; CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; Hb, hemoglobin; LFS, leukemia-free survival; MDAPS, MD Anderson prognostic score; OS, overall survival; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell.

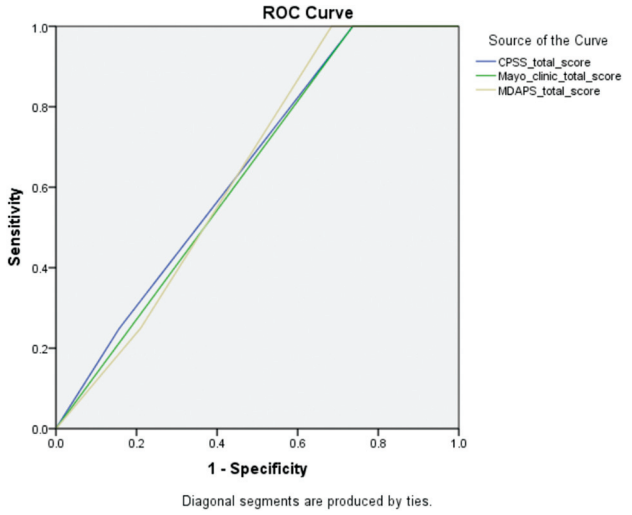

Fig. 2 Receiver operating characteristic (ROC) curve for all the three prognostic tool with area under curve for each. CPSS, chronic myelomonocytic leukemia-specific prognostic scoring system; MDAPS, MD Anderson prognostic score.

tool called as modified CPSS, in which to the existing CPSS system they added platelet count less than 100 × 10^9/L.[9,12] A similar study was also done by Padron et al on a larger study population, in which they compared seven prognostic tools and found Revised International Prognostic Scoring System (IPSS-R) to have the maximum area under ROC curve followed by CPSS.[13] The IPSS-R is a revised prognostic tool developed primarily for myelodysplastic syndrome patients, and in many studies it had been used for CMML patients also. However, its applicability is questionable for the proliferative type CMML.[9,14]

Newer molecular updates have been given to both Mayo prognostic model and CPSS. In Mayo molecular model, ASXL-1 has been added as an independent parameter, while for the CPSS-Mol, the cytogenetic risk group has been replaced with genetic risk group that calculates a cumulative score.[15,16] In present series, two cases with mutation had leukemic transformation and both the cases showed high risk scoring for CPSS-Mol and Mayo Molecular model, while on GFM scoring system the one with ASXL1 mutation had high risk scoring and the one with IDH2 and NRAS mutation had intermediate scoring. Both the cases expired within a year of leukemic transformation. Since NGS was not available for majority, we did not apply the above scoring system for rest of the cases.

The various scoring systems not only provide prognosis but also therapeutic recommendations. For high-risk patients, hematopoietic stem cell transplantation (HSCT) is recommended and considered to be curative provided they are medically fit. While for the low-risk patients, if they are asymptomatic a wait and watch policy is recommended, while for others hydroxyurea or hypomethylating agents are considered over and above HSCT, considering its complications.[16] In this study, a similar approach was applied accordingly and HSCT was done in total seven cases.

Conclusion

Thus, to summarize, we present a new set of parameters (AMC > 10 × 109/L, IMC in PB, Hb10g/dl, platelet100 × 109/L, and ALC > 2.5 × 109/L) that we found significant. In the

future, more research with a larger study population is required so that this can be validated. We discovered CPSS to be the most specific and sensitive (based on ROC-curve) out of the three well-known prognostic tools. The size of the study population and, in the majority of instances, the lack of NGS data were the study's limitations. And lastly, to the best of our knowledge, this is the first time such a study has been conducted in an Indian setting.

Declarations

Authors Declarations: The manuscript has been read thoroughly and contributed by all the concerned authors. The requirement for authorship as mentioned in the instructions has been met duly. Authors are responsible for correctness of the statements provided in the manuscript.

Internal Ethics Committee Approval: All the approvals had been taken from the institutional review board. Ethical approval was waived by the local ethics committee of institute in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. All the necessary permission has been taken for collection and analysis of materials and data from the concerned authorities.

Consent to Participate: All necessary informed written consent has been taken priorly.

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All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Conflict of Interest
Nil.

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