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RESEARCH ARTICLE

THE PROGNOSTIC SIGNIFICANCE OF CD10+ MUM1+ GCB SUBTYPE OF DIFFUSE LARGE B-CELL LYMPHOMAS

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ABSTRACT

PURPOSE - Diffuse Large B-Cell Lymphoma can be subclassified into the prognostically distinct groups of GCB and non-GCB using the immunohistochemical Hans algorithm. However, in real life, patients classified as GCB show differing outcomes even when treated with the same chemotherapy regimen. CD10 is a GCB marker, while MUM1 is a non-GCB marker, but Hans algorithm classifies CD10+ MUM1+ patients as GCB DLBCL. We explored whether CD10+ MUM1+ GCB DLBCL patients had different outcomes compared to rest of the GCB DLBCL patients.

METHODS - In this study, we retrospectively analyzed the clinical records of 427 DLBCL patients treated with standard chemo-immunotherapy at Kidwai Memorial Institute of Oncology, Bengaluru from 2013 to 2019. The clinical characteristics, response rate and overall survival of CD10+ MUM1+ GCB group was compared with MUM1-ve GCB group and non-GCB group.

RESULTS - Among the patients studied, 187 (43%) patients were of GCB subtype, whereas 240 (57%) patients belonged to the non-GCB subtype. Additionally, 61 (14.3%) patients were of the CD10+ MUM1+ GCB immune-phenotype. No significant differences could be demonstrated in the clinical characteristics of CD10+ MUM1+ GCB and MUM1- GCB patients. Patients with CD10+ MUM1+ GCB subtype exhibited a significantly inferior response rate compared to those with MUM1- GCB subtype (81% versus 92%; p=0.04). Although, both non-GCB and CD10+ MUM1+ GCB subtypes displayed diminished overall survival in comparison to MUM1- GCB patients, (non-GCB = 33 months, CD10+ MUM1+ GCB = 33 months and MUM1-ve GCB = 40.4 months, p = 0.21) it did not reach statistical significance

CONCLUSION - CD10+ MUM1+ GCB patients may be prognostically more similar to non-GCB patients, as suggested by the inferior response rates and numerically inferior OS compared to other GCB patients. This needs further confirmation in prospective studies.

Keywords - Immunohistochemistry, Gene expression, Cell of origin, chemo-immunotherapy, Germinal centre B- cell

Abbreviations

DLCBL - Diffuse Large B-cell Lymphoma
RR - Response rate
OS - Overall Survival
GCB - Germinal centre B-cell
IPI - International prognostic index
ECOG - Eastern cooperative oncology group
LDH - Lactate dehydrogenase
IHC - Immunohistochemistry
GEP - Gene expression profiling
FFPE - Fixed formalin paraffin embedded
KFT - Kidney function test
LFT - Liver function test
RCHOP - Rituximab, Cyclophosphamide, Adriamycin, Oncovorin and Prednisolone
DA-REPOCH - Dose adjusted Rituximab, Etoposide, Prednisolone, Oncovorin, Cyclophosphamide and Adriamycin
RCHEOP - Rituximab, Cyclophosphamide, Adriamycin, Etoposide, Oncovorin and Prednisolone

Introduction

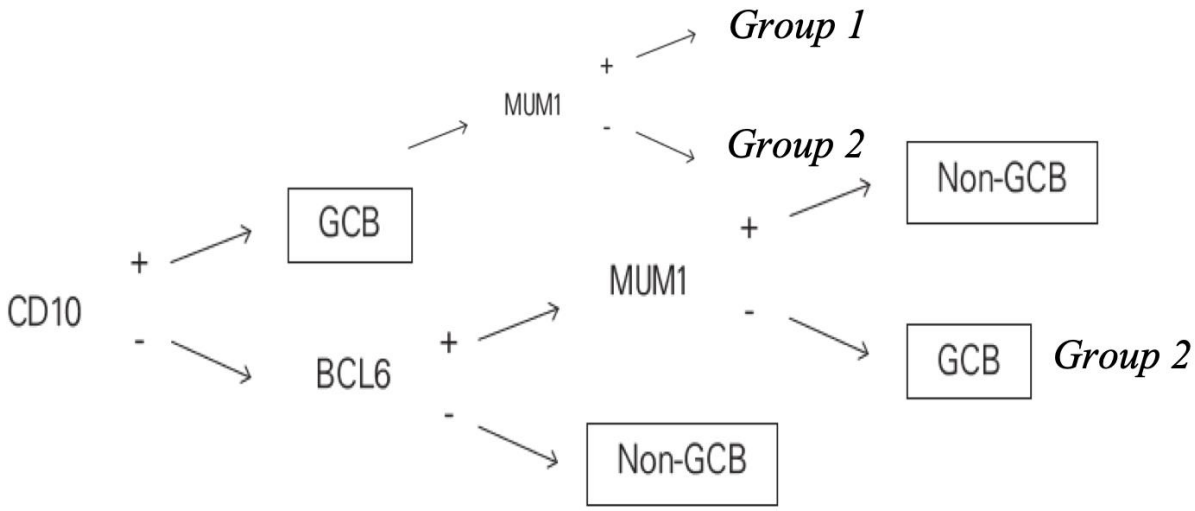
Diffuse large B-cell lymphoma (DLBCL) is one of the most common types of non-Hodgkin's lymphoma that is prevalent in the developing world today.[1] According to some sources it constitutes around 40% of the total lymphomas in the world.[2] DLBCL is inherently heterogeneous in nature and survival of this disease ranges from 38% to 96% depending on the subtype and stage of the disease.[3] The treatment of this disease is centred around the standard chemo-immunotherapy regimen (R-CHOP) and its modifications. This has helped us to improve the outcomes of this disease drastically in the last two decades. However, despite these advances, many of these patients are intrinsically refractory to the common chemo-immunotherapy regimens that we use today.

Till date, many different methods have been tried by the scientific community to identify the poor prognostic groups. One such method is gene expression profiling (GEP), which is used to identify various genes that play an important role in various oncologic mechanisms. The ultimate aim of gene expression studies is to provide a unique molecular signature of the of tumour cells, which will help us to identify various subgroups that have a common cell of origin and similar methods of transformation. GEP studies helped us to classify DLBCL into three distinct subtypes, the GCB, the non-GCB and the type 3 DLBCL, the latter two having much poorer prognosis.[4] However, GEP analysis is cumbersome and is not feasible in daily clinical practice. As a result, immunohistochemistry (IHC) algorithms using formalin-fixed, paraffin-embedded (FFPE) tissue have been proposed to predict the GEP subtypes.

Various algorithms like Hans et al,[5] Choi et al,[6] Muris et al[7] use IHC to sub classify DLBCL in clinical practice. The Hans criteria are widely used in clinical practice for categorizing DLBCL. This method relies on three markers: CD10, BCL6, and MUM1/IRF4. Patients who test positive for CD10 are classified as having the germinal center B-cell (GCB) subtype. This includes people who are positive or negative for MUM1, as well as those who are positive or negative for BCL6. CD10 negative patients are characterized as GCB if they are BCL6 positive and MUM1 negative. Interestingly, in this classification system, patients who test positive for both CD10 and MUM1/IRF4 are still classified as GCB subtype. Therefore, there

are two distinct types of GCB patients: one group comprises individuals who are CD10 positive and MUM1 positive (CD10+ MUM1+ GCB - Group 1), while the other encompasses those who are MUM1-ve (CD10-ve, BCL6+, MUM1-ve & CD10+ MUM1-ve [MUM1-ve GCB - Group 2]). (FIGURE 1).

Fig-1: Hans algorithm



Choi and colleagues added two extra markers, GCET1 and FOXP1, to the ones already used by the Hans algorithm to classify DLBCL into GCB and ABC subgroups. Their method had a concordance of 93% with GEP based classification, which was higher than the 88% accuracy achieved by the Hans algorithm.[6] Muris et al. employed BCL2 markers instead of BCL6 to prognosticate outcomes in DLBCL and stratify them into favourable and unfavourable subgroups.[7]

The clinical characteristics and prognosis of CD10+ MUM1+ GCB type is largely unknown. Hence in this study we try to find out the clinical profile of CD10+ MUM1+ GCB subtype and its relation with other GCB DLBCL patients. We also analysed and compared the differences in survival of CD10+ MUM1+ GCB; MUM1-ve GCB and non-GCB patients when treated with standard chemo-immunotherapy regimen.

Methods

The study was approved by the Institutional Ethics committee (No KMIO/MEC/2022/07/PG/MO/12). This was a retrospective observational study in which the medical records of adult patients (aged >18 years) diagnosed with de novo DLBCL between January 2013 and January 2019 at the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru were retrieved and analysed. Cases of special variants or subtypes, such as primary central nervous system lymphoma, primary mediastinal B-cell lymphoma, HIV-positive DLBCL, Burkitt's lymphoma and primary cutaneous DLBCL were excluded from the study. Also, patients

with deranged KFT and LFT were excluded from the study.

A case record form was filled for each patient which included socio-demographic data, date of diagnosis, clinical parameters (like sites of disease, ECOG PS, IPI, stage, LDH etc.), IHC markers, chemotherapy administered, the response rate and the overall survival. The IHC panel for lymphomas included: LCA, CD20, CD3, CD5, CD23, Cyclin D1, Ki67, MUM1, CD10, BCL2. BCL6 and Tdt. These patients were categorised as GCB or non-GCB subtype according to Hans algorithm. (5) Using Hans algorithm, CD10, Bcl-6 and MUM1/IRF4 were each considered positive if 30% or more of the tumour cell stained positive. Patients who were both CD10+ and MUM1/IRF4+ on immunohistochemistry were categorised as CD10+ MUM1+ GCB DLBCL while the rest were categorised as MUM1-ve GCB subtype. IPI was calculated using NCCN-IPI score.[8] The end of treatment response was recorded and designated as complete response, partial response, stable disease and progressive disease in accordance with the Lugano classification.[9] Objective response rate included complete response and partial response according to the post treatment imaging. The patients were followed up for the entire period of the study. Survival data was analysed for all the subgroups.

Statistical analysis

Statistical analyses were performed with SPSS software, version 20.0. Chi-square and Fisher exact tests were used to determine correlation in the frequencies between groups. The survival analysis was performed according to the Kaplan-Meier method, and the survival curves were compared with the help of log-rank test. For all tests, a *P* value less than 0.05 was considered statistically significant.

Results

A total of 427 DLBCL patients were analyzed as part of the study. The mean age of the study group was 52 years, with 144 (33.7%) patients being older than 60 years. Among the patient cohort, 270 (63.2%) patients were male with a male to female ratio 1.7:1. In our study,187 (43%) patients were of the GCB subtype, while 240 (57%) belonged to the non-GCB subtype. Majority of the patients ((243 (57%)) presented with advanced stage disease - Ann Arbor stage (III/IV) and 156 (36%) had a high IPI score (>2). Approximately 256 (60%) patients received R-CHOP while 86 (20%) received only CHOP chemotherapy. Other chemotherapy regimens included dose adjusted R-EPOCH, RCEOP, and R mini-CHOP. The median duration of follow-up was 39 months. The number of patients having a CD10+ MUM1+ GCB immune-phenotype was 61(14.3%), MUM1-ve GCB was 126 (29.5%) and non-GCB was 240 (56%). (FIGURE 2)

There were no statistically significant differences between CD10+ MUM1+ GCB, MUM1-ve GCB and non-GCB patients when compared for age, sex, elevated LDH (>220units/L), high IPI score (>2) and advanced stage (III/IV). The response rate of CD10+ MUM1+ GCB patients was significantly worse when compared to patients of MUM1-ve GCB subtype. (TABLE 1)

The overall survivals of CD10+ MUM1+ GCB and non-GCB patients were less than MUM1–ve GCB subtype but the result did not reach statistical significance (33 months vs 33 months vs 40.4 months, p=0.21) (FIGURE 3).

Fig-2: DLBCL subtypes (Percentage %)

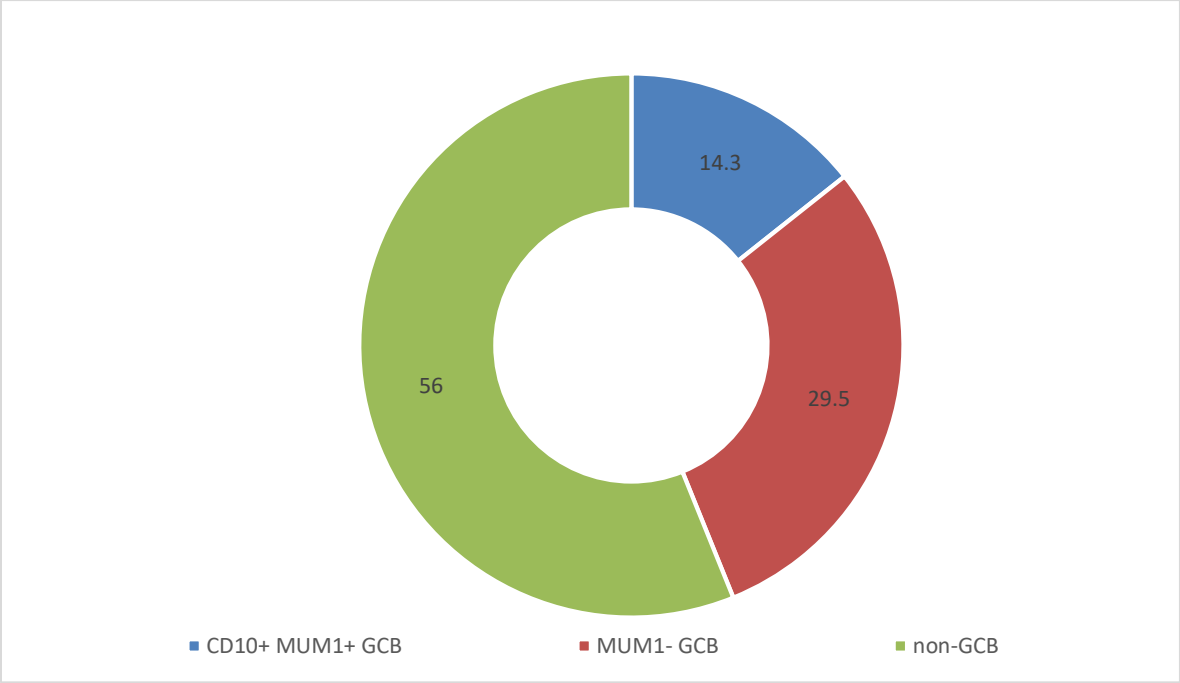
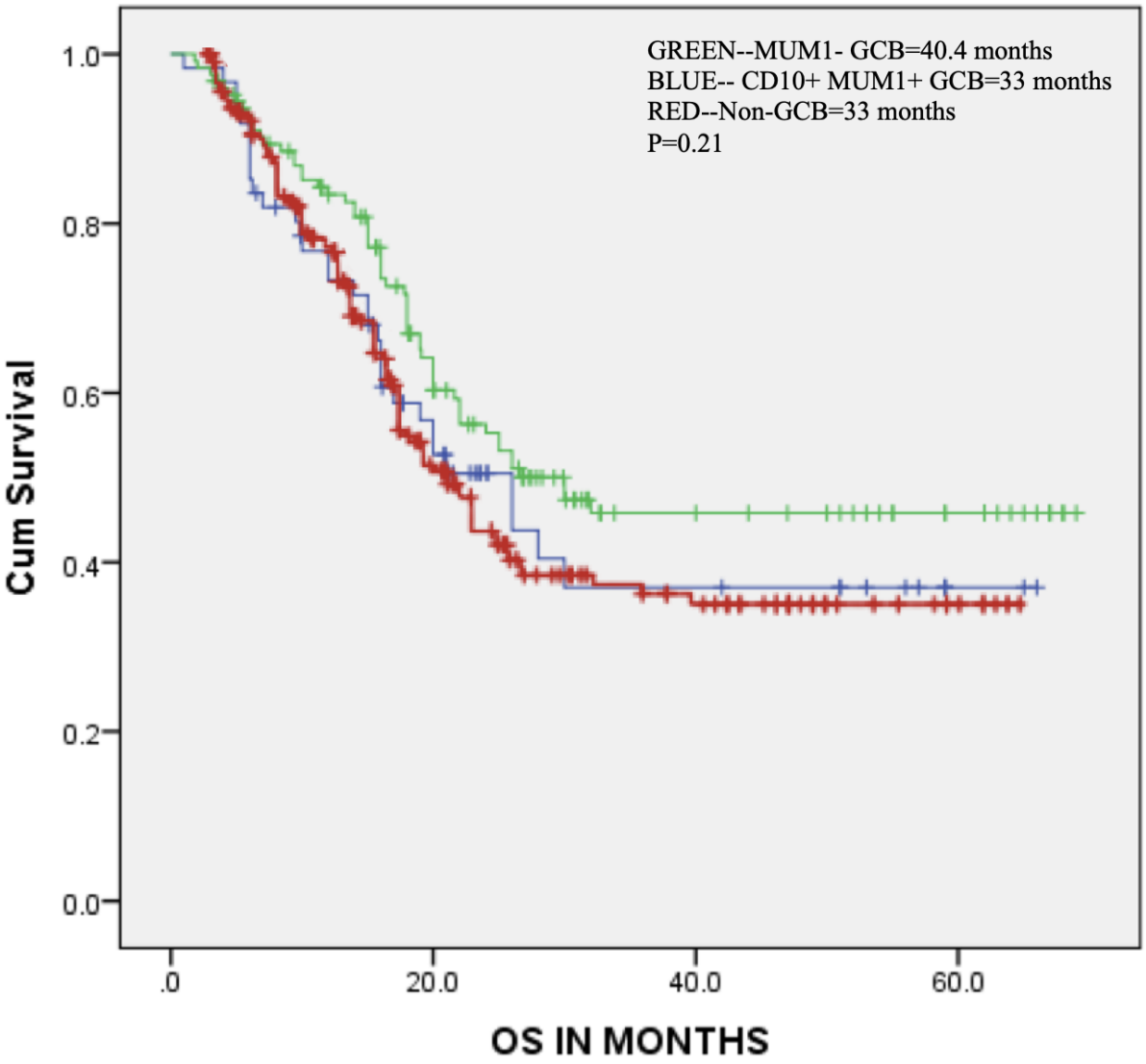


TABLE 1: The clinical characteristics of CD10+ MUM1+ GCB, MUM1- GCB and non-GCB subtype.

Sr Num.	Variables	CD10+ MUM1+ GCB (n=61)	Vs MUM1- GCB (n=126)	p-value (Chi square)	Vs Non-GCB (n=240)	p-value (Chi square)
1.	Age (%)					
	<60 years	43(70)	84(66)	0.599	156(65)	0.418
	>60 years	18(30)	42(34)		84(35)	
2.	Sex (%)					
	Male	37(60)	82(65)	0.627	151(63)	0.744
	Female	24(40)	44(35)		89(37)	
3.	Elevated LDH (%)					
	Yes	24(39)	38(30)	0.210	81(34)	0.413
	No	37(61)	88(70)		159(66)	
4.	IPI score (%)					
	1-2	38(62)	84(66)	0.556	149(62)	0.879
	3-5	23(38)	42(34)		91(38)	
5.	Ann Arbor stage (%)					
	1-2	37(60)	83(65)	0.555	104(43)	0.052
	3-4	24(40)	43(35)		136(57)	
6.	Response Rate (%)					
	Yes	50(81)	116(92)	*0.04*	194(80)	0.840
	No	11(19)	10(8)		46(20)	

Fig 3: Survival analysis of MUM1- GCB vs CD10+ MUM1+ GCB subtype and non-GCB subtype



Discussion

Hans criteria is one the most commonly used algorithms for classification of DLBCL patients into GCB and non-GCB subtypes. Recently, the validity of the algorithm has been questioned as many patients grouped within the same subtype showed differing outcomes.[10],[11]. This led to the realisation that each marker utilized in the Hans criteria has a unique contribution to the prognosis of the patient. CD10 is a GCB marker, while MUM1 is a non-GCB marker, but Hans algorithm classifies CD10+ MUM1+ patients as GCB DLBCL. We explored whether CD10+ MUM1+ GCB DLBCL patients had different outcomes compared to rest of the GCB DLBCL patients. Hence in this study, we retrospectively analysed the clinical characteristics and outcomes of CD10+ MUM1+ GCB DLBCL patients and compared it with that of MUM1-ve GCB and non-GCB patients.

This study revealed that 43% of the DLBCL patients had a GCB subtype. In comparison, Western literature has shown a higher incidence of GCB subtype, the reasons of which are unknown.[12] while Indian literature demonstrated

a comparable incidence of GCB subtype with our study[13] There were no statistically significant differences between GCB and non-GCB subtypes with respect to clinical characteristics like stage and IPI score in this study. This was in contrast to the study conducted by Moonho Kim et all, which showed that non-GCB subtype presented with advanced stage, high IPI score and elevated LDH[17]. The better prognosis of GCB subtype compared to non-GCB subtype has been demonstrated in numerous studies and many explanations have been offered for the same.[14] Firstly, it has been seen that non-GCB subtype patients are generally older when compared to GCB subtype.[15] Older patients are unlikely to tolerate chemo regimens well and have less than acceptable outcomes. Secondly, the intrinsic resistance of non-GCB subtype to chemotherapy is thought to be due to constitutive action on NFKB gene. This in turn leads to activation of anti-apoptotic pathway and poor response to chemotherapy. [16] Poorer prognosis of non-GCB subtype has led to evolution of many novel therapies in the treatment of DLBCL. Drugs like Lenalidomide[18], Ibrutinib[19] etc. have been tried in non-GCB patients with some success.

In our study, 14.3% of the total patients were CD10+ MUM1+ GCB. End of treatment imaging showed that CD10+ MUM1+ GCB patients had a poorer response rate to therapy compared to MUM1-ve GCB patients. Survival analysis also demonstrated a poorer OS for CD10+ MUM1+ GCB and non-GCB patients compared to that of MUM1-ve GCB, even though it did not reach statistical significance. In a study conducted by TX Lu et al. the fraction of CD10+ MUM1+ GCB patients (13.3%) was similar to that seen in the present study. However, the CD10+ MUM1+ GCB or Double Positive (DP) subtype correlated with adverse clinical characteristics, such as advanced age (p=0.04) and poor PS (p=0.0192), in comparison to rest of the GCB patients. The DP group was associated with a poorer survival compared to the rest of the GCB group (p=0.0481), and an overall survival comparable to that of the non-GCB group (p=0.3650) [20]. In other studies, the incidence of DP ranged from 14-17%.[5],[21],[22]

The principal factor contributing to the poorer outcomes observed in CD10+ MUM1+ DLBCL is the intrinsic cell of origin of these patients. CD10 serves as a marker for the germinal center, whereas MUM1/IRF4, a NFkB target gene, is expressed by activated B cells [21],[23]. Consequently, the CD10+ MUM1+ GCB subgroup is presumed to share closer prognostic characteristics with the non-GCB subtype. We observed that patients with CD10+ MUM1+ GCB subtype exhibited a comparable overall survival rate to those with the non-GCB subtype. The trend towards an inferior outcome in comparison to patients with the MUM1-ve GCB subtype, however was not statistically significant.

Yet another entity that can challenge the prognostic value of Hans algorithm is the so-called triple negative (TN) DLBCL. DLBCL without positive staining for CD10, BCL6, and MUM1 constitutes the TN DLBCL. According to Hans algorithm, TN DLBCL is classified as non-GCB subtype. However, in the study by TX Lu et al[20] TN DLBCL patients (8.8%) showed a better OS and PFS than the non-GCB group. A study conducted by Chang et al. which tried to show a correlation between IHC and outcome in DLBCL had a lower incidence of TN patients (4%).[21]

There are several limitations in our study which include 1) single centre study, 2) the retrospective nature, 3) smaller sample size, 4) confounding factors like double expressor and double hit characteristics (which were not looked into, 5) non-rituximab-based regimens (20%), and 6) varying chemotherapy regimens

Despite the limitations, this current study represents the first attempt to systematically study CD10+ MUM1+ GCB patients in an Indian population. The relative high prevalence of these subtypes emphasizes its importance in the Indian clinical scenario. The poorer prognosis of CD10+ MUM1+ GCB subtype reiterates the importance of early recognition of these patients.

Conclusion

CD10+ MUM1+ GCB patients may be prognostically more similar to non-GCB patients, as suggested by the inferior response rates and numerically inferior OS compared to MUM1-ve GCB patients. This needs further confirmation in prospective studies. The Hans algorithm-based classification of DLBCL into GCB and non-GCB subtypes may not always be prognostically accurate, as outcomes differ for patients within these subgroups. CD10+ MUM1+ GCB may represent one such subtype that merits further investigation.

Conflict of Interest Statement:

None

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Declaration of Interest Statement:

The authors have no relevant financial or non-financial interests to disclose.

Compliance and Ethical standards:

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. The study was approved by the Ethics Committee of Kidwai Memorial Institute of Oncology, Bengaluru (No KMIO/MEC/2022/ 07/PG/MO/12).

Informed consent was obtained from all individual participants included in the study.

Dr. Linu Jacob-Conceptualization and Methodology; Dr. Animesh Gupta- Formal analysis, writing-original draft, writing-review, editing and data curation; Dr. Kanika Sharma- resources Dr Usha Amtitham-Methodology Dr. M C Suresh Babu, Dr. Rudresha, Dr. Lokesh, Dr. Smitha- resources, supervision.

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