774P High MTV and low CD4/CD8 ratio before apheresis are poor prognostic factors in patients with r/r LBCL treated with CAR T-cell therapy

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Background: Previous studies have identified prognostic factors before lymphodepleting chemotherapy in patients with relapsed/refractory large B-cell lymphoma (r/r LBCL) undergoing chimeric antigen receptor (CAR) T-cell therapy, including metabolic tumor volume (MTV) and CD4/CD8 ratio. However, there are limited reports on prognostic factors before apheresis. This study evaluated the prognostic impact of MTV and CD4/CD8 ratio prior to apheresis. Additionally, we assessed the influence of bridging therapy (BT) on prognosis according to pre-apheresis risk status.

Methods: We retrospectively studied r/r LBCL patients who received CAR T-cell therapy at our institution from October 2020 to March 2024. All patients had FDG-PET/CT scans and CD4/CD8 ratio before apheresis. SUVmax was measured, and MTV was summed using 41% of SUVmax as the threshold.

Results: 43 patients were analyzed with a median follow-up of 12.4 months for survivors (IQR: 6.6—20.6 months). The overall response rate was 70%. At the last follow-up, 16 patients (37%) had experienced progression and 12 (28%) had died. The median progression-free survival (PFS) was 26.6 months (95% confidence interval [CI]: 11.8—not reached). Using a median MTV cutoff value of 26.62mL (IQR; 1.74—93.3), patients were divided into high and low MTV groups. Patients with low MTV had significantly superior PFS (hazard ratio [HR], 0.25; 95% CI, 0.09—0.70). Based on a median CD4/CD8 ratio cutoff value of 0.64 (IQR: 0.31—0.84), patients were divided into high and low CD4/CD8 groups. Those with high CD4/CD8 had significantly superior PFS (HR, 0.37; 95% CI, 0.14—0.96). A new prognostic model combining MTV and CD4/CD8 ratio stratified patients into low risk (zero or one risk factor) and high risk (two risk factors) subgroups. The low-risk group (n = 30) had significantly superior PFS (HR, 0.14; 95% CI, 0.05—0.37). The response to BT was not significant for PFS in low-risk patients but was significant in high-risk patients (HR,0.19; 95% CI, 0.04—0.83).

Conclusions: High MTV and low CD4/CD8 ratio before apheresis correlated with poorer prognosis in CAR T-cell therapy for r/r LBCL. Effective BT improved outcomes in high-risk patients.

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775P CD58 alterations govern antitumor immune responses by inducing PD-L1 and IDO in diffuse large B-cell lymphoma

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Background: Recurrent abnormalities of immune surveillance-related genes play a crucial role in DLBCL progression. Prior studies have shown that CD58, a key adhesion molecule that acts as a ligand for the T-cell costimulatory molecule CD2, is frequently mutated or deleted in certain hematological malignancies. Downregulation or loss of CD58 is linked to resistance to ICB therapy in melanoma and CAR-T therapy in B-cell malignancies. Nevertheless, the role of CD58 in cancer is not yet well understood.

Methods: Comprehensive analysis of the genetic characteristics of *CD58* were performed through targeted deep sequencing (n=176), whole exome sequencing (n=38), and RNA-sequencing (n=162) in patients with de novo DLBCL. To investigate the mechanistic impacts of CD58 alterations on co-inhibitory molecules expression and immune cell function, we performed bulk and single-cell RNA-sequencing analysis of tumor samples and conducted co-IP, flow cytometry and co-culture assays in vitro.

Results: We identified that *CD58* mutation rate was 9.1%, and the copy number loss rate was 44.7% among all enrolled DLBCL patients. Notably, *CD58* genetic alterations, along with low CD58 expression, significantly correlated with reduced rates of response to R-CHOP therapy and inferior progression-free and overall survival. Single-cell RNA sequencing revealed that CD58 expression in tumor cells was negatively correlated with $CD8^+$ T cell exhaustion/dysfunction status. CD58 inhibited the activity of the JAK2/STAT1 pathway by activating the Lyn/CD22/SHP1 axis, thereby limiting PD-L1 and IDO expression. Elevated PD-L1 and IDO expression in CD58 deficient DLBCL cells led to immune evasion and tumor-intrinsic resistance to CAR T-cell therapy. Direct activation of CD58-CD2 costimulatory signaling in combination with anti-PD-L1 blockade or IDO inhibitor sensitized CD58-deficient DLBCL to CAR T-cell therapy.

Conclusions: Our study comprehensively characterized *CD58* genetic alterations in DLBCL. We demonstrated that CD58 downregulation or mutation led to upregulation of PD-L1 and IDO expression mainly by regulating the LYN/CD22/SHP1 axis. Our findings provide novel insights for individualized therapy for DLBCL patients with CD58 mutation or deletion.

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776P Prognostic significance of baseline vitamin D level on the outcome of diffuse large B cell lymphoma

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Background: DLBCL is the most common subtype of NHL. There have been reports on vitamin D deficiency(VDD) as a negative prognostic factor in patients with aggressive B cell lymphomas. In this study we aim to look at the baseline Vitamin D level of patients with DLBCL treated with chemoimmunotherapy and to look into its association with treatment response and survival outcome.

Methods: This was a prospective study of patients diagnosed with DLBCL treated in our centre. Serum samples for Vitamin D were collected at the time of diagnosis and was assayed for Vitamin D using Chemo-luminescent assay. A value less than 30ng/ml as deficient and those more than or equal to 30ng/ml as sufficient. Those with deficient vitamin D were graded as critically low (<20ng/ml) and low (20-29ng/ml). Patients were treated with R-CHOP chemoimmunotherapy. End of treatment response (EOT) assessment was done with PET-CT, 6 weeks after completion of treatment and was correlated with baseline vitamin D level. DFS and OS at 1 year was estimated. Survival at 1 year was correlated with baseline vitamin D level.

Results: 76 patients were included. The median age was 48 years. There were 35 males and 41 females.M:F ratio was 1:1.17. The most symptom was cervical lymphadenopathy.35% had B symptoms. The Ann Arbor stage was I in 6, II in 21, III in 25, and IV in 24 patients. VDD was seen in 70 (92%) patients. critically low value in 58% and low in 34.2%. 61 patients attained CR, 1 had PR, 8 had progressive disease. Among the 8 with progression 7 had insufficient vitamin D and those with CR; 60 patients had deficient Vitamin D. There was no significant association of Vitamin D level with EOT response.DFS at 1 year was 87.2%. There was no significant difference in DFS with respect to Vitamin D level. Those with critically low , low and normal pretreatment levels of Vitamin D showed no statistical significance in relation to DFS. Overall survival at 1 year was 98%. Among the prognostic variables LDH and extranodal involvement were significant predictors of DFS.

Conclusions: In our study majority of patients (92%) had vitamin D deficiency and among them, more than 50% of patients had a critically low level. No significant difference was observed in the end of treatment response rate and DFS with respect to level and grades of vitamin D.

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777P Glasgow prognostic score in diffuse large B cell lymphoma: Single institutional observational study

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Background: Diffuse large B cell lymphoma (DLBCL) is an aggressive lymphoma and the most important prognostic factor in predicting outcome is the Revised International Prognostic Index (R-IPI). In this study we looked at the significance of Glasgow prognostic score in patients with DLBCL.

Methods: This is a prospective study of 110 patients with newly diagnosed DLBCL, treated at Regional Cancer Centre Trivandrum with R-CHOP chemoimmunotherapy. The Glasgow prognostic score was calculated at baseline using CRP and Serum albumin, as follows: patients with both elevated CRP (≥10 mg/L) and low albumin (<3.5 g/dL) levels were allocated a score of 2, patients with either elevated CRP (≥10 mg/L) or low albumin (<3.5 g/dL) were allocated a score of 1, and those with normal CRP and albumin levels were allocated a score of 0. The baseline GPS distribution and its association with treatment response and survival were studied.

Results: This study included 110 patients with a median age of 55 years with a male-to-female ratio of 1:1.1. The Ann Arbor stage was I in 7.2%, II in 35.4%, III in 20%, and IV in 37.2% patients. The Revised International Prognostic Index (R-IPI) risk group was very good in 18.2%, good in 54.5%, and poor in 27.3% of patients. The baseline GPS score was zero in 59.3%, one in 22.7%, and two in 18% of patients. All patients received R-CHOP chemoimmunotherapy. The end of treatment PET-CT showed complete response in 86.3%, persistent disease in 7.3%, and progressive disease in 6.4%. GPS of one or two correlated with persistent or progressive disease and poor risk group of R-IPI ($p<0.05$). Progression-free survival at 18 months for GPS scores of zero, one, and two (96.4% vs 73.3% vs 58.3%)($p<0.001$). Overall survival at 18 months for GPS scores of zero, one, and two were 98.8%, 93.3%, and 83.3% respectively ($p<0.001$).

Conclusions: This study demonstrated that a GPS score of one or two correlated with poor risk R-IPI, persistent or progressive disease, and inferior PFS and OS at 18 months compared with patients having a GPS score of zero. Hence GPS could act as a prognostic marker which could help categorize patients who have poor outcomes with standard chemoimmunotherapy.

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779P Prognostic value of micro-vessel density in classical Hodgkin Lymphoma: A systematic review

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Background: Angiogenesis plays a role in cancer progression and metastasis. In Hodgkin lymphoma, micro-vessel density (MVD) has been widely used to estimate the degree of angiogenesis. The role of MVD in classical Hodgkin lymphoma is not well defined. The aim of this study is to review prognostic value of MVD in classical Hodgkin lymphoma.

Methods: We searched systematic in several databases for instance PubMed, Science Direct, Google Scholar, Cochrane with relevant keywords related to, classical Hodgkin lymphoma, micro-vessel density, and survival, progression free survival and overall survival. The observational studies last twenty years that reported the association between MVD and survival in classical Hodgkin lymphoma were included. The quality of included study was assessed using Newcastle Ottawa Scale tool.

Results: We included 10 studies with total 968 patients. Five studies were using CD31 as marker for MVD, while the other five were using CD34. There was 6 studies using overall survival as end point. Two studies (402 patients) concluded that MVD negatively correlated with overall survival (OS), while one study with 167 patients concluded that MVD negatively correlated in event free survival (EFS). Three other studies (236 patients) showed no significant correlation between MVD with OS, progression free survival (PFS), relapse and recurrent rate, or disease free survival (DFS). MVD was negatively correlated with stadium, and MVD was shown higher in relapsed refractory HL, however, no correlation between MVD with clinical and pathological profile.

Conclusions: There were conflicting results between studies. However, several studies shown microvascular density associated with worse survival in classical Hodgkin lymphoma. Further multi centre prospective study is needed to see a real association between MVD and survival parameter in classical Hodgkin lymphoma.

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780P Comparative assessment of machine learning model performance in clinical classification of acute lymphoblastic leukemia subtypes

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Background: B-cell precursor acute lymphoblastic leukemia (BLL) is a heterogeneous disease, harboring 26 molecular subtypes characterized by unique gene expression profiles (GEPs) and diverse genetic alterations. Diagnosing subtypes defined as GEPs through traditional genetic tests can be challenging. Therefore, there is a need to consider the bioinformatics analysis of the RNA sequencing (RNA-seq) method with subtype diagnosis in detail. Recently, machine learning models for subtype classification based on GEPs have been developed, but comparisons of their performance can be inaccurate due to overlapping test and training datasets.

Methods: Our study included 69 patients diagnosed with BLL at our institution. RNA-seq analysis identified subtypes with genomic events like gene fusions, hotspot SNVs, and virtual karyotypes. We evaluated the performance of several open-source BLL subtype classifiers (ALLCatchR, ALLSorts, ALLIUM, and ALLSpice) on our RNA-seq data. The difficulties in assessing each model came from the different numbers and types of classifiable subtypes and their very own methods to represent prediction results. So, we introduced a method of multi-label encoding to turn it into a unified format of prediction results. A label based evaluation was then conducted to assess the reprocessed multi-label prediction results by calculating the evaluation index for each subtype and averaging these values.

Results: Molecular subtypes were assigned based on analysis of leukemic cells at the time of diagnosis concerning morphology, immunophenotype, molecular genetics, and cytogenetics. A total of 62 patients (89.9 %) had an established molecular subtype, and 7 patients (10.1%) were denoted as Not Other Specified. To validate subtype classifiers, only samples categorized into certain subtypes ($n = 62$) were used. As a result, ALLSorts showed the highest accuracy at 97.7%. All models performed well but they had lower sensitivity than accuracy and specificity.

Conclusions: In conclusion, the positive predictive results and performance of these GEP-based BLL subtype classifiers have shown potential relevance in clinical decisions. However, several considerations remain before applying these to actual clinical decisions.

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781P Prognostic role of targeted amino acids as oncometabolites in acute lymphoblastic leukemia

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