

## Original Article

# miR-193-5p, miR-1307-5p, and miR-671-5p: Potential biomarkers for chemoresistance in diffuse large B-cell lymphoma

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**Background and objectives:** Diffuse large B-cell lymphoma presents a significant challenge due to its high rate of treatment failure in 40% of patients. In this study we screened microRNAs as biomarkers in chemotherapy non-responding patients, to allow their early prognostication.

**Methods:** In the exploratory phase, whole transcriptome microRNA profiling was conducted on 10 diffuse large B-cell lymphoma cases. Three patients achieved complete remission, while seven had refractory or relapsed disease. The differentially expressed miRNAs were validated in 41 retrospective, treatment-naive diffuse large B-cell lymphoma biopsies, including the original 10 cases. Additionally, 33 cases with paired biopsy and plasma samples were prospectively evaluated using qRT-PCR to correlate miRNA expression with clinical outcomes. Functional validation to identify downstream pathways was done by knocking down identified miRNAs in JM-1 cells by semi-quantitative proteomics.

**Results:** miR-193b-5p, miR-1307-5p, and miR-671-5p expression were downregulated in refractory/relapsed diffuse large B-cell lymphoma biopsies. Plasma miRNA levels did not reflect prognosis. *In vitro* proteomics showed their impact on key oncogenic pathways, revealing significant enrichment of replication and transcription-related proteins.

**Interpretation and conclusions:** The expression of miR-193b-5p, miR-1307-5p, and miR-671-5p miRNAs in diffuse large B-cell lymphoma tissues may serve as predictive biomarkers.

**Keywords** Biomarkers; Deregulated miRNA expression; Diffuse large B cell lymphoma; miRNA profiling; Quantitative proteomics; Treatment outcome

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and can be classified further according to the Hans algorithm into the germinal centre (GCB) and activated B cell (ABC) types that are of prognostic relevance.<sup>1-4</sup> Although R-CHOP has improved survival, one-third of patients relapse or do not respond to the treatment.<sup>5,6,7</sup> These refractory and relapse cases demand a personalised treatment approach. Studies have reported that genetic alterations and deregulated gene expression correlate with treatment outcomes and can serve as potential biomarkers.<sup>8-11</sup> Beyond the International Prognostic Index, tumour genetic features hold promises for

improved risk stratification and accurate prediction of therapy response.<sup>12</sup>

MicroRNAs (miRNAs) bind to the 3' untranslated region (3'UTR) of target genes and inhibit translation, making them emerging biomarkers and therapeutic candidates.<sup>13,14</sup> The interaction of miRNAs with their target genes regulate the key pathways of the cell, including apoptosis, cell division, metastasis, and angiogenesis. This accentuates its importance as a driver of lymphomagenesis.<sup>15-17</sup> Distinct miRNA profiles differentiate ABC and GCB subtypes,<sup>18</sup> and comparing responder vs. non-responder signatures may

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help elucidate resistance pathways. Deep sequencing has identified miRNAs linked to treatment outcomes independent of cell of origin.<sup>19-21</sup> Differentially expressed miRNA clusters have been identified for driving lymphoma, and their mechanism of action has also been deciphered.<sup>22-27</sup> Circulating miRNAs share these deregulations and offer a stable, non-invasive biomarker source.<sup>28-31</sup>

Several studies have evaluated miRNAs in diffuse large B-cell lymphoma, but they differ in the study design and methodology. Leivonen *et al*<sup>25</sup> studied paired diagnostic and relapsed biopsies without remission controls. Lim *et al*<sup>19</sup> stratified prognostic groups using NMF rather than direct clinical outcome comparisons. Fajardo-Ramirez *et al*<sup>20</sup> analysed responder and non-responder plasma without survival data or independent validation. Bento *et al*<sup>27</sup> used microarrays to assess chemoresistance, a less sensitive platform than next-generation sequencing.

This study undertook to identify differentially expressed miRNAs in pre-treatment biopsies of patients with long-term remission (>2 yr), relapse within one year, or progressive disease, generating first-time data from the North Indian population. We evaluated these miRNAs in both tissue and plasma as predictive biomarkers in a prospective cohort and used in vitro knockout with quantitative proteomics to delineate affected pathways in non-responders. While diffuse large B-cell lymphoma mutations are well characterised, miRNA-based predictors of treatment response remain underexplored. Our findings highlight key deregulated miRNAs and support the development of a focused panel to improve patient management.

## Methods

**Patients and samples:** This study was conducted at the department of Histopathology, Post Graduate Institute of Medical Education and Research, between 2019-2022 after obtaining clearance from the Institute Ethics committee. A total of 41 cases with histopathological diagnosis of diffuse large B-cell lymphoma based on World Health Organization (WHO) criteria<sup>2</sup> were enrolled in this study after obtaining informed consent. Cases with secondary diffuse large B-cell lymphoma, post-transplant lymph proliferative disorder, diffuse large B-cell lymphoma in HIV positive and paediatric patients were excluded from the study. Prospective formalin-fixed primary lymph node biopsy samples and paired blood samples in 36 cases were collected from year 2018-2021. All retrospective cases from

year 2008-2015 were treated by CHOP chemotherapy or R-CHOP and followed up from 7-2273 days (mean 874 days). Cases in sustained complete remission for  $\geq 1095$  days were identified as responders (n=17), whereas cases with partial response/stable disease or primary progressive disease were identified as non-responders (n=24).

**Study design:** The study comprised three parts (**Supplementary Fig. 1**). Initially, whole-transcriptome miRNA profiling was performed on 10 diffuse large B-cell lymphoma cases (3 complete remission, 3 refractory, 4 relapsed). Differentially expressed miRNAs were identified by comparing responders (complete remission) with non-responders (relapse and refractory). Selected miRNAs were validated by qRT-PCR in a retrospective cohort of 17 responders and 24 non-responders, irrespective of their cell of origin. Receiver operator characteristic (ROC) analysis was used to determine  $\Delta$ Ct cut-off values. The selected  $\Delta$ Ct cut-off values of miRNAs were further tested for their predictive value in a prospective cohort with pre-treatment paired primary biopsy and plasma (**Supplementary Fig. 2**). Patients were followed for up to 730 days, and clinical outcomes were recorded (**Supplementary Tables I-III**).

**Small RNA Sequencing:** Total RNA was isolated from formalin fixed DLBCL tissues (Thermo Fisher Scientific, MA, USA), and 1  $\mu$ g RNA per sample was used. RNA was quantified using a Bioanalyzer (Agilent Technologies, CA, USA); RIN was not considered. Libraries were prepared with the Ion Total RNA-Seq Kit v2 and sequenced single-end on the Ion Torrent S5 platform. An average of 1.5 million mapped reads per sample was obtained. Data were deposited in GEO (GSE179760).<sup>32</sup> Reads <17 bp were filtered using FASTX-Toolkit (<https://bio.tools/fastx-toolkit>), aligned to hg19 with Bowtie (<https://bowtie-bio.sourceforge.net/index.shtml>), and differential miRNA expression between non-responders and complete responders was analysed using DESeq2 (<https://bioconductor.org/packages/release/bioc/html/DESeq2.html>). The *P* values were not adjusted but, the cut-off for miRNA selection was  $P < 0.01$  (Wald test of significance). miRNA target genes were predicted using miRWalk 2.0.<sup>33</sup>

**Isolation of miRNAs from tissue biopsy and cell-free plasma samples:** Total RNA was isolated from formalin-fixed tissues of prospective and retrospective cohorts. For cell-free miRNAs, blood samples were collected in PAX gene CF DNA tubes (BD Biosciences, CA,

USA). Plasma was separated the same day and stored at  $-80^{\circ}\text{C}$  and cf-miRNAs was isolated from miRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany), using 200  $\mu\text{L}$  of plasma, and final total RNA was eluted in 10  $\mu\text{L}$ . Tumour RNA was isolated from tissues using The Recover All Total Nucleic acid isolation kit (Invitrogen, Thermo Fisher Scientific, MA, USA).

*Validation of miRNAs by Real-time reverse transcription PCR:* Short listed miRNAs from top 30 significant miRNAs in non-responding cohort were validated by q-RT-PCR. Reverse transcription of tumour RNA and cfRNA was performed using MystiCq microRNA cDNA Synthesis Mix (Sigma, MO, USA). qRT-PCR Brilliant III Syber Master Mix (Agilent, CA, USA) was used for qRT-PCR and performed on Aria Mx Real-Time PCR System. Reactions were run in 1000ng RNA concentration for tissue.  $\Delta\text{Ct}$  normalisation was done with SNORD44 (Sigma, MO, USA) and  $2^{-\Delta\Delta\text{CT}}$  method was used to calculate fold change (primer sequence given in **Supplementary Table IV**).

*In vitro proteomic analysis of miR-1307-5p and miR-193b-5p knockdown:* To identify oncogenic proteins affected by loss of expression of miRNAs, *in vitro* quantitative proteomic analysis was done on JM1. Cells were maintained in Iscove Modified Dulbecco Media (IMDM) supplemented with 10% FBS in T-75 flask till 70% confluency was achieved. Lipofectamine RNAi max was used for transfection (Thermo Fisher Scientific, MA, USA), 10  $\mu\text{M}$  of anti-miRs were commercially synthesised. For transfection serum starved  $5 \times 10^5$  cells were seeded in each well of 12 well plates in 450  $\mu\text{L}$  Opti-MEM without antibiotic and 45 pmol antimiRs. After 7h complete media (up to 1 mL) was added, and cells were grown for 30 h. Transfection was confirmed using a positive control let-7c miRNA antimir, with a known target HMGA2, at 30 h time point upregulated expression of HMGA2 was observed by qRT-PCR. For LC-MS/MS cells were washed and collected in 1x PBS, a negative control in which only lipofectamine was also plated.

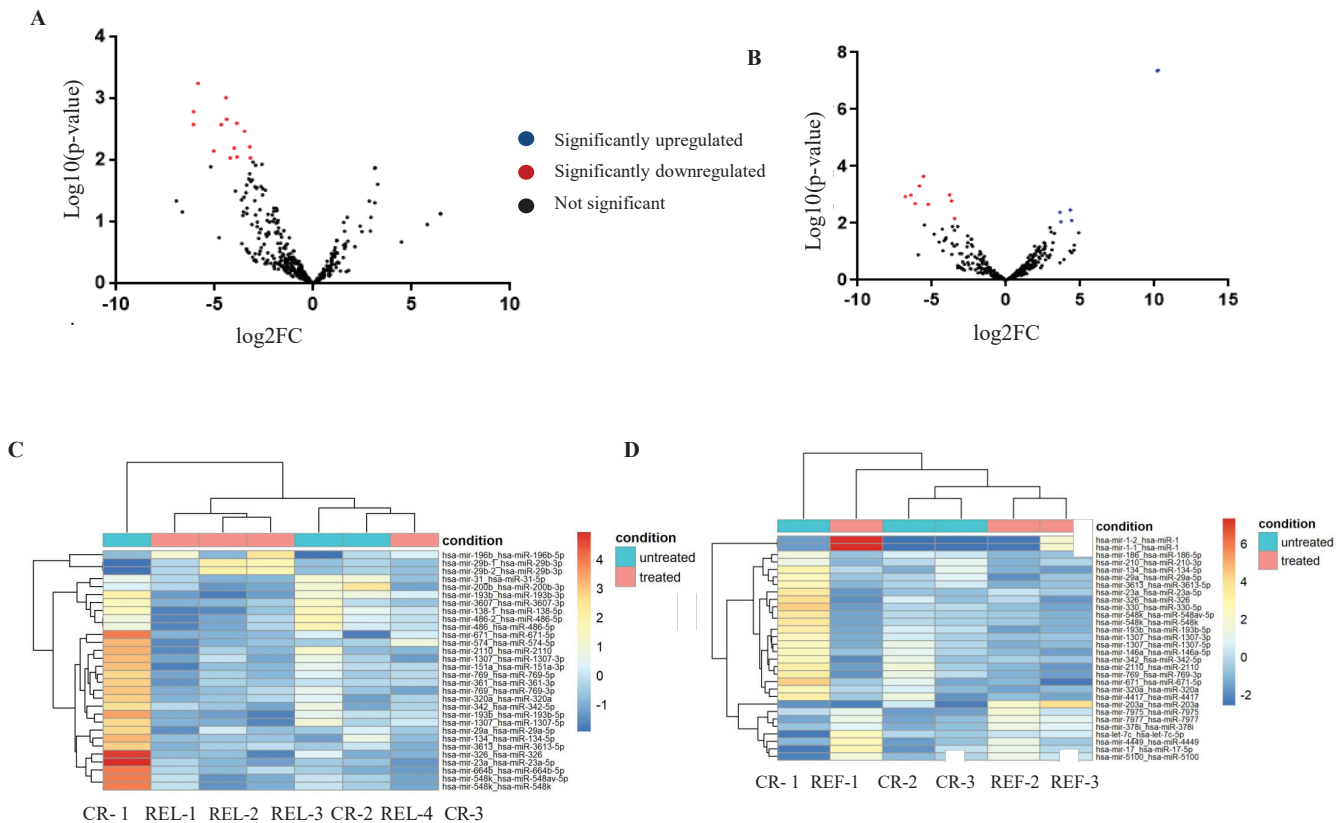
*Sample preparation for proteomics:* Cells were harvested, washed with PBS, lysed in hot 6 M GnHCl/0.1 M Tris (pH 8.5) with protease inhibitors, heat-denatured at  $90^{\circ}\text{C}$ , sonicated, and clarified by centrifugation. 25 mg protein were reduced (10 mM DTT), and alkylated (50 mM IAA), and digested with 1  $\mu\text{g}$  ( $37^{\circ}\text{C}$ , 16 h). LC-MS/MS was done on Orbitrap Fusion LumosTribid Mass Spectrometer. Data was processed in Proteome discoverer 2.0 and fold change were calculated relative to lipofectamine-only

negative controls.<sup>34</sup> Differentially expressed proteins were defined as  $\geq 1.5$ -fold change with  $\text{FDR} < 0.001$  using a target-decoy strategy. For identification of enriched biological process by knockdown of miRNAs ShinyGO 0.82 software was used.<sup>35</sup>

*Statistical analysis:* Statistical analysis was done with Graphpad Prism version 8. We aimed to compare the mean  $\Delta\text{Ct}$  values between two independent cohorts: (i) remission and (ii) non-responders (relapse and refractory). The assumption of normality of qRT-PCR data were tested visually by Q-Q plots and statically by Shapiro-Wilk test. After the confirmation of data normality, unpaired t-test was used to compare delta Ct values of each miRNA between both independent cohorts. Unpaired t-test was chosen over other test as (i) mean delta Ct was compared between independent cohorts -remission and non-responders (ii) qRT-PCR data followed normal distribution. The delta Ct values of each miRNA were compared between both the cohorts, and miRNAs with a  $P < 0.05$  were considered significant. Spearman correlation was used to determine an association between a miRNA expression and progression-free survival. Progression-free survival time was calculated between treatment end and progression or death due to disease. ROC analysis was done to assess the clinical utility of validated miRNAs as a biomarker.<sup>36</sup> Clinical parameters including presence/absence of B symptoms, disease stage, and nodal/extranodal origin of diffuse large B-cell lymphoma were also analysed done by unpaired t-test. For prospective samples, based on the selected Ct value, a prediction for treatment outcome was done and matched with the final clinical assessment. Lastly, a correlation between cell-free and biopsy miRNAs levels was evaluated by Spearman correlation.

## Results

Whole miRNAs transcriptome sequencing of 10 cases of DLBCL including three in CR (responders), three refractory, and four relapsed cases (non-responders) was done and the differentially expressed miRNAs are depicted in the volcano plot (**Figs. 1A and B**) and heatmaps in relapsed (**Fig. 1C**) and refractory cases (**Fig. 1D**). There was no significantly upregulated miRNAs in non-responders (refractory and relapse) compared to complete responders. Out of 30 downregulated miRNAs, the top four miRNAs in refractory and relapsed diffuse large B-cell lymphoma cases- miR-671-5p, miR1307-5p, miR-326, and miR-193b-5p were selected for further analysis and validation



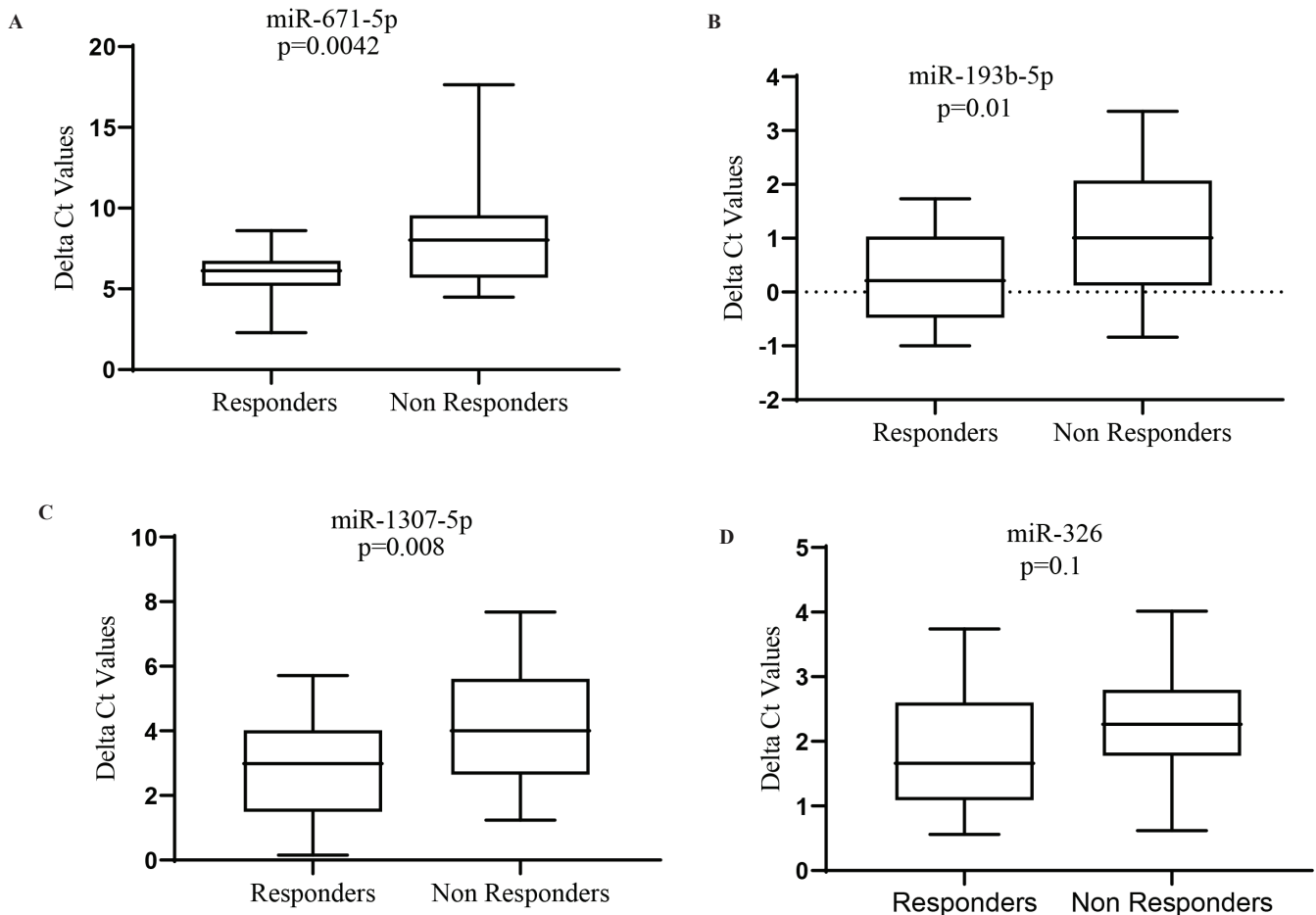
**Fig. 1.** miRNA sequencing results and differential miRNA expression of DLBCL responders (n=3) versus non-responders (3 refractory and 4 relapse). (A) and (B) Volcano plots, red data points indicate significantly downregulated miRNA with  $P$  value  $<0.01$  and (C) and (D) corresponding heat maps. (A) and (C) show results comparing responders with relapse cases and (B) and (D) show results comparing responders with refractory cases.

(Supplementary Table V). The genes targeted by these differentially expressed miRNAs were predicted by mirwalk2.0 and are shown in the Supplementary Table VI.

**Validation of selected miRNAs:** The selected miRNAs were evaluated in biopsy samples of 41 responders or non-responders DLBCL cases and the  $\Delta C_t$  values were compared. miR-671-5p, miR-1307-5p, and miR-193b-5p were found to be significantly down-regulated in non-responders (Fig. 2, Supplementary Table V), implicating them in chemotherapy resistance. There was no correlation of stage, B-symptoms or nodal/extranodal origin with any of the miRNAs validated (Fig. 3), with the sole exception of miR-671-5p with B symptoms. Receiver operator characteristic curve analysis enabled the selection of the best  $\Delta C_t$  cut-off values for prognostic and predictive utility (Supplementary Fig. 2). Downregulation of all three miRNAs correlated negatively with poor progression-free survival (Fig. 4; 4A, C, and E) and poor treatment outcome (Fig. 4B, D and F).

**Tissue versus plasma cell-free miRNAs:** We evaluated 36 paired prospective biopsy and plasma cell-free miRNAs samples for the expression of miR-671-5p, miR-193b-5p, miR-1307-5p by qRT-PCR. A significant correlation between expression of cell-free miRNA and biopsy was observed for miR-193b-5p and miR-1307-5p but not for miR-671-5p (Supplementary Fig. 3).

**Prediction of treatment outcome:** The cut-off Ct values from ROC analysis for outcome prediction were 7.2 for miR-671-5p, 4.35 for miR-1307-5p, and 0.44 for miR-193b-5p. Patients whose all three miRNAs levels were above the selected cut-off were considered non-responders. The prediction was done on 33 cases after excluding three lost to follow up (13 cases were predicted as non-responders and 20 as responders). The prediction for non-responders was correct in 11/13 (84.6%) cases and two cases showed only partial response. The prediction for responders was correct in 18/20 (90%) cases as only two turned non-responders on follow up. However, plasma miRNAs expression did not correlate with clinical outcome as only 4/13(30%)



**Fig. 2.** Validation of differentially expressed miRNA by qRT-PCR in 17 responders and 24 non-responders. Box and whisker plots with bar representing mean of  $\Delta$ Ct values for each miRNA (A) 5.8 and 8.07; (B) 0.28 and 1.1; (C) 2.7 and 4.2; (D) 1.9 and 2.3 in the respective cohorts.

cases were predicted to be non-responders based on the selected cut-offs.

**Identification of pathways and genes enriched by miR-193b-5p and miR-1307-5p knockdown:** LC-MS/MS revealed upregulation of 486 proteins by knockdown of miR-1307-5p and of 632 proteins by knockdown of miR-193b-5p compared with the negative control). Gene ontology of miR-1307-5p and miR-193b-5p revealed top 20 pathways that can influence cancer progression and its response to chemotherapy (**Supplementary Fig. 4 A and B**).

### Discussion

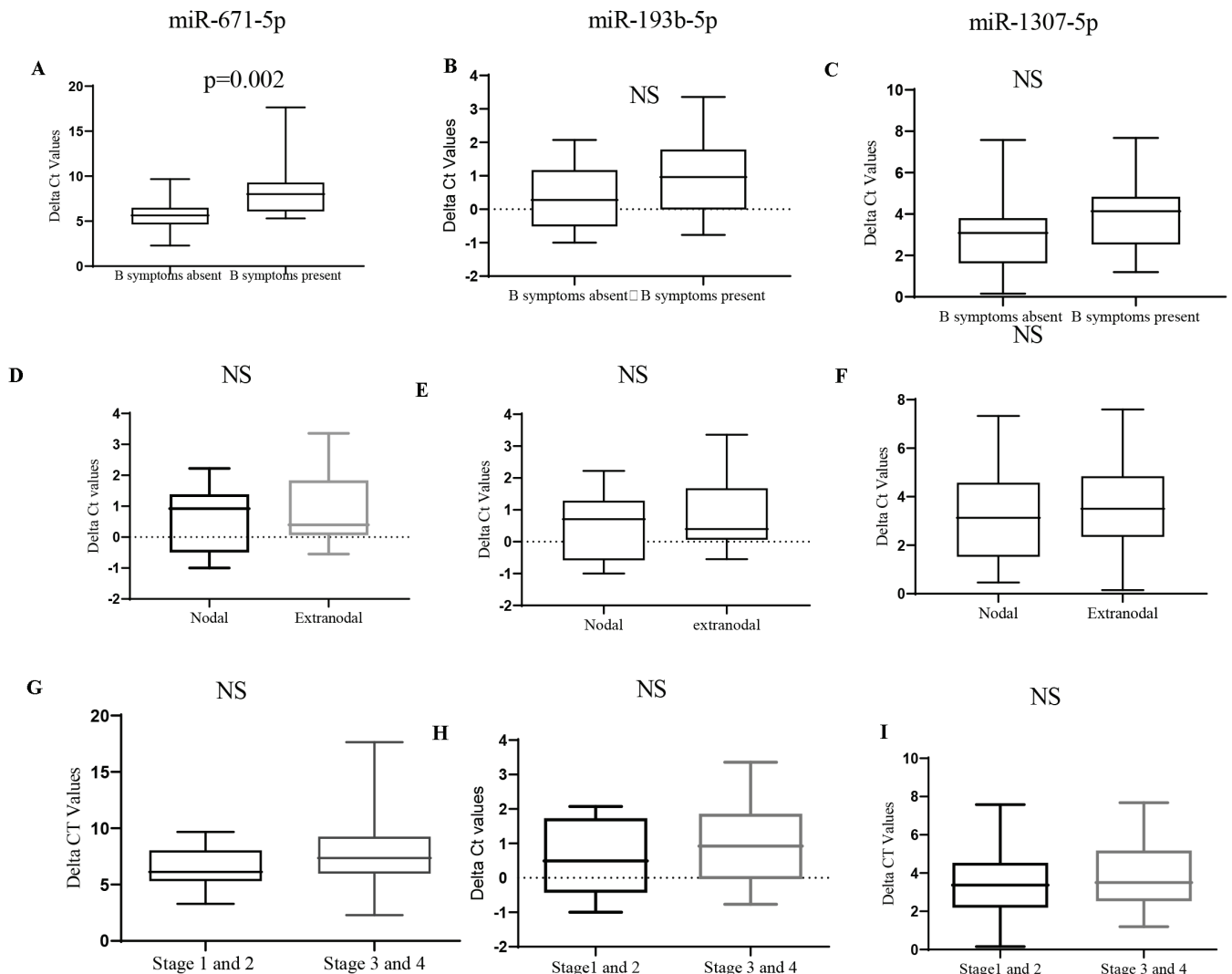
This pilot study is a comparative expression profile of miRNAs to distinguish chemotherapy-resistant from chemosensitive cohorts in diffuse large B-cell lymphoma. Specifically, the downregulation of miR-193b-5p, miR-1307-5p, and miR-671-5p was associated

with poor treatment response. From a clinical point of view, tissue-based miRNA profiling may provide a useful prognostication tool for stratifying patients prior to treatment initiation.

Downregulation of all three miRNAs above the defined  $\Delta$ Ct cut-offs in tissue biopsies predicted non-response to treatment and correlated with clinical outcome, as shown by Kaplan-Meier plots (**Fig. 4**).

Previous studies in diffuse large B-cell lymphoma have largely focused on oncogenic miRNAs such as miR-155, miR-21, and the miR-17~92 cluster. These miRNAs have been validated as prognostic markers across different cohorts.<sup>16,21,26</sup> Recently, upregulated expression of miR-193b-5p has been reported in a recent study with diffuse large B-cell lymphoma treatment failure.<sup>37</sup>

Lack of cell-free miRNA and their respective tissue expression in patients can be a result of multiple

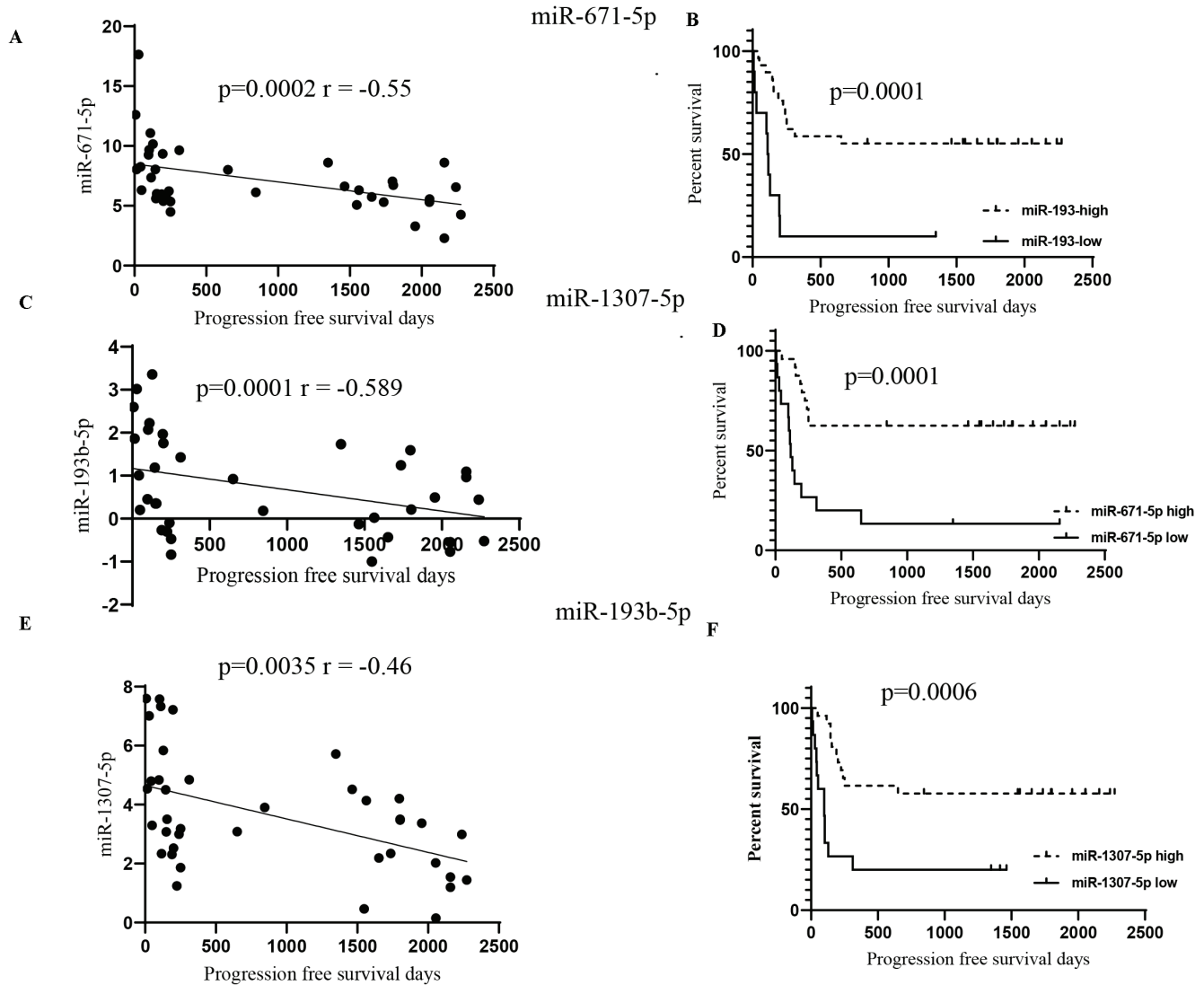


**Fig. 3.** miRNA expression and association with clinical parameters in DLBCL (n=41). Plots showing association with (A), (B), (C) B symptoms; (D), (E), (F) nodal/extranodal presentation; (G), (H), (I) disease stage. Downregulated miR-671-5p correlated with presence of B symptoms.

factors. miRNAs may be degraded in circulation, and the expression of miRNA might be affected by disease stage and its progression in patients, contributing to the heterogeneity in expression. The discrepancies can also be observed due to freeze-thaw degradation. Wang *et al*<sup>38</sup> has elucidated various confounding factors such as sample source, patient characteristic differences (age, gender, lifestyle, and history of diseases). For establishing miRNA as a non-invasive biomarker for disease progression, a large sample size is required following whole transcriptome profiling of cell-free miRNA rather than screening targeted miRNA. Then, deregulated miRNA can be selected and validated as a biomarker in an independent cohort.

In this study miRNA knockdown revealed the oncogenic pathways disrupted by miRNA knockdown. The *in silico* analysis indicated that miR-193b-5p and miR-1307-5p broadly regulate DNA replication and chromatin assembly, highlighting genomic instability and epigenetic dysregulation through the downregulation of miRNA (**Supplementary Fig. 4 A and B**). Comprehensive validation and investigation of the pathways and proteins controlled by these miRNAs will facilitate the identification of enhanced therapeutic targets.

The total number of samples evaluated in this study was small due to the fact that it was a single-centre study, and the actual numbers required for the results



**Fig. 4.** miRNA expression and progression free survival (PFS). Negative correlation of PFS with expression ( $\Delta$ Ct) of (A) miR-671-5p, (C) miR-1307-5p and (E) miR-193b-5p (Spearman correlation test). Kaplan-Meier curves showing progression free survival curve of patients with high and low expression of micro-RNA (B) miR-671-5p (n=25 high expression, n=16 low expression) (D) miR-193b-5p (n=30 high expression, n=11 low expression) and (F) miR-1307-5p (n=26 high expression, n=15 low expression; Log Rank test), n=number of cases.

to observe a have statistical significance would be much larger. This was a limitation since we combined refractory and relapsed lymphoma patients, their separate assessment may provide miRNAs unique to relapse and refractory conditions as compared to remission. Hence, this study may be viewed as a pilot study, and our observations need to be validated in a larger cohort of diffuse large B-cell lymphoma patients.

**Author contributions:** AD: Supervision, conception, data interpretation, writing manuscript; AS: Conception, data interpretation, writing manuscript; AB: Supervision, data interpretation, writing manuscript, critical revision; RS: Supervision, data interpretation,

writing manuscript; PM: Supervision; GP: Supervision; RK: Supervision. All authors have read and approve the final printed version of the manuscript.

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**Conflicts of Interest:** None.

**Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation:** The authors confirm that there was no use of AI-assisted technology for assisting in the writing of the manuscript and no images were manipulated using AI.

### शोध-संदेश

यह अध्ययन डिफ्यूज लार्ज बी-सेल लिम्फोमा (DLBCL) में उपचार विफलता की उच्च दर को ध्यान में रखते हुए किया गया, जिसमें लगभग 40% रोगियों में कीमोथेरेपी पूर्ण रूप से सफल नहीं हो पाती। शोध का उद्देश्य ऐसे रोगियों में माइक्रो-आरएनए (miR) को संभावित बायोमार्कर के रूप में पहचानना था, जिससे उपचार-प्रतिक्रिया का प्रारंभिक पूर्वानुमान लगाया जा सके। अध्ययन में पाया गया कि DLBCL ऊतकों में miR-193b-5p, miR-1307-5p और miR-671-5p की अभिव्यक्ति कीमोथेरेपी के प्रति प्रतिक्रिया की भविष्यवाणी करने में सहायक हो सकती है। ये माइक्रो-आरएनए उपचार-रोधी रोगियों की शीघ्र पहचान में उपयोगी साबित हो सकते हैं और रोग-प्रबंधन रणनीतियों को बेहतर बनाने में योगदान दे सकते हैं।

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