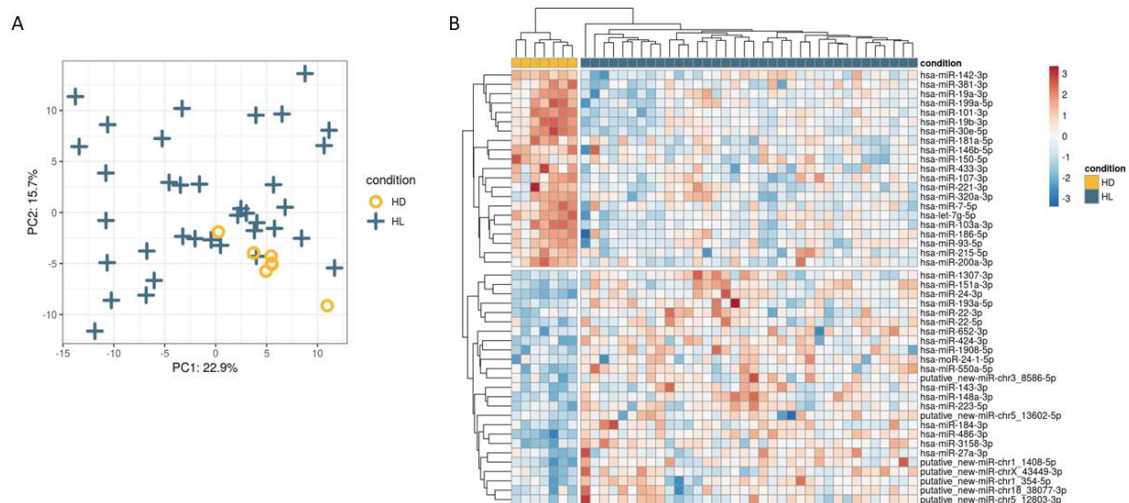
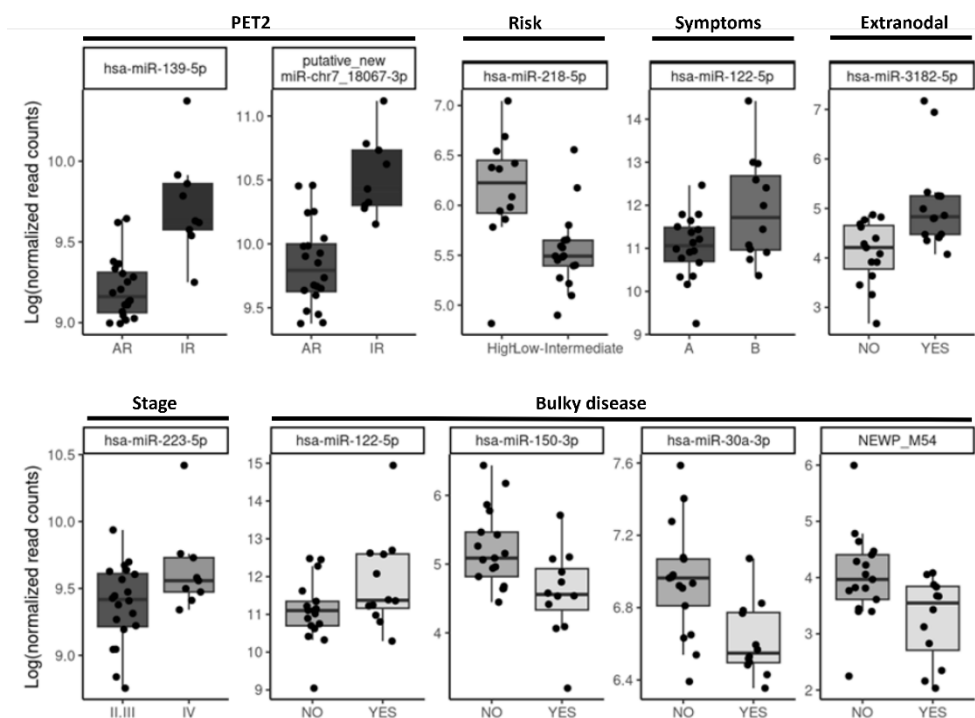
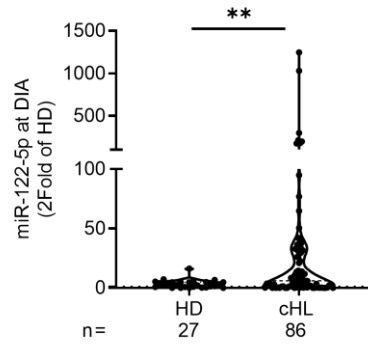




**Figure S1.** Small RNA (sRNA) sequencing of plasma circulating small extracellular vesicles derived RNA in 36 pediatric classical Hodgkin Lymphoma (cHL) cases and 7 healthy donors (HDs). **(A)** Principal component analysis of sRNA sequencing reveals a heterogeneous profile of cHL and similarity with HDs. **(B)** In cHL, 21 microRNAs (miRNAs) are less and 25 miRNAs/new putative miRNAs are more abundant compared to HDs.



**Figure S2.** Integration of sRNA sequencing analysis with clinical data. Boxplots showing the differentially abundant microRNAs (miRNAs) in plasma sEVs samples from sRNA sequencing data in PET 2; High and low intermediate risk; patients presenting and not presenting B-symptoms, nodal vs. extranodal involvement, patients staged at diagnosis as stage IV vs. stages II and III; (F) bulky vs. non-bulky disease.



**Figure S3.** RT-qPCR analysis of miR-122-5p in 86 pediatric cHL plasma samples, 27 pediatric healthy donor (HD) plasma samples. At day of diagnosis (DIA) miR-122-5p expression is significantly different in plasma small extracellular vesicles of cHL patients compared to HDs. Mann–Whitney analysis of cHL vs. HDs: significant ( $p$ -value: 0.0098, \*\*).

**Table S1.** The body mass index (BMI) and 2-fold of miR-122-5p at day of diagnosis (DIA) as a fold of healthy donors (HDs) positively correlate ( $p$ -value: 0.0033, \*\*). Plasma small extracellular vesicle miR-122-5p levels were measured at DIA and follow-up (FUP) in 43 patients. The 2-fold at FUP is significantly increased compared to FUP. Data were analyzed using a Mann–Whitney test ( $p$ -value: 0.001, \*\*\*).

|                  | BMI vs. DIA miR-122-5p (2-fold of HDs) | DIA miR-122-5p (2-fold of HD) vs. FUP miR-122-5p (2-fold of HD) |
|------------------|----------------------------------------|-----------------------------------------------------------------|
| Statistical test | Spearman r                             | Mann–Whitney                                                    |
| Number of pairs  | 62                                     | 43                                                              |
| $p$ -value       | 0.0033 (**)                            | <0.0001 (****)                                                  |