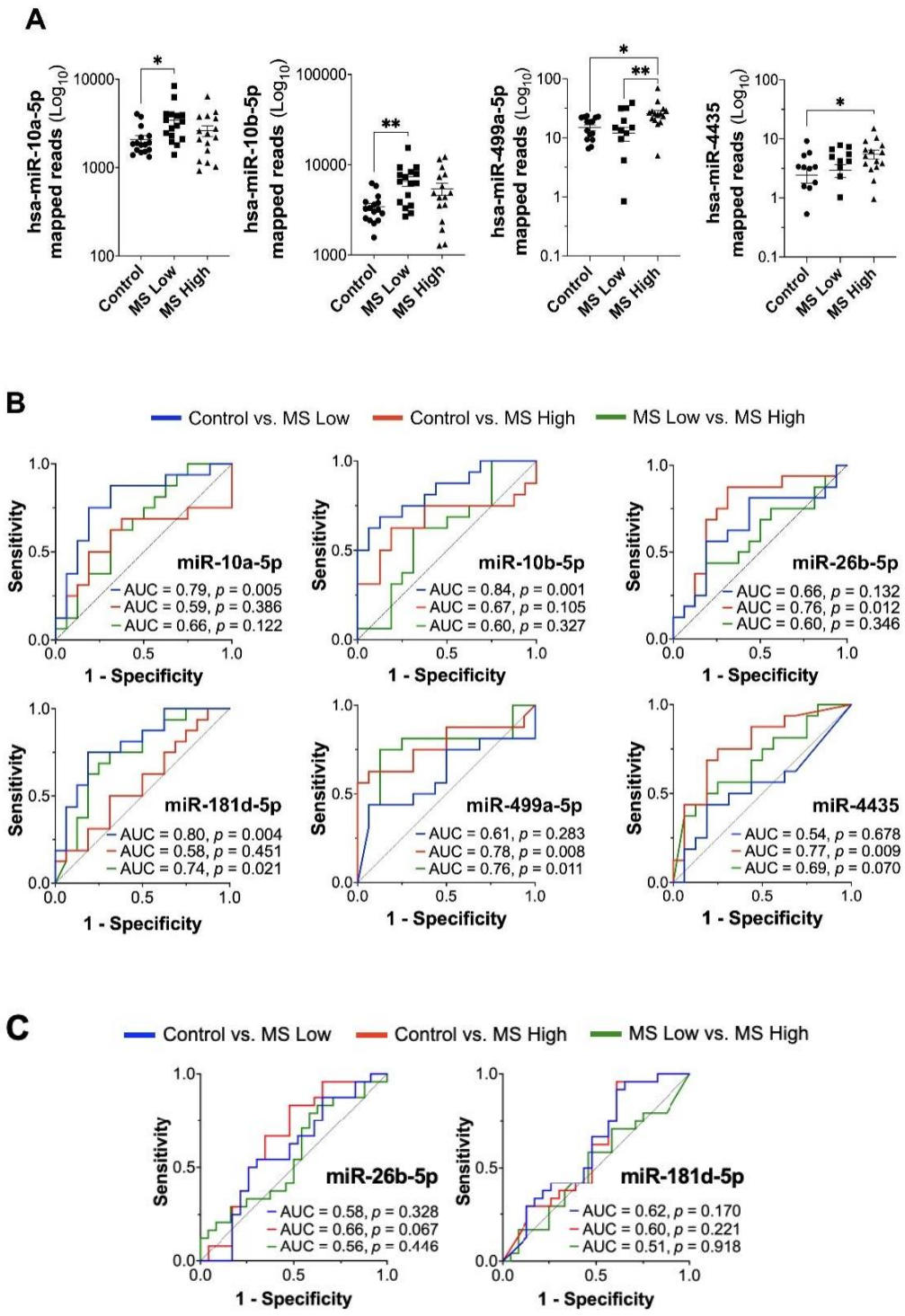
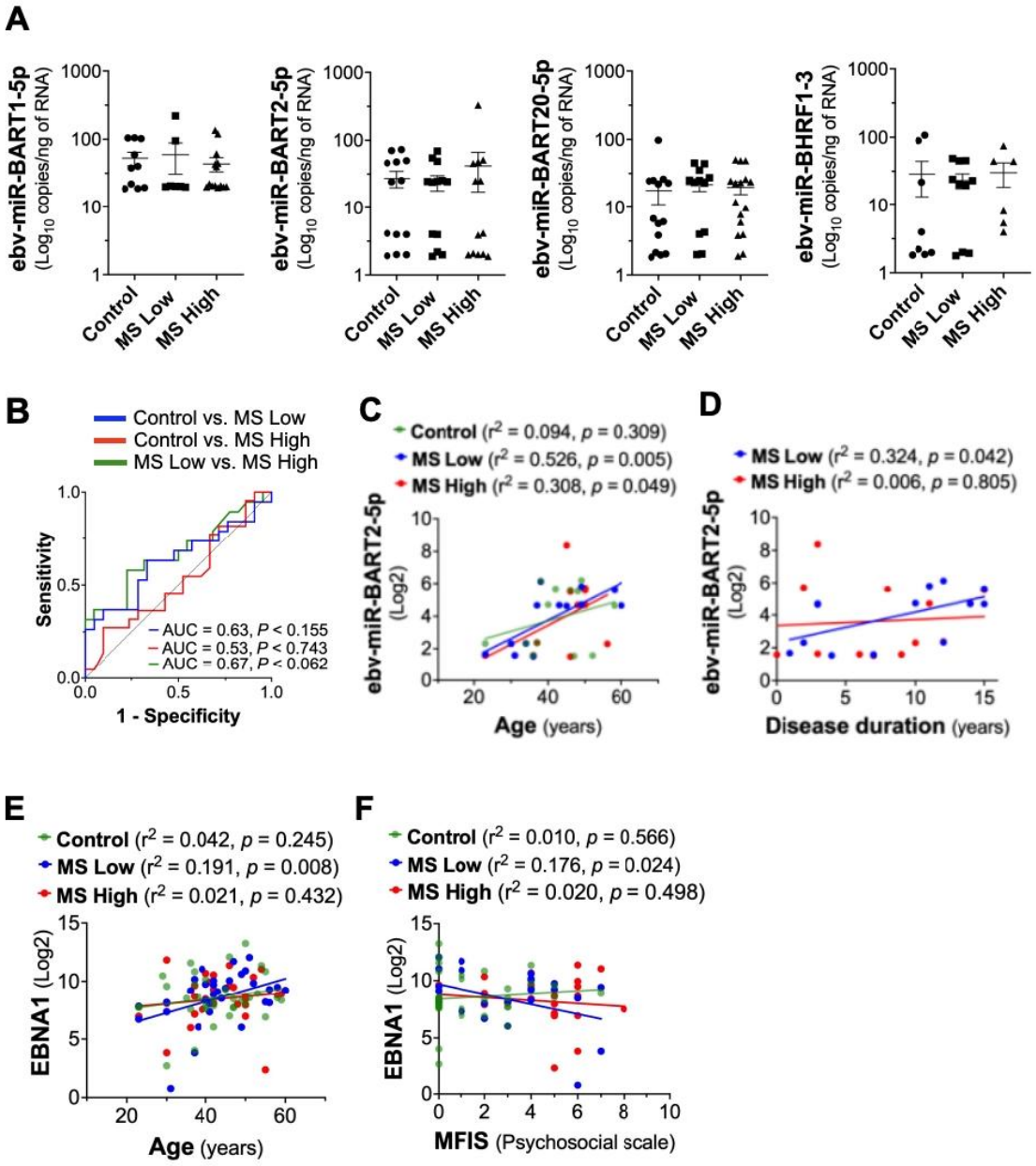
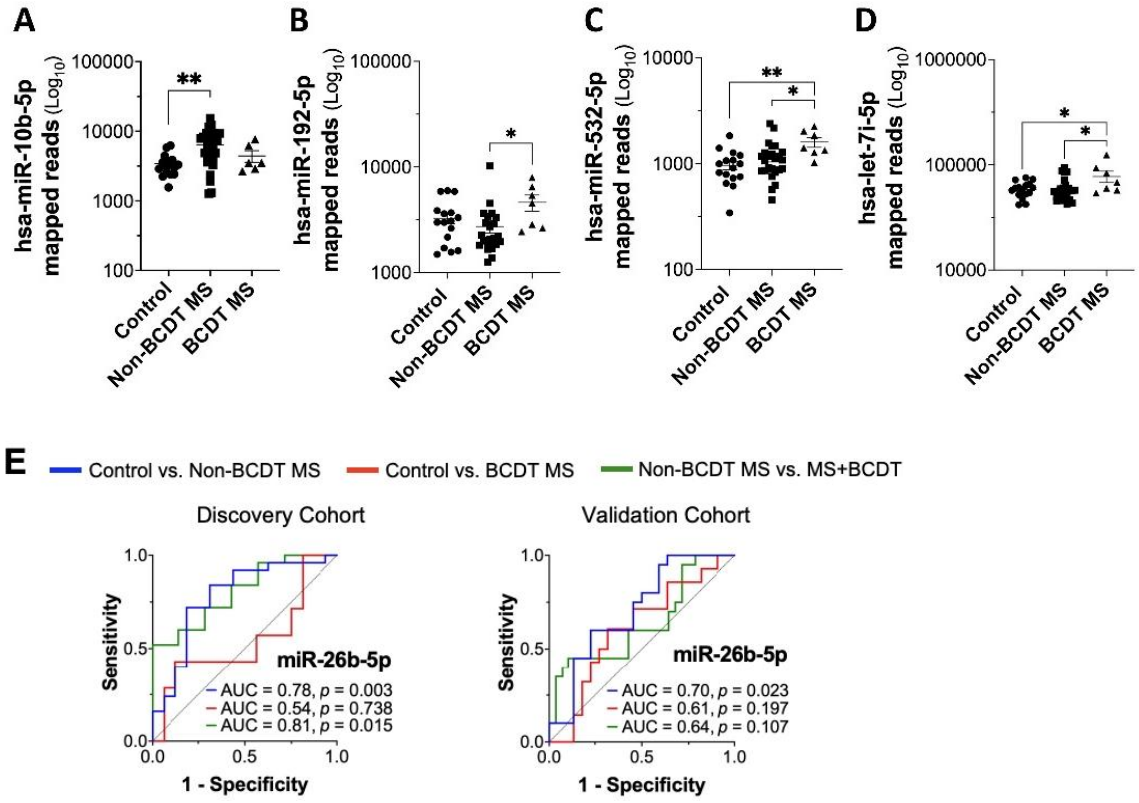
Supplementary Figures



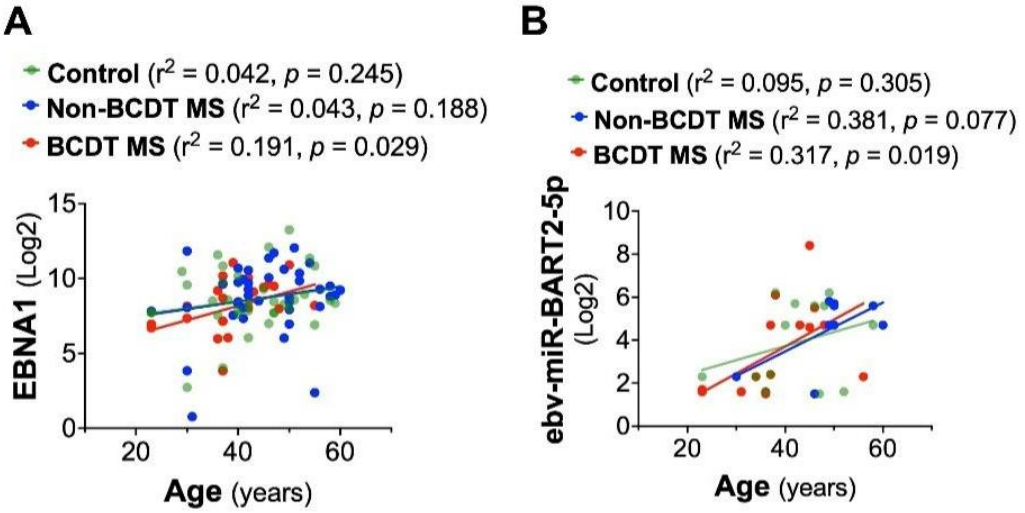
Supplementary Figure S1. ***Differential expression of serum host-encoded miRNAs in the Discovery Cohort.*** **(A)** Differential expression of identified host-encoded miRNAs. Data are presented as mean ± SEM; **p*<0.05, ***p*<0.01. **(B,C)** ROC curves of host-encoded miRNAs for discriminating persons with MS (low and high disability) from control PwoMS **(B)** in the Discovery Cohort and **(C)** Validation Cohort. The area under the ROC curve (AUROC) reflects the predictive potential of miRNAs.



Supplementary Figure S2. ***Serum levels of EBV-encoded miRNAs and EBV DNA quantities.*** **(A)** In the Validation Cohort, levels of EBV-encoded miRNAs were quantified using ddPCR. Data are presented as absolute values (mean ± SEM). **(B)** ROC curves of ebv-miR-BART11-5p for discriminating persons with MS (low and high disability) from control PwoMS. **(C-F)** Linear regression (r^2) analysis showing correlations between EBV-encoded miRNAs and clinical variables in PwMS (low and high EDSS) compared to PwoMS ($p<0.05$). Levels of ebv-miR-BART2-5p correlated with **(C)** age, and **(D)** disease duration. *EBNA1* copy numbers associated with **(E)** age, and **(F)** MFIS (psychosocial scale).



Supplementary Figure S3. ***Impact of B cell depletion therapies (BCDT) on serum host-encoded miRNAs.*** **(A-D)** Host-encoded miRNA expression, showing differential expression of the identified host-encoded miRNAs, was profiled by sequencing in the Discovery Cohort. Data are presented as mean ± SEM; *p<0.05, **p<0.01. **(E)** The area under the ROC curve (AUROC) reflects the predictive potential of miRNA in both the Discovery and Validation Cohorts.



Supplementary Figure S4. ***Impact of B cell depletion therapies (BCDT) on serum EBV-encoded DNA and miRNAs.*** Linear regression (r^2) analysis displayed association(s) between **(A)** EBNA1 copy numbers and age in the Discovery and Validation Cohorts, and **(B)** levels of ebv-miR-BART2-5p and age in the Validation Cohort in non-BCDT-treated PwMS compared to PwoMS (p<0.05).