Supplemental Figures for

Chemotherapy delivery time affects treatment outcomes of female patients with diffuse large B-cell lymphoma

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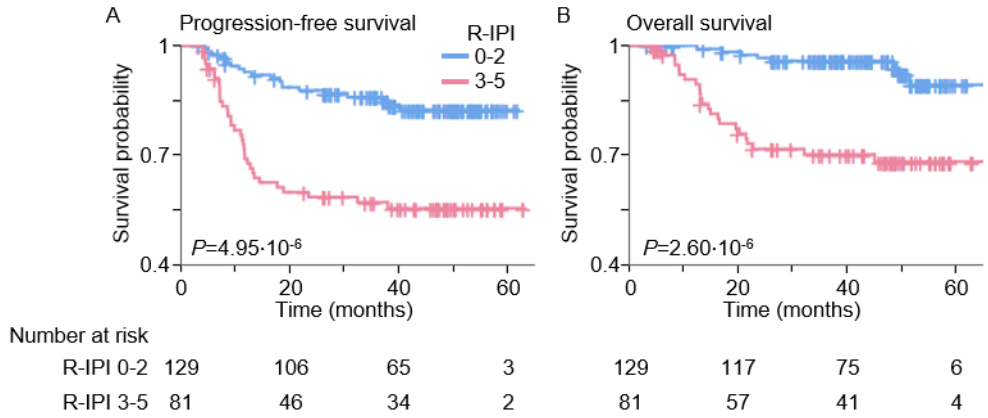
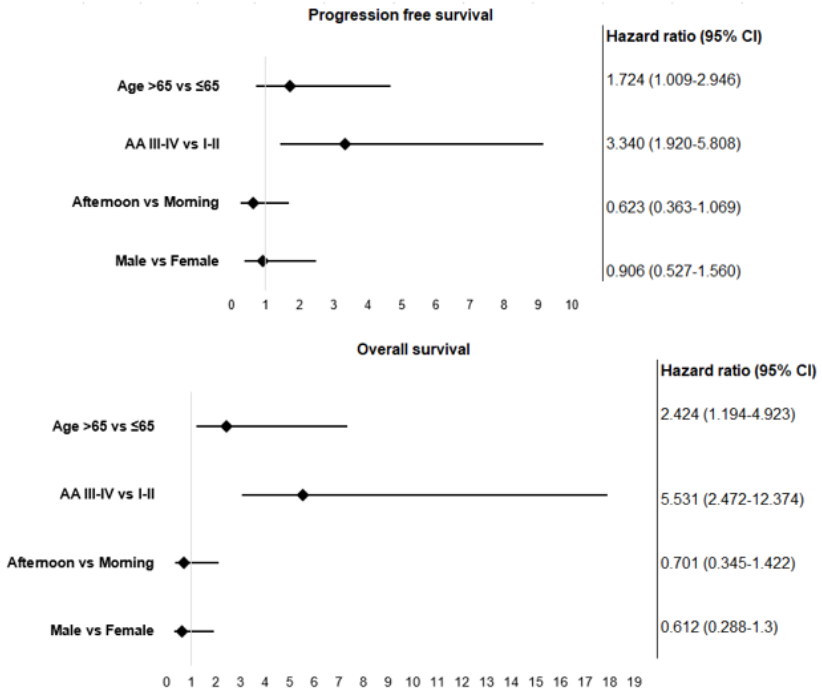
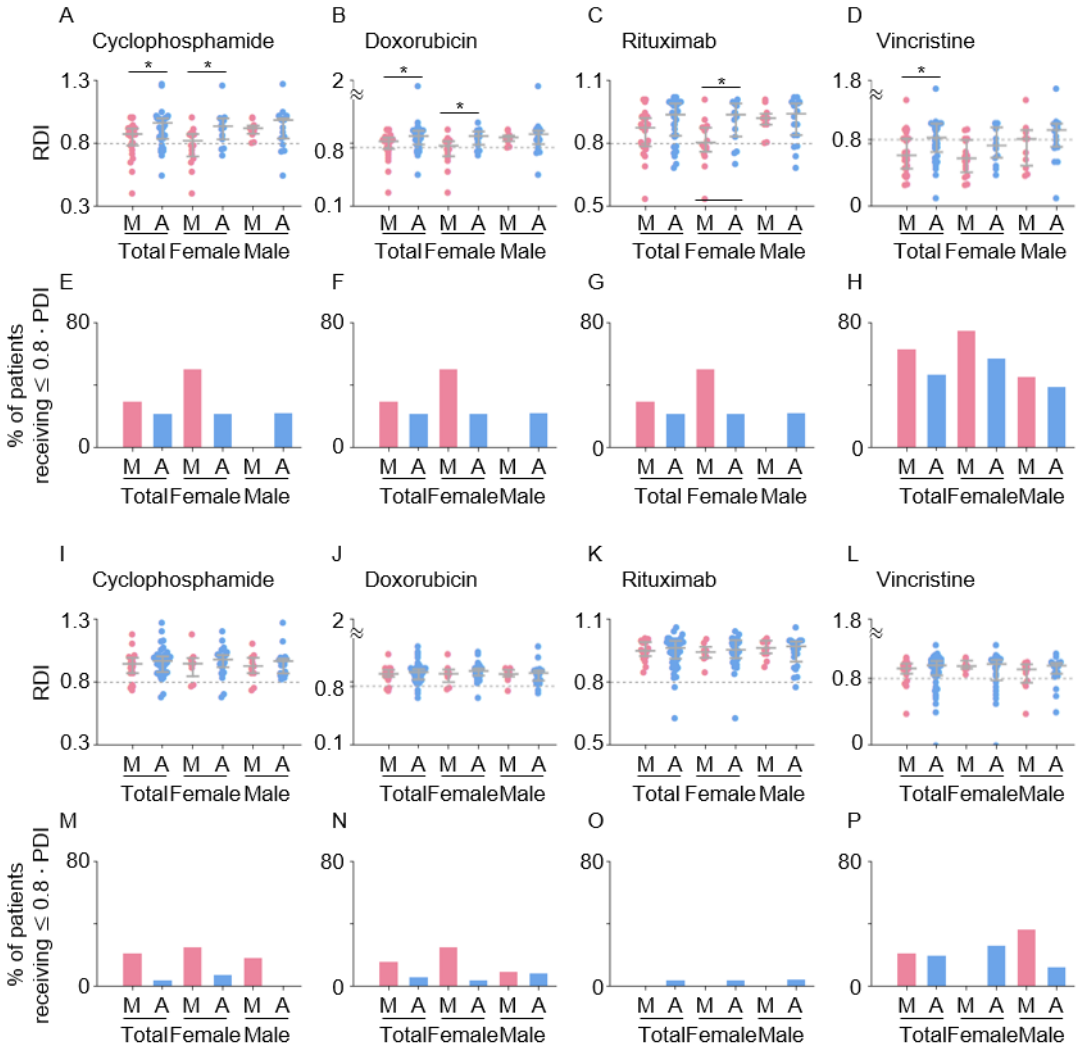


Supplemental Figure 1. Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to R-IPI. PFS and OS decreased in patients with R-IPI 0-2 compared to patients with R-IPI 3-5. Cross (+) indicates censoring of data. Here, 129 patients with R-IPI 0-2 and 81 patients with R-IPI 3-5 in the survival cohort were analyzed. *P*-values were calculated by log-rank test.

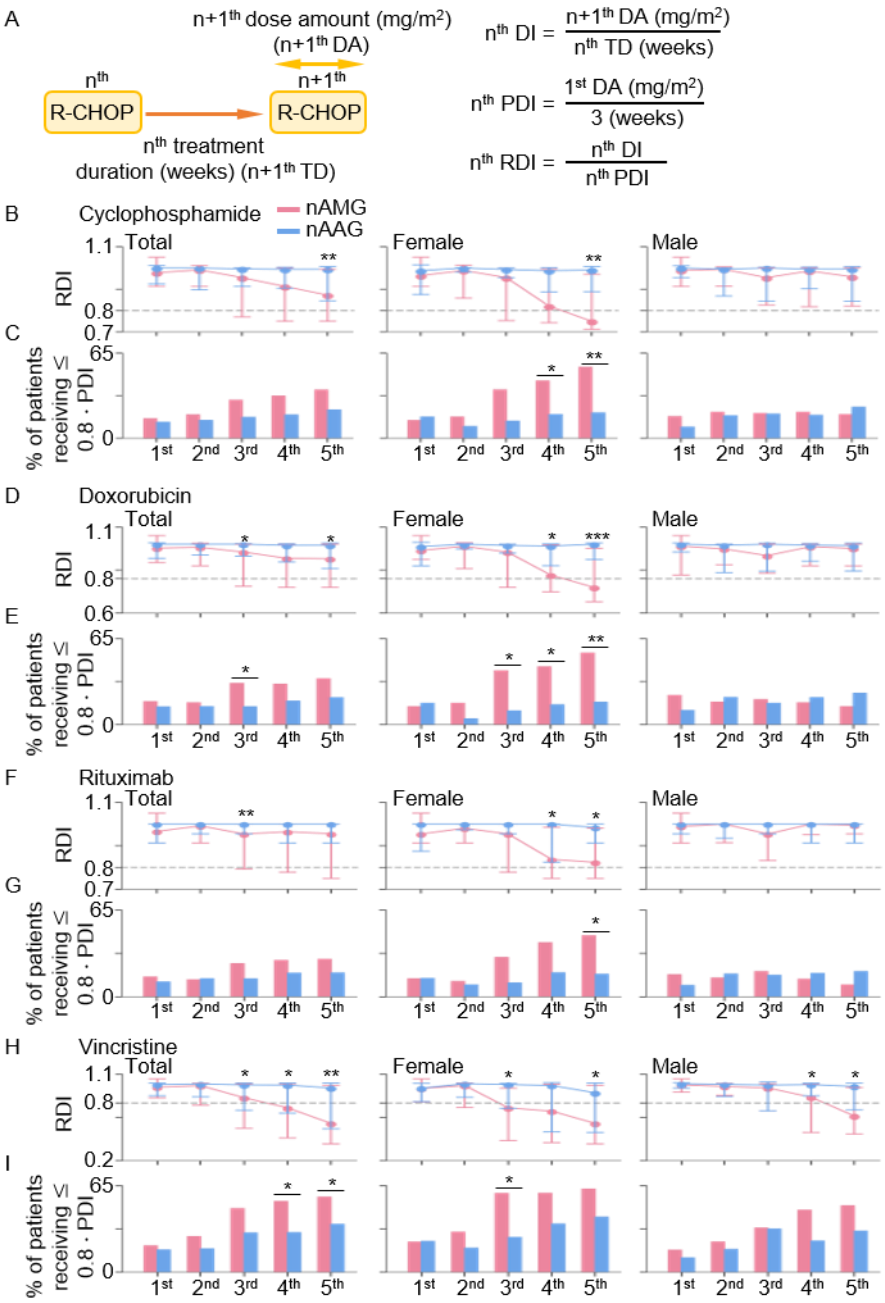


Supplemental Figure 2. Forest plots showing hazard ratios for survival. The upper and lower panels show the hazard ratios for progression-free survival and overall survival, respectively. Here, 210 patients in the survival cohort were analyzed.



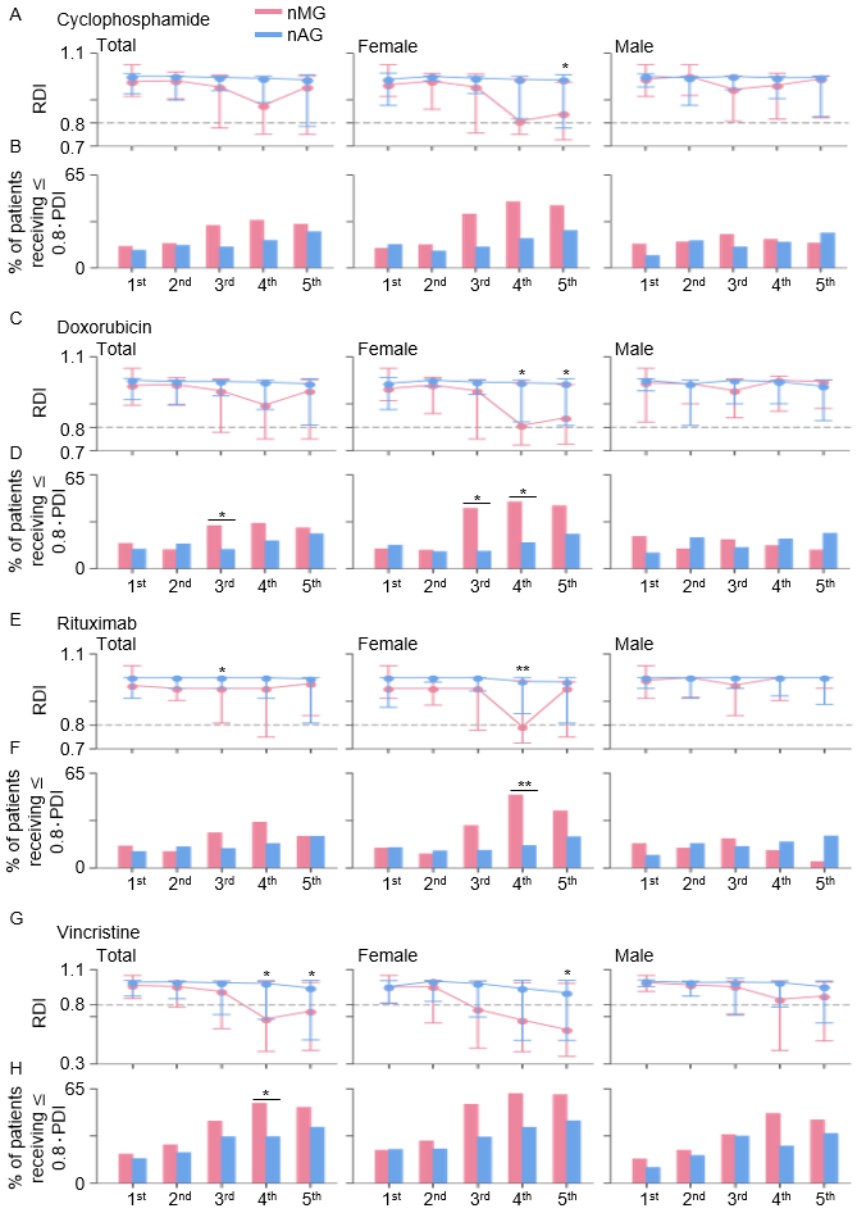
Supplemental Figure 3. Dose intensity according to sex and the time of the day of R-CHOP delivery in the two independent cohorts. (A-D) RDI (relative dose intensity) of cyclophosphamide (A), doxorubicin (B), rituximab (C), and vincristine (D) in MG and AG, female MG and AG, and male MG and AG of the Seoul National University Hospital adverse event cohort. **(E-H)** The fraction of patients receiving less than 80% of PDI (planned dose intensity) of cyclophosphamide (E), doxorubicin (F), rituximab (G), and vincristine (H) in MG and AG, female MG and AG, and male MG and AG of the Seoul National University Hospital adverse event cohort. **(I-L)** RDI of cyclophosphamide (I), doxorubicin (J), rituximab (K), and vincristine (L) in MG and AG, female MG and AG, and male MG and AG of the Seoul National

University Bundang Hospital adverse event cohort. **(M-P)** The fraction of patients receiving less than 80% of PDI of cyclophosphamide (M), doxorubicin (N), rituximab (O), and vincristine (P) in MG and AG, female MG and AG, and male MG and AG of the Seoul National University Bundang Hospital adverse event cohort. Here, RDI was calculated as in Figure 4. 129 patients in the adverse event cohort were analyzed. *P*-values in (A-D) and (I-L) were calculated by Mann-Whitney *U* test. *P*-values in (E-H) and (M-P) were calculated by Chi-square test. Error bar denotes IQR.



Supplemental Figure 4. Dose intensity for a treatment cycle according to sex and the accumulated number of morning treatments before the cycle. (A) Definition of n^{th} DI (dose intensity), n^{th} PDI (planned dose intensity), and n^{th} RDI (relative dose intensity). **(B-I)** n^{th} RDI and the fraction of patients receiving less than 80% of n^{th} PDI of cyclophosphamide (B and C), doxorubicin (D and E), rituximab (F and G), and vincristine (H and I) for each cycle. Here,

when analyzing the n^{th} RDI, patients are subgrouped into the n^{th} accumulated morning group (nAMG) if the number of morning treatments is equal to or larger than that of afternoon treatments until the n^{th} treatment. Otherwise, they are subgrouped into the n^{th} accumulated afternoon group (nAAG). RDI decreases in the nAMG but not in the nAAG when treatment is ongoing (B, D, F, and H left). Thus, RDI becomes lower in the nAMG than in the nAAG for the latter part of the R-CHOP chemotherapy (i.e., 3^{rd}, 4^{th} and 5^{th} therapies). In particular, it becomes statistically significant in the last (i.e., 5^{th}) measured RDI except for rituximab. Such lower RDI of cyclophosphamide, doxorubicin, and rituximab in the nAMG than in the nAAG is mainly due to the lower RDI in the female nAMG than in the female nAAG in the latter part of the therapy (B, D, and F center); RDI in male patients is not different between the nAMG and the nAAG (B, D, and F right). Accordingly, the fraction in the latter part becomes higher in the female nAMG than in the female nAAG (C, E, and G center) while there is no difference between the male nAMG and the male nAAG (C, E, and G right). Unlike other drugs, RDI of vincristine decreases in both the female nAMG and the male nAMG (H). However, the fraction in the latter is not statistically different between the nAMG and the nAAG in either female or male patients (I). Here, 129 patients in the adverse event cohort were analyzed. *P*-values in (B, D, F, and H) and those in (C, E, G, and I) were calculated by Mann-Whitney *U* test and Chi-square test, respectively. Solid circles and error bars in B, D, F, and H denote median and IQR.



Supplemental Figure 5. Dose intensity for a specific treatment cycle according to sex and time of the day of R-CHOP before the cycle. (A-H) n^{th} RDI and the fraction of patients receiving less than 80% of n^{th} PDI of cyclophosphamide (A and B), doxorubicin (C and D), rituximab (E and F), and vincristine (G and H) for each cycle. Here, when analyzing the n^{th} RDI, patients are subgrouped into the n^{th} morning group (nMG) if their previous treatment time is morning. Otherwise, they are subgrouped into the nth afternoon group (nAG). When

79 treatment is in progress, RDI of cyclophosphamide, doxorubicin, and rituximab decreases in
80 the nMG, in particular after the 4^{th} treatment, while it does not in the nAG (A, C, E, and G left).
81 This is mainly due to the lower RDI in the female nMG than in the female nAG in the later
82 treatments (A, C, and E center); there is no difference between the male nMG and the male
83 nAG (A, C, and E right). Accordingly, there is a higher fraction in the female nMG receiving
84 less than 80% of PDI than in the female nAG; the majority show a very slight trend toward
85 significance ($P < 0.2$) in the latter parts of the therapy (B, D, and F center). In contrast, there is
86 no such trend for the male patients (B, D, and F right). The RDI of vincristine decreases in both
87 the female nAMG and the male nAMG (G). However, the fraction receiving less than 80% of
88 PDI in the later treatments is not statistically different between the nAMG and the nAAG in
89 either female or male patients (H). Here, 129 patients in the adverse event cohort were analyzed.
90 *P*-values in (A, C, E, and G) and those in (B, D, F, and H) were calculated by Mann-Whitney
91 *U* test and Chi-square test, respectively. Solid circles and error bars in A, C, E, and G denote
92 median and IQR.