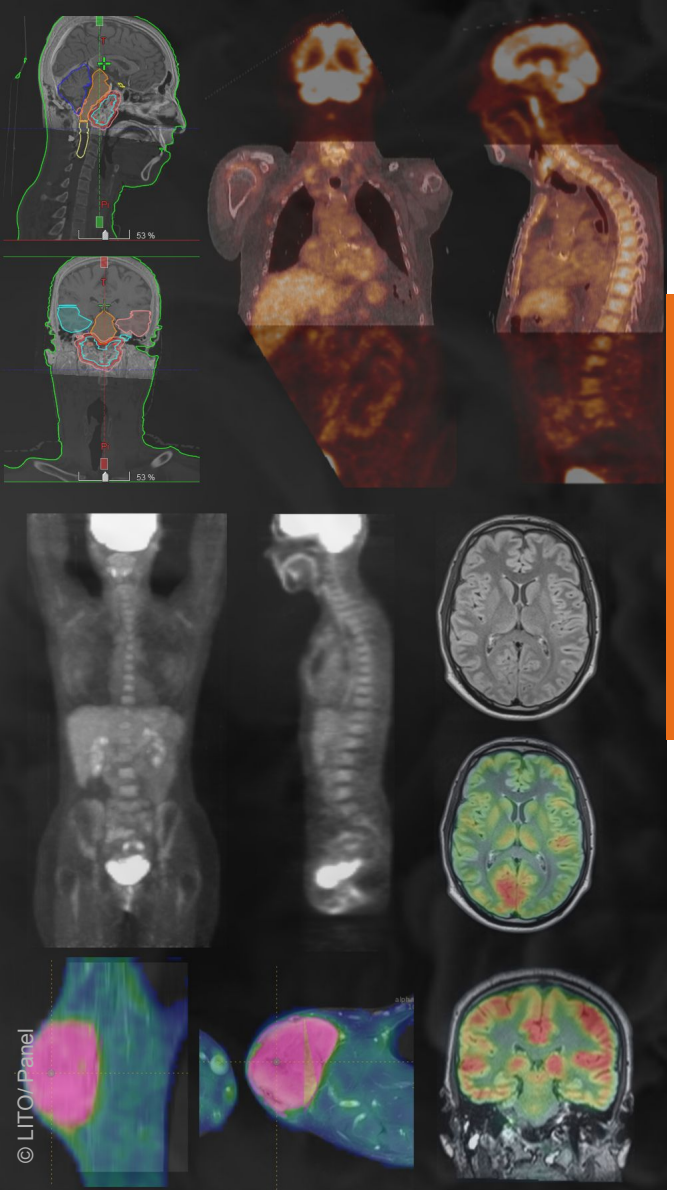


[18F]FDG-PET/CT Tumor Spread and Dissemination Measured from the Spleen in Lymphoma: How predictive of the outcome?

Kibrom B. Girum[1] and Irène Buvat[1]

[1] Laboratory of Translational Imaging in Oncology (LITO), U1288, Institut Curie, Inserm, Université Paris-Saclay, Orsay, France

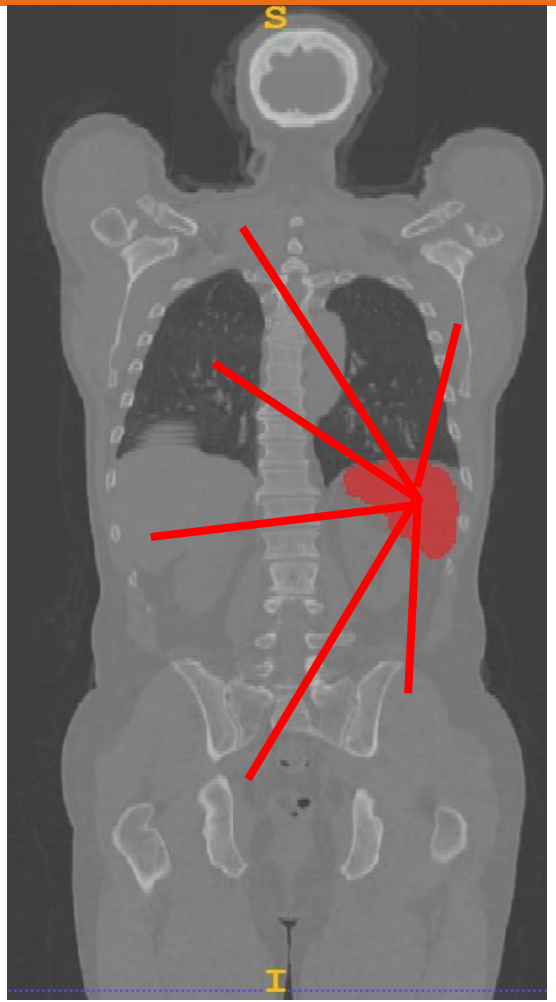
Experiment to model tumor spread and dissemination in DLBCL

- **Organ segmentation using Totalsegmentator** [Wasserthal et al. 2022]
- Tumor segmentation from the experts (Nuclear medicine experts)
- Tumor segmentation and anatomical segmentations are overlapped
- Is the spread of the tumor with respect to the spleen predictive of outcome in DLBCL patients?
- Consider the Spleen as reference organ
- We can include patients with single tumor region in the calculation
- Consider average of the spleen coordinates for the missed spleen segmentation for some cases
    - no complete CT-scan
    - no spleen segmentation from Totalsegmentator



Lesion and Spleen segmentation from PET/CT

- **Organ segmentation using Totalsegmentator** [Wasserthal et al. 2022]
- Totalsegmentator results **(REMARC data):**
  - 13 cases with wrong segmentation of the spleen
  - The spleen and other organs considered as the spleen
  - All 13 cases were corrected using LIFEx and fully automated image processing method and visually verified
  - 3 cases with no segmentation of the spleen
    - Median value of the centroid of all other cases were used
    - 1 initial included into the survival analysis
    - 2 cases removed for verification (analysis with and without)
  - 295 cases correctly segmented, visually verified

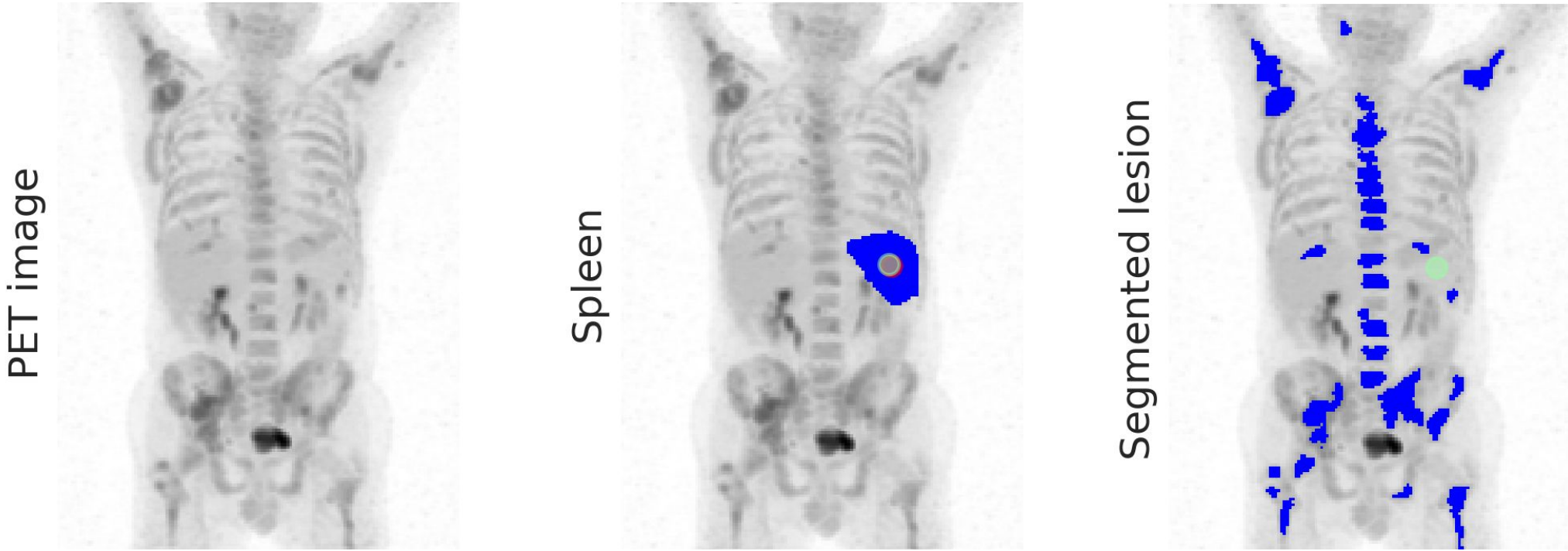


Definitions

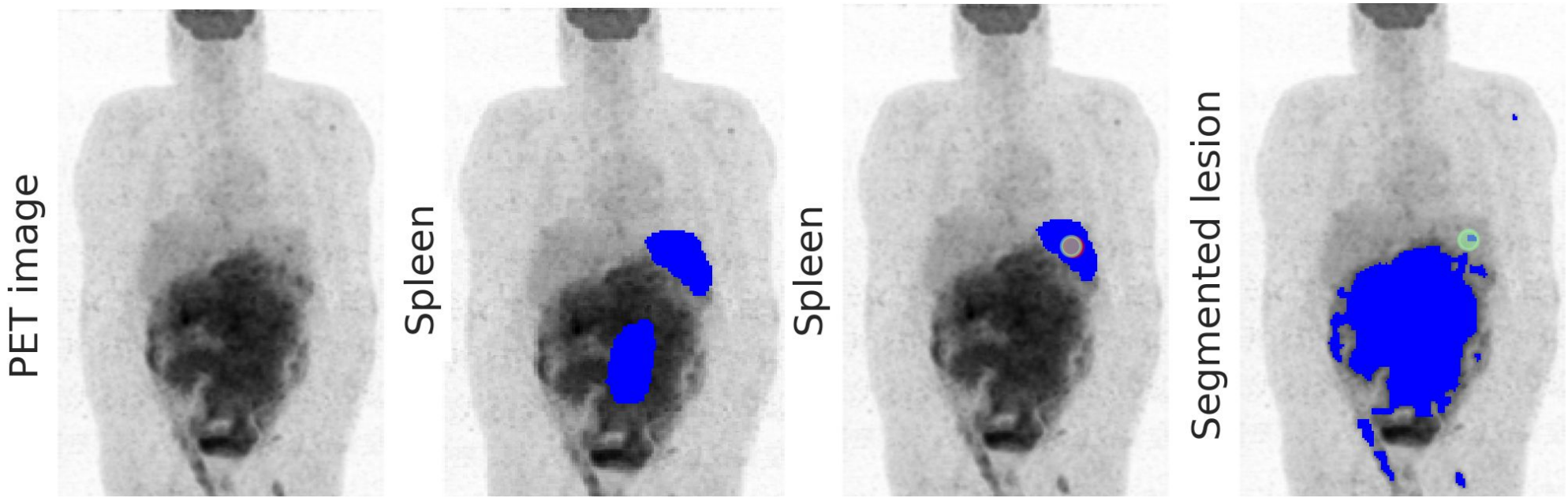
- The distance between the centroid of the Spleen and all other lesions was measured
- The standard deviation (SD) of the measured distances was defined as the Lesion Spread (LS)
- The distance of the farthest lesion from the Spleen reflects the Disseminated Lesion from the Spleen (DLS)



Lesion and Spleen segmentation results



Lesion and Spleen segmentation results



Wrong segmentation of the spleen

Corrected segmentation of the spleen

Concordance index: Univariate analysis

[18F]FDG-PET/CT features	Metric	Progression-free survival (PFS)	Overall survival (OS) Concordance index (C-index)
Total metabolic tumor volume **(TMTV)**	Concordance index (C-index)	0.657	0.661
The distance between the spleen and the farthest lesion from the spleen **(DLS)**	Concordance index (C-index)	0.655	0.637
Standard deviation of the distances calculated between all lesions and the spleen **(LS)**	Concordance index (C-index)	0.645	0.630
The distance between two farthest lesions **(Dmax)**	Concordance index (C-index)	0.635	0.600
The distance between the bulk and other farthest lesion from the bulk **(Dbulk)**	Concordance index (C-index)	0.620	0.603
International prognostic index **(IPI)**	Concordance index (C-index)	0.587	0.606

- Standardized values of Dspleen and Dspleen_spread also gave approximately the same results (squareroot((height*weight)/3600)

Correlation between image-based biomarkers
REMARC data (282 patients, 6 patients excluded)

	IPI	Dmax	TMTV	Dstd	Dbulk	Dbulk_std	DLS	LS
IPI	1.000000	0.265829	0.386894	0.155463	0.175869	0.060760	0.117074	0.152860
Dmax	0.265829	1.000000	0.350418	0.887710	0.927239	0.762420	0.758522	0.777060
TMTV	0.386894	0.350418	1.000000	0.170495	0.176012	0.002982	0.220611	0.207102
Dstd	0.155463	0.887710	0.170495	1.000000	0.888058	0.898042	0.672325	0.764432
Dbulk	0.175869	0.927239	0.176012	0.888058	1.000000	0.902704	0.698086	0.730711
Dbulk_std	0.060760	0.762420	0.002982	0.898042	0.902704	1.000000	0.569455	0.665889
DLS	0.117074	0.758522	0.220611	0.672325	0.698086	0.569455	1.000000	0.749965
LS	0.152860	0.777060	0.207102	0.764432	0.730711	0.665889	0.749965	1.000000

Time-dependent AUC (tdAUC) and hazard ratios (HR)

PET/CT Features	Metric	Progression-free survival (PFS)	Overall survival (OS)
Total metabolic tumor volume **(TMTV)**	tdAUC	0.66 (0.60-0.73)	0.66 (0.56-0.75)
	HR	11.37 (1.85-50.12)	17.56 (2.07-82.45)
The distance between the spleen and the farthest lesion from the spleen **(DLS)**	tdAUC	0.66 (0.59-0.72)	0.64 (0.58-0.73)
	HR	17.82 (3.17-53.12)	19.37 (2.91-90.74)
Standard deviation of the distances calculated between all lesions and the spleen **(LS)**	tdAUC	0.64 (0.57-0.71)	0.63 (0.55-0.72)
	HR	6.60 (1.60-18.39)	10.28 (1.64-46.05)
The distance between two farthest lesions **(Dmax)**	tdAUC	0.65 (0.58-0.71)	0.61 (0.52-0.69)
	HR	8.32 (2.10-23.92)	6.41 (1.04-18.75)
International prognostic index **(IPI)**	tdAUC	0.60 (0.54-0.66)	0.60 (0.52-0.69)
	HR	3.47 (1.19-8.13)	5.88 (1.34-16.34)

Multivariate analysis

New

PET/CT features	Metric	score_pfs	score_os	Pval_PFS	Pval_OS
LS	tdAUC	0.692000	**0.687281**	0.000020	0.000320
DLS	tdAUC	0.699088	**0.663547**	0.000010	0.001811
Dmax	tdAUC	0.685941	**0.648667**	0.000020	0.005093
Dbulk	tdAUC	0.663712	**0.647577**	0.000150	0.000150
TMTV	tdAUC	0.6699408	0.669406	-	-

Multivariate analysis

New

PET/CT features	Metric	Mean_base_PFS **(TMTV + IPI)**	mean_new_PFS	mean_base_OS **(TMTV + IPI)**	**mean_new_OS**
LS	tdAUC	0.669518	0.719673	0.669406	**0.727752**
DLS	tdAUC	0.669518	0.723126	0.669406	**0.708878**
Dmax	tdAUC	0.669518	0.694279	0.669406	**0.676047**
Dbulk	tdAUC	0.669518	0.693513	0.669406	**0.688138**

mean_new_os/pfs indicates the value of the combined model (new biomarker plus the baseline biomarkers (TMTV +IPI))

Multivariate analysis

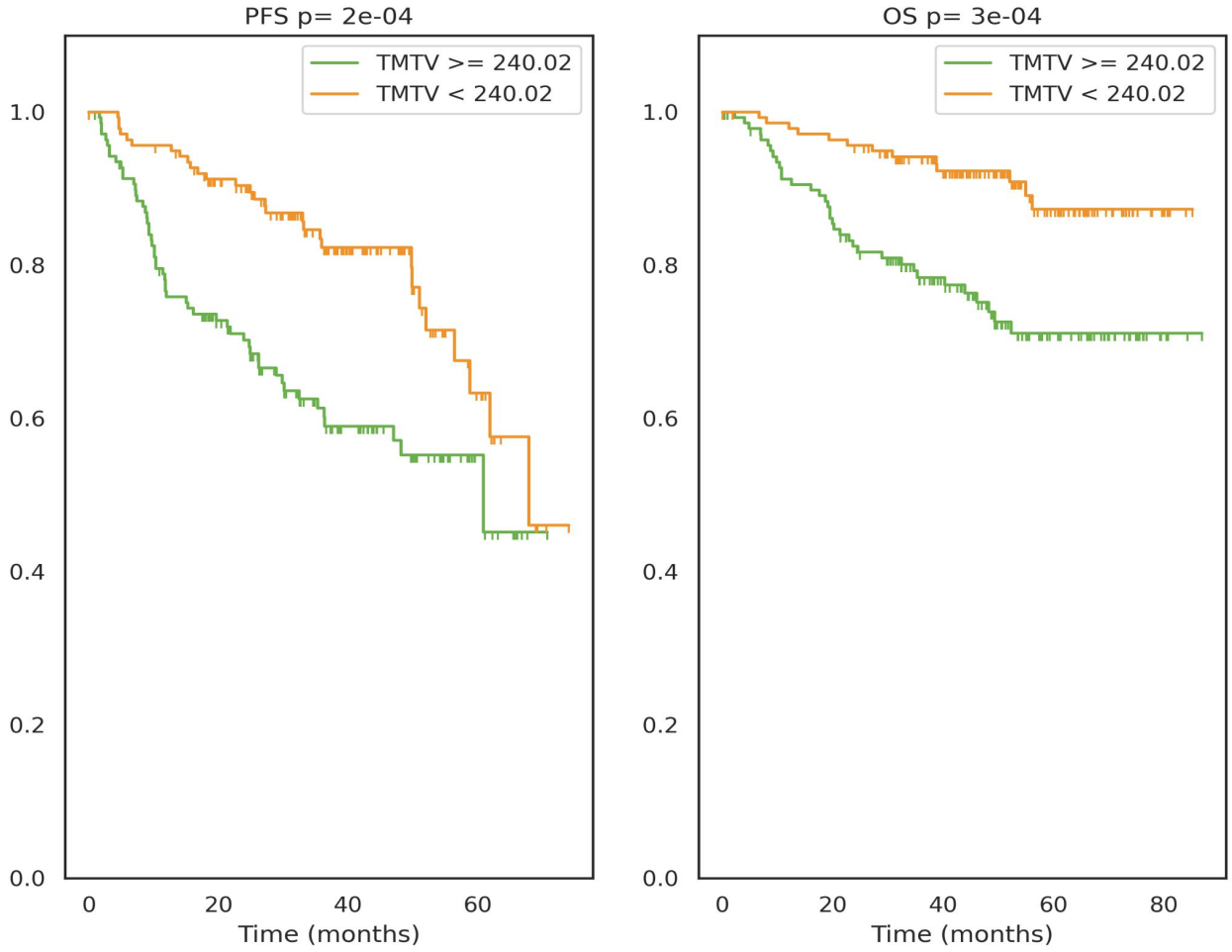
New

Image-driven biomarker	Metric	Mean_base_PFS **(TMTV)**	mean_new_PFS	mean_base_OS **(TMTV)**	**mean_new_OS**
LS	tdAUC	0.669940851	0.7324347	0.672639189	**0.7289708999**
DLS	tdAUC	0.669940851	0.7342246	0.672639189	**0.7184582198**
Dmax	tdAUC	0.669940851	0.7028790	0.672639189	**0.6737697171**
Dublk	tdAUC	0.669940851	0.7003769	0.672639189	**0.6870213808**

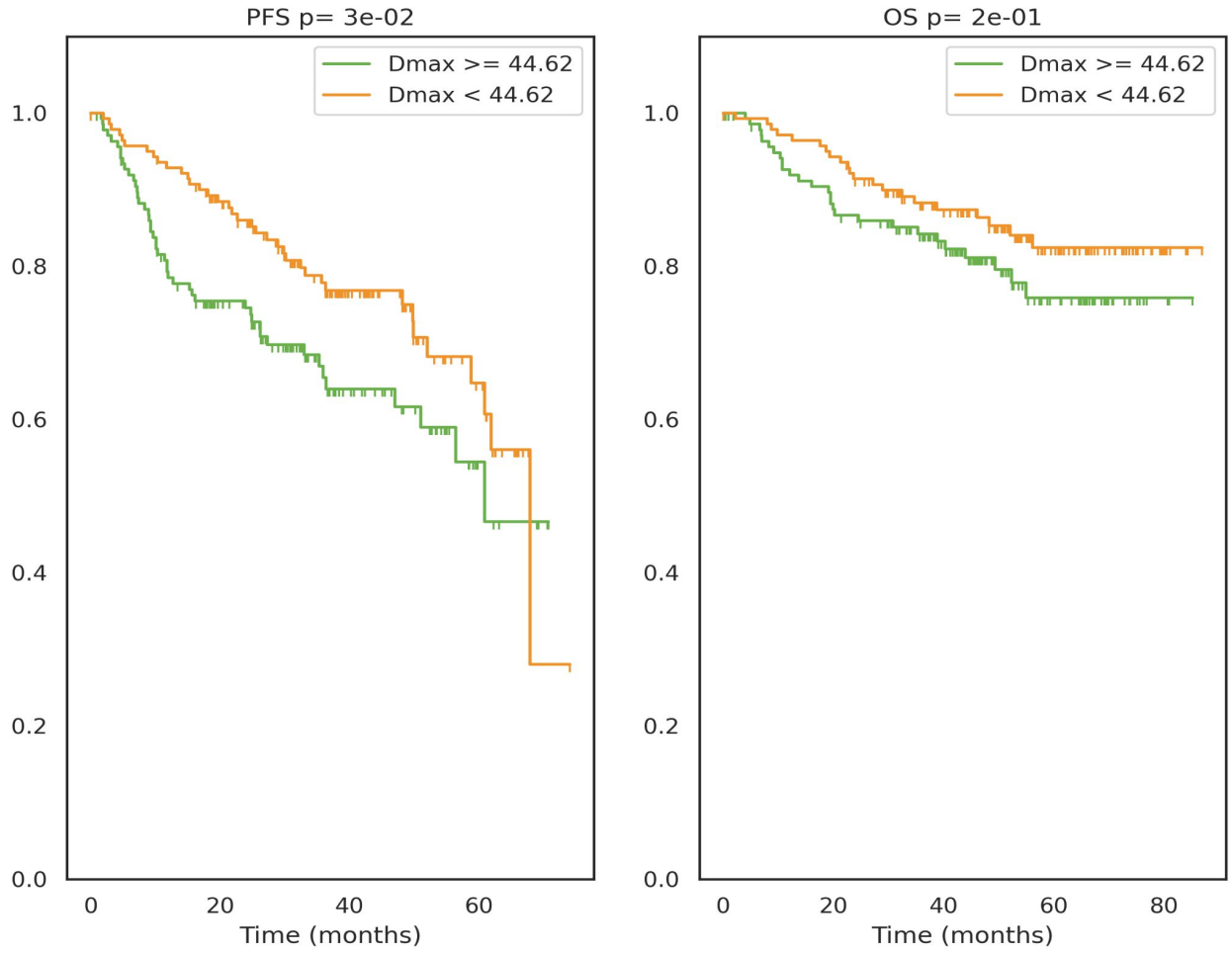
mean_new_os/pfs indicates the value of the combined model (new biomarker plus the baseline biomarkers (TMTV))

Kaplan-Meier estimator

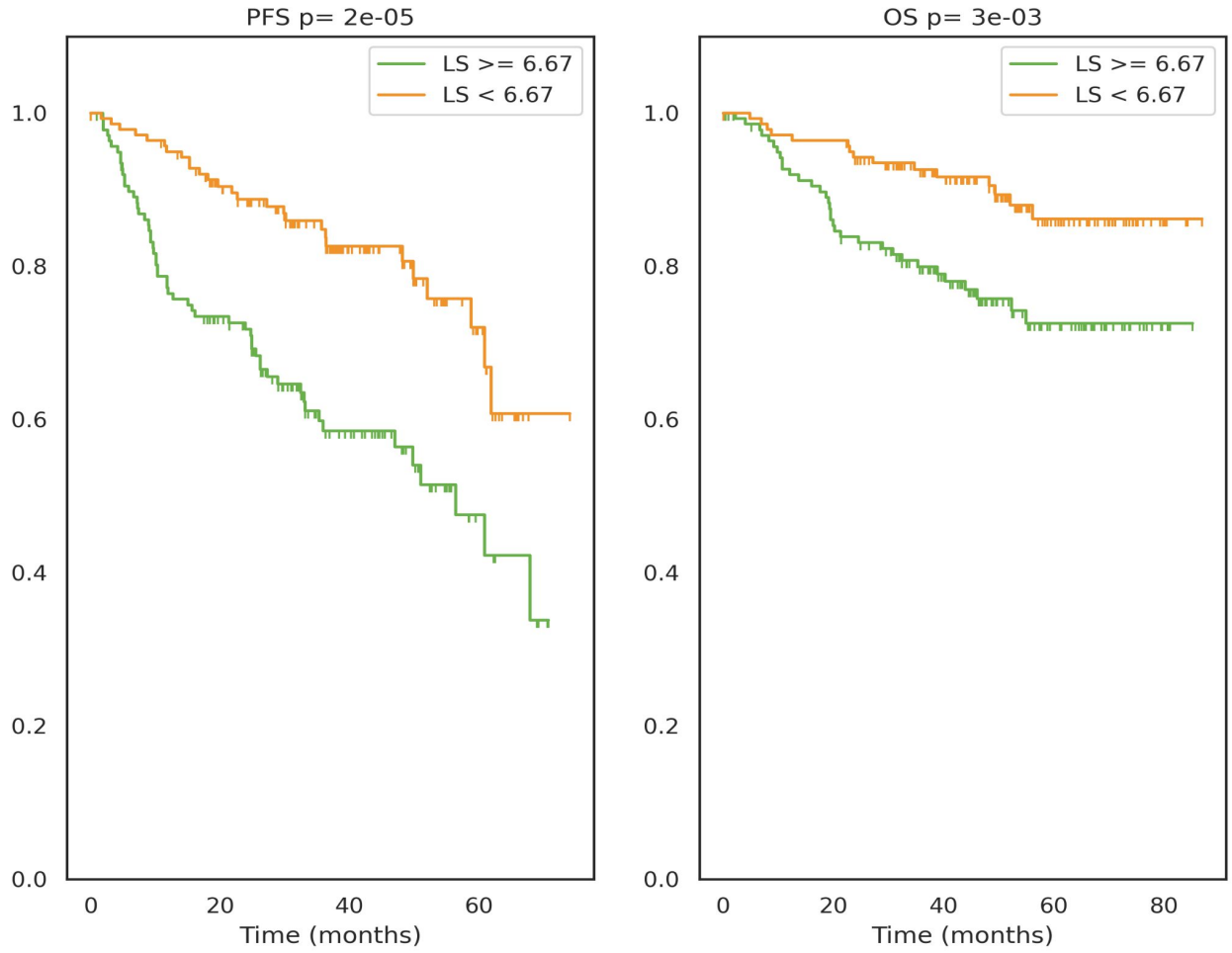
1. Considering the median values, Dmax scored high P-values but not DLS,and LS
2. Considering the optimally selected thresholds shows improved P values
3. These results are based on the new analysis (282 cases). The results are the same as it was done before.



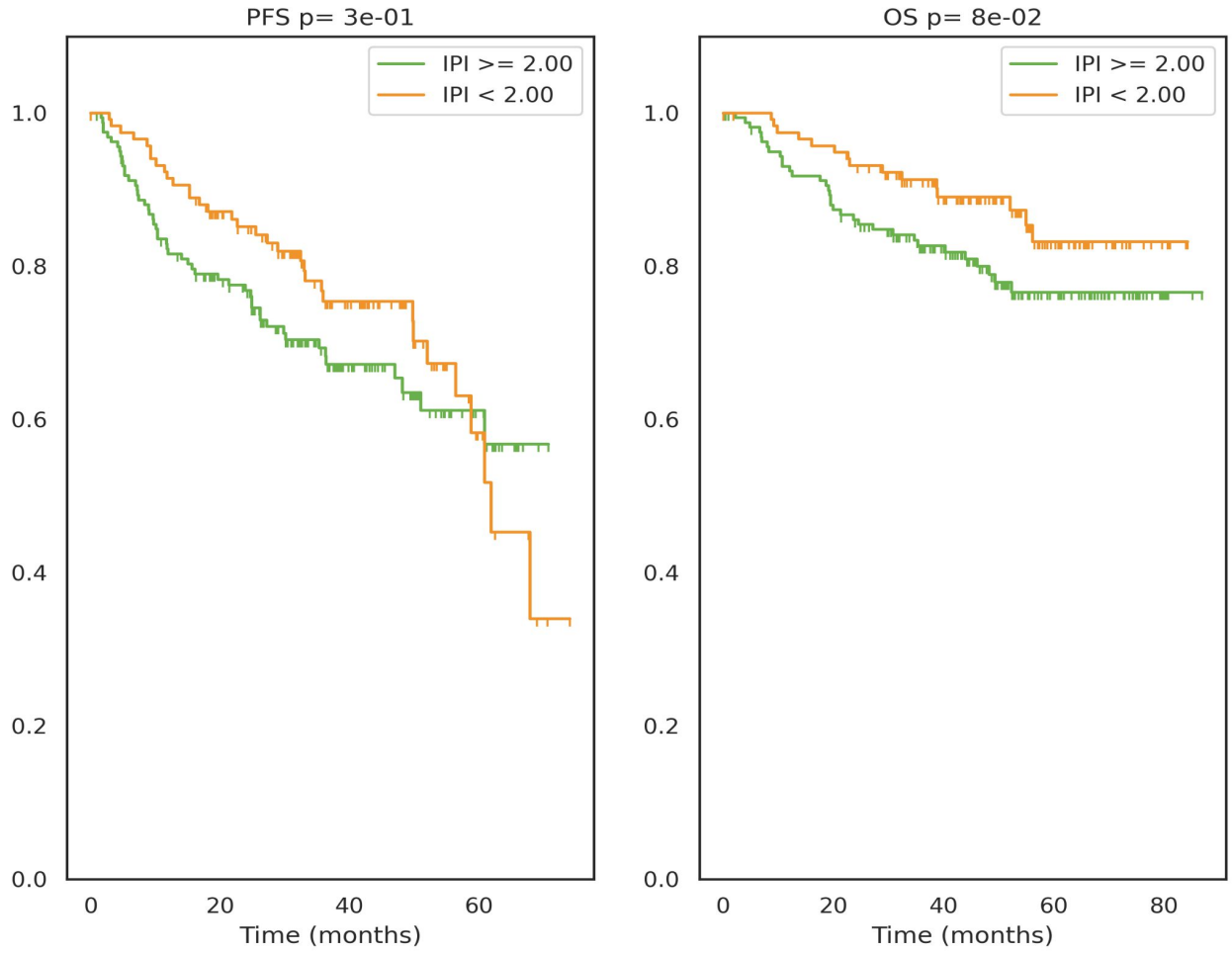
Kaplan-Meier estimator: Dmax



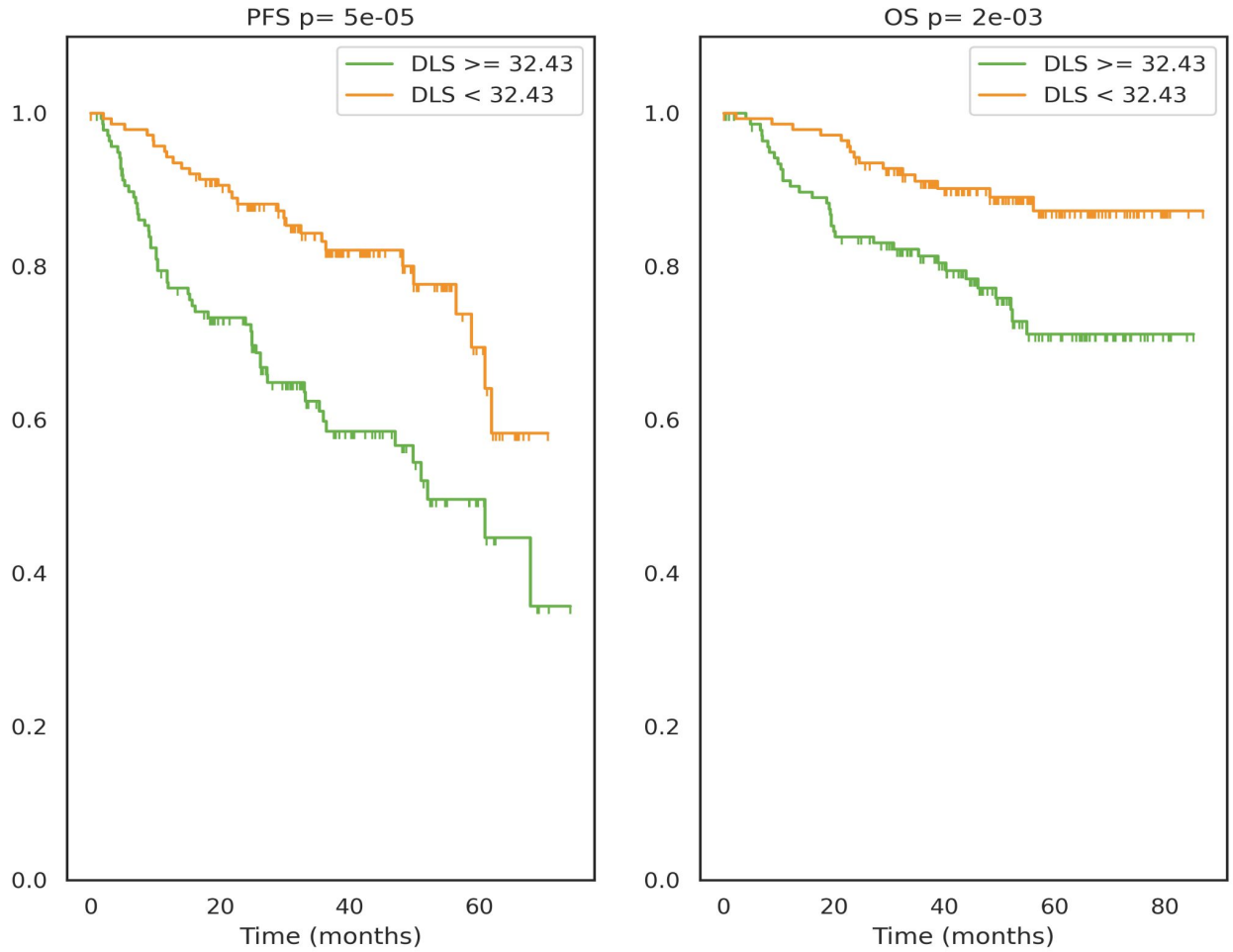
Kaplan-Meier estimator: Lesion spread



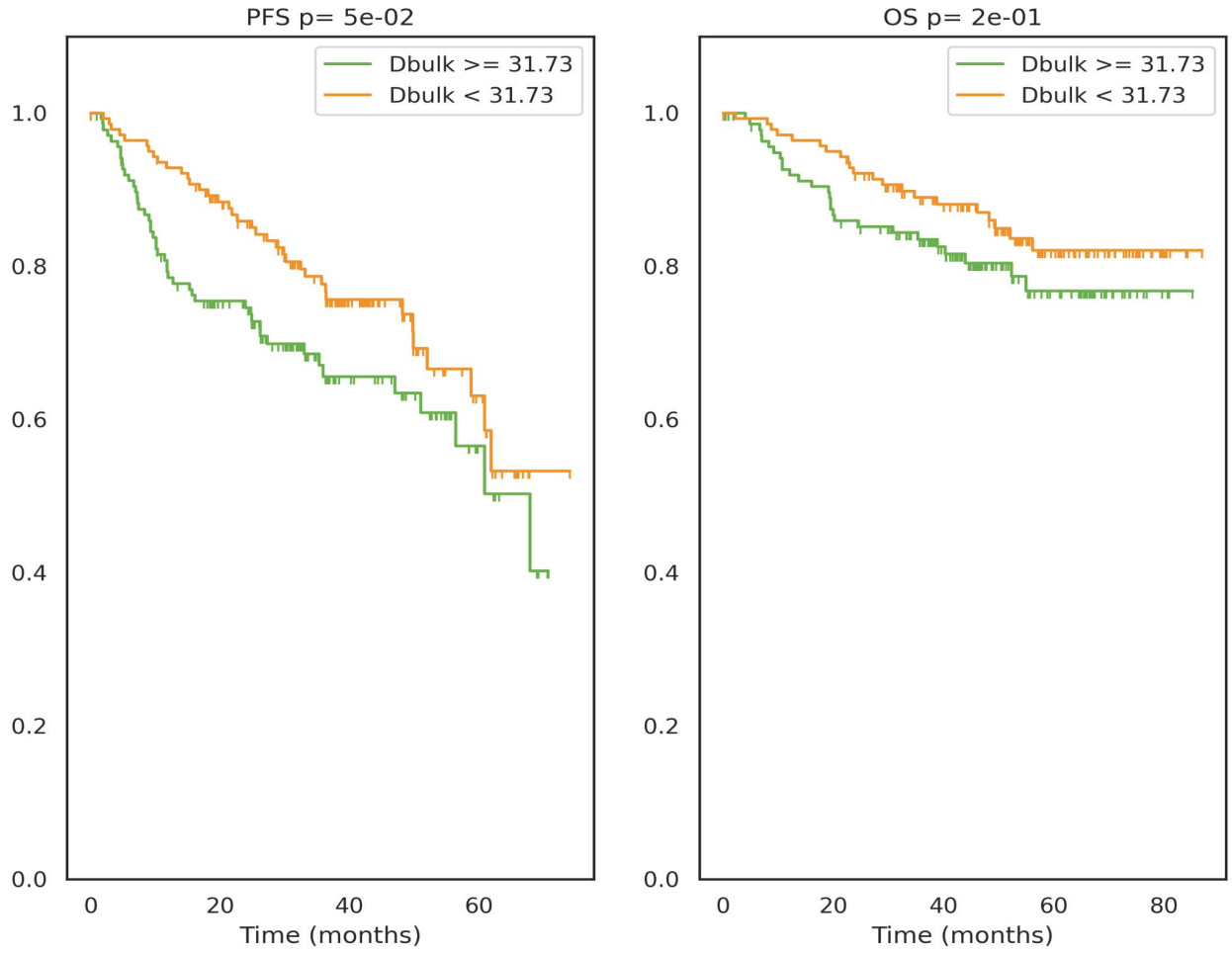
Kaplan-Meier estimator: IPI



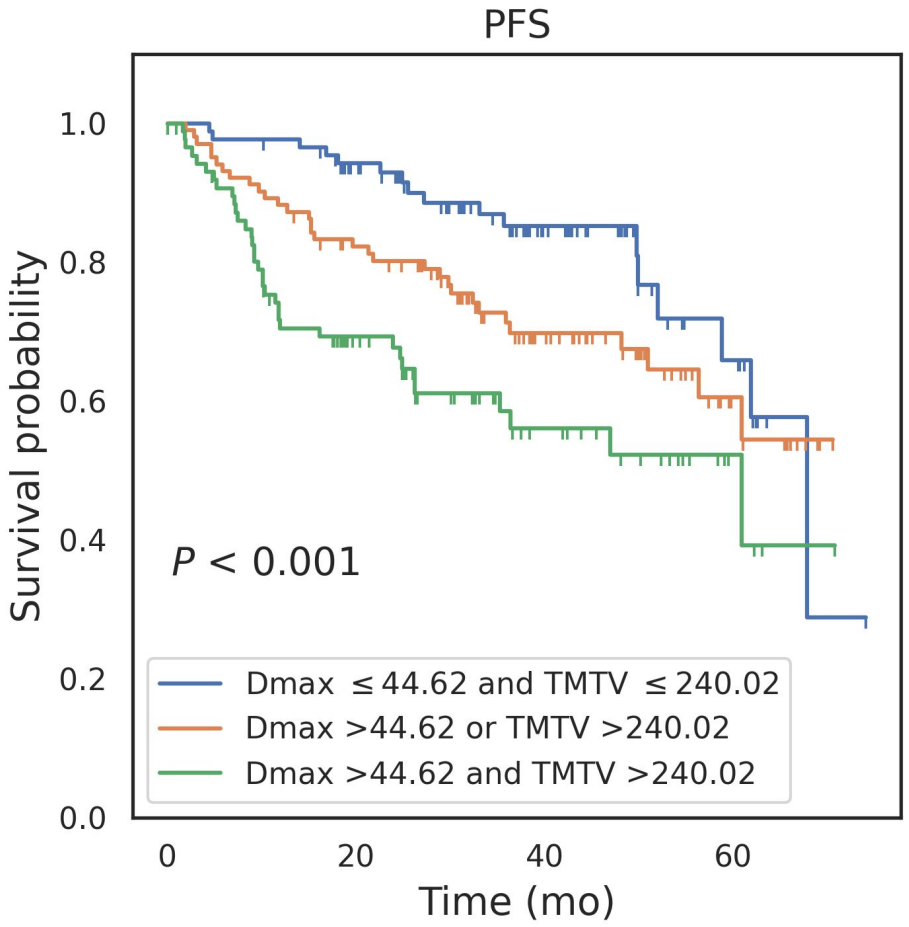
Kaplan-Meier estimator: distance of disseminated lesion from spleen

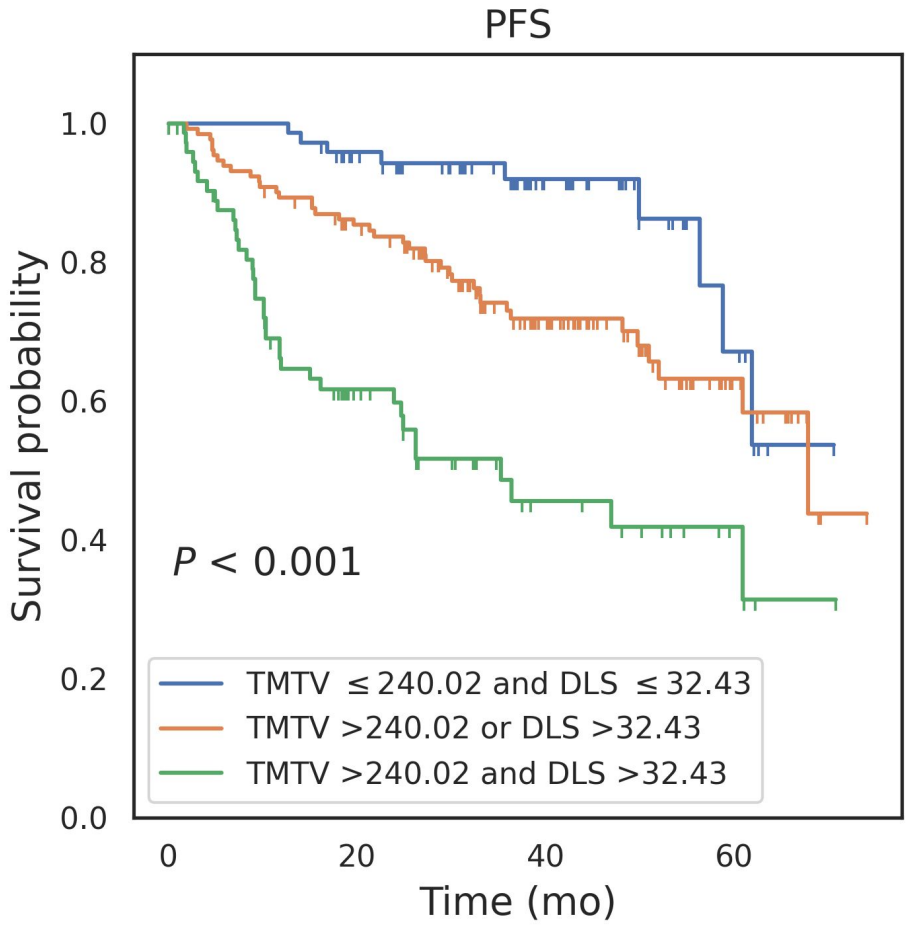


Kaplan-Meier estimator: Dbulk

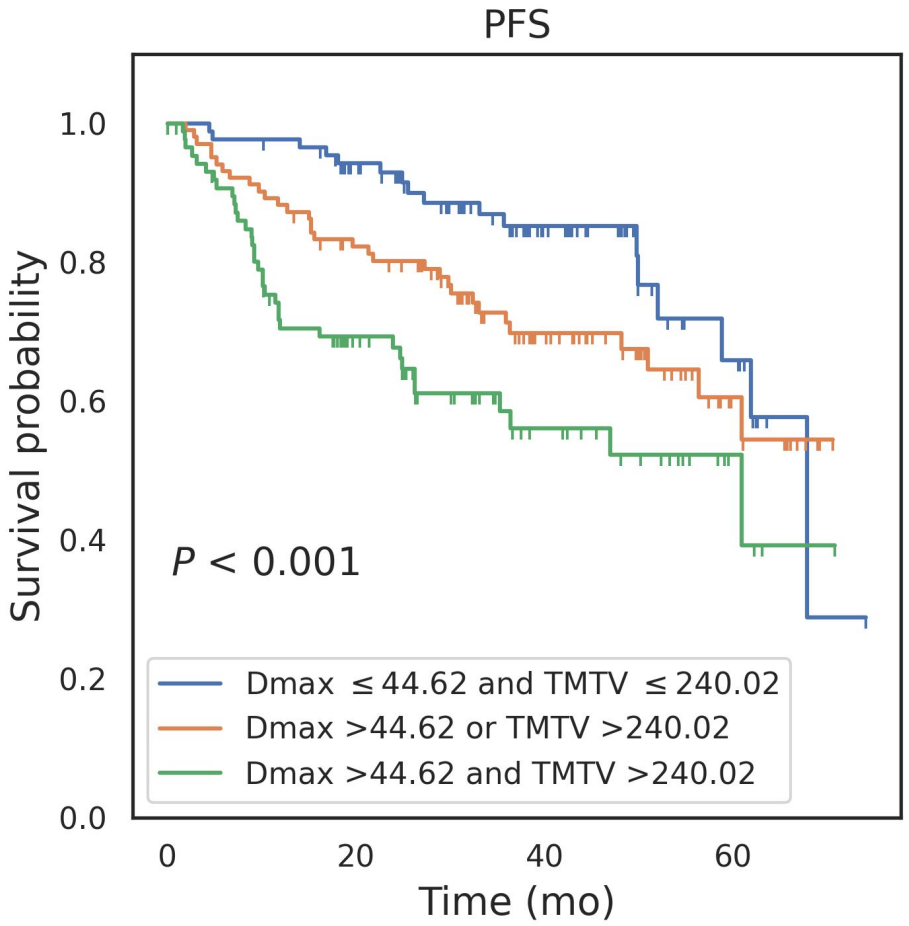


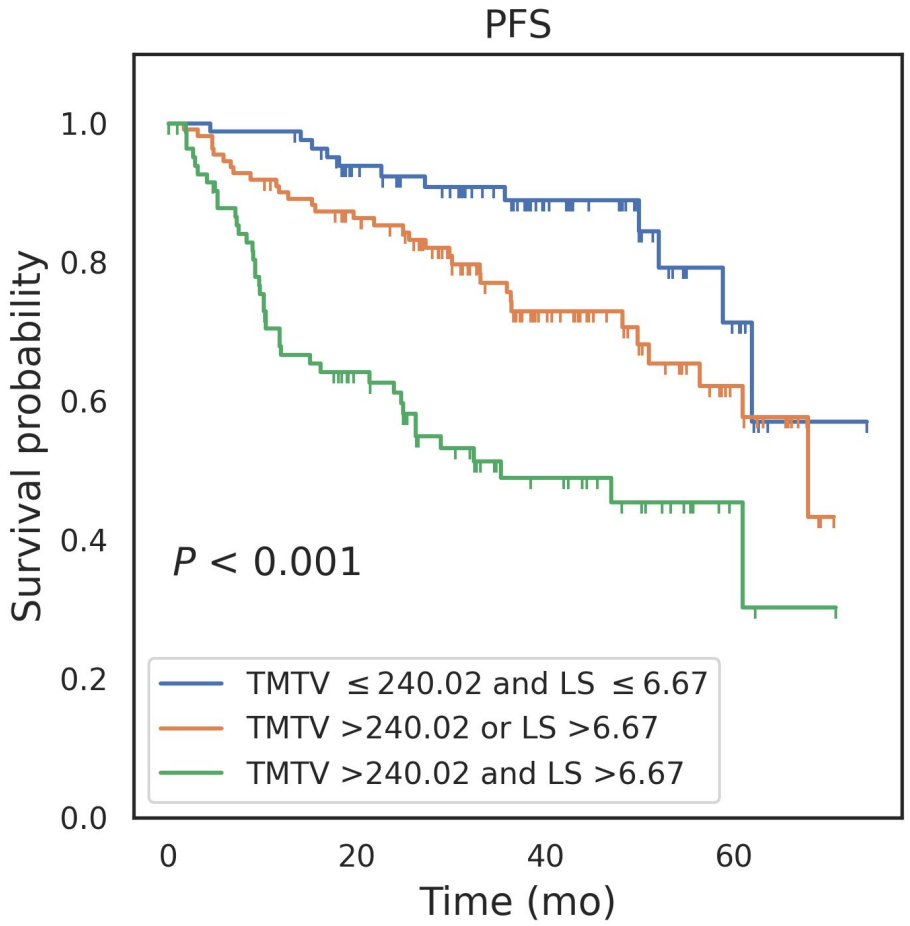
Three-risk factor analysis



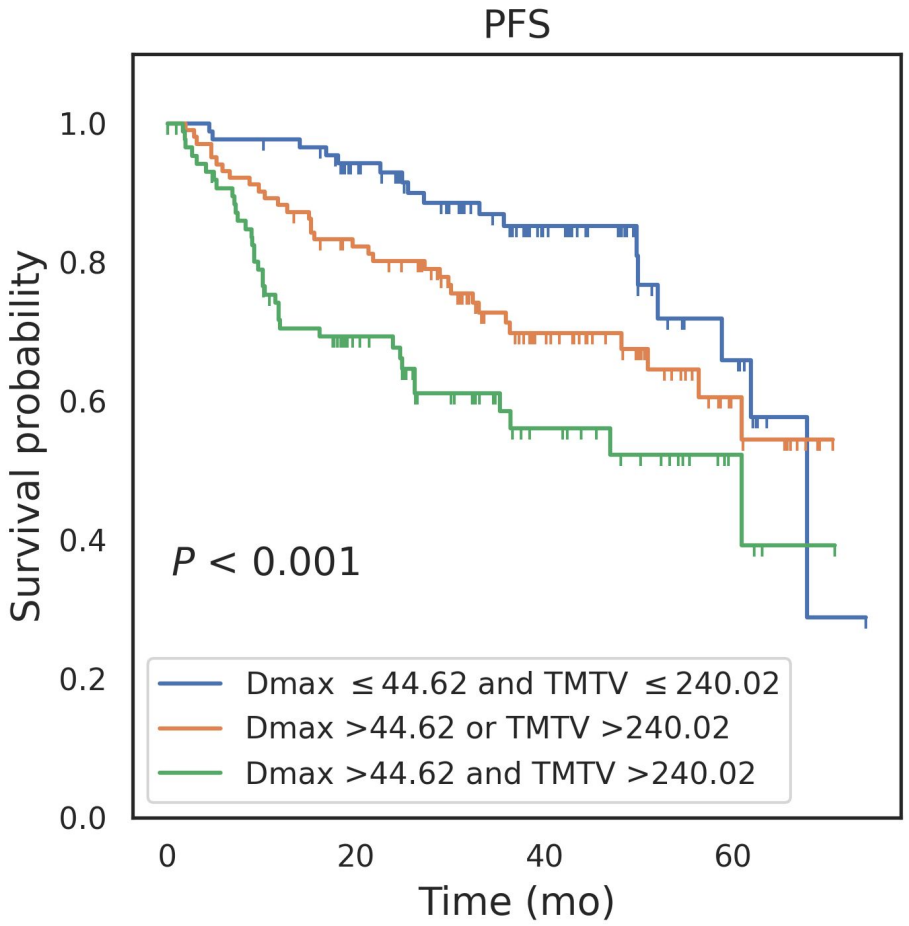


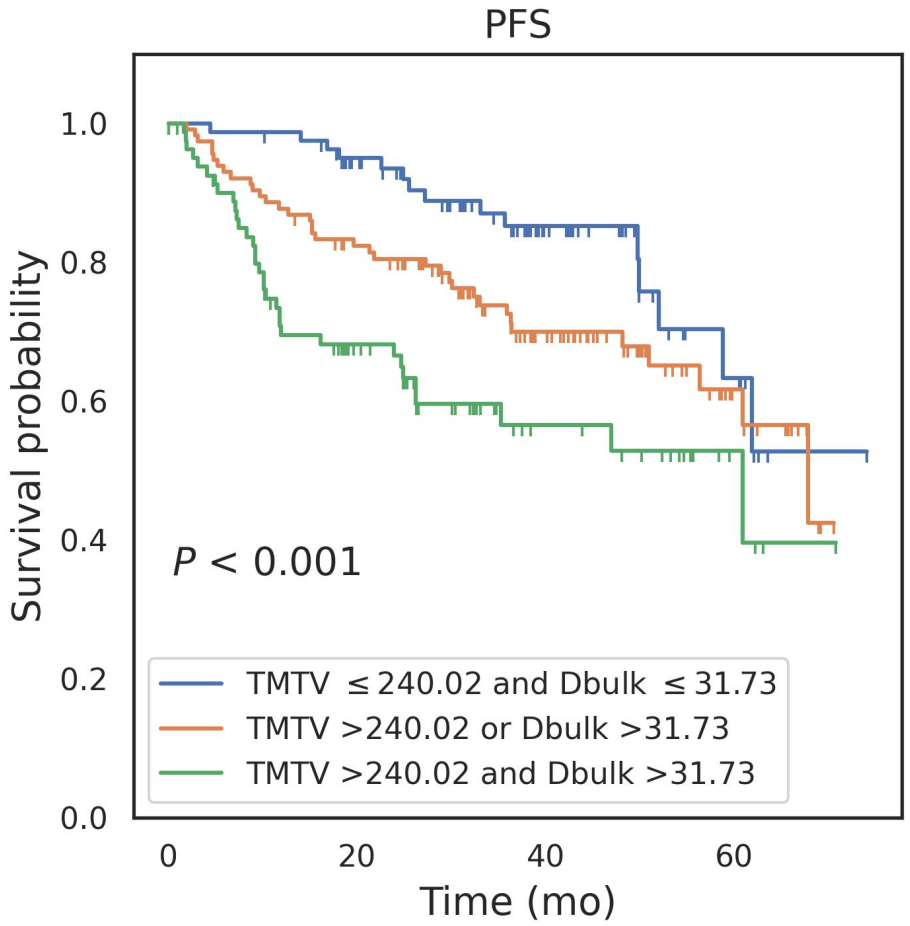
Three-risk factor analysis



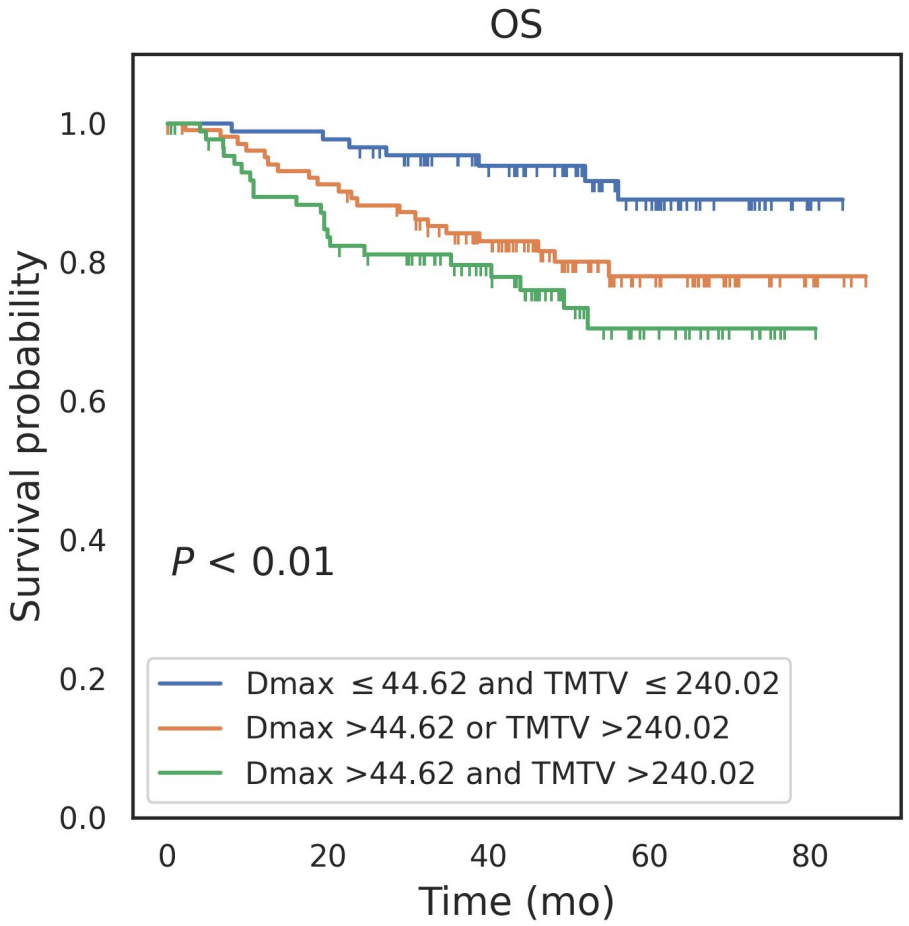


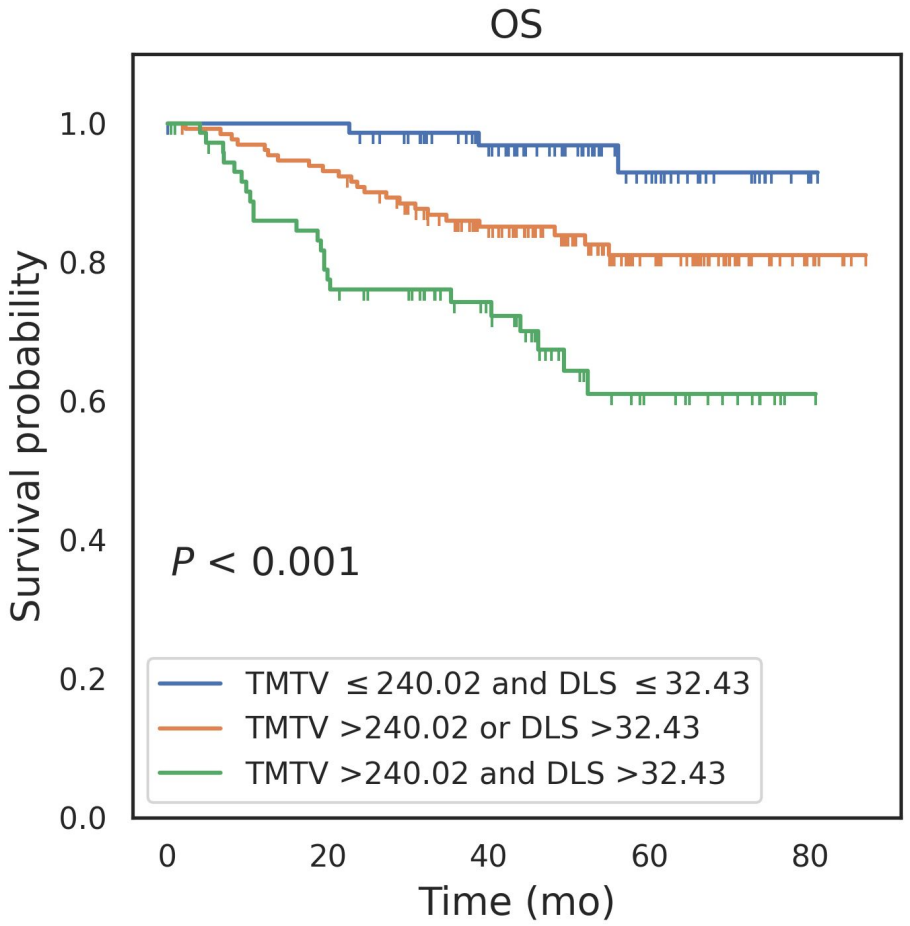
Three-risk factor analysis



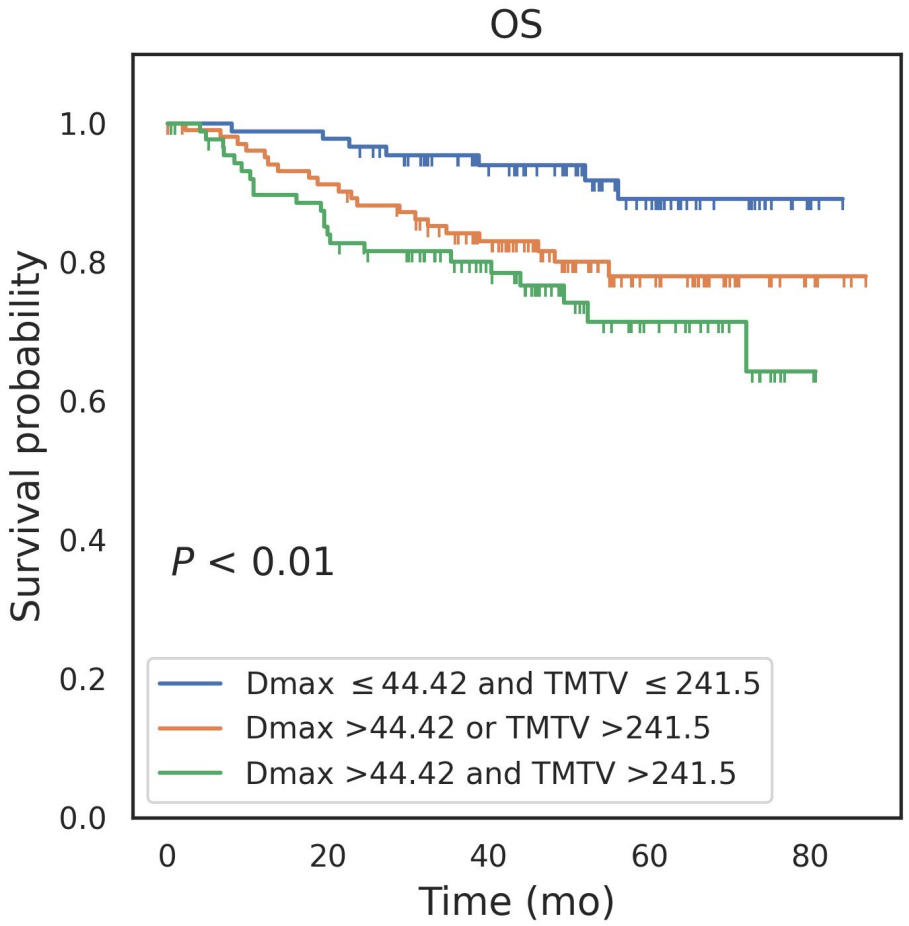


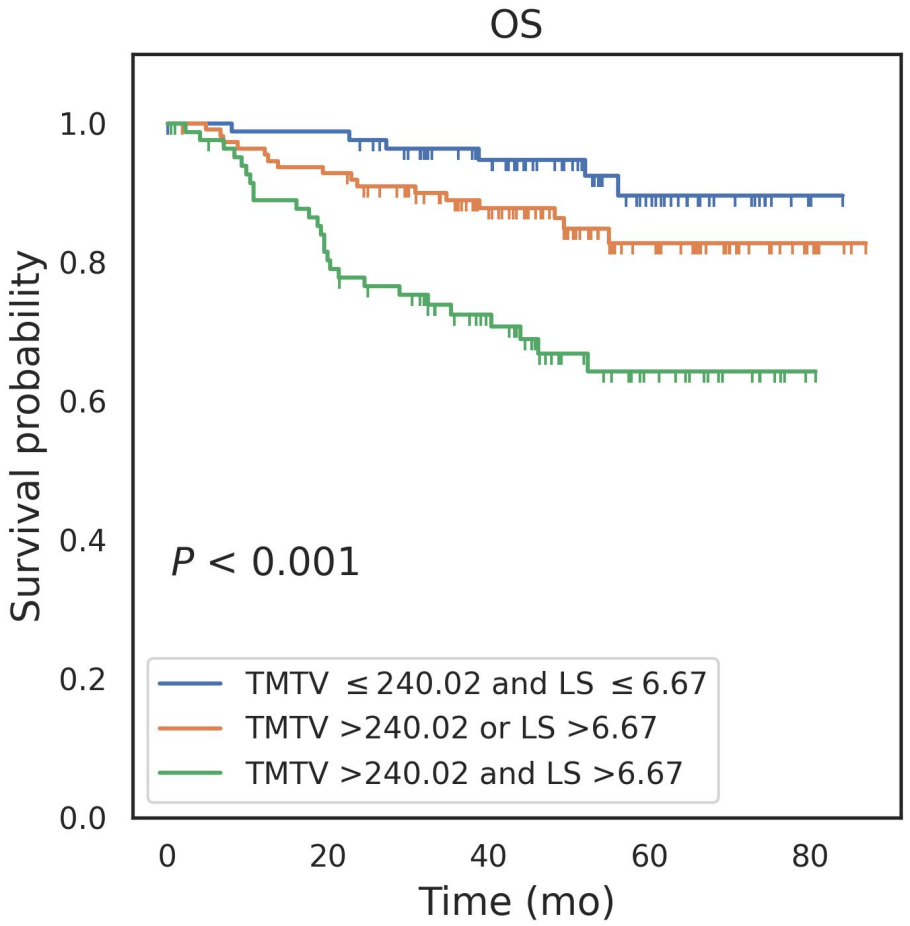
Three-risk factor analysis



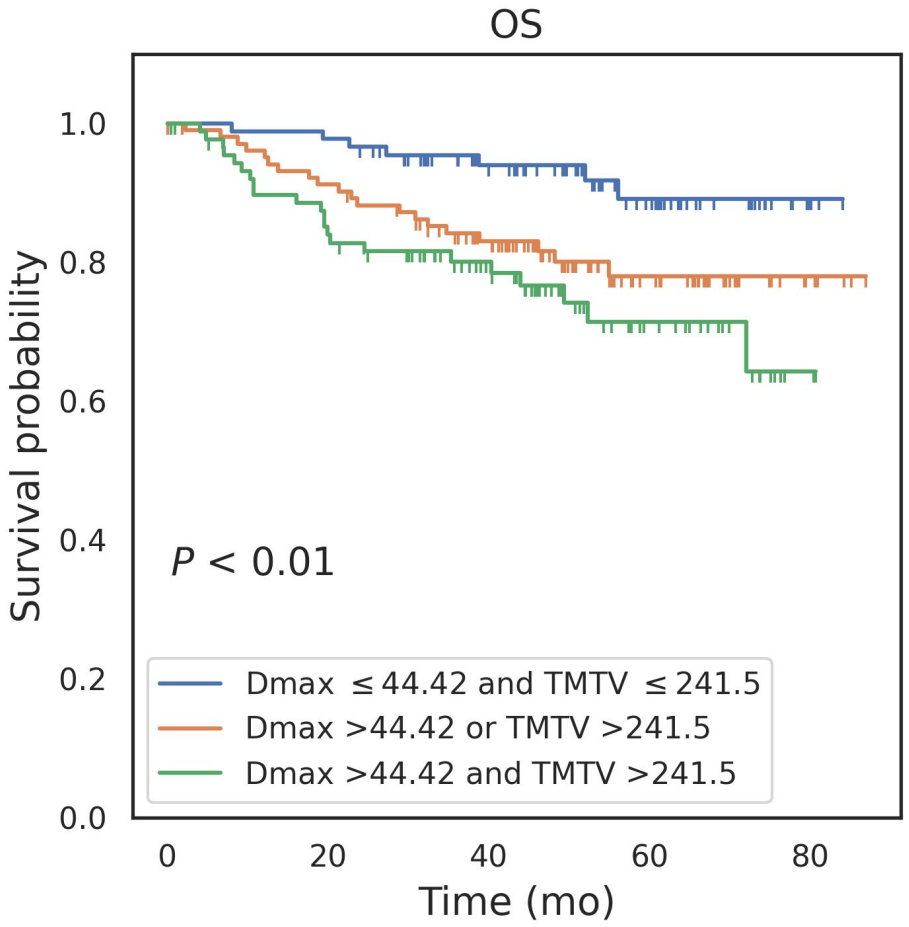


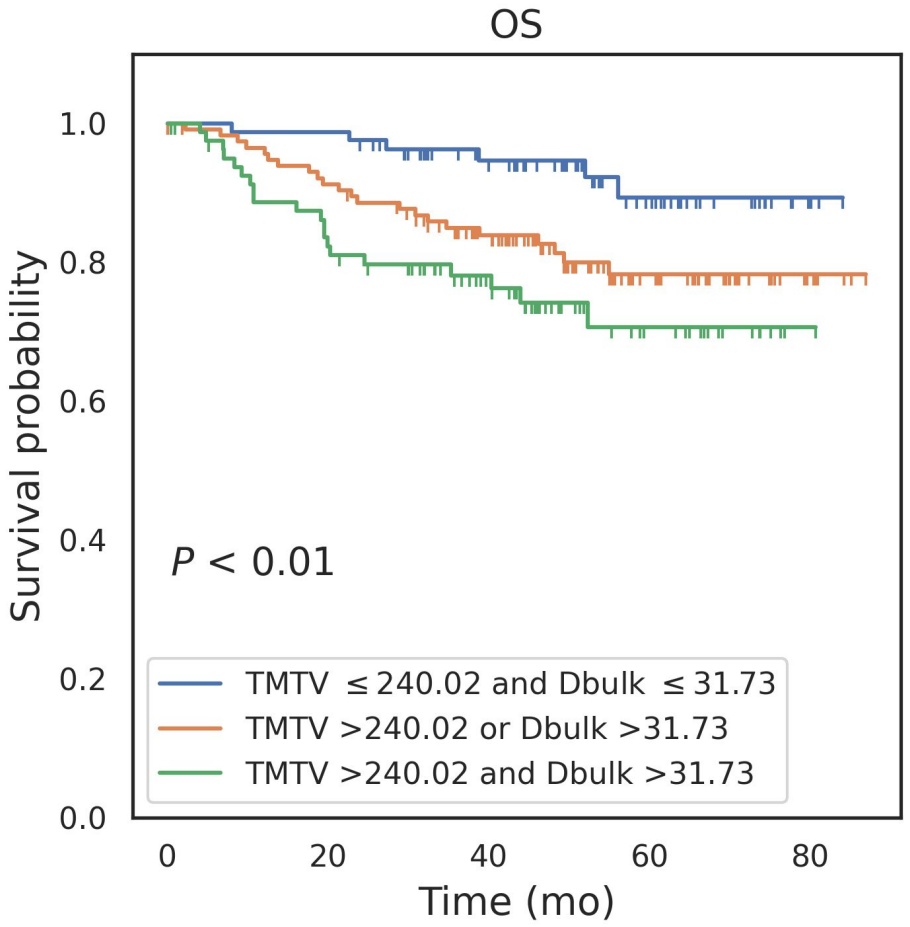
Three-risk factor analysis





Three-risk factor analysis





Conclusions and future works

- **Conclusions**
  - DLS adn LS are two simple PET/CT features showing how cancer disseminates and spreads from the spleen, respectively, and are predictive of PFS and OS in DLBCL patients
  - Both features are uncorrelated and complementary to TMTV and improved patient stratification when combined with TMTV
- **Future directions**
  - Further evaluation is needed on external cohort, e.g., RELEVANCE, LNH073B (elementary results are promising)
  - Further evaluation of the proposed features on other lymphatic disease such as the Hodgkin lymphoma is undergoing and showed promising results
  - Determination of the best way to combine them all (**ICARE**, **logistic regression)**
  - The whole process could be automated using **artificial intelligence in 3D**

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Merci beaucoup pour votre attention!