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Onset-subtype-dependent diagnostic performance of serum hyaluronic acid for sinusoidal obstruction syndrome/veno-occlusive disease after allogeneic hematopoietic cell transplantation

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Artificial Intelligence: OpenAI ChatGPT (GPT-5 series; OpenAI, San Francisco, CA, USA; commercial software) was used to assist with drafting, revising, and linguistic refinement of portions of the manuscript and responses to reviewers. Prompts were used to improve clarity, conciseness, grammatical accuracy, and scientific English while preserving the authors' intended scientific content. All AI-assisted text was critically reviewed, verified, and edited by the authors. Artificial intelligence was not used for data generation or statistical analysis. The authors take full responsibility for the accuracy, integrity, and originality of the final manuscript.

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To the Editor

Sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) remains a serious and potentially life-threatening complication after allogeneic hematopoietic cell transplantation (HCT)(1, 2), and reliable biomarkers for early detection are lacking. Hyaluronic acid (HA), an endothelial glycocalyx component cleared by liver sinusoidal endothelial cells(3, 4), has been proposed as an early biomarker of SOS/VOD in previous studies(5-10); however, its diagnostic performance according to onset subtype remains unclear (Supplementary Table S1). Here, we evaluated the diagnostic performance of serial serum HA according to SOS/VOD onset subtype in adult umbilical cord blood transplantation (CBT) recipients. We retrospectively analyzed adult patients undergoing CBT at a single center. Serum HA was measured serially using a standardized enzyme-linked immunosorbent assay but was available only in selected patients as part of routine clinical practice. Classical SOS was diagnosed according to the EBMT 2016 criteria, or, in patients without hyperbilirubinemia who did not fulfill the EBMT 2016 criteria, the revised Seattle criteria, whereas all late-onset SOS cases were diagnosed according to the EBMT 2016 criteria. Further details of patient selection and eligibility criteria are provided in the legend to Supplementary Figure S1. Baseline (pre-HCT) serum samples were collected before graft infusion, either before or after initiation of conditioning. Further details regarding HA measurement and longitudinal sample collection are provided in the legend to Figure 1. All patients received ursodeoxycholic acid and dalteparin prophylaxis. Receiver operating characteristic (ROC) analysis used day-9 HA for classical SOS and day-9 and day-21 HA for late-onset SOS; details of ROC analyses are provided in the legend to Figure 2. Statistical analyses were performed using EZR (version 1.67; May 31, 2024)(11). The study was approved by the Institutional Review Board of Toranomon Hospital (approval No. 1183), with an opt-out consent procedure.

A total of 118 transplants with serial serum HA measurements were analyzed. Patient selection is summarized in Supplementary Figure S1. Baseline characteristics are summarized in Supplementary Table S2A. Clinical characteristics of SOS/VOD patients are summarized in Supplementary Table

S2B, and individual clinical characteristics and diagnostic findings of late-onset SOS are provided in Supplementary Table S2C. Of the 118 patients, 55 developed SOS/VOD, including 16 with classical SOS and 39 with late-onset SOS. The overall frequency of SOS/VOD in the present study was higher than expected because the analysis was restricted to a selected biomarker cohort with longitudinal serum HA measurements rather than an unselected transplant population. Among patients with SOS/VOD, late-onset disease accounted for the majority of cases, consistent with our previous institutional analysis of an unselected transplant cohort, which also demonstrated that late-onset SOS/VOD was the predominant subtype.(12) Serum HA levels increased significantly after transplantation compared with baseline and were consistently higher in patients who subsequently developed SOS/VOD than in those who did not (Figure 1A). However, HA elevations were also observed in a subset of patients without SOS/VOD, indicating limited specificity as a standalone biomarker. Longitudinal analysis revealed distinct HA kinetics between the two SOS subtypes (Figure 1B). In classical SOS, HA levels increased rapidly after transplantation, reaching peak levels within the first three weeks. In contrast, late-onset SOS showed a more gradual and heterogeneous increase, with delayed peak values and substantial inter-individual variability. Although not statistically significant, these patterns suggest biological heterogeneity between SOS/VOD subtypes. We next evaluated the diagnostic performance of HA. Patients who had already fulfilled the diagnostic criteria for SOS/VOD on or before day 9 (n = 1) were excluded from the day-9 ROC analysis to ensure that biomarker assessment preceded clinical diagnosis. For overall SOS/VOD, day-9 HA demonstrated moderate discriminative ability, with an area under the curve (AUC) of 0.76 (95% CI, 0.67–0.85) and an optimal threshold of 353 ng/mL, yielding a sensitivity of 0.66 (95% CI, 0.52–0.79), specificity of 0.79 (95% CI, 0.66–0.88), positive predictive value of 0.73 (95% CI, 0.58–0.85), and negative predictive value of 0.73 (95% CI, 0.60–0.83). When stratified according to onset subtype, marked differences in discriminative performance emerged. After excluding the single patient who had already met the diagnostic criteria on or before day 9, day-9 HA showed strong discriminative performance for classical SOS, with an AUC of 0.89 (95% CI, 0.83–0.96). A threshold of 433 ng/mL achieved a sensitivity of 1.00 (95% CI, 0.70–

1.00), specificity of 0.80 (95% CI, 0.70–0.88), positive predictive value of 0.46 (95% CI, 0.28–0.64), and negative predictive value of 1.00 (95% CI, 0.93–1.00) (Figure 2A). Thus, low HA levels effectively excluded subsequent classical SOS, whereas elevated HA showed only modest positive predictive value. In contrast, HA demonstrated more limited discriminative performance for late-onset SOS, with AUC values of 0.68 (95% CI, 0.57–0.79) at day 9 (Figure 2B) and 0.68 (95% CI, 0.57–0.79) at day 21. At day 9, the optimal threshold was 264 ng/mL, yielding a sensitivity of 0.71 (95% CI, 0.54–0.85), specificity of 0.64 (95% CI, 0.51–0.76), positive predictive value of 0.55 (95% CI, 0.40–0.69), and negative predictive value of 0.78 (95% CI, 0.64–0.89). At day 21, the optimal threshold was 305 ng/mL, with a sensitivity of 0.68 (95% CI, 0.51–0.83), specificity of 0.71 (95% CI, 0.59–0.82), positive predictive value of 0.59 (95% CI, 0.43–0.74), and negative predictive value of 0.79 (95% CI, 0.66–0.89). Although threshold-based stratification identified significant differences in cumulative incidence, overall discriminative performance remained modest. Exploratory analyses according to disease severity and clinical outcomes are summarized in Supplementary Table S2D.

The differing diagnostic performance of HA according to SOS onset subtype likely reflects underlying pathophysiological heterogeneity. Previous studies have shown that serum HA increases within the first week after transplantation and is associated with the subsequent development of SOS/VOD.(5-10) The present study extends these observations, showing distinct diagnostic performance according to SOS/VOD onset subtype. Classical SOS is characterized by acute injury to liver sinusoidal endothelial cells early after transplantation, consistent with rapid HA elevation resulting from impaired hepatic clearance(4). In contrast, late-onset SOS is thought to involve more complex mechanisms, including delayed endothelial injury, cumulative treatment-related toxicity, and interactions with other post-transplant complications such as graft-versus-host disease, which may contribute to systemic inflammation and endothelial perturbation(13). This biological heterogeneity may explain why single time-point HA measurements perform well in classical SOS but substantially less well in late-onset disease. Early HA elevation around day 9 may help identify patients at increased risk of

classical SOS before overt disease develops, supporting closer monitoring and earlier diagnostic evaluation. Because serum HA may reflect liver sinusoidal endothelial cell injury, these findings also provide a biological rationale for investigating whether serial HA monitoring could help identify patients who may benefit from endothelial-protective therapeutic strategies. Defibrotide has been reported to preserve endothelial integrity through modulation of heparanase activity and extracellular matrix remodeling during SOS/VOD progression.(14) Although this study was not designed to evaluate treatment response or guide therapy, our findings support future studies investigating the relationship between serial HA kinetics and endothelial-protective therapies, including defibrotide. In contrast, the more modest performance observed in late-onset SOS suggests that HA should be interpreted together with serial clinical assessment and imaging findings rather than as a standalone diagnostic marker. An important limitation is the non-specific nature of HA elevation. Serum HA concentrations may increase in sepsis, hepatic congestion, renal dysfunction, and other transplant-related complications(15). Although early bacteremia occurred at similar frequencies in patients with and without SOS/VOD during the primary evaluation period (32/55 [58.2%] vs. 34/63 [54.0%]), residual confounding cannot be excluded. Accordingly, HA should be interpreted within the overall clinical context. In addition, because of the retrospective design and heterogeneous clinical backgrounds of transplant recipients, we were unable to systematically determine the underlying causes of elevated HA in individual non-SOS/VOD patients with false-positive HA elevations. Future studies incorporating detailed clinical adjudication of these cases will be important to improve the clinical interpretation of serum HA. Our previous institutional study identified several independent pre-transplant risk factors for late-onset SOS, whereas no independent predictors, including busulfan-containing conditioning, were identified for classical SOS.(12) Whether HA provides information beyond established clinical risk factors could not be determined because only 16 patients developed classical SOS, precluding reliable multivariate analyses. Additional limitations include the retrospective single-center design, selection bias related to selective HA measurements, and restriction to adult umbilical cord blood transplantation recipients. As summarized in Supplementary Table S1, previous

studies have evaluated HA either alone or in combination with other biomarkers. Whether combining HA with established endothelial biomarkers, such as EASIX, further improves the early detection and risk stratification of SOS/VOD remains unknown and should be evaluated in future prospective studies. Accordingly, external validation in prospective multicenter studies including other graft sources is warranted before routine clinical implementation.

In conclusion, serum HA demonstrates onset-subtype-dependent diagnostic performance for SOS/VOD after allogeneic HCT, with better discriminative performance for classical SOS than for late-onset SOS. These findings support further evaluation of HA as an adjunctive biomarker for early post-transplant risk assessment while underscoring the importance of considering disease heterogeneity when evaluating endothelial biomarkers. However, the present analysis should be considered hypothesis-generating, and prospective multicenter validation in adult UCBT recipients is required before the proposed diagnostic thresholds can be applied in routine clinical practice. Studies in other graft sources are required to establish generalizability.

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Figure legend

Figure 1. Changes in serum hyaluronic acid levels over time

Changes in serum hyaluronic acid levels over time. Serum hyaluronic acid (HA) concentrations were measured serially using a standardized enzyme-linked immunosorbent assay performed by a certified external clinical laboratory. The same assay method and standardized laboratory procedures were applied consistently throughout the study period in accordance with laboratory quality-control procedures. Baseline (pre-HCT) serum samples were obtained before graft infusion according to routine clinical practice when available. Baseline samples were available for 70 of the 118 transplants, including 52 collected before initiation of conditioning and 18 after conditioning had begun. Subsequent samples were collected as part of routine post-transplant monitoring, and no additional blood samples were obtained specifically for research. Longitudinal analyses focused on predefined post-transplant time points, particularly days 9 and 21, which were selected according to routine clinical sampling schedules and their relevance to the expected timing of classical and late-onset SOS. Baseline values were used only for descriptive analyses of longitudinal HA kinetics. The percentages shown at the bottom of the figure indicate the proportion of patients in whom serum hyaluronic acid values were measured at each time point. The Y-axis scales differ between panels. Red boxes indicate patients with SOS/VOD in panel A and patients with classical SOS in panel B, while black boxes indicate non-SOS/VOD (panel A) and late-onset SOS (panel B).

A. Serum hyaluronic acid levels stratified by the presence or absence of SOS/VOD.

B. Serum hyaluronic acid levels stratified by SOS/VOD onset subtype (classical vs. late-onset).

Figure 2. Diagnostic performance for classical and late-onset SOS

Receiver operating characteristic (ROC) analyses were performed to evaluate the discriminative performance of serum hyaluronic acid (HA) at predefined post-transplant time points. The area under the ROC curve (AUC) and diagnostic performance measures were calculated with 95% confidence intervals (CIs), and

optimal cutoff values were determined by maximizing the combined sensitivity and specificity.

A. Receiver operating characteristic (ROC) curve for classical SOS based on serum hyaluronic acid levels on day 9 post-transplant (AUC = 0.89; 95% CI, 0.83–0.96).

B. ROC curve for late-onset SOS based on serum hyaluronic acid levels on day 9 post-transplant (AUC = 0.68; 95% CI, 0.57–0.79).

Figure 1

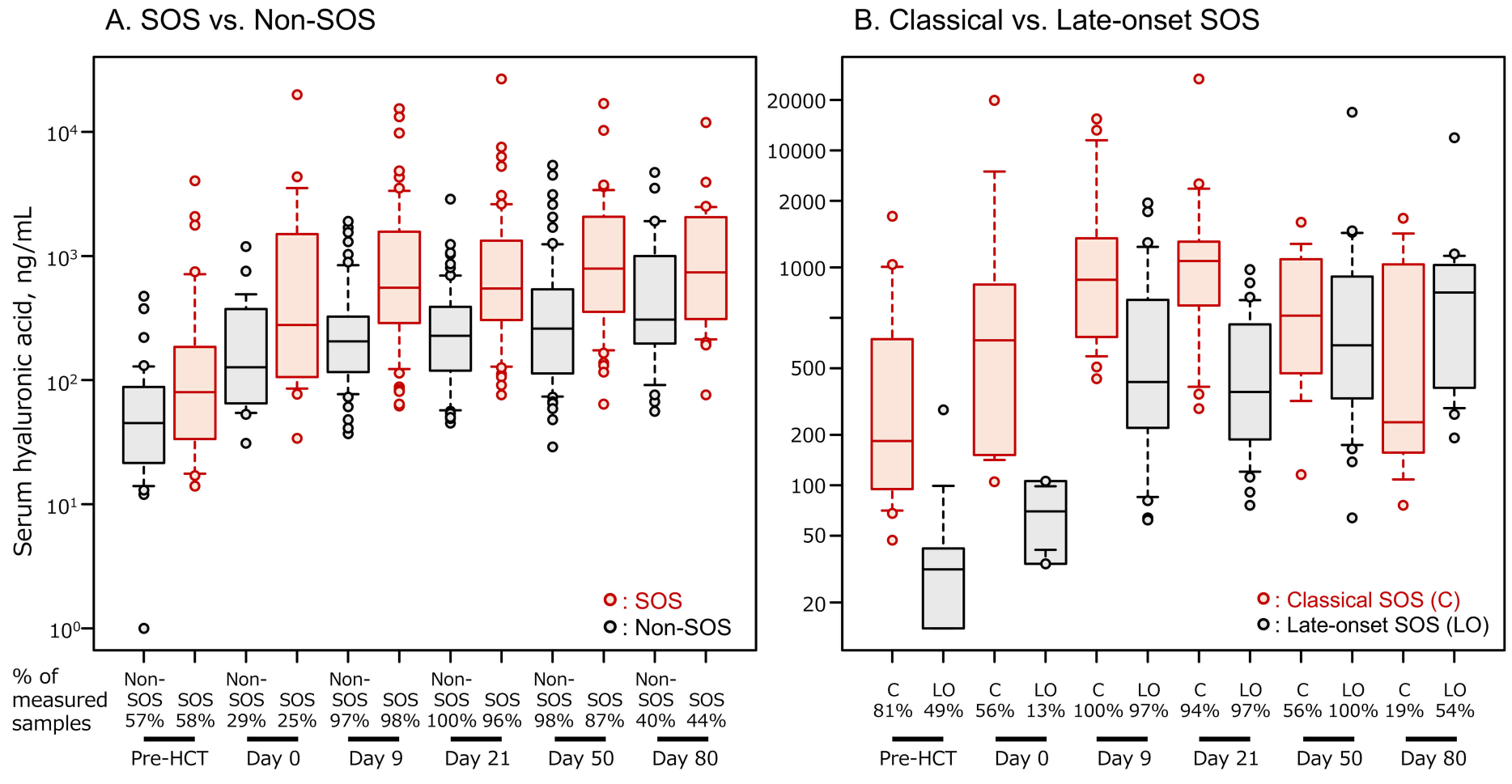
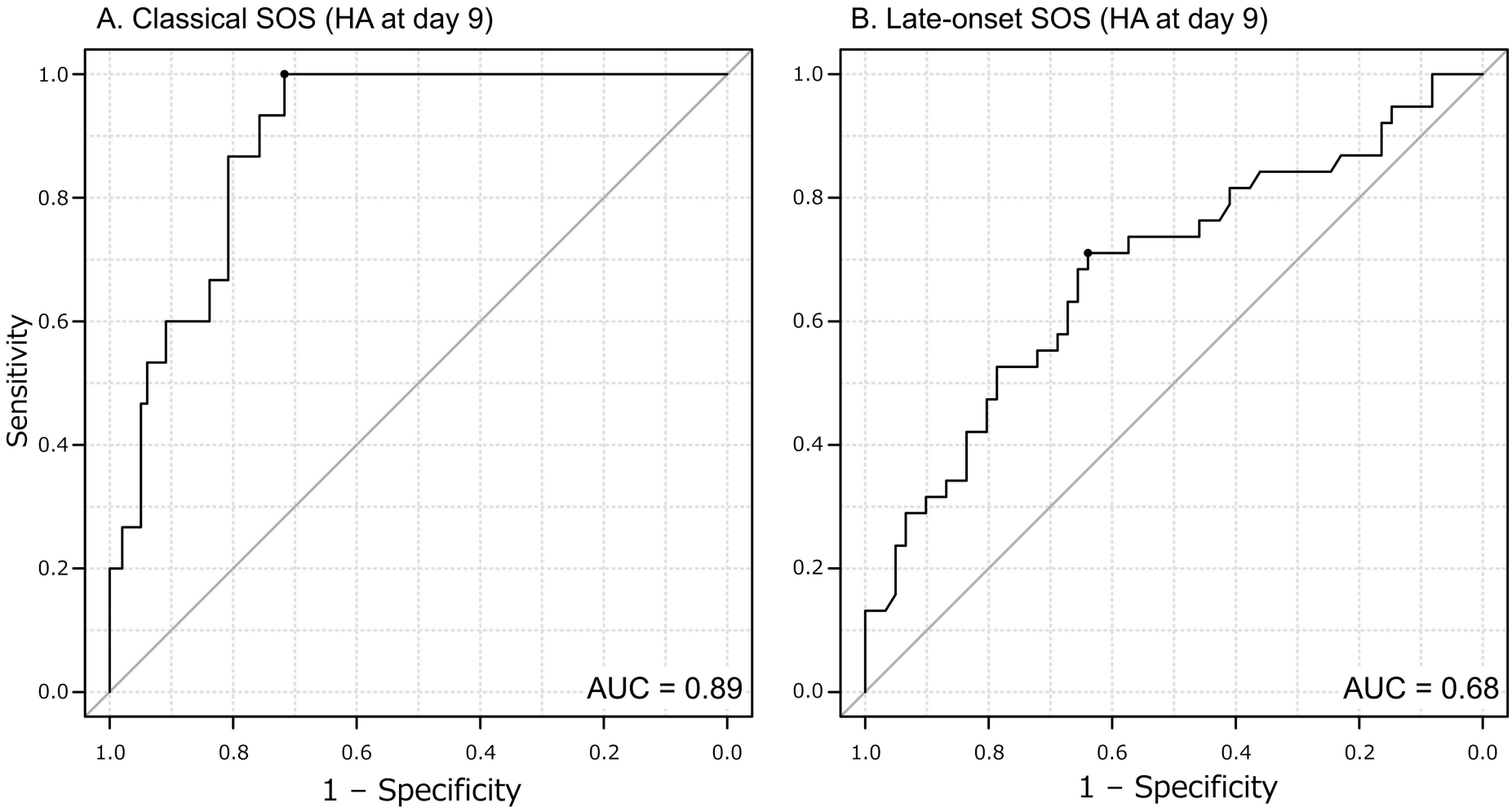
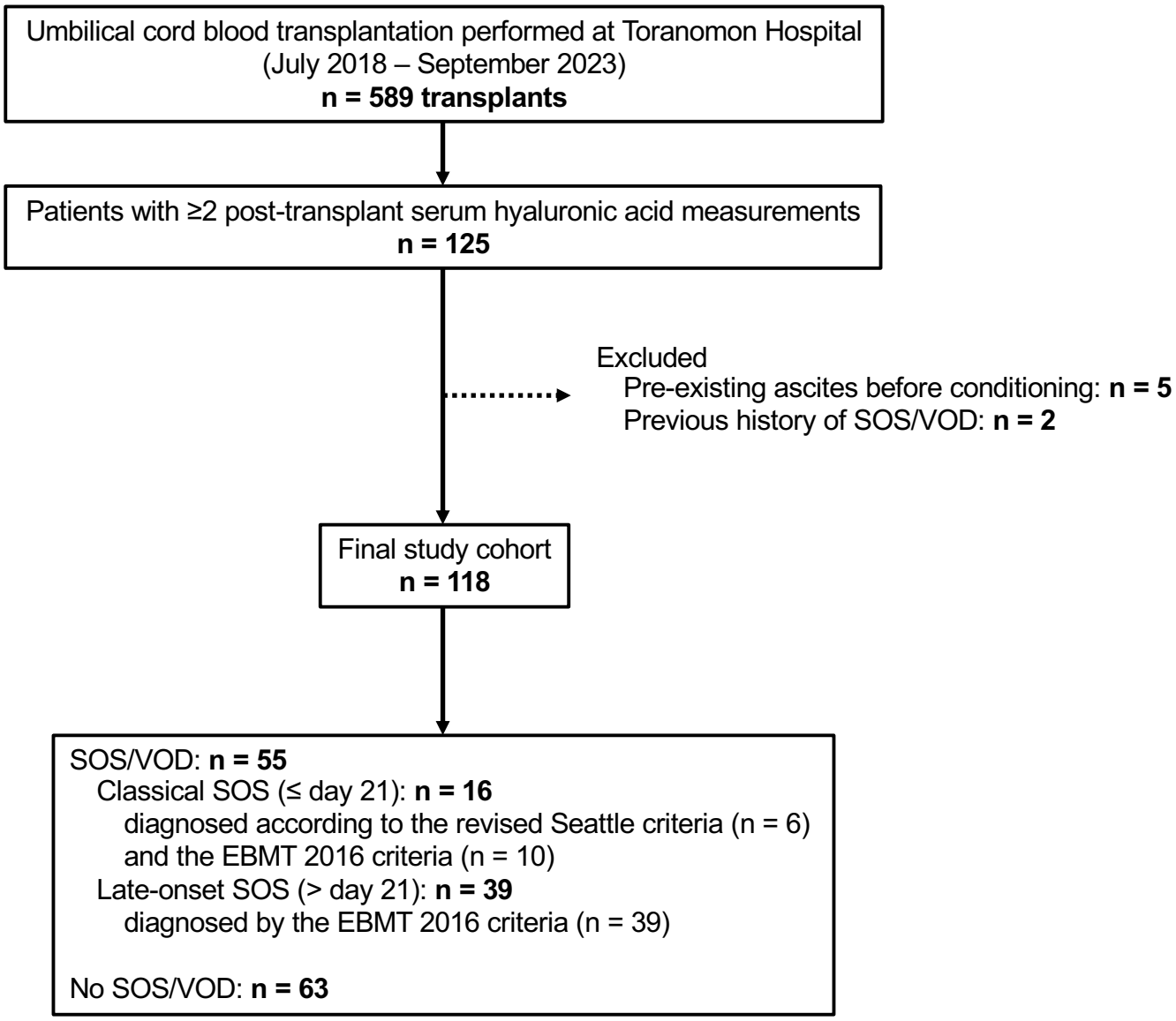

A. SOS vs. Non-SOS
Serum hyaluronic acid, ng/mL
10^4
10^3
10^2
10^1
10^0
: SOS
: Non-SOS
% of measured samples
Non-SOS 57% SOS 58%
Non-SOS 29% SOS 25%
Non-SOS 97% SOS 98%
Non-SOS 100% SOS 96%
Non-SOS 98% SOS 87%
Non-SOS 40% SOS 44%
Pre-HCT
Day 0
Day 9
Day 21
Day 50
Day 80
B. Classical vs. Late-onset SOS
20000
10000
2000
1000
500
200
100
50
20
: Classical SOS (C)
: Late-onset SOS (LO)
C 81% LO 49%
C 56% LO 13%
C 100% LO 97%
C 94% LO 97%
C 56% LO 100%
C 19% LO 54%
Pre-HCT
Day 0
Day 9
Day 21
Day 50
Day 80

Figure 2


A. Classical SOS (HA at day 9)
B. Late-onset SOS (HA at day 9)
Sensitivity
1 − Specificity
AUC = 0.89
AUC = 0.68
1.0
0.8
0.6
0.4
0.2
0.0



Supplementary Figure S1. Patient selection flow diagram
Adult patients who underwent umbilical cord blood transplantation at Toranomon Hospital between July 2018 and September 2023 were retrospectively screened. Serum hyaluronic acid (HA) measurements were performed serially as part of routine post-transplant clinical practice in selected patients. Patients with at least two serial serum HA measurements, including at least one obtained after transplantation, were eligible for analysis. Patients with pre-existing ascites before initiation of conditioning or a previous history of sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) were excluded. Clinical data were retrospectively obtained from electronic medical records. Classical SOS was defined as disease occurring within 21 days after transplantation and was diagnosed according to the EBMT 2016 criteria or, in patients without hyperbilirubinemia who did not fulfill these criteria, the revised Seattle criteria. Late-onset SOS was defined as disease developing after day 21 according to the EBMT 2016 criteria and was further classified as icteric (total bilirubin ≥2 mg/dL) or anicteric (total bilirubin <2 mg/dL). SOS severity was graded according to the EBMT 2016 severity criteria.

Supplementary Table S1. Previous studies of hyaluronic acid as a biomarker for SOS/VOD

Ref	Biomarker	Sampling point	Details
5	HA	Day 7, 17, 25	Mean peak value: 1173.4 in SOS vs. 444.9 in non-SOS (p=0.01)
6	ST2, ANG2, L-Ficolin, HA, VCAM1	Day 0, 7	AUC=0.98 (for diagnosis)
	L-Ficolin, HA, VCAM1	Day 0, 7	AUC=0.90 (for prognosis)
7	Combination biomarker (L-Ficolin, HA, ST2)*	Day 3	Sensitivity 80%, Specificity 73%
8	HA, ICAM1, ANG2, TIMP1, VEGF	Day 7	HA: AUC=0.81
9	Combination biomarker (HA, TM, ANG2)**	Day 7	VODCheck: AUC=0.815
Present study	HA	Day 9	AUC=0.76 (overall SOS); 0.89 (classical SOS); 0.68 (late-onset SOS)
		Day 21	AUC=0.68 (late-onset SOS)

* Patients with L-ficolin levels <1100 ng/mL were classified as high risk for SOS/VOD. In patients with L-ficolin ≥1100 ng/mL, hyaluronic acid (HA) was assessed, and levels >200 ng/mL indicated high risk. If both markers were within the normal range, ST2 was subsequently evaluated, and levels >45 ng/mL indicated high risk; otherwise, patients were classified as low risk.

** VODCheck model: predicted probability = 1 / [1 + exp(–A)], where A = -8.380 + 1.365 × log10(HA) + 1.306 × log10(ANG2) + 3.902 × log10(TM).

Abbreviations: AUC, area under the receiver operating characteristic curve; ANG2, angiopoietin-2; EBMT, European Society for Blood and Marrow Transplantation; HA, hyaluronic acid; ICAM1, intercellular adhesion molecule-1; L-ficolin, L-ficolin; SOS, sinusoidal obstruction syndrome; ST2, suppression of tumorigenicity 2; TIMP1, tissue inhibitor of metalloproteinase-1; TM, thrombomodulin; VCAM1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VOD, veno-occlusive disease.

Supplementary Table S2. Clinical characteristics and exploratory analyses

A. Baseline patient and transplant characteristics

Variable	Number	%
Times of transplantation	118	
Median age, years (range)	61	(23–77)
Sex, male/female	72/46	
Primary disease		
AML	70	59.3%
MDS or MPN	21	17.8%
ALL	15	12.7%
NHL	7	5.9%
CML	5	4.2%
Disease status		
In remission	33	28.0%
Not in remission	85	72.0%
Previous exposure		
Gemtuzumab ozogamicin	1	0.8%
Inotuzumab ozogamicin	5	4.2%
Previous history of transplantation		
No	101	85.6%
Autologous	5	4.2%
Allogeneic	12	10.2%
Intensity of conditioning		
MAC	37	31.4%
RIC	81	68.6%
Busulfan-containing conditioning	97	82.2%
TBI-containing conditioning	90	76.3%
Baseline liver function		
AST, U/L, median (IQR)	16	(14–24)
ALT, U/L, median (IQR)	16	(10–30)
Total bilirubin, mg/dL, median (IQR)	0.6	(0.5–0.8)
Baseline Ferritin		
Ferritin, ng/mL, median (IQR)	955	(441–1865)
GVHD prophylaxis		
Tacrolimus and MMF	118	100%
SOS/VOD prophylaxis		
Ursodeoxycholic acid	118	100%
Dalteparin	118	100%
Defibrotide	0	0%
Antifungal prophylaxis		
Fluconazole	0	0%
Voriconazole	15	12.7%
Posaconazole	18	15.3%
Micafungin	80	67.8%
Liposomal amphotericin B	5	4.2%

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma; RIC, reduced-intensity conditioning; SOS, sinusoidal obstruction syndrome; TBI, total body irradiation; VOD, veno-occlusive disease.

B. Clinical characteristics, management, and outcomes of patients with SOS/VOD according to onset subtype

Variable	Classical SOS (n=16)	Late-onset SOS (n=39)
EBMT 2016 severity at SOS/VOD diagnosis		
Mild	0	0
Moderate	1 (6.3%)	2 (5.1%)
Severe	4 (25.0%)	14 (35.9%)
Very severe	11 (68.8%)	23 (59.0%)
Multi-organ dysfunction *	10 (62.5%)	16 (41.0%)
Clinical course and outcomes		
Received defibrotide	7 (43.8%)	8 (20.5%)
ICU admission following SOS/VOD diagnosis	8 (50.0%)	14 (35.9%)
Day-100 mortality	9 (56.3%)	4 (10.3%)

* Pulmonary dysfunction was defined as the requirement for new supplemental oxygen, and renal dysfunction as a serum creatinine level ≥2 times the pre-transplant baseline, both assessed at the time of SOS/VOD diagnosis.

Abbreviations: HA, hyaluronic acid; ICU, intensive care unit; IQR, interquartile range; MOD, multi-organ dysfunction; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.

C. Individual clinical characteristics and diagnostic findings of patients with late-onset SOS

ID	Age	Sex	Primary disease	Conditioning	GVHD prophylaxis	Day of diagnosis	Supporting findings *					
							Painful hepato-megaly	Weight gain ≥ 5%	Bilirubin ≥2 mg/dL	Ascites	Supportive imaging findings	Diagnostic procedures
1	47	F	ALL	Flu/Mel/TBI	Tac/MMF	35	Yes	Yes	Yes	Yes	Asc, HVN	US, CT
2	58	F	ALL	Flu/Bu/Mel/TBI	Tac/MMF	105	Yes	Yes	Yes	Yes	Asc, GBWT	US, CT
4	63	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	83	No	Yes	No	Yes	Asc, GBWT	US, CT
15	64	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	144	No	Yes	No	Yes	Asc, HVN, GBWT	US, CT
19	71	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	71	Yes	Yes	No	Yes	Asc, GBWT	US, CT
22	64	M	MDS	Flu/Bu/Mel/TBI	Tac/MMF	63	Yes	Yes	No	Yes	Asc, RPFV, GBWT	US, CT
25	63	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	39	No	Yes	No	Yes	Asc, DHA	US, CT
26	66	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	27	Yes	Yes	Yes	Yes	Asc	CT
27	71	F	MDS	Flu/Bu/Mel/TBI	Tac/MMF	54	Yes	Yes	Yes	Yes	Asc, HVN	US, CT
34	67	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	161	Yes	Yes	No	Yes	HMG, Asc, GBWT	US, CT
37	69	M	MDS	Flu/Bu/Mel/TBI	Tac/MMF	26	Yes	Yes	Yes	Yes	Asc, GBWT	CT
42	49	M	ALL	Flu/Bu/Mel/TBI	Tac/MMF	47	No	Yes	No	Yes	HMG, Asc, RPFV	US, CT
43	56	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	34	No	Yes	No	Yes	HMG, Asc, GBWT	US, CT
47	70	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	27	No	Yes	No	Yes	Asc, HVN	US, CT
49	72	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	108	Yes	Yes	No	Yes	HMG, Asc, GBWT	US, CT
50	60	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	22	No	Yes	Yes	Yes	Asc, DHA, GBWT	US, CT
53	77	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	51	No	Yes	Yes	Yes	Asc, RPFV	US, CT
54	69	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	32	Yes	Yes	No	Yes	HMG, Asc, DHA, GBWT	US, CT
57	72	F	MDS	Flu/Bu/Mel/TBI	Tac/MMF	180	Yes	Yes	No	Yes	Asc, HARI, DPV	US, CT
58	58	F	AML	Flu/Mel	Tac/MMF	34	Yes	Yes	No	Yes	HMG, Asc, DHA	US, CT
62	65	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	189	No	Yes	No	Yes	Asc, HARI	US, CT
64	50	F	MDS	Flu/Bu/Mel/TBI	Tac/MMF	46	Yes	Yes	No	Yes	HMG, Asc, DMPV	US, CT
70	29	M	ALL	Flu/Mel/HDCA	Tac/MMF	33	Yes	Yes	Yes	Yes	HMG, Asc, PVF	US, CT
72	67	M	MDS	Flu/Bu/Mel/TBI	Tac/MMF	173	No	Yes	Yes	Yes	HMG, Asc, RPFV, HARI	US, CT
76	50	F	NHL	Flu/Mel/TBI	Tac/MMF	178	No	Yes	No	Yes	Asc, GBWT, DPV	US, CT
78	38	M	ALL	Flu/Mel/HDCA	Tac/MMF	49	Yes	Yes	No	Yes	Asc, DMPV, RPFV, GBWT, DPV	US, CT
80	70	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	33	Yes	No	No	Yes	HMG, Asc, HARI, PVF; HVPG elevation	US, CT, HVPG
81	67	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	72	No	Yes	No	Yes	HMG, Asc, DMPV, RPFV, HARI	US, CT
84	39	M	AML	Flu/Mel/TBI/HDCA	Tac/MMF	61	Yes	Yes	No	Yes	HMG, Asc, HARI, PVF	US, CT
89	56	M	AML	Flu/Bu/Mel	Tac/MMF	27	Yes	Yes	No	Yes	HMG, Asc, HARI	US, CT
95	57	M	AML	Flu/Bu/Mel	Tac/MMF	22	Yes	Yes	No	Yes	HMG, Asc, RPFV, HARI	US, CT
97	64	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	127	No	Yes	No	Yes	HMG, Asc, HARI, GBWT, DPV, PVF	US, CT
101	72	F	MDS	Flu/Bu/Mel/TBI	Tac/MMF	95	No	Yes	No	Yes	Asc, RPFV, HARI, DPV	US, CT
102	66	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	200	No	Yes	Yes	Yes	Asc, DMPV, HARI	US, CT
103	66	M	AML	Flu/Bu/Mel/TBI	Tac/MMF	48	No	Yes	No	Yes	HMG, Asc, DMPV, HARI	US, CT
104	60	F	AML	Flu/Bu/Mel/TBI	Tac/MMF	347	No	Yes	No	Yes	Asc, DMPV, RPFV, GBWT	US, CT
113	62	F	NHL	Flu/Mel/TBI	Tac/MMF	22	No	Yes	No	Yes	HMG, Asc, DMPV, RPFV, HARI	US, CT
114	43	M	MDS	Flu/Bu/Mel/TBI	Tac/MMF	54	No	Yes	No	Yes	HMG, Asc, DMPV, RPFV, HARI	US, CT
116	61	M	CML	Flu/Bu/Mel/TBI	Tac/MMF	46	Yes	No	No	Yes	HMG, Asc, DMPV, RPFV, HARI, GBWT, PVF	US, CT

* Late-onset SOS was diagnosed according to the 2016 EBMT criteria based on the overall clinical assessment, including compatible imaging findings and exclusion of alternative diagnoses. The imaging findings listed represent the principal supportive findings identified by ultrasonography, computed tomography, and, where applicable, hepatic venous pressure gradient measurement.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Asc, ascites; Bu, busulfan; CML, chronic myeloid leukemia; CT, computed tomography; DHA, dilated hepatic artery; DMPV, dilated main portal vein; DPV, dilated paraumbilical vein; Flu, fludarabine; GBWT, gallbladder wall thickening; HARI, increased hepatic arterial resistive index; HDCA, high-dose cytarabine; HMG, hepatomegaly; HVN, hepatic vein narrowing; HVPG, hepatic venous pressure gradient; MDS, myelodysplastic syndrome; Mel, melphalan; MMF, mycophenolate mofetil; NHL, non-Hodgkin lymphoma; PVF, abnormal paraumbilical venous flow (stagnant or hepatofugal); RPFV, reduced portal venous flow velocity; Tac, tacrolimus; TBI, total body irradiation; US, ultrasonography.

D. Exploratory analyses of serum HA levels according to disease severity and clinical outcomes in patients with SOS/VOD

Classical SOS

Comparison	Group	N	Day-9 HA, median (IQR), ng/mL	P value
Disease severity at diagnosis	Non-very severe	5	1010 (765–1810)	
	Very severe	11	2050 (1112–6655)	0.267
Multi-organ dysfunction at diagnosis	No	6	1410 (826–1990)	
	Yes	10	2010 (942–8223)	0.368
ICU admission following diagnosis	No	8	1810 (951–2398)	
	Yes	8	1630 (741–5940)	1
Day-100 mortality	Alive	7	1570 (888–2215)	
	Dead	9	1810 (773–3520)	0.837

Late-onset SOS

Comparison	Group	N	Day-9 HA, median (IQR), ng/mL	P value	Day-21 HA, median (IQR), ng/mL	P value
Disease severity at diagnosis	Non-very-severe	16	373 (183–666)		279 (149–349)	
	Very severe	23	410 (249–1310)	0.626	595 (346–969)	0.022
Multi-organ dysfunction at diagnosis	No	23	353 (129–1036)		315 (142–477)	
	Yes	16	501 (292–1290)	0.232	645 (491–1073)	0.014
ICU admission following diagnosis	No	25	292 (183–544)		353 (156–779)	
	Yes	14	838 (319–1425)	0.106	409 (233–862)	0.639
Day-100 mortality	Alive	35	353 (197–1180)		361 (171–645)	
	Dead	4	533 (264–2540)	0.585	740 (337–895)	0.585

Data are presented as median (interquartile range). Comparisons were performed using the Mann–Whitney U test. Because of the limited sample size, these analyses were considered exploratory and were not adjusted for multiple comparisons.

Abbreviations: HA, hyaluronic acid; ICU, intensive care unit; IQR, interquartile range; MOD, multi-organ dysfunction; SOS, sinusoidal obstruction syndrome; VOD, veno-occlusive disease.