Rituximab, dexamethasone, etoposide, ifosfamide and carboplatin (R-DeVIC) in relapsed or refractory central nervous system lymphoma: a retrospective multicentre clinical study

High-dose methotrexate (HD-MTX)-based first-line treatment followed by thiotepa (TT)-based high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT) is established as standard of care for eligible patients with untreated primary diffuse large B-cell lymphoma of the central nervous system (PCNSL).[1] However, up to one-third of PCNSL patients fail first-line treatment and 25-50% eventually relapse after initial complete remission (CR).[2] In the relapse / refractory (rr) setting, standard of care has not been established, and outcomes remain poor.[3,4] Although a few phase II trials demonstrated promising overall response rates (ORR) for novel agents such as Bruton's tyrosine kinase inhibitors (BTK) or immunomodulatory drugs (IMiD) in rrCNSL, response duration was short.[5,6] In the absence of data from randomized trials, treatment recommendations for CNS involvement of systemic B-cell lymphoma (secondary central nervous system lymphoma [SCNSL]) rely on prospective, single-arm trials, retrospective series or expert consensus. In the phase II MARIETTA trial, SCNSL patients received sequential MATRix (HD-MTX, HD-AraC, TT, rituximab) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide) followed by consolidating TT-based HCT-ASCT. While progression-free survival (PFS) rates were promising overall, outcome for the 43 patients who relapsed was significantly inferior, with a 1-year PFS rate of 28%.[7] The DeVIC regimen (dexamethasone, ifosfamide, carboplatin, and etoposide) uses the same agents as ICE, but at slightly different dosages. In a retrospective cohort of 21 untreated PCNSL patients, DeVIC achieved a 95% ORR and a median PFS of 49 months for patients who achieved CR prior to consolidating whole-brain radiotherapy.[8] Given its non-cross-resistant agents, DeVIC was also evaluated with rituximab as non-myeloablative consolidation *versus* HCT-ASCT in untreated PCNSL patients following MATRix in the phase III MATRix / IELSG43 trial.[9] However, its efficacy and tolerability in rrPCNSL / SCNSL remain unknown. Thus, we performed a retrospective multicenter study at four German tertiary referral centers and identified 100 patients by chart review who received at least one R-DeVIC cycle between January 2010 and June 2024 for remission induction in either rrPCNSL or rrSCNSL: rituximab (375 mg/m^2) day (d) 0, dexamethasone (40 mg/d) days 1-3, etoposide (100 mg/m^2/d) days 1-3, ifosfamide (1500 mg/m^2/d) days 1-3, and carboplatin (300 mg/m^2) day 1, intravenously, every three weeks. Patients with rrSCNSL were included regardless of isolated CNS or synchronous systemic lymphoma manifestations prior to R-DeVIC. Refractory disease was defined as progression within three months after prior therapy. Inclusion criteria were: 1) histologically confirmed high-grade B-cell lymphoma at initial diagnosis; 2) CNS progression assessed by local neuroradiological imaging evaluation. The study was conducted in accordance with the principles of the Declaration of Helsinki of 1975, as revised in 2008, and was approved by the central ethics committee.

The primary endpoint was the best overall response rate (BORR), defined as the proportion of patients who achieved CR or partial remission (PR) of the patients in whom response assessment was performed prior to any other anti-lymphoma therapy, and assessed by local neuroradiological evaluation according to the response criteria of the International Primary CNS Lymphoma Collaborative Group (IPCG). Consolidation therapy was defined as any planned treatment administered after completion of induction therapy, excluding patients with progressive disease after R-DeVIC. Secondary endpoints were PFS, defined as time from the start of R-DeVIC until progression or death from any cause, and overall survival (OS), defined as time from the start of R-DeVIC until death from any cause. Patients without an event were censored at their last follow-up. Toxicity was assessed in clinically relevant categories, graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and are only shown if severe (≥ grade 3).

This was a descriptive study without formal hypothesis testing. All statistical comparisons, including subgroup analyses, were exploratory, and *P* values are descriptive only. Categorical variables are reported as frequencies and proportions; continuous variables are reported as medians and ranges. PFS and OS were estimated using the Kaplan-Meier method, and groups were compared using the log-rank test and Cox regression analysis. Analyses were performed in R version 4.1.1.

Prior therapy lines contained HD-MTX in 99/100 (99%) patients, and 40/100 (40%) patients had already received HCT-ASCT consolidation. Of the 100 patients, 97 were evaluable for response, while the remaining 3 died within one week after starting R-DeVIC. Further patient characteristics are summarized in Table 1.

Table 1. Patient characteristics before the first cycle of R-DeVIC.

	All patients	PCNSL	SCNSL
Patient characteristics prior to R-DeVIC, N=100			
PCNSL N (%) SCNSL N (%) Synchronous systemic lymphoma manifestation	55 (55) 45 (45) 14 (31)	55 - -	- 45 14
Age, years, median (range)	63 (35-85)	63 (35-83)	63 (36-85)
Sex, N (%) Female	39 (39)	26 (47)	13 (29)
ECOG Median (range) ≥ 2, N (%)	1 (0-4) 46 (46)	1 (0-4) 25 (45)	1 (0-3) 21 (46)
Prior treatment lines, median (range)	1 (1-3)	1 (1-3)	1 (1-3)
Median time from end of prior therapy line to start of R-DeVIC, months (range)	4 (0.3-65)	5 (0.3-52)	3 (1-65)
Reasons for R-DeVIC therapy, N (%) Relapse Refractory CNSL	44 (44) 56 (56)	26 (47) 29 (53)	18 (40) 27 (60)
Treatment from start of R-DeVIC, N=100			
R-DeVIC cycles, median (range)	2 (1-3)	2 (1-3)	2 (1-3)
Consolidation/maintenance reached, N (%) HCT-ASCT CAR T-cell therapy Radiotherapy Single agent maintenance therapy	32 (32) 21 (21) 5 (5) 3 (3) 3 (3)	17 (31) 12 (22) 0 (0) 3 (5) 2 (4)	15 (33) 9 (20) 5 (11) 0 (0) 1 (1)
Response rates after a median of 2 cycles of R-DeVIC, N=97			
ORR, N (%) CR PR	46 (47) 9 (9) 37 (38)	30 (55) 6 (11) 24 (44)	16 (37) 3 (7) 13 (30)
SD, N (%)	10 (10)	6 (11)	4 (9)
PD, N (%)	41 (42)	18 (33)	23 (53)

CAR: chimeric antigen receptor; CNSL: central nervous system lymphoma; CR: complete remission; ECOG: Eastern Co-operative Oncology Group; HCT-ASCT: high-dose chemotherapy and autologous stem cell transplantation; N: number; ORR: overall response rate; PCNSL: primary diffuse large B-cell lymphoma of the central nervous system; PD: progressive disease; PR: partial remission; R-DeVIC: rituximab, dexamethasone, etoposide, and carboplatin; SCNSL: secondary central nervous system lymphoma; SD: stable disease.

The BORR was 47% (CR: N=9, PR: N=37) after the application of a median number of 2 R-DeVIC cycles (range: 1-3). rrPCNSL patients showed higher response rates than rrSCNSL patients (55% *vs*. 37%). Prior HCT-ASCT exposure was associated with lower ORR (42% *vs*. 51%). After a median follow-up period of 16.4 months (range: 0.2-107.1), median PFS and OS for the entire cohort were 2.0 months (95% confidence interval [CI]: 1.3-2.7) and 8.0 months (95%CI: 5.8-10.1), respectively. Thirty-two out of the 100 patients (32%) received consolidation / maintenance treatment following R-DeVIC: 21/32 (66%) patients received HCT-ASCT, 5/32 (16%) patients CD19-directed chimeric antigen receptor (CAR) T-cell therapy, while the remaining patients (6/32) received either radiotherapy (N=3) or lenalidomide maintenance (N=3). The rate of patients reaching consolidation was comparable between rrPCNSL and rrSCNSL patients. Among the 26 patients who underwent consolidation with HCT-ASCT or CAR T-cell therapy, median PFS and OS were 7.8 months (95%CI: 0.0-21.0) and 52.8 months (95%CI: 0.0-115.5), respectively. After HCT-ASCT or CAR T-cell therapy, 12/26 (46%) patients relapsed and 16/26 (62%) received additional salvage treatment. Of the 3 patients who received consolidating radiotherapy, 2 had sustained responses at last follow-up four and 39 months after radiotherapy, and one patient experienced progressive disease (PD) one month after radiotherapy. Median PFS for the 3 patients receiving lenalidomide maintenance was six months (range: 4-10). Of the 42 patients with documented PD following R-DeVIC, 25 (60%) received no further anti-lymphoma therapy, yet 11 (26%) received HCT-ASCT or CAR T-cell therapy. Of these 11 patients, 9 received HCT-ASCT (8 without intercalated salvage treatment, 1 with intercalated R-MTX/AraC),

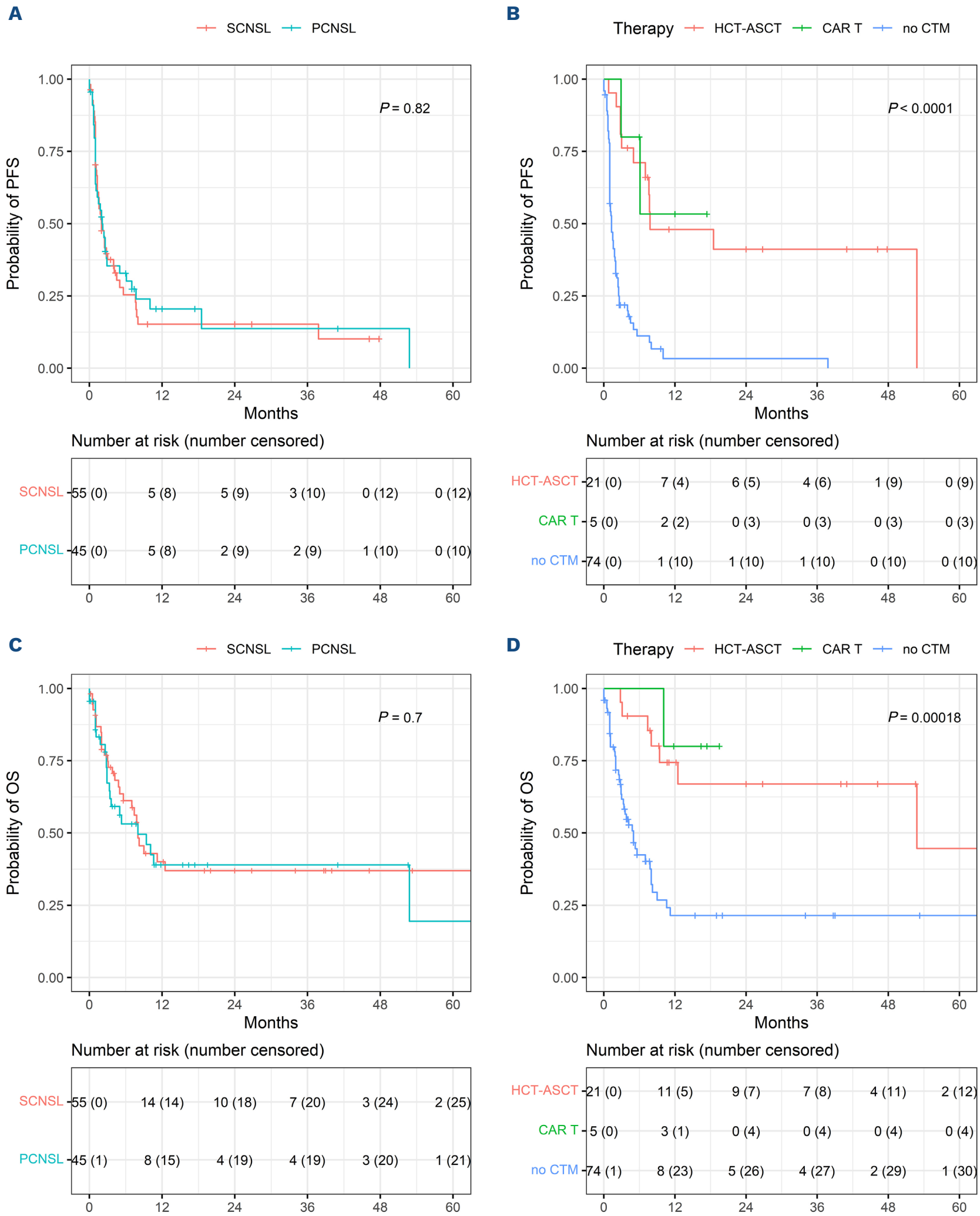

Figure 1. Kaplan-Meier curves for progression-free survival and overall survival. (A and C) Progression-free survival (PFS) and overall survival (OS) for the primary and secondary central nervous system lymphoma (PCNSL/SCNSL) subgroups, and (B and D) show PFS and OS according to consolidation therapy with high-dose chemotherapy and autologous stem cell transplantation (HCT-ASCT), chimeric antigen receptor (CAR) T-cell therapy, or no cellular therapy modality (CTM) after R-DeVIC (rituximab, dexamethasone, etoposide, and carboplatin). There was no significant difference in PFS or OS between patients with PCNSL and those with SCNSL. By contrast, patients who received consolidation with HCT-ASCT or CAR T-cell therapy had significantly longer PFS and OS than those who either underwent consolidation with radiotherapy or lenalidomide maintenance or did not receive consolidation.

and 2 received CAR T-cell therapy (1 following intercalated treatment with ibrutinib/radiotherapy and 1 following ViPOR [venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide]).

Patients receiving consolidative HCT-ASCT or CAR T-cell therapy achieved significantly superior PFS (hazard ratio [HR] 0.19, 95%CI: 0.10-0.35, *P*<0.001) and OS (HR 0.22, 95%CI: 0.10-0.48, *P*<0.001) compared with the remainder of the cohort, including those who proceeded to these therapies despite failing to respond to R-DeVIC. Among the non-responder subset who nonetheless underwent consolidation, median PFS was 1.3 months (95%CI: 0.5-7.7) and median OS was 6.4 months (95%CI: 3.4-11.2). Survival for the described subgroups is shown in Figure 1 and post-consolidation response rates and subsequent treatments in *Online Supplementary Table S1*.

Multivariate analysis, including age, performance status, number of prior treatment lines, median time from prior therapy, classification as PCNSL or SCNSL, and relapse *versus* refractory status could not identify prognostic factors for PFS and OS or high-risk patient subgroups for treatment-related mortality.

Seven patients were admitted to intensive care during R-DeVIC, and 8 died, mostly due to infectious complications some of which were possibly related to R-DeVIC treatment. All deaths occurred during the first R-DeVIC cycle (Table 2).

Several salvage regimens have been explored in rrPCNSL (*Online Supplementary Table S2*). Single-agent therapies such as pemetrexed, temozolomide, topotecan, and poly-(immuno)chemotherapy with (R)-GemOx (rituximab, gemcitabine, oxaliplatin) have shown ORR of 31-55% and median PFS of 2.0-5.7 months, similar to our study results.[10-13] By contrast, prospective phase II trials of BTK inhibitor ibrutinib or IMiD lenalidomide in rrPCNSL (and some rrSCNSL) reported higher ORR (48-77%) but PFS of only 4.6-6.0 months; these targeted therapies were better tolerated than R-DeVIC in our study.[5,6] Moreover, the comparable ICE regimen was evaluated in a retrospective study by the French LOC network.[14] Despite a promising BORR of 70%, long-term remissions were confined to patients who proceeded to consolidative strategies, which is in line with our results. Notably, only 6% in the LOC network study received prior HCT-ASCT *versus* 40% in our cohort, and only rrPCNSL were included, which may explain the superior efficacy in their results.

The substantial toxicity of R-DeVIC, including severe infectious complications leading to treatment discontinuation and death, does not support its use as standard salvage therapy for r/r CNS lymphoma. While R-DeVIC may still be considered as a bridging option in PCNSL patients who have been carefully selected and have shown good tolerance to previous chemotherapy approaches, the inferior response rates in SCNSL patients strongly favor the use of alternative salvage approaches in this subgroup.

The main limitations of our study include the retrospective design, the heterogeneous study population of rrPCNSL and rrSCNSL patients, and the small numbers of patients in analyzed subgroups. The survival benefit observed in our patients receiving consolidative therapy (N=26) should be interpreted with caution due to selection bias because patients with better performance status and those with better responses to R-DeVIC were more likely to receive intensive consolidation. The small subgroup size means that these findings remain exploratory and require validation in larger cohorts.

Given the promising response rates but limited durability of single-agent therapies, future studies should assess these agents as bridging to consolidation. BTK inhibitors show particular promise given their excellent CNS penetration and favorable toxicity profile; they warrant priority evaluation in future clinical trials as bridging to consolidating HCT-ASCT or CAR T-cell therapy for rrCNSL patients.[15]

Table 2. Toxicity: overview of serious adverse events (grade ≥3) after treatment with R-DeVIC.

Toxicity N=100	N (%)
Hematologic toxicity ≥grade 3	63 (63)
Infections ≥grade 3 After 1st R-DeVIC cycle After 2nd R-DeVIC cycle After 3rd R-DeVIC cycle	43 (43) 34/100 (34) 21/64 (33) 3/15 (20)
Neurotoxicity ≥grade 3	10 (10)
Acute kidney injury ≥grade 3*	4 (4)
Dose reductions or treatment-related delay	28 (28)
Treatment-related deaths**	8 (8)

N: number; R-DeVIC: rituximab, dexamethasone, etoposide, and carboplatin. *1 patient developed terminal renal insufficiency requiring hemodialysis. **Sepsis / infection (N=7) and heart failure (N=1).

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Contributions

ST, ESc and GI developed the study; KK, HT, AK, JW, ST, SW, JF, ESh, GL, GW, LKI and AA provided resources; KK, HT, JW, ST and AJ analyzed patient data; KK, JW, HT, ST, LKI and ESc wrote the manuscript. All authors revised and agreed to the final version of the manuscript for publication.

Data-sharing statement

Primary individual participant data may be shared to researchers whose proposed use of the data has been approved by an independent review committee identified for this purpose upon request. All secondary data derived from these primary individual participant data are available within this article.

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