Clinicopathological implications of immunohistochemical expression of TBX21, CXCR3, GATA3, CCR4, and TCF1 in nodal follicular helper T-cell lymphoma and peripheral T-cell lymphoma, not otherwise specified

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Background: The classification of nodal peripheral T-cell lymphoma (PTCL) has evolved according to histology, cell-of-origin, and genetic alterations. However, the comprehensive expression pattern of follicular helper T-cell (Tfh) markers, T-cell factor-1 (TCF1), and Th1- and Th2-like molecules in nodal PTCL is unclear. **Methods:** Eighty-two cases of nodal PTCL were classified into 53 angioimmunoblastic T-cell lymphomas (AITLs)/nodal T-follicular helper cell lymphoma (nTFHL)-AI, 18 PTCLs-Tfh/nTFHL–not otherwise specified (NOS), and 11 PTCLs-NOS according to the revised 4th/5th World Health Organization classifications. Immunohistochemistry for TCF1, TBX21, CXCR3, GATA3, and CCR4 was performed. **Results:** TCF1 was highly expressed in up to 68% of patients with nTFHL but also in 44% of patients with PTCL-NOS (p > .05). CXCR3 expression was higher in AITLs than in non-AITLs (p = .035), whereas GATA3 expression was higher in non-AITL than in AITL (p = .007) and in PTCL-Tfh compared to AITL (p = .010). Of the cases, 70% of AITL, 44% of PTCL-Tfh/nTFHL-NOS, and 36% of PTCL-NOS were subclassified as the TBX21 subtype; and 15% of AITL, 38% of PTCL-Tfh/nTFHL-NOS, and 36% of PTCL-NOS were subclassified as the GATA3 subtype. The others were an unclassified subtype. CCR4 expression was associated with poor progression-free survival (PFS) in patients with PTCL-Tfh (p < .001) and nTFHL (p = .023). The GATA3 subtype showed poor overall survival in PTCL-NOS compared to TBX21 (p = .046) and tended to be associated with poor PFS in patients with non-AITL (p = .054). **Conclusions:** The TBX21 subtype was more prevalent than the GATA3 subtype in AITL. The GATA3 subtype was associated with poor prognosis in patients with non-AITL and PTCL-NOS.

Key Words: Angioimmunoblastic T-cell lymphoma; Nodal peripheral T-cell lymphoma of TFH phenotype; Nodal T-follicular helper (TFH) cell lymphoma, angioimmunoblastic-type; Nodal T-follicular helper (TFH) cell lymphoma, not otherwise specified; Peripheral T-cell lymphoma, not otherwise specified

Nodal peripheral T-cell lymphoma (PTCL) consists of distinct entities, and its classification has evolved in recent decades by considering clinicopathological features, genetic alterations, and the cell-of-origin [1-3]. In particular, many advances in nodal PTCL of follicular helper T-cell (Tfh) origin have been made [2,3]. Conventionally, nodal PTCL other than angioimmuno-

blastic T-cell lymphoma (AITL) and anaplastic lymphoma kinase (ALK)(+) or ALK(–) anaplastic large cell lymphoma (ALCL) was classified into PTCL–not otherwise specified (NOS). The revised 4th World Health Organization (WHO) classification of lymphomas introduced a category of AITL and other nodal lymphoma of TFH cell origin, which included AITL, follicular

T-cell lymphoma, and nodal PTCL with Tfh phenotype (PTCL-Tfh) [1]. Despite distinct histologic and genetic features, these three entities share unique genetic alterations and gene expression profiles, which are not shared by PTCL-NOS. Tfh-like PTCLs exhibit gene expression signatures similar to normal Tfh and AITL and frequently show genetic mutations in *TET2*, *DNMT3A*, and *RHOA* [4-10]. Thus, the current 5th WHO classification and the International Consensus Classification (ICC) of lymphomas changed the terminology of nodal PTCLs of Tfh origin to nodal T-follicular helper cell lymphoma (nTFHL; WHO5) and Tfh lymphoma (TFHL; ICC) of the angioimmunoblastic-type, follicular-type, and NOS, respectively [2,3].

In clinical practice, the identification of the Tfh phenotype is made by immunohistochemical analysis. The expression of two or more (preferably 3 or more) Tfh-related markers (represented by programmed death-1 [PD-1], inducible T cell costimulator [ICOS], C-X-C motif chemokine ligand 13 [CXCL13], CD10, BCL6, and C-X-C motif chemokine receptor 5 [CXCR5]) with a cutoff value of 5%–20% (usually 10%) in neoplastic CD4 T cells, is considered to represent the Tfh phenotype [11-13]. However, none of these markers are specific for Tfh cells, and there is no gold standard cutoff value. Given that the differential diagnosis of nTFHL-NOS and PTCL-NOS only depends on the determination of the Tfh phenotype, further studies to define the Tfh phenotype using clinical samples (especially formalin-fixed paraffin-embedded tissue [FFPE]) may be required.

T-cell factor 1 (TCF1, encoded by the *TCF7* gene) plays an important role in T-cell development and malignant transformation. TCF1 is expressed in CD4 and CD8 naïve T cells, Tfh cells, CD8 memory T cells, and stem-like exhausted T cells [14]. TCF1 plays a role in Tfh-cell differentiation and function [15]. However, the potential role of TCF1 expression in the diagnosis of PTCL remains unclear. Thus, we addressed this issue in this study.

Excluding nTFHL-NOS, PTCL-NOS remains a heterogeneous entity. Previous studies on PTCL-NOS often included nTFHL-NOS other than AITL, thus hampering our understanding of the biology of PTCL-NOS. Despite this, recent studies on the gene expression profiling of PTCL-NOS led to the identification of two major subtypes of PTCL-NOS, including PTCL–T-box transcription factor 21 (TBX21) (i.e., Th1-like subtype) and PTCL–GATA binding protein 3 (GATA3) (i.e., Th2-like subtype) [16-19]. They showed distinct oncogenic pathway alterations and pathologic features, with a less favorable prognosis for patients with PTCL-GATA3 [18,19]. These subtypes could be classified using immunohistochemical markers for PTCL-TBX21 (including TBX21 and CXCR3) and PTCL-GATA3 (including GATA3 and C-C motif chemokine receptor 4 [CCR4]) [20]. However, further validation is needed. Tfh cells may also co-express Th1- and Th2-transcription factors and chemokines under certain differentiation stages and circumstances, although the biological role of Th1 and Th2 transcription factor expression in Tfh cells needs more investigation [21-24]. However, the expression of these markers in nTFHL remains unclear.

Thus, in this study, we comprehensively investigated the immunohistochemical expression of TBX21, CXCR3, GATA3, CCR4, and TCF1 in nTFHL and PTCL-NOS cases classified according to the conventional and current nodal PTCL classifications.

MATERIALS AND METHODS

Patients

A total of 82 nodal PTCL patients diagnosed from 2001 to 2021 at the Seoul National University Hospital (SNUH) were enrolled. The patients' diagnoses were reviewed and classified based on the revised 4th and 5th WHO classification guidelines (WHO4R and WHO5, respectively). Some of the patients were included in our previous studies [25,26]. All cases were classified as having AITL (i.e., nTFHL-AI by WHO5), PTCL-Tfh (i.e., nTFHL-NOS by WHO5), or PTCL-NOS (i.e., PTCL-NOS by WHO5). For comparison, AITL and PTCL-Tfh were grouped into nTFHL, whereas PTCL-Tfh and PTCL-NOS were classified as non-AITL.

Immunohistochemistry

Immunohistochemical (IHC) studies were performed using FFPE with the following antibodies: CD10 (clone 56C6, Novocastra, Newcastle, UK), BCL6 (clone LN22, Novocastra), PD-1 (clone MRQ-22, Cell Marque, Rocklin, CA, USA), CXCR5 (clone 51505, R&D Systems, Minneapolis, MN, USA), ICOS (clone EPR20560, Abcam, Cambridge, UK), TCF1 (C63D9, Cell Signaling Technology, Danvers, MA, USA), T-bet/TBX21 (4B10, Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA), CXCR3 (clone CD183, BD PharMingen, Heidelberg, Germany), GATA3 (Clone L50-823, Biocare Medical, Concord, CA, USA), CCR4 (polyclonal, catalog #: HPA031613, Sigma-Aldrich, St. Louis, MO, USA). Immunostaining was performed using a Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ, USA) or a Bond-Max Autostainer (Leica Microsystems, Melbourne, Australia). The expression of Tfh markers (CD10, BCL6, PD-1, CXCR5, and ICOS) in CD3+ cells were considered positive if they were above 10% [25]. According to the IHC subclassification algorithm in PTCL-NOS [20], TBX21 and

CXCR3 were considered positive above a 20% threshold, and GATA3 and CCR4 were considered positive beyond a 50% cutoff of CD3+ cells. The proportion of positive cells for TCF1 in the total CD3+ cells were graded as 0 (0%–10%), 1+ (10%–30%), 2+ (30%–50%), and 3+ (>50%).

Statistical analysis

Statistical analyses were performed using SPSS ver. 27 (IBM Corp., Armonk, NY, USA). Correlations of categorical variables were assessed using Pearson's χ^2 test and Fisher's exact test. Correlation among the markers for classification was calculated using Spearman's correlation. Survival analysis was conducted using the Kaplan-Meier method with the log-rank test. Two-sided p-values of less than .05 were considered statistically significant.

RESULTS

Clinical characteristics of patients with nodal PTCL

The distribution of the 82 patients with nodal PTCL and their clinical characteristics are summarized in Table 1. Fifty-three patients were diagnosed with AITL (i.e., nTFHL-AI by WHO5), 18 with PTCL-Tfh (i.e., nTFHL-NOS by WHO5), and 11 with PTCL-NOS. Seventy-one patients were classified as having nT-FHL, including AITL and PTCL-Tfh, while 29 patients, including PTCL-Tfh and PTCL-NOS, were grouped as non-AITL. The majority of these patients presented with an advanced Ann Arbor stage (3–4; 87.8%), elevated serum lactate dehydrogenase levels (76.3%), older age (>60 years; 61.0%), high international prognostic index (IPI) score (3–5; 61.0%), and bone marrow involvement (57.0%). PTCL-NOS had male predominance (90.9%) compared to other PTCL entities (p < .05, all). Patients with AITL and nTFHL exhibited significantly higher Ann Arbor stages compared to patients with PTCL-NOS (p = .009 and p = .008, respectively). Patients with PTCL-Tfh demonstrated higher IPI score and Eastern Cooperative Oncology Group Performance Status (ECOG PS) compared to patients with PTCL-NOS (p = .026 and p = .055, respectively). B symptoms were most common in patients with AITL (vs. non-AITL, p = .016; vs. PTCL-Tfh, p = .002, respectively), but less common in patients with PTCL-Tfh than PTCL-NOS (p = .013).

Analysis of Tfh markers and TCF1 expression in nodal PTCL

Representative TCF1 IHC images are shown in Supplementary Fig. S1. The IHC results of five conventional Tfh markers (CD10, BCL6, PD-1, CXCR5, and ICOS) and TCF-1 are summarized in Table 2 and Supplementary Fig. S2. The expression of the five conventional Tfh markers was positively correlated with variable statistical significances (Supplementary Fig. S2). As a diagnostic marker for nTFHL, CXCR5, and PD-1 showed the highest sensitivity, whereas CD10 and BCL6 exhibited high specificity but less sensitivity. AITL expressed more Tfh markers than PTCL-Tfh (average, 3.6 and 3.1), which is consistent with a previous report [25]. TCF1 expression was positively correlated with CXCR5 (Pearson's r = 0.317, p = .026) and ICOS expression (Pearson's r = 0.386, p = .006). However, there was no correlation between TCF1 and CD10, BCL6, or PD-1 expression (Supplementary Fig. S2). TCF1 was frequently expressed in up to 67.8% of nTFHL cases (63.6% of AITL and 80% of PTCL-Tfh) but was also expressed in 44.4% of the PTCL-NOS cases (Table 2). No difference in TCF1 expression levels was seen between the AITL, PTCL-Tfh, and PTCL-NOS cases (Supplementary Fig. S1). Together, these findings suggest that TCF1 expression is highly expressed in nTFHL, but specificity is low.

Expression pattern of Th1-like (TBX21 and CXCR3) and Th2-like (GATA3 and CCR4) markers in nodal PTCL

Representative IHC images of TBX21, CXCR3, GATA3, and CCR4 in AITL, PTCL-Tfh, and PTCL-NOS cases are shown in Fig. 1, and the results are summarized in Table 2 and Fig. 2. TBX21 and GATA3 expression demonstrated a significant positive correlation with the expression of their respective target proteins, CXCR3 and CCR4, respectively (Fig. 2A–C). TBX21 showed low expression in the range of 0%–30% in suspected neoplastic cells, except for one case (Fig. 2D). While the expression levels of CXCR3 and CCR4 were not significantly different among the 3 PTCL entities, the GATA3 expression level was significantly lower in AITL compared to PTCL-Tfh and PTCL-NOS (p < .05, both) (Fig. 2E–G). When the cases were identified as positive or negative for each marker expression as described in Materials and Methods, AITL showed the lowest GATA3 positivity (vs. PTCL-NOS, p = .041; vs. PTCL-Tfh, p = .010; vs. non-AITL, p = .007) (Table 2). In contrast, AITL cases showed higher CXCR3 positivity compared to non-AITL cases (p = .035) (Table 2).

Subclassification of nodal PTCL into TBX21 and GATA3 subtypes and their clinicopathological characteristics

Cases were subclassified based on the TBX21, CXCR3, GATA3, and CCR4 IHC results into TBX21, GATA3, and unclassified subtypes according to the algorithm by Amador et al. [20]. Overall, 70% of AITL, 44% of PTCL-Tfh (i.e., nTFHL-NOS by WHO5), and 36% of PTCL-NOS were subclassified as the

Table 1. Clinical characteristics of patients with nodal peripheral T-cell lymphoma

Variable	PTCL (n=82)	AITL (n=53)	PTCL-Tfh (n=18)	nTFHL (n=71)	PTCL-NOS (n=11)	Non-AITL (n=29)	p-value Three groups[a]	AITL vs. PTCL-NOS	PTCL-Tfh vs. PTCL-NOS	AITL vs. PTCL-Tfh	nTFHL vs. PTCL-NOS	AITL vs. non-AITL
Sex												
Female	34 (41.5)	22 (41.5)	11 (61.1)	33 (46.5)	1 (9.1)	12 (41.4)	.022	.041	.006	.150	.019	.991
Male	48 (58.5)	31 (58.5)	7 (38.9)	38 (53.5)	10 (90.9)	17 (58.6)						
Age (yr)												
≤60	32 (39.0)	22 (41.5)	5 (27.8)	27 (38.0)	5 (45.5)	10 (34.5)	.526	.809	.331	.300	.638	.533
>60	50 (61.0)	31 (58.5)	13 (72.2)	44 (62.0)	6 (54.5)	19 (65.5)						
Ann Arbor stage												
1–2	10 (12.2)	4 (7.5)	2 (11.1)	6 (8.5)	4 (36.4)	6 (20.7)	.029	.009	.103	.639	.008	.082
3–4	72 (87.8)	49 (92.5)	16 (88.9)	65 (91.5)	7 (63.6)	23 (79.3)						
IPI score												
0–2	32 (39.0)	21 (39.6)	4 (22.2)	25 (35.2)	7 (63.6)	11 (37.9)	.084	.144	.026	.182	.072	.881
3–5	50 (61.0)	32 (60.4)	14 (77.8)	46 (64.8)	4 (36.4)	18 (62.1)						
Extranodal site												
≤1	58 (71.6)	39 (75.0)	11 (61.1)	50 (71.4)	8 (72.7)	19 (65.5)	.528	.875	.523	.261	.929	.364
>1	23 (28.4)	13 (25.0)	7 (38.9)	20 (28.6)	3 (27.3)	10 (34.5)						
Serum LDH												
Normal	19 (23.8)	10 (19.6)	4 (22.2)	14 (20.3)	5 (45.5)	9 (31.0)	.186	.069	.189	.813	.069	.248
Elevated	61 (76.3)	41 (80.4)	14 (77.8)	55 (79.7)	6 (54.5)	20 (69.0)						
≥2	12 (20.3)	8 (20.0)	4 (36.4)	12 (16.9)	0	4 (21.1)						
B symptoms												
Absent	48 (60.8)	26 (51.0)	16 (94.1)	42 (61.8)	6 (54.5)	22 (78.6)	.006	.083	.013	.002	.649	.016
Present	31 (39.2)	25 (49.0)	1 (5.9)	26 (38.2)	5 (45.5)	6 (21.4)						
BM involvement												
Absent	34 (43.0)	20 (39.2)	7 (41.2)	27 (39.7)	7 (63.6)	14 (50.0)	.328	.138	.246	.886	.137	.354
Present	45 (57.0)	31 (60.8)	10 (58.8)	41 (60.3)	4 (36.4)	14 (50.0)						

Values are presented as number (%) unless otherwise indicated.

PTCL, peripheral T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; nT-FHL, nodal T-follicular helper (TFH) cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; IPI, International Prognostic Index; LDH, lactate dehydrogenase; BM, bone marrow.

[a]AITL vs. PTCL-Tfh vs. PTCL-NOS.

TBX21 subtype; 15% of AITL, 38% of PTCL-Tfh (i.e., nTFHL-NOS by WHO5), and 36% of PTCL-NOS into the GATA3 subtype; and the others into the unclassified subtype (Table 2). AITL frequently showed a TBX21 subtype (70%), which was statistically significant compared to non-AITL cases (p = .035) (Table 2). No difference in the proportion of TBX21 and GATA3 subtypes between PTCL-Tfh and PTCL-NOS was found (Table 2).

We analyzed clinical features according to TBX21 and GATA3 subtype classifications (Table 3, Supplementary Table S1). In AITL, the unclassified subtypes exhibited a higher ECOG PS compared to the TBX21 and GATA3 subtypes (p = .048). Within PTCL-Tfh and non-AITL, the GATA3 subtype displayed male predominance compared to TBX21 and unclassified subtypes (p = .012 for PTCL-Tfh; p = .040 for non-AITL). In PTCL-NOS, B symptoms tended to be more common in the unclassified subtype (p = .084). Otherwise, there was no significant difference in clinical features according to TBX21 and GATA3 subtype in

nodal PTCL (Table 3, Supplementary Table S1).

Amador et al. reported that monomorphic morphology was common in PTCL-NOS of GATA3 subtype and polymorphic morphology with mixed inflammatory background was common in PTCL-NOS of TBX21 subtype [20]. In this study, no significant histologic difference was observed in PTCL-NOS according to the two subtypes.

Survival analysis according to immunohistochemical markers and subtype classification in patients with AITL, PTCL-Tfh, nTFHL, PTCL-NOS, and non-AITL

Survival analysis according to the IHC markers and subtype classification was performed in patients with AITL, PTCL-Tfh, nTFHL, PTCL-NOS, and non-AITL. Progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier method according to GATA3, CCR4, and TCF1 expression are shown in Fig. 3 and Supplementary Fig. S3. GATA3 positivity was sig-

Table 2. Immunohistochemical features of patients with nodal peripheral T-cell lymphoma

Variable	AITL (n=53)	PTCL-Tfh (n=18)	nTFHL (n=71)	PTCL-NOS (n=11)	Non-AITL (n=29)	p-value					
						Three groups[a]	AITL vs. PTCL-NOS	PTCL-Tfh vs. PTCL-NOS	AITL vs. PTCL-Tfh	nTFHL vs. PTCL-NOS	AITL vs. non-AITL
CD10											
Negative	19 (46.3)	11 (68.8)	30 (52.6)	5 (100)	16 (76.2)	.038	.023	.152	.128	.041	.025
Positive	22 (53.7)	5 (31.3)	27 (47.4)	0	5 (23.8)						
BCL6											
Negative	19 (46.3)	13 (81.3)	32 (56.1)	5 (100)	18 (85.7)	.009	.023	.296	.017	.055	.003
Positive	22 (53.7)	3 (18.8)	25 (43.9)	0	3 (14.3)						
PD-1											
Negative	7 (17.1)	1 (6.3)	8 (14)	5 (100)	6 (28.6)	<.001	<.001	<.001	.290	<.001	.293
Positive	34 (82.9)	15 (93.8)	49 (86)	0	15 (71.4)						
CXCR5											
Negative	0	0	0	5 (100)	5 (23.8)	<.001	<.001	<.001	-	<.001	.001
Positive	41 (100)	16 (100)	57 (100)	0	16 (76.2)						
ICOS											
Negative	10 (24.4)	5 (31.3)	15 (26.3)	4 (80.0)	9 (42.9)	.039	.011	.055	.597	.013	.136
Positive	31 (75.6)	11 (68.8)	42 (73.7)	1 (20.0)	12 (57.1)						
TCF1											
Negative	16 (36.4)	3 (20.0)	19 (32.2)	5 (55.6)	8 (33.3)	.204	.283	.074	.241	.172	.803
Positive	28 (63.6)	12 (80.0)	40 (67.8)	4 (44.4)	16 (66.7)						
TBX21											
Negative	42 (91.3)	14 (87.5)	56 (90.3)	11 (100)	25 (92.6)	.500	.310	.223	.658	.281	.847
Positive	4 (8.7)	2 (12.5)	6 (9.7)	0	2 (7.4)						
CXCR3											
Negative	16 (34.0)	9 (56.3)	25 (39.7)	7 (63.6)	16 (59.3)	.101	.071	.701	.117	.139	.035
Positive	31 (66.0)	7 (43.8)	38 (60.3)	4 (36.4)	11 (40.7)						
GATA3											
Negative	44 (93.6)	11 (68.8)	55 (87.3)	8 (72.7)	19 (70.4)	.025	.041	.824	.010	.210	.007
Positive	3 (6.4)	5 (31.3)	8 (12.7)	3 (27.3)	8 (29.6)						
CCR4											
Negative	30 (63.8)	7 (43.8)	37 (58.7)	6 (60.0)	13 (50.0)	.369	.820	.420	.159	.940	.250
Positive	17 (36.2)	9 (56.3)	26 (41.3)	4 (40.0)	13 (50.0)						
Subclassification											
TBX21	33 (70.2)	7 (43.8)	40 (63.5)	4 (36.4)	11 (40.7)	.135	.102	.860	.112	.239	.035
GATA3	7 (14.9)	6 (37.5)	13 (20.6)	4 (36.4)	10 (37.0)						
Unclassified	7 (14.9)	3 (18.8)	10 (15.9)	3 (27.3)	6 (22.2)						

Values are presented as number (%) unless otherwise indicated.

AITL, angioimmunoblastic T-cell lymphoma; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; nTFHL, nodal T-follicular helper (TFH) cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PD-1, programmed death-1; CXCR5, C-X-C motif chemokine receptor 5; ICOS, inducible T cell costimulator; TCF1, T-cell factor-1; TBX21, T-box transcription factor 21; GATA3, GATA binding protein 3; CCR4, C-C motif chemokine receptor 4.

[a]AITL vs. PTCL-Tfh vs. PTCL-NOS.

nificantly associated with poor PFS in patients with non-AITL (p = .040). CCR4 positivity was significantly associated with poor PFS in patients with PTCL-Tfh (p < .001), nTFHL (p = .023), and non-AITL (p = .004) (Fig. 3). CCR4 positivity was also significantly associated with poor OS in patients with non-AITL (p = .016) (Supplementary Fig. S3). TCF1 positivity tended to

be associated with a favorable prognosis with marginal statistical significance for PFS in patients with PTCL-NOS (p = .046) (Fig. 3L) and for OS in patients with AITL (p = .031) (Supplementary Fig. S3C). No significant difference in PFS and OS was found according to the expression of TBX21 and CXCR3 (Supplementary Figs. S4, S5).
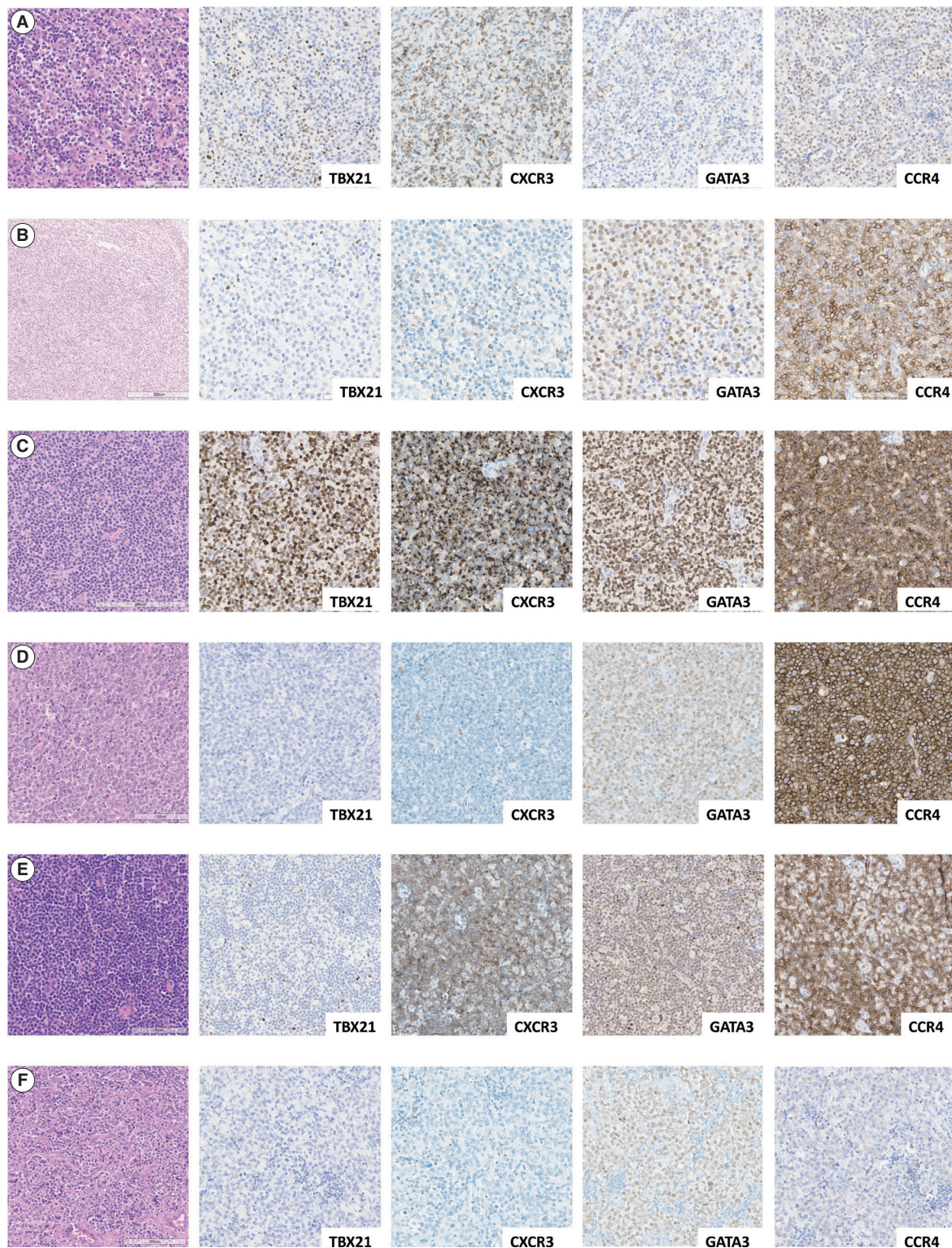
Fig. 1. Representative immunostaining for TBX21, CXCR3, GATA3, and CCR4 within TBX21 and GATA3 subtypes in three PTCL entities. Hematoxylin and eosin and TBX21, CXCR3, GATA3, and CCR4 immunostaining within the TBX21 subtype in AITL (A), GATA3 subtype in AITL (B), TBX21 subtype in PTCL-Tfh (C), GATA3 subtype in PTCL-Tfh (D), TBX21 subtype in PTCL-NOS (E), and GATA3 subtype in PTCL-NOS (F). AITL, angioimmunoblastic T-cell lymphoma; CCR4, C-C motif chemokine receptor 4; CXCR3, C-X-C motif chemokine receptor 3; GATA3, GATA binding protein 3; PTCL, peripheral T-cell lymphoma; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TBX21, T-box transcription factor 21.

PFS and OS using the Kaplan-Meier method according to TBX21 and GATA3 subtypes are shown in Fig. 4. The GATA3 subtype was significantly associated with poor OS in patients with PTCL-NOS (vs. TBX21 subtype, p = .046; vs. unclassified subtype, p = .033) (Fig. 4G). The GATA3 subtype was associated with poor OS in patients with non-AITL (vs. unclassified subtype, p = .008) and poor PFS (vs. TBX21 subtype, p = .054) (Fig. 4I, J).
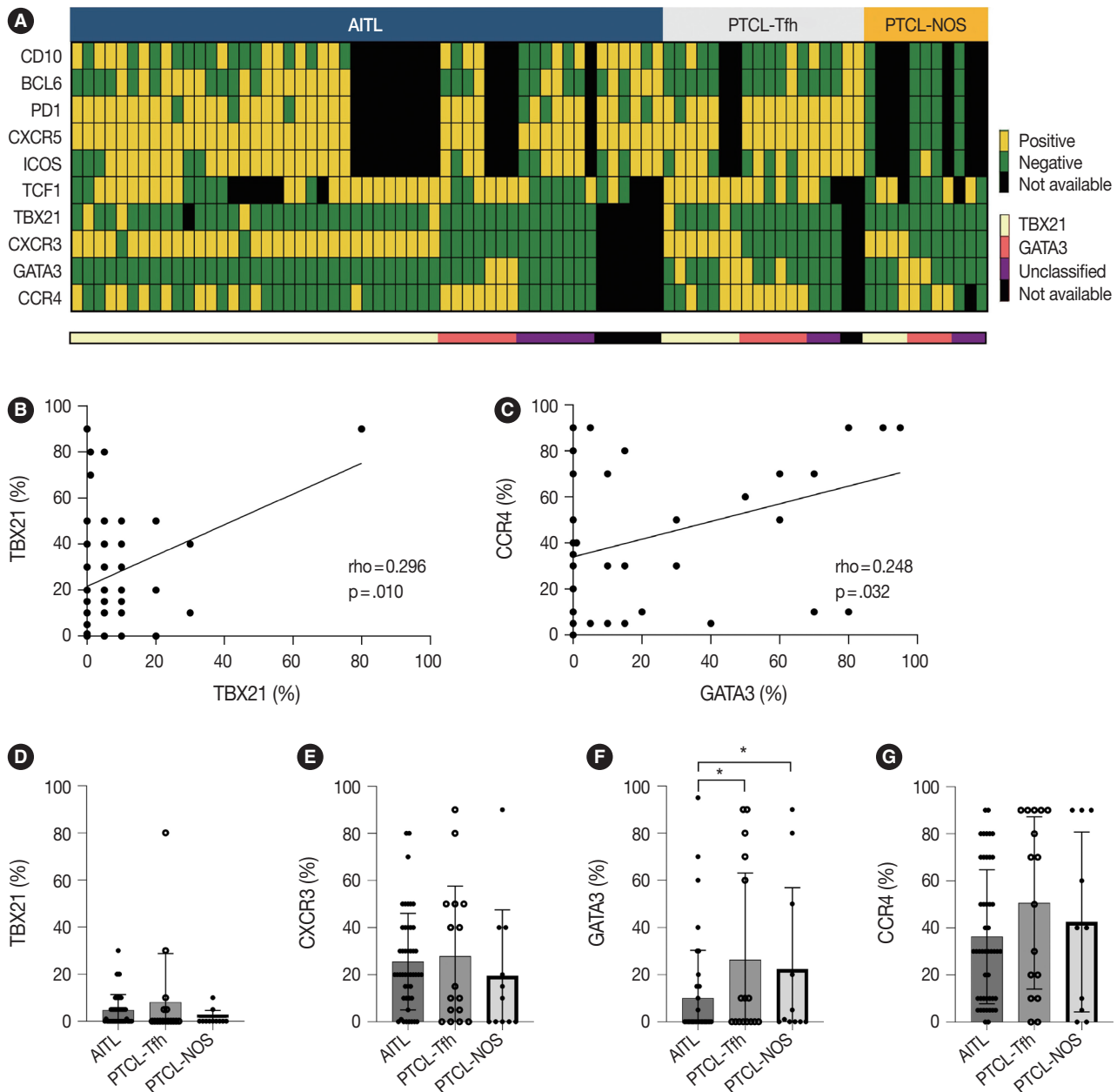

Fig. 2. Expression and distribution of IHC staining in patients with three PTCL entities. The heatmap presents the distribution of IHC markers related to Tfh (CD10, BCL6, PD-1, CXCR5, and ICOS), TCF1, and classifications (TBX21, CXCR3, GATA3, and CCR4) across three PTCL entities and subtypes (A). Correlation between TBX21 and CXCR3 (B), and GATA3 and CCR4 (C). Expression patterns for TBX21 (D), CXCR3 (E), GATA3 (F), and CCR4 (G) in three PTCL entities. AITL, angioimmunoblastic T-cell lymphoma; CCR4, C-C motif chemokine receptor 4; CXCR5, C-X-C motif chemokine receptor 5; GATA3, GATA binding protein 3; ICOS, inducible T cell costimulatory; IHC, immuno-histochemistry; PD-1, programmed death-1; PTCL, peripheral T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; TBX21, T-box transcription factor 21; TCF1, T-cell factor-1. *p < .05, **p < .01, ***p < .001.

Table 3. Clinical characteristics of nodal peripheral T-cell lymphoma according to TBX21 and GATA3 subtype classifications

	AITL				PTCL-Tfh				nTFHL				PTCL-NOS			
	TBX21 (n=33)	GATA3 (n=7)	Unclassified (n=7)	p-value	TBX21 (n=7)	GATA3 (n=6)	Unclassified (n=3)	p-value	TBX21 (n=40)	GATA3 (n=13)	Unclassified (n=10)	p-value	TBX21 (n=4)	GATA3 (n=4)	Unclassified (n=3)	p-value
Sex				.916				.012				.374				.231
Female	12 (36.4)	3 (42.9)	3 (42.9)		6 (85.7)	1 (16.7)	3 (100)		18 (45.0)	4 (30.8)	6 (60.0)		0	0	1 (33.3)	
Male	21 (63.6)	4 (57.1)	4 (57.1)		1 (14.3)	5 (83.3)	0		22 (55.0)	9 (69.2)	4 (40.0)		4 (100)	4 (100)	2 (66.7)	
Age (yr)				.197				.382				.254				.535
≤60	16 (48.5)	4 (57.1)	1 (14.3)		1 (14.3)	3 (50.0)	1 (33.3)		17 (42.5)	7 (53.8)	2 (20.0)		2 (50.0)	1 (25.0)	2 (66.7)	
>60	17 (51.5)	3 (42.9)	6 (85.7)		6 (85.7)	3 (50.0)	2 (66.7)		23 (57.5)	6 (46.2)	8 (80.0)		2 (50.0)	3 (75.0)	1 (33.3)	
Ann Arbor stage				.507				.356				.494				.441
1–2	3 (9.1)	0	0		1 (14.3)	0	1 (33.3)		4 (100)	0	1 (10.0)		1 (25.0)	1 (25.0)	2 (66.7)	
3–4	30 (90.9)	7 (100)	7 (100)		6 (85.7)	6 (100)	2 (66.7)		36 (90.0)	13 (100)	9 (90.0)		3 (75.0)	3 (75.0)	1 (33.3)	
IPI score				.539				.768				.915				.757
0–2	13 (39.4)	4 (57.1)	2 (28.6)		1 (14.3)	1 (16.7)	1 (33.3)		14 (35.0)	5 (38.5)	3 (30.0)		3 (75.0)	2 (50.0)	2 (66.7)	
3–5	20 (60.6)	3 (42.9)	5 (71.4)		6 (85.7)	5 (83.3)	2 (66.7)		26 (65.0)	8 (61.5)	7 (70.0)		1 (25.0)	2 (50.0)	1 (33.3)	
Extranodal site				.693				.635				.696				.337
≤1	24 (72.7)	5 (83.3)	6 (85.7)		3 (42.9)	4 (66.7)	2 (66.7)		27 (67.5)	9 (75.0)	8 (80.0)		3 (75.0)	2 (50.0)	3 (100)	
>1	9 (27.3)	1 (16.7)	1 (14.3)		4 (57.1)	2 (33.3)	1 (33.3)		13 (32.5)	3 (25.0)	2 (20.0)		1 (25.0)	2 (50.0)	0	
Serum LDH				.343				.445				.275				.323
Normal	8 (25.0)	1 (14.3)	0		1 (14.3)	2 (33.3)	0		9 (23.1)	3 (23.1)	0		3 (75.0)	1 (25.0)	1 (33.3)	
Elevated	24 (75.0)	6 (85.7)	6 (100)		6 (85.7)	4 (66.7)	3 (100)		30 (76.9)	10 (76.9)	9 (100)		1 (25.0)	3 (75.0)	2 (66.7)	
ECOG PS				.048				.392				.303				>.99
<2	21 (80.8)	6 (100)	2 (40.0)		7 (100)	2 (40.0)	1 (100)		24 (80.0)	8 (72.7)	3 (50.0)		4 (100)	3 (100)	1 (100)	
≥2	5 (19.2)	0	3 (60.0)		0	3 (60.0)	0		6 (20.0)	3 (27.3)	3 (50.0)		0	0	0	
B symptoms				.862				.343				.991				.084
Absent	16 (51.6)	3 (42.9)	3 (42.9)		7 (100)	4 (80.0)	3 (100)		23 (60.5)	7 (58.3)	6 (60.0)		3 (75.0)	3 (75.0)	0	
Present	15 (48.4)	4 (57.1)	4 (57.1)		0	1 (20.0)	0		15 (39.5)	5 (41.7)	4 (40.0)		1 (25.0)	1 (25.0)	3 (100)	
BM involvement				.329				.700				.388				.308
Absent	13 (39.4)	4 (57.1)	1 (16.7)		2 (28.6)	3 (50.0)	1 (50.0)		15 (37.5)	7 (53.8)	2 (25.0)		2 (50.0)	2 (50.0)	3 (100)	
Present	20 (60.6)	3 (42.9)	5 (83.3)		5 (71.4)	3 (50.0)	1 (50.0)		25 (62.5)	6 (46.2)	6 (75.0)		2 (50.0)	2 (50.0)	0	

Values are presented as number (%).

TBX21, T-box transcription factor 21; GATA3, GATA binding protein 3; AITL, angioimmunoblastic T-cell lymphoma; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper (TFH) cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group performance status; BM, bone marrow.
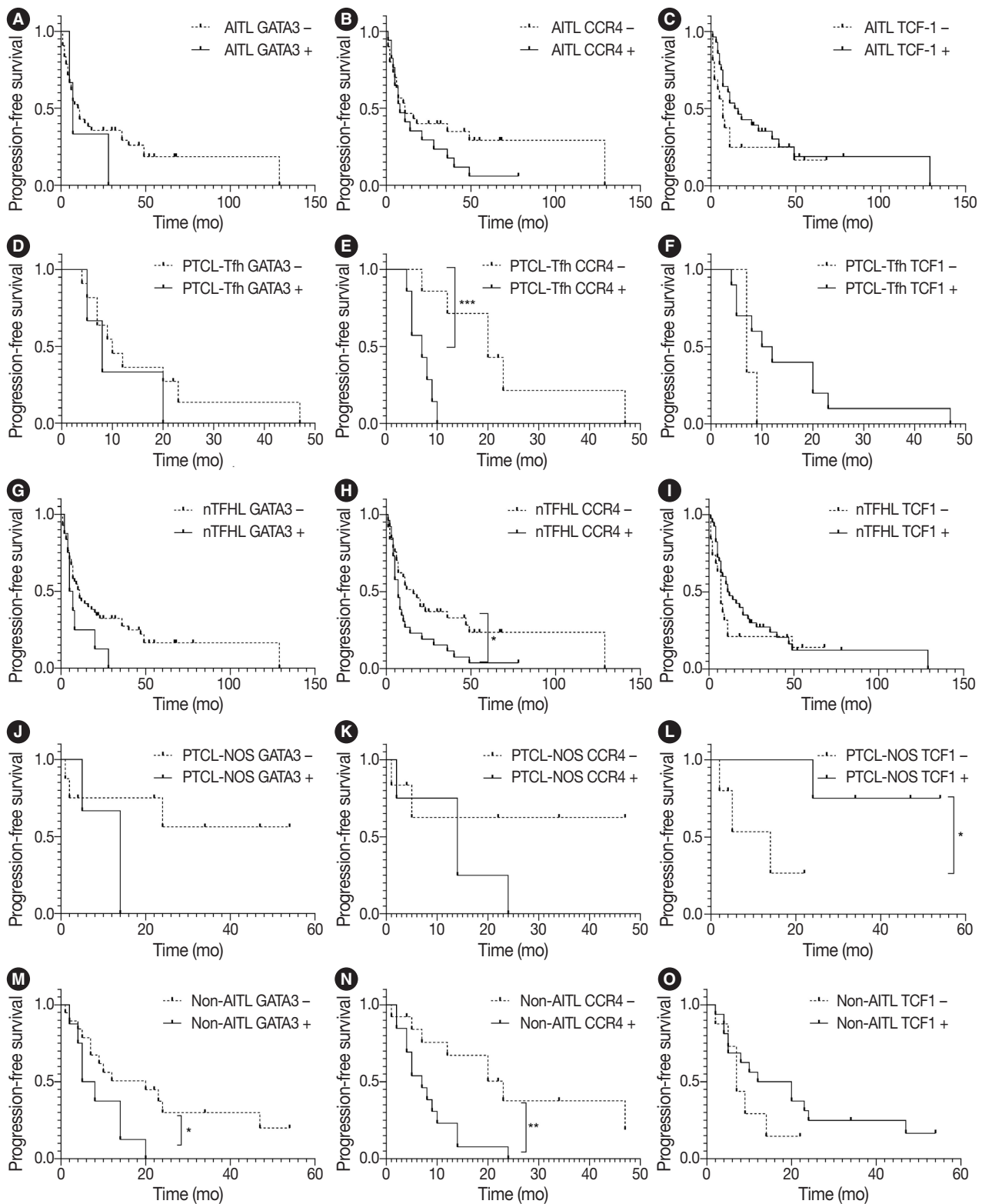
Fig. 3. Survival analysis of progression-free survival in patients with nodal peripheral T-cell lymphoma according to Th2-like markers and TCF1. Kaplan-Meier curves display progression-free survival according to GATA3, CCR4, and TCF1 in AITL (A–C), PTCL-Tfh (D–F), nTFHL (G–I), PTCL-NOS (J–L), and non-AITL (M–O). AITL, angioimmunoblastic T-cell lymphoma; CCR4, C-C motif chemokine receptor 4; GATA3, GATA binding protein 3; nTFHL, nodal T-follicular helper cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; TCF1, T-cell factor-1. *p < .05, **p < .01, ***p < .001.
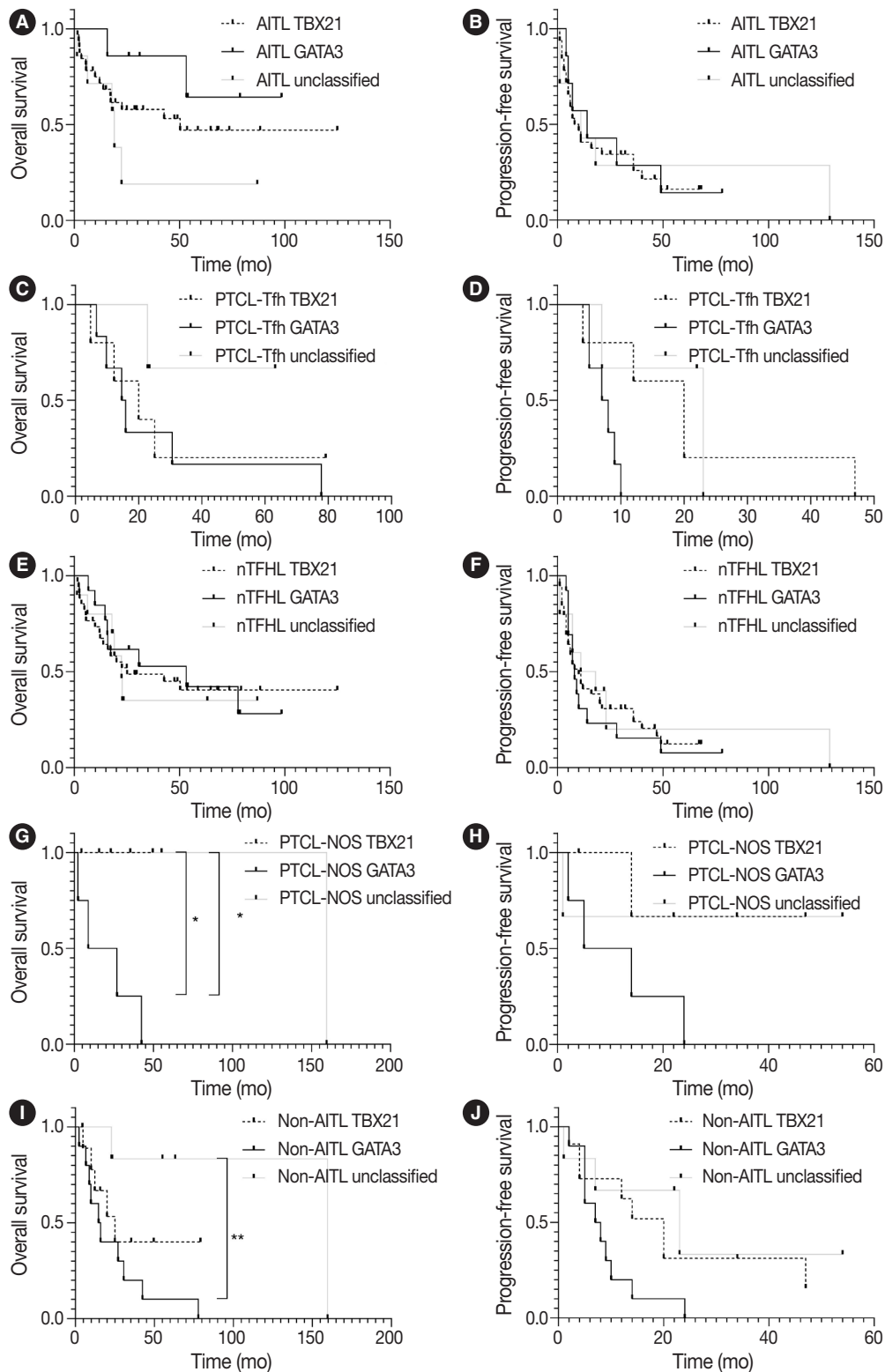
Fig. 4. Survival analysis of patients with nodal peripheral T-cell lymphoma according to TBX21 and GATA3 subtype classification. Kaplan-Meier curves displays overall survival and progression-free survival according to classification in AITL (A, B), PTCL-Tfh (C, D), nTFHL (E, F), PTCL-NOS (G, H), and non-AITL (I, J). AITL, angioimmunoblastic T-cell lymphoma; GATA3, GATA binding protein 3; nTFHL, nodal T-follicular helper cell lymphoma; PTCL-Tfh, peripheral T-cell lymphoma of follicular helper T-cell phenotype; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; TBX21, T-box transcription factor 21. *p<.05, **p<.01.

DISCUSSION

According to the latest 5th WHO and ICC classification, AITL and PTCL-Tfh/nTFHL-NOS belong to the nTFHL family. However, they show partially overlapping and some distinct clinicopathological and genetic features. For example, genetic mutations in epigenetic modifiers (i.e., *DNMT3A* and *TET2*) and *RHOA*, are shared, whereas IDH^{R172} mutations are considered exclusive to AITL [9,27]. PTCL-Tfh/nTFHL-NOS could be differentiated from PTCL-NOS based on Tfh marker expression, and approximately 40%–63% of cases previously diagnosed as PTCL-NOS are now deemed to be PTCL-Tfh/nTFHL-NOS [25,27]. Clinical studies indicated that nTFHL showed improved responsiveness to treatment involving epigenetic modifiers, such as histone deacetylase inhibitors and demethylating agents, compared to PTCL-NOS [28,29]. Therefore, nTFHL subtypes must be differentiated, and nTFHL must be distinguished from non-TFHL, particularly PTCL-NOS, for accurate diagnosis and effective management in the future. Given the importance of IHC markers for determining the Tfh phenotype in the diagnosis of PTCL, we evaluated the expression pattern of TCF1 in PTCL to explore its potential utility as a diagnostic and prognostic biomarker. TCF1 was highly expressed in up to 68% of nTFHL but also in 44% of PTCL-NOS, with no statistical difference. Thus, TCF1 may have limited diagnostic value as a potential novel marker for the Tfh phenotype, warranting further studies using a larger PTCL-NOS cohort.

TCF1 was reported to play a role in T-cell lymphomagenesis, as well as T-cell development [30-32]. A previous study explored TCF1 expression in PTCLs (including AITL, ALCL, and PTCL-unspecified), where CXCR3 and CCR4 were used as Th1 and Th2 markers, respectively. These two markers were expressed in a mutually exclusive manner [33]. In that study, TCF1 was expressed in 46% of PTCL, particularly in 76% of Th1-like PTCL but none of Th2-like PTCL [33]. Consistently, in our present study, TCF1 expression was significantly positively correlated with CXCR3 expression (Supplementary Fig. S2) and the TBX21 subtype (Supplementary Fig. S1C) in nodal PTCLs. Although not exclusive, as in the previous study, the higher expression of TCF1 in Th1-like PTCL might suggest a potential role of TCF1 in the pathogenesis of Th1-like PTCL, requiring further studies. TCF1 is implicated in T-cell lymphomagenesis, and a study claimed that TCF1 functions as a T-cell-specific tumor suppressor [31]. In this study, we observed that TCF1 expression was associated with favorable PFS in patients with PTCL-NOS and OS in AITL, suggesting the potential of TCF1 as a positive prog-

nostic marker and emphasizing the need for further investigations into the role of TCF1 in T-cell lymphomagenesis.

PTCL-NOS, excluding nTFHL, still remains a heterogeneous entity. Using comprehensive gene expression profile analysis, unique subtypes of PTCL-NOS, including PTCL-TBX21 and PTCL-GATA3, have been identified [18,19]. These subtypes show distinct oncogenic pathway alterations, which may be implicated in the prognosis of patients [2,3]. Recently, subclassifications of PTCL-TBX21 and PTCL-GATA3 were validated by IHC analysis for TBX21, CXCR4, GATA3, and CCR4 [20]. However, the comprehensive expression patterns of these molecules remain unclear in nodal PTCL. We compared the expression of four IHC markers and TBX21 vs. GATA3 subtypes among AITL, PTCL-Tfh, and PTCL-NOS. Consistent with previous reports [21-24], Th1- and Th2-transcription factors and cytokines were also expressed in nTFHL. CXCR3 expression was significantly higher in AITLs than non-AITLs, whereas GATA3 expression was higher in non-AITL than in AITL and in PTCL-Tfh than in AITL. Based on the algorithm by Amador et al. [20], AITL frequently showed the TBX21 subtype (70%, 33/53) rather than the GATA3 subtype (15%, 7/53), whereas PTCL-Tfh and PTCL-NOS revealed comparable frequencies of TBX21 and GATA3 subtypes. These findings were partly consistent with a previous study by Yoon et al. [34], where both AITL and other TFHL frequently showed the TBX21 subtype (31/41, 75.6% and 10/11, 90.9%, respectively) compared to the GATA3 subtype.

GATA3 acts as a proto-oncogene in T-cell lymphoma [35], and GATA3 expression and GATA3 subtype were reported to be associated with the poor prognosis of patients with PTCL-NOS [16,18,20,35]. This may be partly attributable to higher genomic complexity including *PTEN* and *CDKN2A/B* deletions, aberrant TP53 pathway (biallelic deletions/mutations), gains/amplifications of MYC and STAT, and high proliferation signature in PTCL-GATA3 cases [18,27,36]. In the present study, the GATA3 subtype was significantly associated with poor survival compared to TBX21 and unclassified subtypes in patients with PTCL-NOS and non-AITL but not in patients with AITL. These observations suggest that the prognostic implication of the GATA3 subtype might differ in the context of disease entities.

In the present study, CCR4 expression was significantly associated with poor prognosis in patients with PTCL-Tfh, nTFHL, as well as non-AITL. CCR4 expression is reported in the majority of adult T-cell leukemia/lymphoma (ATLL), cutaneous T-cell lymphoma (CTCL), and 30%–40% of PTCL cases [37-40]. CCR4 expression was associated with the poor prognosis of patients with PTCL, unspecified, and ATLL [38,41]. Mogamuli-

zumab, a humanized monoclonal antibody against CCR4, has been approved for the treatment of ATLL and CTCL (mycosis fungoides/Sezary Syndrome) [42,43] and also showed clinical efficacy in patients with relapsed CCR4-positive PTCL [44]. Thus, mogamulizumab could be a potential therapeutic option in CCR4-positive nodal PTCL patients with a poor prognosis [45].

This study had some limitations. First, due to the disease's rarity and data collection from a single institution, the sample size was restricted, particularly in the case of PTCL-NOS. Second, while the identification of shared molecular alterations is critical in categorizing nTFHL, this study did not explore genetic alterations. Third, PTCL often consists of heterogeneous cell populations and tumor cells with mild atypism. Thus, it sometimes is not easy to distinguish between neoplastic cells and reactive cells. Consensus interpretation of IHC results was performed after independent evaluations by two pathologists to overcome this shortening.

In summary, our comprehensive IHC analysis of TCF1, Th1- and Th2-like markers may contribute to the evolving understanding of nodal PTCL, emphasizing the applicability and importance of these markers for accurate diagnosis and predicting prognosis and potential therapeutic targets.

Supplementary Information

The Data Supplement is available with this article at https://doi.org/10.4132/jptm.2024.01.04.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of SNUH (No. 1506-080-681). The requirement for informed consent for participation in the study was waived by the IRB of SNUH.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

Code Availability

Not applicable.

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Conflicts of Interest

The authors declare that they have no potential conflicts of interest.

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