


Clinical and pathological characteristics of peripheral T-cell lymphomas in a Spanish population: a retrospective study

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Abstract

We investigated the clinicopathological features and prognostic factors of patients with peripheral T-cell lymphoma (PTCL) in 13 sites across Spain. Relevant clinical antecedents, CD30 expression and staining pattern, prognostic indices using the International Prognostic Index and the Intergruppo Italiano Linfomi system, treatments, and clinical outcomes were examined. A sizeable proportion of 175 patients had a history of immune-related disorders (autoimmune 16%, viral infections 17%, chemo/radiotherapy-treated carcinomas 19%). The median progression-free survival (PFS) and overall survival (OS) were 7.9 and 15.8 months, respectively. Prognostic indices influenced PFS and OS, with a higher number of adverse factors resulting in shorter survival ($P < 0.001$). Complete response (CR) to treatment was associated with better PFS (62.6 vs. 4 months; $P < 0.001$) and longer OS (67.0 vs. 7.3 months; $P < 0.001$) compared to no CR. CD30 was expressed across all subtypes; >15% of cells were positive in anaplastic lymphoma kinase-positive and -negative anaplastic large-cell lymphoma and extranodal natural killer PTCL groups. We observed PTCL distribution across subtypes based on haematopathological re-evaluation. Poor prognosis, effect of specific prognostic indices, relevance of histopathological subclassification, and response level to first-line treatment on outcomes were confirmed. Immune disorders amongst patients require further examination involving genetic studies and identification of associated immunosuppressive factors.

Keywords: peripheral T-cell lymphoma, anaplastic lymphoma kinase, anaplastic large-cell lymphoma, progression-free survival, overall survival, complete response.

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T-cell lymphomas (TCLs) are a heterogeneous group of lymphoid diseases that include nodal entities, extranodal lymphomas and T-cell leukaemia. The differences in cellular origin and the broad phenotypical and morphological spectrum make it difficult to subclassify TCLs. Despite the wide use of reference guidelines, including the World Health Organization (WHO) classification of lymphoid neoplasms,^{1,2} accurate diagnosis requires expert haematopathologists and various clinical and molecular tests. Experienced pathologists may need to refer cases for central review to reach a final diagnosis.

Reports related to the International Non-Hodgkin Lymphoma (NHL) Prognostic Factors Project³ have identified several features of TCLs, including outcome trends,⁴ risk groups,⁵ and potential therapeutic targets, such as CD30. CD30, originally identified as a Reed-Sternberg and Hodgkin cell-surface marker in classic Hodgkin lymphoma,⁶ is expressed in several types of NHLs. CD30 expression also has prognostic value in diffuse large B-cell lymphoma.^{7,8}

In Spain, there are insufficient epidemiological data regarding peripheral TCL (PTCL) and several years have passed since the publication of the available reports.^{9,10} Our

present multicentre retrospective study aimed to characterise this patient setting in a descriptive manner and to remark on the issue of the potential diagnostic differences associated with a second (central) review of samples, by analysing PTCL cases from several Spanish centres using the 2016 WHO classification criteria. We studied the frequency, clinical and biological behaviours, and prognostic factors (including CD30 expression) of PTCL. Considering the low frequency and wide heterogeneity of PTCL, identifying histological subtypes through local diagnosis and expert central review has been assessed as a prognostic factor.

Patients and methods

Data collection

Medical records from 13 Spanish centres were searched to identify PTCL patients diagnosed between 1 January 2008 and 31 December 2013 using the 2008 WHO classification of lymphoid neoplasms.¹ The inclusion criteria included biopsy specimens from the initial diagnosis (node or 16–18 mm core biopsy in paraffin) and histologically confirmed PTCL, involving subtypes including extranodal natural killer (NK) TCL nasal type, enteropathy-associated TCL (EATCL), hepatosplenic TCL, PTCL not-otherwise-specified (PTCL-NOS), angioimmunoblastic TCL (AITL), anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma (ALK+ ALCL), or ALK-negative ALCL (ALK– ALCL). Clinical data included sex, age, relevant clinical history, Ann Arbor Stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), treatments, and outcomes [complete response (CR) or partial response (PR), stable disease or progression of disease (PD)]. In order to calculate progression-free survival (PFS), date of PD or date of death were recorded, and the latter of these was used to calculate overall survival (OS). The International Non-Hodgkin Lymphoma Prognostic Factors Project system³ and the Intergruppo Italiano Linfomi system¹¹ were used to calculate the International Prognostic Index (IPI) and the Prognostic Index for TCL (PIT), respectively.

Central review

Tissue microarrays were constructed using archival formalin-fixed and paraffin-embedded patient samples originating from the local pathology laboratory. Immunohistochemical staining and assessment were performed by an expert central pathology committee. Positive tumour cells were scored in percentage classes including programmed cell death protein 1 (PD1), lymphoid enhancer binding factor-1 (LEF1), Ki67, B-cell lymphoma 6 (BCL6), cluster of differentiation 10 (CD10), and percentage of Epstein–Barr virus (EBV)-encoded small nuclear RNAs (EBERs) cells. CD30 was considered positive with $\geq 15\%$ tumour cells (no expression, negative >0 –14%), while intensity of staining was estimated visually and scored as no expression (negative), weak, moderate and strong.

Expression of tumour protein p53 (p53) was included during the samples assessment^{12,13} and was classified into: negative, positive (1–50%) and very positive ($>50\%$). The expert committee also reviewed and re-classified and/or updated the PTCL specimens into subtypes according to the 2016 WHO criteria² and based on their evaluation and the available evidence, diagnoses were categorised into one of the following six subtypes: (i) PTCL-NOS, (ii) AITL plus nodal PTCL with T follicular helper (TFH) phenotype,^{14,15} (iii) ALK+ ALCL, (iv) ALK– ALCL, (v) extranodal NK/T (including EBV-associated TCLs)² and (vi) intestinal TCL (including patients diagnosed with EATCL and those with monomorphic epitheliotrophic intestinal TCL).

Statistics

Categorical variables are reported as percentages and analysed using binomial regression. Continuous variables are reported as mean \pm standard deviation (SD) or median (range). Follow-up was calculated based on overall observation time, on censoring times for surviving patients, and on reserve censoring by Kaplan–Meier curve analysis.^{16,17} Time-to-event analyses (OS, PFS, and time-to-PD) were performed using the Kaplan–Meier method and the log-rank test. Estimated mean with 95% confidence interval (95% CI) was used when the median value was not reached. The Cox proportional hazards model allowed the assessment of the potential prognostic covariates for OS and PFS. Univariate and multivariate analyses are reported using hazard ratios (HRs) with 95% CIs. Factors with $P \leq 0.1$ in univariate analyses were included in the multivariate analyses using two approaches: firstly excluding potential confounding factors that were already included in further variables, i.e. ECOG PS for the IPI score or bone marrow disease for the PIT score and, secondly, by excluding the IPI and PIT scores. Logistic regression models considering CR as ‘the event’ were presented as odds ratio (ORs) with 95% CIs. As previously, only potential confounding factors were taken into account in the multivariate logistic regression analyses. Differences were considered statistically significant at $P < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS®), version 22.0 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Ethical approval

All patients provided written informed consent prior to inclusion. The study protocol was approved by the ethics committees at all participating sites.

RESULTS

The study population and PTCL clinical features

A total of 198 patients were diagnosed with PTCL, and 175 patients fulfilled the eligibility criteria and were included in

the study Fig 1. PTCL subtypes were mostly found in males (63.4%). The median (range) age at first PTCL diagnosis was 62.8 (18.3–88.7) years Table I; however, the ALK+ ALCL group had the youngest median (range) age, at 31.6 (18.3–81.6) years, amongst all subtypes.

A relevant clinical history including previous neoplasms was reported in 18.9% of the enrolled patients, and most frequently in the extranodal NK/T group (25%). Viral infections were relatively frequent (17.7%), particularly hepatitis C virus (7.4%). Other autoimmune factors, including inflammatory or rheumatological disorders (16%), and immunosuppressive treatments were also reported Table I at PTCL diagnosis (4.6%) and at any other time (7.4%).

At diagnosis, most patients had advanced Ann Arbor Stages (III and IV). Bone marrow infiltration was confirmed in 32 patients (18.3%). Serum lactic acid dehydrogenase (LDH) levels were elevated in 92 (52.6%) patients and B symptoms were present in 95 (54.3%). Other PTCL clinical characteristics are detailed in Table II.

The median (range) follow-up interval was 12.4 (0.1–92.3) months in all patients (observation time), 42.3 (0.5–92.3) months amongst surviving patients (censoring times), and 53.0 (42.4–63.7) months by reverse censoring. Only three patients received palliative treatments, while 158 received curative treatment Fig 1. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens (69.7%) were most commonly used Table S1).

Central review

The final diagnosis in 67.4% of patients involved no classification change after central review and update according to the 2016 WHO classification (Fig 2 and Table S2) PTCL-NOS diagnosis (30.9%) was less frequent after expert review (12%). The remaining cases included new subtypes of PTCL, such as nodal PTCL with TFH phenotype ($n = 23$),

monomorphic epitheliotrophic intestinal TCL ($n = 5$), and others including T-cell prolymphocytic leukaemia ($n = 1$). AITL+ TFH incidence showed a remarkable change after re-evaluation (30.9% vs. 44.6%, respectively), of note, no cases of EBV-associated TCL were centrally reported. The most clinically relevant differences between local and central diagnoses were observed in two cases involving diffuse B-cell NHL (one patient with plasmablastic differentiation), which were previously classified as PTCL-NOS (one) and ALK–ALCL (one), and two other cases where the diagnoses were updated to reactive lymphadenopathies (prior diagnosis was PTCL-NOS and intestinal PTCL, one patient each, samples from these patients were taken from nodes).

Treatments

The best response ($n = 125$) was observed at a median (range) interval of 4.0 (0–65.2) months after first-line therapy; CR, PR, stable disease, and PD were reported in 34.9% ($n = 61$), 22.9% ($n = 40$), nine, and 41 patients, respectively. The median (range) interval from the start of first-line treatment to relapse or PD was 6.0 (0.2–77.3) months.

In all, 90 patients received salvage therapy due to relapse or no CR; 38% received platinum-based regimens [etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP) in 24 patients, and dexamethasone, cytarabine, cisplatin (DHAP) in six patients] (Table S3). Of these 90 patients, 41 had clinical benefit with salvage therapy (CR = 21, PR = 20, stable disease = 15). Autologous stem cell transplantation was used in 21 patients as part of their first-line therapy and in four as part of their salvage therapy, allogeneic stem cell transplantation was reported in five patients during first-line and in two after salvage therapy. A total of 40 patients received treatment beyond the second-line [27, a third-line treatment; and nine, a fourth-line treatment; with a median (range) of 3 (1–10) lines].

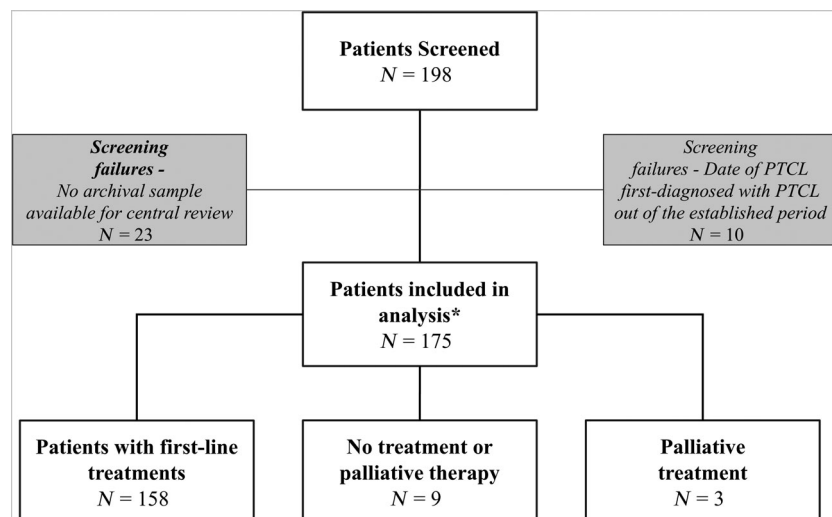


Fig 1. Study flow chart. *One patient died before start of any treatment. Information on four other patients was not available at the time of data collection.

Table I. Patient characteristics.

	Overall sample	AITL+ TFH	PTCL-NOS	PTCL extranodal NK/T	ALK+ ALCL	ALK- ALCL	Intestinal PTCL
Age at diagnosis, years, median (range)	62.8 (18.3-88.7)	65.7 (27.1-88.7)	69.1 (37.2-82.6)	63.2 (22.3-88.1)	31.6 (18.3-81.6)	63.8 (29.6-83.0)	54.1 (21.5-76.0)
N (%):							
Sex							
Male	111 (63.4)	48 (61.5)	14 (66.7)	13 (65.0)	11 (84.6)	16 (88.9)	7 (63.6)
Female	64 (36.6)	30 (38.5)	7 (33.3)	7 (35.0)	2 (15.4)	2 (11.1)	4 (36.4)
Relevant comorbidities							
Any	113 (64.6)	50 (64.1)	14 (66.7)	16 (80.0)	7 (53.9)	14 (77.8)	5 (45.5)
Arterial hypertension	41 (23.4)	18 (23.1)	8 (38.1)	4 (20.0)	2 (15.4)	5 (27.8)	1 (9.1)
Diabetes mellitus type II	22 (12.6)	10 (12.8)	3 (14.3)	2 (10.0)	2 (15.4)	4 (22.2)	1 (9.1)
Appendectomy	15 (8.6)	8 (10.3)	1 (4.8)	3 (15.0)	0 (0.0)	1 (5.6)	2 (18.2)
Dyslipidaemia	12 (6.9)	5 (6.4)	1 (4.8)	1 (5.0)	1 (7.7)	3 (16.7)	0 (0.0)
Hypercholesterolaemia	10 (5.7)	5 (6.4)	2 (9.5)	2 (10.0)	0 (0.0)	1 (5.6)	0 (0.0)
Previous neoplasia*							
Total	33 (18.9)	17 (21.8)	4 (19.1)	5 (25.0)	2 (15.4)	3 (16.7)	1 (9.1)
Genitourinary†	12 (6.9)	6 (7.7)	2 (9.5)	1 (5.0)	1 (7.7)	0 (0.0)	0 (0.0)
Not specified	6 (3.4)	2 (2.6)	1 (4.8)	1 (5.0)	1 (7.7)	1 (5.6)	0 (0.0)
Other lymphomas	5 (2.9)	4 (5.1)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Digestive	4 (2.3)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Breast	3 (1.7)	1 (1.3)	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (9.1)
Skin no melanoma	3 (1.7)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other tumours‡	6 (3.4)	2 (2.6)	1 (4.8)	1 (5.0)	0 (0.0)	2 (11.1)	0 (0.0)
Previous inflammatory, autoimmune or rheumatological disease	28 (16.0)	15 (19.2)	2 (9.5)	4 (20.0)	1 (7.7)	2 (11.1)	2 (18.2)
Solid organ recipient	7 (4.0)	3 (3.9)	1 (4.8)	0 (0.0)	1 (7.7)	1 (5.6)	1 (9.1)
Immunosuppressive treatment							
Viral infections§							
Anytime	13 (7.4)	6 (7.7)	2 (9.5)	0 (0.0)	1 (7.7)	1 (5.6)	2 (18.2)
At time of diagnosis	8 (4.6)	3 (3.9)	2 (9.5)	0 (0.0)	1 (7.7)	1 (5.6)	1 (9.1)
HIV	10 (5.7)	3 (3.9)	2 (9.5)	1 (5.0)	1 (7.7)	3 (16.7)	0 (0.0)
HBV	8 (4.6)	3 (3.9)	1 (4.8)	2 (10.0)	1 (7.7)	0 (0.0)	0 (0.0)
HCV	13 (7.4)	5 (6.4)	3 (14.3)	1 (5.0)	2 (15.4)	2 (11.1)	0 (0.0)
Previous exposure to radiation	14 (8.0)	5 (6.4)	3 (14.3)	3 (15.0)	1 (7.7)	1 (5.6)	1 (9.1)
Previous exposure to chemotherapy	19 (10.9)	6 (7.7)	3 (14.3)	5 (25.0)	1 (7.7)	2 (11.1)	0 (0.0)

AITL, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALK+ ALCL, anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma; ALK- ALCL, ALK-negative ALCL; N, total number of patients; SD, standard deviation; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

*Four patients reported >1 previous neoplasia ($n = 1$, digestive + genitourinary; $n = 1$, other lymphomas + skin no melanoma; $n = 1$, two genitourinary types including prostate and clear cell renal cancer; and $n = 1$, other lymphomas + other tumours + skin no melanoma (2 different types: basal cell carcinoma and Bowen disease).

†Includes renal, bladder, and/or prostate cancer.

‡Includes myeloma ($n = 2$, one patient from the AITL + TFH group and one from the PTCL extranodal NK/T group), thyroid cancer ($n = 1$, AITL + TFH), lung ($n = 1$, ALK- ALCL), acute leukaemia ($n = 1$, PTCL-NOS) and head/neck cancer ($n = 1$, ALK- ALCL).

§17 patients with at least one type of viral infection ($n = 5$, HIV + HBV + HCV; $n = 4$, HIV + HCV; $n = 3$, HBV; and $n = 1$, HIV).

Table II. PTCL clinical features.

	Overall sample (N = 175)	AITL+ TFH (N = 78)	PTCL-NOS (N = 22)	PTCL extranodal		ALK+ ALCL (N = 13)	ALK- ALCL (N = 18)	Intestinal PTCL (N = 11)
				NK/T (N = 20)				
Ann Arbor Stage, n (%)								
I-II	40 (22.9)	12 (15.4)	3 (14.3)	8 (40.0)	3 (23.1)	8 (44.4)	2 (18.2)	
III-IV	128 (73.1)	63 (80.8)	18 (85.7)	11 (55.0)	10 (76.9)	10 (55.6)	7 (63.6)	
N.A./U.K.	7 (4.0)	3 (3.8)	0 (0.0)	1 (5.0)	—	—	2 (18.2)	
Extranodal disease, n (%)								
No	73 (41.7)	33 (42.3)	9 (42.9)	4 (20.0)	10 (76.9)	10 (55.6)	1 (9.09)	
Yes	98 (56.0)	43 (55.1)	12 (57.1)	15 (75.0)	3 (23.1)	8 (44.4)	9 (81.8)	
N.A./U.K.	4 (2.3)	2 (2.6)	0 (0.00)	1 (5.0)	—	—	1 (9.1)	
Extranodal locations								
1	59 (60.2)	24 (55.8)	6 (50.0)	8 (53.3)	3 (100.0)	6 (75.0)	5 (55.6)	
2	29 (29.6)	13 (30.2)	4 (33.3)	5 (33.3)	—	2 (25.0)	3 (33.3)	
3	3 (3.0)	1 (2.3)	1 (8.3)	0 (0.00)	—	—	1 (11.1)	
4	3 (3.0)	2 (4.7)	0 (0.0)	1 (6.7)	—	—	—	
N.A./U.K.	4 (4.1)	3 (7.0)	1 (8.3)	1 (6.7)	—	—	—	
Total	98 (100)	43 (100.0)	12 (100.0)	15 (100.0)	3 (100.0)	8 (100.0)	9 (100.0)	
Bone marrow infiltration								
Yes	32 (18.3)	23 (29.5)	6 (27.3)	1 (5.0)	1 (7.7)	—	—	
No	114 (65.1)	42 (53.8)	14 (63.6)	15 (75.0)	11 (84.6)	16 (88.9)	6 (54.5)	
Not available/ U.K.	29 (16.6)	13 (16.7)	2 (9.1)	4 (20.0)	1 (7.7)	2 (11.1)	5 (45.5)	
Procedure for diagnosis of								
bone marrow disease, n (%)								
Flow cytometry	15 (8.6) ¹	12 (15.4)	3 (14.3)	—	—	—	—	
Histology	19 (10.9) ¹	16 (20.5)	2 (9.5)	—	—	—	—	
Molecular Biology	4 (2.3) ¹	3 (3.9)	1 (4.8)	—	—	—	—	
N.A./U.K.	137 (78.3) ¹	47 (60.3)	15 (71.4)	20 (100.0)	13 (100.0)	18 (100.0)	11 (100.0)	
B Symptoms, n (%)								
Yes	95 (54.3)	35 (44.9)	10 (47.6)	4 (20.0)	7 (53.9)	8 (44.4)	1 (9.1)	
No	69 (39.4)	38 (48.7)	11 (52.4)	14 (70.0)	6 (46.2)	9 (50.0)	8 (72.7)	
N.A./U.K.	11 (6.3)	5 (6.4)	0 (0.0)	2 (10.0)	—	1 (5.6)	2 (18.2)	
Bulky disease, (>10 cm)*, n (%)								
Yes	26 (14.9)	10 (12.8)	5 (23.8)	4 (20.0)	3 (23.1)	2 (11.1)	2 (18.2)	
No	141 (80.6)	65 (83.3)	17 (77.3)	15 (75.0)	9 (69.2)	16 (88.9)	8 (72.7)	
N.A./U.K.	8 (4.6)	3 (3.9)	0 (0.0)	1 (5.0)	1 (7.7)	—	1 (9.1)	
PET at diagnosis (n = 175), n (%)								
Yes	62 (35.4)	31 (39.7)	6 (28.6)	7 (35.0)	8 (61.5)	6 (33.3)	3 (27.3)	
No	102 (58.3)	42 (53.1)	16 (72.7)	11 (55.0)	—	11 (61.1)	7 (63.6)	
N.A./U.K.	11 (6.3)	5 (6.4)	0 (0.0)	2 (10.0)	5 (38.5)	1 (5.6)	1 (9.1)	
ECOG PS at PTCL								
diagnosis (n = 175), n (%)								
0-2	102 (58.3)	48 (61.5)	12 (57.1)	10 (50.0)	9 (69.2)	9 (50.0)	6 (54.5)	
3-4	17 (9.7)	8 (10.3)	3 (14.3)	1 (5.0)	2 (15.4)	1 (5.6)	2 (18.2)	
Low/ intermediate risk	55 (50.0)	23 (42.6)	4 (30.8)	5 (55.6)	9 (90.0)	6 (60.0)	2 (33.3)	
Intermediate/ high risk	55 (50.0)	31 (57.4)	9 (69.2)	4 (44.4)	1 (10.0)	4 (40.0)	4 (66.7)	
Total	110 (100.0)	54 (100.0)	13 (100.0)	9 (100.0)	10 (100.0)	10 (100.0)	6 (100.0)	

Continues

Table II. (Continued)

	Overall sample (N = 175)	AITL+ TFH (N = 78)	PTCL-NOS (N = 22)	PTCL extranodal		
				NK/T (N = 20)	ALK+ ALCL (N = 13)	ALK- ALCL (N = 18)
PTCL* (n = 104), n (%)						Intestinal PTCL (N = 11)
0-1 adverse factors	54 (51.9)	22 (44.9)	4 (30.8)	7 (77.8)	8 (80.0)	3 (60.0)
2-4 adverse factors	50 (48.1)	27 (55.1)	9 (69.2)	2 (22.2)	2 (20.0)	2 (40.0)
Total	104 (100.0)	49 (100.0)	13 (100.0)	9 (100.0)	10 (100.0)	5 (100.0)
Biomarkers						
p53						
Negative	113 (87.6)	71 (98.6)	15 (93.8)	6 (60.0)	9 (81.8)	3 (37.5)
Positive	16 (12.4)	1 (1.4)	1 (6.3)	4 (40.0)	2 (18.2)	5 (62.5)
Total	129 (100.0)	72 (100.0)	16 (100.0)	10 (100.0)	11 (100.0)	8 (100.0)
LDH						
Normal	68 (38.9)	31 (39.7)	5 (23.8)	8 (40.0)	6 (46.1)	4 (36.4)
High	92 (52.6)	44 (56.4)	13 (61.9)	9 (45.0)	5 (38.5)	5 (45.5)
N.A./U.K.	15 (8.6)	3 (3.8)	3 (14.3)	3 (15.0)	2 (15.4)	2 (18.2)
Mean (SD)	n = 155	n = 72	n = 16	n = 12	n = 11	n = 9
CD30 expression	33.9 (37.1)	18.5 (21.0)	25.0 (34.8)	53.1 (41.0)	97.3 (6.5)	31.7 (46.6)
PD1	35.5 (36.9)	49.9 (33.2)	36.6 (41.4)	17.5 (33.3)	0.0 (0.0)	2.2 (6.7)
LEF1	46.0 (35.5)	62.2 (25.6)	39.7 (35.4)	11.0 (29.3)	11.8 (27.1)	18.9 (37.6)
Ki67	39.6 (29.3)	32.3 (25.3)	48.8 (24.4)	45.9 (32.7) [†]	66.8 (24.7)	26.3 (35.7)
BCL6	5.4 (8.3)	6.5 (6.7)	7.4 (17.2)	3.0 (5.7)	3.8 (5.9)	2.4 (5.0)
CD10	6.1 (15.4)	9.1 (17.8)	7.1 (20.2)	1.3 (3.1)	0.2 (0.6)	0.0 (0.0)
Double PD1-LEF1	25.0 (33.2)	39.7 (33.5)	14.4 (27.8)	7.7 (25.9)	0.0 (0.0)	10.6 (31.7)
% EBER-positive cells	12.2 (26.5)	7.2 (13.0)	12.3 (31.5)	75.0 (32.5)	0.0 (0.0)	0.1 (0.3)

*% based on total patients (n = 175).

AITL, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; ALK- ALCL, anaplastic lymphoma kinase (ALK)-negative anaplastic large-cell lymphoma; N, total number of patients; SD, standard deviation; HIV, Human immunodeficiency virus; BHV, hepatitis B virus; CHV, hepatitis C virus. N.A., Not available; U.K., Unknown; n.s., not statistically significant.

*Location included NOS (42.3%), spleen (15.3%; among whom one patient with a 14 cm lesion and one with splenomegaly), retroperitoneal (11.5%; including one patient with mesenteric disease) and other locations (30.8%).

†Based on 11 patients.

*IPI and PIT is presented based on the total number of patients with complete information to calculate both indices (n = 110 and n = 104, respectively).

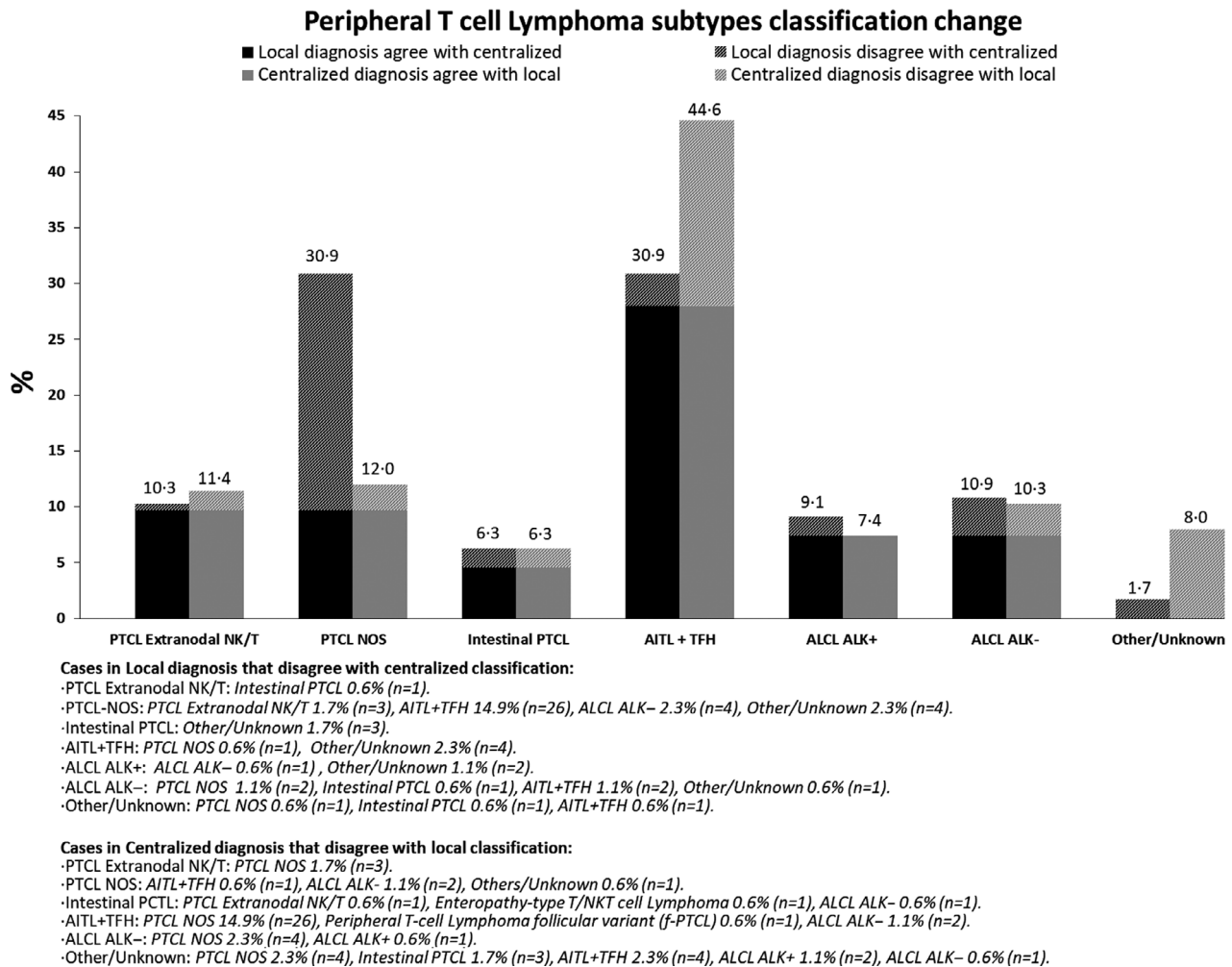


Fig 2. Peripheral T-cell Lymphoma subtypes and results from experts' central review. Two patients were reported with follicular T-cell lymphoma ($n = 1$) and enteropathic T-cell lymphoma ($n = 1$) by the local diagnosis. These subtypes were not considered in the central review due to the WHO classification update. Central review also confirmed new subtypes such as nodal PTCL with TFH phenotype ($n = 23$) and other included in the graphic as 'Other entities' including monomorphic epitheliotrophic intestinal T-cell lymphoma ($n = 5$), T-cell prolymphocytic leukaemia ($n = 1$), reactive lymphadenopathy ($n = 2$), and diffuse B-cell lymphoma ($n = 2$, one with plasmablastic differentiation).

Prognostic factors for outcome: PFS and OS

The median PFS among 157 patients was 7.9 (95% CI 5.0–10.7) months. The intermediate/high-risk group had a significantly shorter PFS according to the IPI (6.3 months, 95% CI 3.7–8.8) than the low/intermediate-risk group (71.7 months, 95% CI 22.3–121.1; $P < 0.001$) (Fig 3A). Similar findings were seen for patients with 0–1 PIT adverse factors, with a median PFS of 22.7 months (95% CI 0–82.3) vs. 6.7 months (95% CI 2.0–11.4) for PIT 2–4 ($P < 0.001$) (Fig 3B).

A CR after first-line therapy was significantly associated with a better median PFS (62.6 months, 95% CI 20.2–105.1) compared with reaching PR (7.1 months, 95% CI 5.8–8.4) or stable disease (6.3 months, 95% CI 1.1–11.4; $P < 0.001$) Fig 3C. When different PTCL subtypes were compared, patients with ALK+ ALCL showed a significantly better PFS

(22.7 months, 50% of patients had PD throughout the study period) than those with other subtypes ($P < 0.001$), while intestinal forms of PTCL showed a poorer outcome (median PFS of 2.6 months, 95% CI, 1.1–4.0) Fig 3D.

The median OS for all the 175 patients was 15.8 months (95% CI 10.2–21.3). The most frequent causes of death ($n = 114$) were PD (65.8%) and infections (18.4%).

Being classified into the intermediate/high-risk groups (IPI) and having 2–4 adverse factors (PIT) were both associated with shorter OS (median 7.9 months, 95% CI 3.9–11.9; and 13.9 months, 95% CI 8.8–18.9, respectively) compared with the lower-risk groups (IPI low/intermediate risk, median 59.4 months, 95% CI 49.0–70.4; $P < 0.001$; and PIT 0–1 adverse factors, mean 57.5 months, 95% CI 46.5–68.6; $P < 0.001$) (Fig 4A,B).

Reaching CR after first-line therapy was associated with longer OS (mean 67.0 months, 95% CI 58.2–75.9) vs.

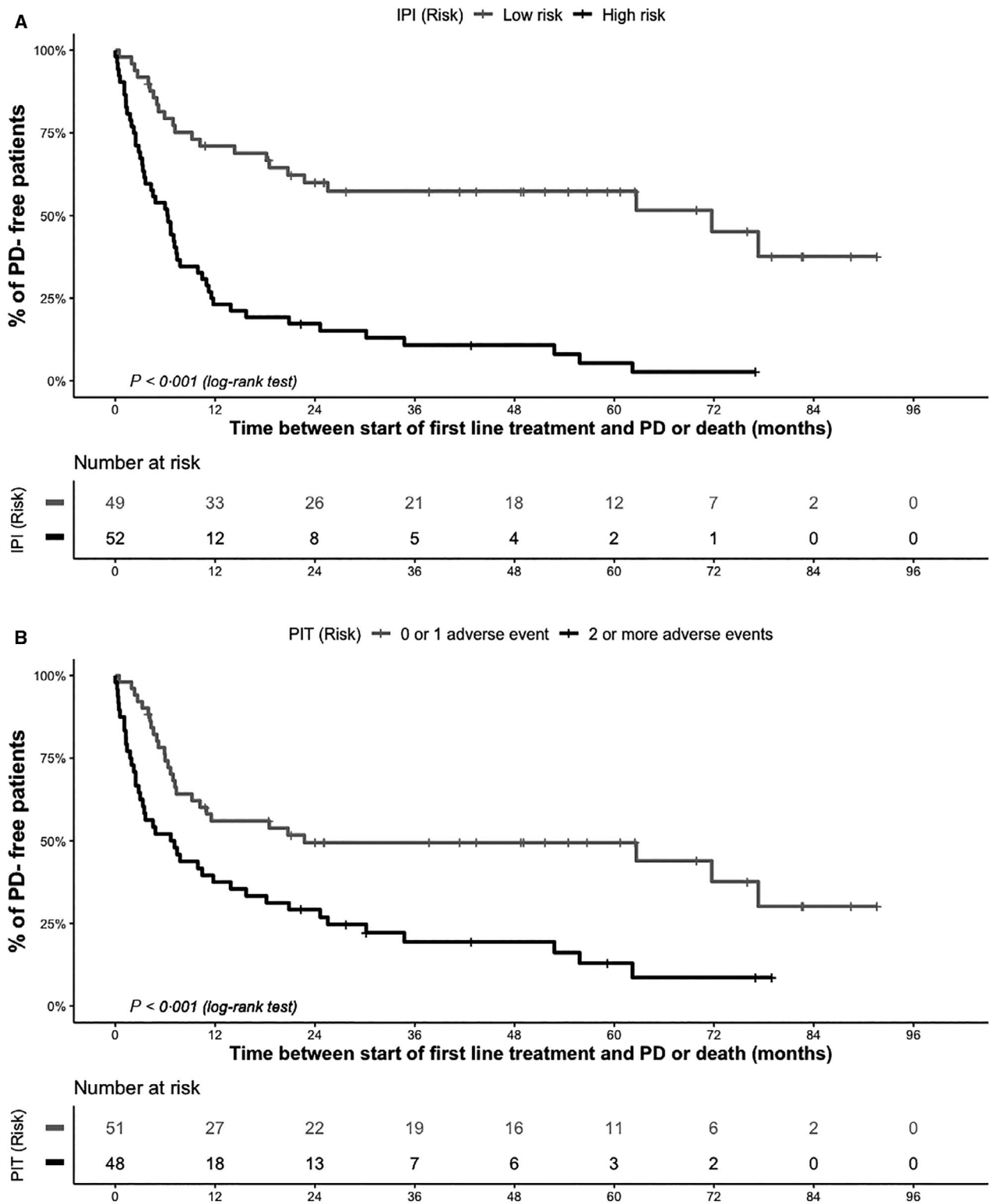


Fig 3. Progression-free survival (PFS) curves. (A) PFS according to IPI score groups; (B) PFS according to PIT groups; (C) PFS according to response intention-to-cure chemotherapy as first-line treatment; (D) PFS of clinically relevant diagnostic groups after central review.

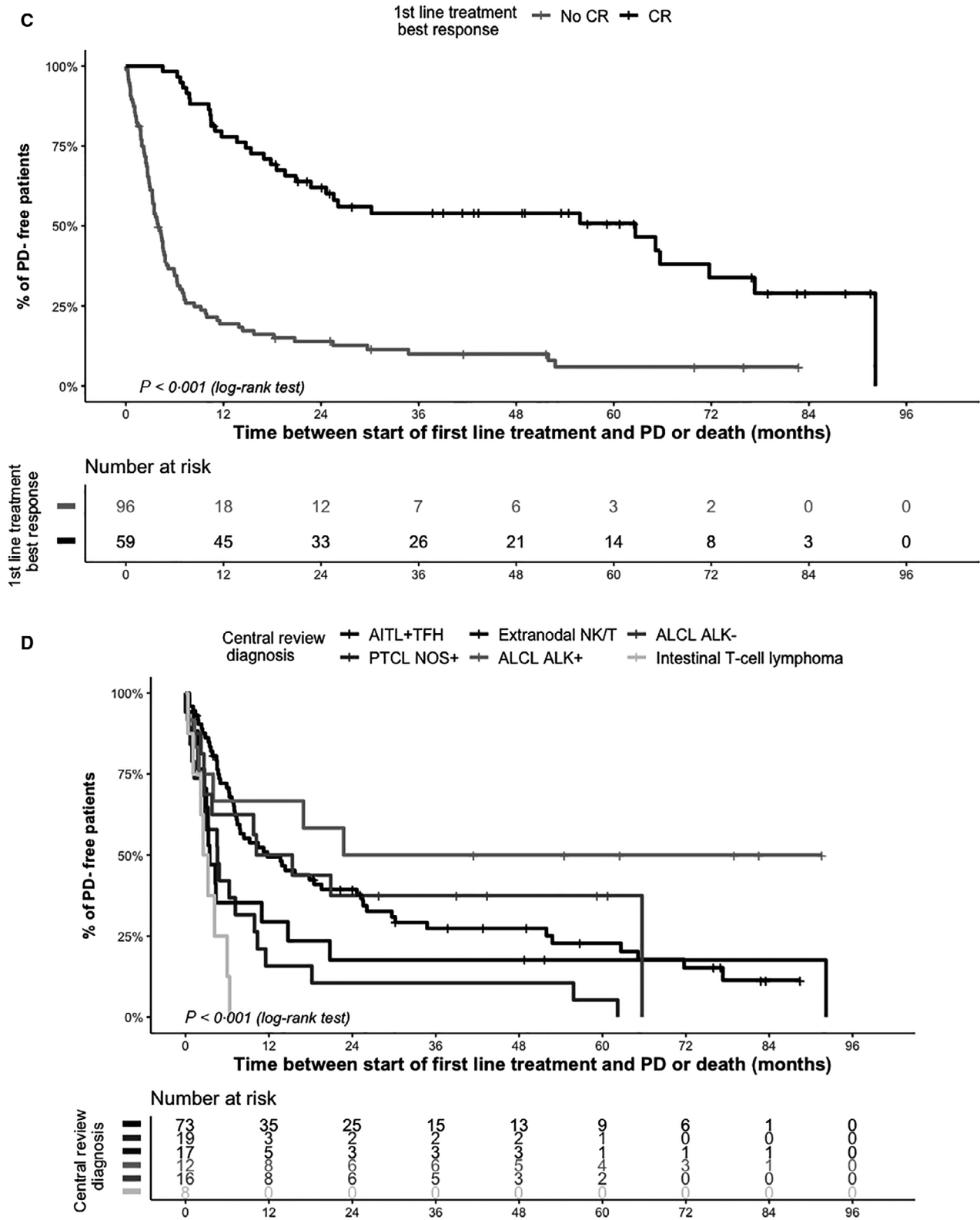


Fig 3. (Continued).

median 7.3 months, 95% CI 5.9–8.8; $P < 0.001$) (Fig 4C). Histological subtypes associated with the shortest survival corresponded to those re-classified as intestinal PTCL (median 6.2 months, 95% CI 3.9–8.5) and extranodal NK/T PTCL (median 6.4 months, 95% CI 2.9–9.8; $P < 0.001$) (Fig 4D).

Univariate and multivariate analyses for PFS Table III also confirmed that reaching a CR was overall associated with a lower risk of PD in multiple multivariate testing, early Ann Arbor Stages I–II, an ECOG PS 0–2 were also significant for PFS when IPI and PIT were excluded as factors. When OS was evaluated, the predictive factors for survival were: CR after the first PTCL treatment, low/intermediate risk based on IPI, and normal/low LDH values. Patients with very positive p53 showed a longer OS and a trend to significance with respect to those with negative results when excluding the IPI and PIT scores from the analysis; however, limited sample size compromises its interpretation.

Prognostic factors for CR to first-line treatment

Univariate logistic regression analysis for evaluating factors associated with CR after the first therapeutic approach revealed significant differences between the proportion of CR and non-CR patients, particularly for PTCL subtypes, including ALK+ ALCL (odds ratio [OR] 18, 95% CI 2.7–119.2; $P = 0.003$), ALK– ALCL (OR 10.1, 95% CI 1.8–57.9; $P = 0.009$), and angioimmunoblastic + TFH (OR 6.9, 95% CI 1.5–31.7; $P = 0.014$); reference cohort, PTCL-NOS ($P = 0.032$). Other factors with significant differences in univariate analysis regarding CR included: a younger age (OR 0.99, 95% CI 0.97–1.0; $P = 0.093$), an IPI low/intermediate risk (OR 2.9, 95% CI 1.3–6.7; $P = 0.01$), a negative p53 expression (OR 4.7, 95% CI 1.0–22.0; $P = 0.050$), a low/normal LDH value (OR 2.8, 95% CI 1.4–5.5; $P = 0.003$), Ann Arbor Stages I–II (OR 2.4, 95% CI 1.1–5.1; $P = 0.025$), an absence of extranodal infiltration (OR 2.5, 95% CI 1.3–4.9; $P = 0.006$) and no bone marrow disease (OR 2.7, 95% CI 1.1–6.5; $P = 0.029$). Despite these results, when using multivariate analysis, only the ALK + ALCL subtype was statistically associated with high probability of CR by excluding the potential confounders as explained in the methods section (Fig 5A,B).

CD30 expression

CD30 expression was scored as positive (68/132 patients) for patients with >15% positive neoplastic cells. The intensity of CD30 expression was graded in positive patients from weak, 35/121 patients; moderate, 57/121 patients, or intense, 29/121 patients. An association between the IPI groups and CD30 expression was found, showing higher average and median values for the low/intermediate-risk groups [mean (SD) 36.4 (38.6) vs. 18.3 (26.6) for the high/intermediate groups; $P = 0.004$]; also, a higher CD30 intensity was more

frequently reported in the low/intermediate-IPI group (Table S4). Neither CD30 expression ($P = 0.082$) nor CD30 intensity ($P = 0.361$) showed significant differences in the PIT groups. A comparison of CD30 expression across clinically relevant groups showed significant differences between median values, being particularly high for ALK+ ALCL (100%, range, 80–100%), ALK– ALCL (80%; range, 15–100%), and extranodal NK/T (70%; range, 0–100%) groups.

DISCUSSION

Among the various lymphoid neoplasms, PTCL is associated with poor prognosis compared to B-cell lymphomas.¹⁸ The rarity of this disease with limited data regarding outcomes and limited treatments has made it difficult to identify factors for classifying patients with high-risk disease. Analysis of epidemiological and baseline characteristics at diagnosis have led to relevant prognostic indices, including IPI and PIT. Here, the prognostic values of IPI and PIT for the identification of patients at a higher risk of PD or death were confirmed, as previously reported.^{10,19} We showed that a large proportion of patients with PTCL had a previous medical history of immune-related conditions, including autoimmune diseases (16%), viral infections (17%), or previous chemo/radiotherapy for the treatment of other carcinomas (almost 19%), as described previously.²⁰ These findings warrant an in-depth study, along with relevant genetic studies and research, into associated immunosuppressive factors.

There were mixed results when considering the distribution amongst various PTCL subtypes.^{21,22} Comparison of our present results to those of the International TCL Project²¹ showed a higher frequency of PTCL-NOS (30.9% vs. 25.9%) and AITL (30.9% vs 18.5%), while Carson *et al.*²³ recently reported that 51.3% of patients with PTCL were diagnosed with PTCL-NOS. Undoubtedly, PTCL-NOS diagnosis requires careful consideration.²⁴ Its heterogeneous cytological and phenotypic characteristics may result in subjective biases and discrepancies in diagnosis between different pathologists despite the widespread use of immunophenotyping;^{21,25} therefore, appropriate pathological review is recommended. In relation to the present study, updated classification criteria and central review by experienced haematopathologists could ensure high reproducibility of diagnoses. This approach also reduced the number of patients with PTCL without specific features, that is, in PTCL-NOS cases (from 54 cases to 21). However, TCL may show 'overlapping phenotypes' and its clinical course might lead to differences in diagnosis, especially in gamma-delta and EBV-related lymphomas. Therefore, access to the extranodal location of origin is also necessary to subclassify TCLs effectively.

Although almost 58% of the patients showed some response to first-line therapy (CR or PR), The PFS and OS were low (7.9 and 15.8 months, respectively). When we analysed the variables influencing PFS and OS, CR to first-line

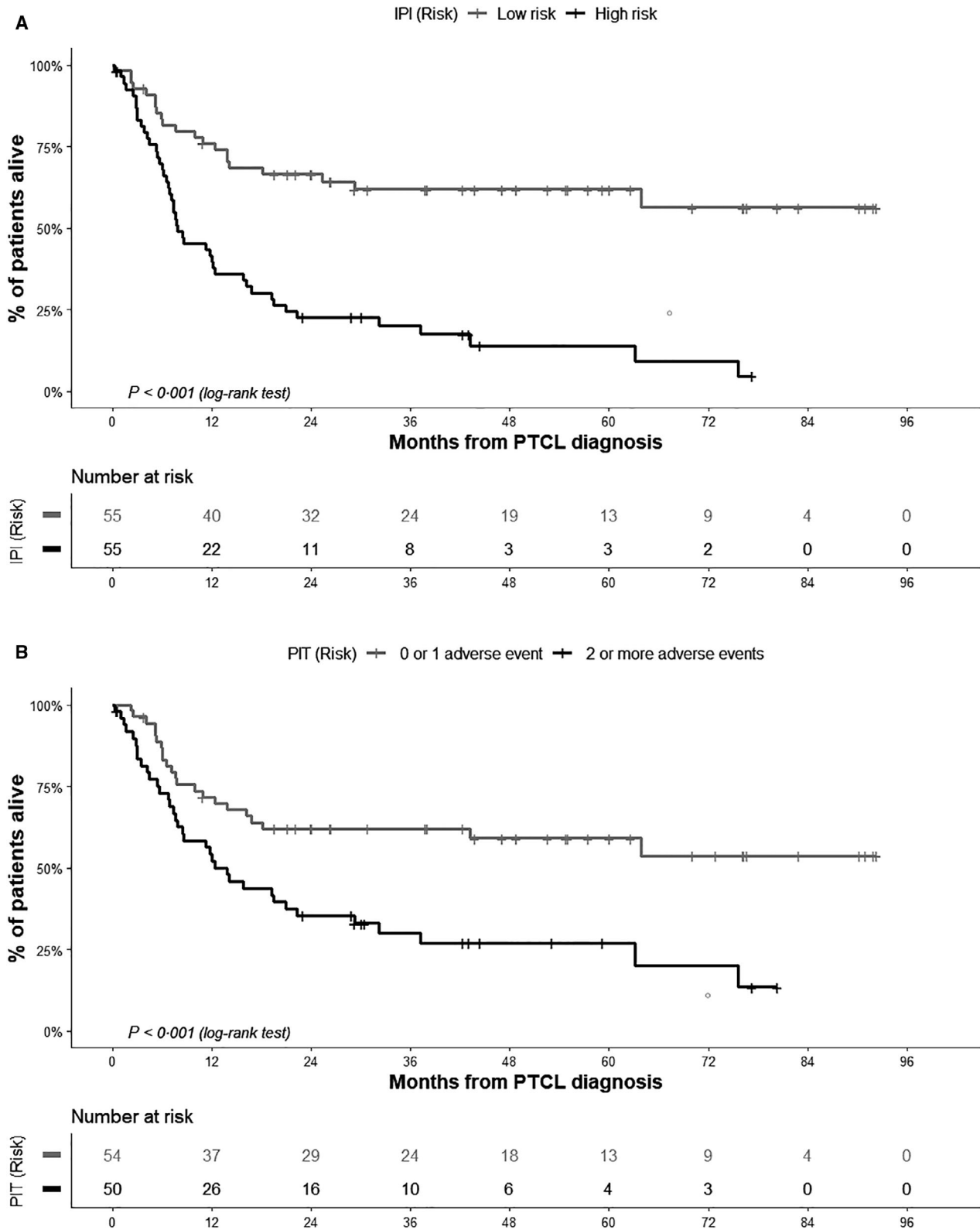


Fig 4. Overall survival (OS) curves. (A) OS according to IPI score groups; (B) OS according to PIT groups; (C) OS according to response intention-to-cure chemotherapy as first-line treatment; (D) OS of clinically relevant diagnostic groups after central review.

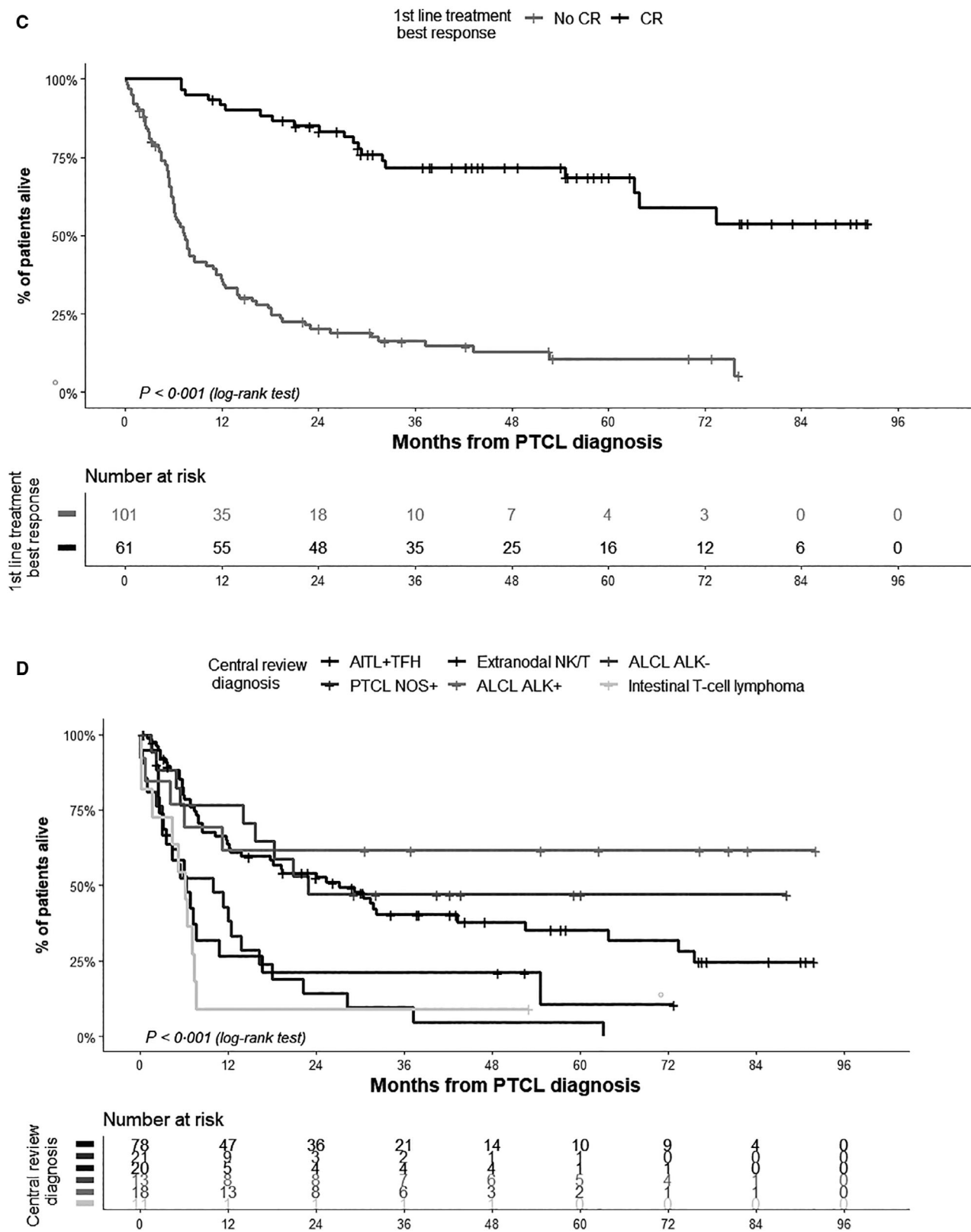


Fig 4. (Continued).

Table III. Multivariate Cox regression model for progression-free survival and overall survival.

Factors	Progression-free survival (PFS)					Overall survival (OS)				
	Univariate			Multivariate (1)		Multivariate (2)			Univariate	
	Median PFS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	Median OS, months (95% CI)	HR (95% CI)	P
Age	7.8 (4.7–10.9)	1.01 (1.00–1.02)	0.071	–	–	–	n.s.	13.9 (5.7–19.1)	1.02 (1.00–1.03)	0.013
Central review diagnosis										
ALK+ ALCL*	22.7 (–)	Reference	<0.001	–	n.s.	–	n.s.	58.5 (32.3–81.8)	Reference	<0.001
Angioimmunoblastic + TFH	11.8 (4.2–19.3)	1.97 (0.84–4.60)	n.s.	–	–	–	–	27.1 (14.9–39.4)	1.89 (0.75–4.78)	n.s.
PTCL-NOS	4.6 (1.9–7.3)	4.42 (1.74–11.21)	0.002	–	–	–	–	10.0 (0.9–19.2)	5.13 (1.91–13.80)	0.001
Extranodal NK/T	3.5 (2.1–4.9)	15 (1.20–8.26)	0.019	–	–	–	–	6.4 (2.9–9.8)	4.22 (1.53–11.64)	0.005
PTCL										
ALK-negative	10.2 (0–21.1)	1.87 (0.69–5.08)	n.s.	–	–	–	–	47.8 (29.4–66.1)	1.55 (0.52–4.65)	n.s.
ALCL										
Intestinal PTCL	2.6 (1.1–4.0)	8.67 (2.91–25.90)	<0.001	–	–	–	–	6.2 (3.9–8.5)	6.52 (2.19–19.42)	<0.001
Ann Arbor Stage										
I–II*	25.6 (0–86.7)	Reference	0.003	–	–	Reference	0.016	54.6 (0–109.4)	–	n.s.
III–IV	6.6 (5.3–8.0)	2.14 (1.28–3.55)	–	–	–	3.07 (1.23–7.61)*	–	11.9 (5.6–18.3)	–	n.s.
Extranodal disease										
No	17.8 (8.8–26.8)	Reference	0.025	–	–	–	n.s.	63.1 (6.9–119.4)	Reference	<0.001
Yes	6.4 (3.7–7.0)	1.69 (1.15–2.49)	0.007	–	–	–	–	8.5 (4.0–13.0)	2.13 (1.41–3.22)	<0.001
N.A./U.K.	6.3 (3.2–9.4)	1.80 (0.56–5.85)	n.s.	–	–	–	–	5.7 (0–11.7)	5.26 (1.83–15.10)	0.002
Bone marrow infiltration at PTCL diagnosis										
No*	10.5 (2.6–18.4)	Reference	0.031	–	n.s.	–	n.s.	27.1 (14.6–39.7)	Reference	<0.001
Yes	7.3 (3.1–11.6)	1.30 (0.84–2.03)	n.s.	–	–	–	–	12.4 (0.8–24.0)	1.42 (0.89–2.28)	n.s.
N.A./U.K.	3.8 (3.0–4.6)	2.10 (1.19–3.71)	0.011	–	–	–	–	5.4 (2.3–8.4)	3.32 (2.00–5.50)	n.s.
ECOG PS										
0–2*	11.8 (4.1–19.5)	Reference	<0.001	–	–	Reference	<0.001	20.9 (2.5–39.4)	Reference	<0.001
3–4	1.8 (0.1–3.5)	3.39 (1.80–6.42)	–	–	–	7.64 (3.16–18.48)	–	3.5 (2.2–4.9)	3.96 (2.20–7.15)	–
Best response to first-line tx.										
Complete response (CR)*	62.6 (20.2–105.1)	Reference	<0.001	Reference	<0.001	Reference	<0.001	67.0 (58.2–75.9)	Reference	<0.001
No CR (PR and stable disease)	4.0 (3.1–4.9)	4.62 (3.00–7.12)	–	5.14 (2.61–10.13)	–	5.42 (2.60–11.28)	–	7.3 (5.9–8.8)	6.35 (3.78–10.67)	–

Continues

Table III. (Continued)

Factors	Progression-free survival (PFS)					Overall survival (OS)				
	Univariate			Multivariate (1)		Multivariate (2)			Univariate	
	Median PFS, months (95% CI)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	Median OS, months (95% CI)	HR (95% CI)	P
IPI										
Low/intermediate risk	71.7 (22.3–121.1)	Reference	<0.001	Reference	0.010	–	–	59.5 (48.5–70.4)	Reference	<0.001
(0–2 points)*										
Intermediate/high risk	6.3 (3.7–8.8)	3.81 (2.24–6.48)		2.89 (1.29–6.50)		–	–	7.9 (3.9–11.9)	3.31 (1.93–5.67)	
(3–5 points)										
PIT										
0/–1 adverse factors*	22.7 (0–82.3)	Reference	0.002	–	n.s.	–	–	57.5 (46.5–68.6)	Reference	0.003
2–4 adverse factors	6.7 (2.0–11.4)	2.17 (1.32–3.58)		–		–	–	13.9 (8.8–19.0)	2.29 (1.32–3.99)	
LDH										
Low/normal LDH*	17.0 (8.0–25.9)	Reference	0.024	–	–	–	n.s.	52.6 (19.0–86.3)	Reference	<0.001
High LDH	6.0 (3.7–8.3)	1.57 (1.06–2.33)		–		–		8.5 (4.8–12.2)	2.22 (1.44–3.41)	
p53										
Negative*	10.4 (4.9–15.8)	–	n.s.	–	–	–	–	19.3 (6.3–32.3)	Reference	0.005
Low positive	4.3 (2.2–6.4)	–		–		–		55.0 (19.3–90.7)	0.50 (0.12–2.05)	n.s.
Very positive	4.2 (0.9–7.5)	–		–		–		5.3 (0.2–10.4)	3.24 (1.54–6.83)	0.002

IPI groups: low risk 0–1 point, low/intermediate risk 2 points, high/intermediate risk 3 points and high risk 4–5 points.

Multivariate PFS (1): including IPI/PIT but excluding factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. Multivariate PFS (2): excluding IPI/PIT and including factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. Multivariate OS (3): excluding IPI/PIT and including factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), variables without significant result are not shown. OS multivariate model including IPI/PIT but excluding factors involved in their calculation (age, LDH, ECOG PS, Ann Arbor Stage and extranodal disease), was also calculated (data not shown) and only best response to first-line treatment remained significant in the model, (HR 12.05, 95% CI 4.33–33.48; $P < 0.001$).

HR, hazard ratio; CI, confidence interval; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; PTCL, peripheral TCL; NOS, not otherwise specified; ALK– ALCL, ALK-negative anaplastic large-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CR, complete response; PR, partial response; IPI, International prognostic index; PIT, Prognostic Index for TCL. n.s., not statistically significant; N.A., Not available; U.K., Unknown.

Bold to highlight statistically significant values from reference categories.

*Reference category.

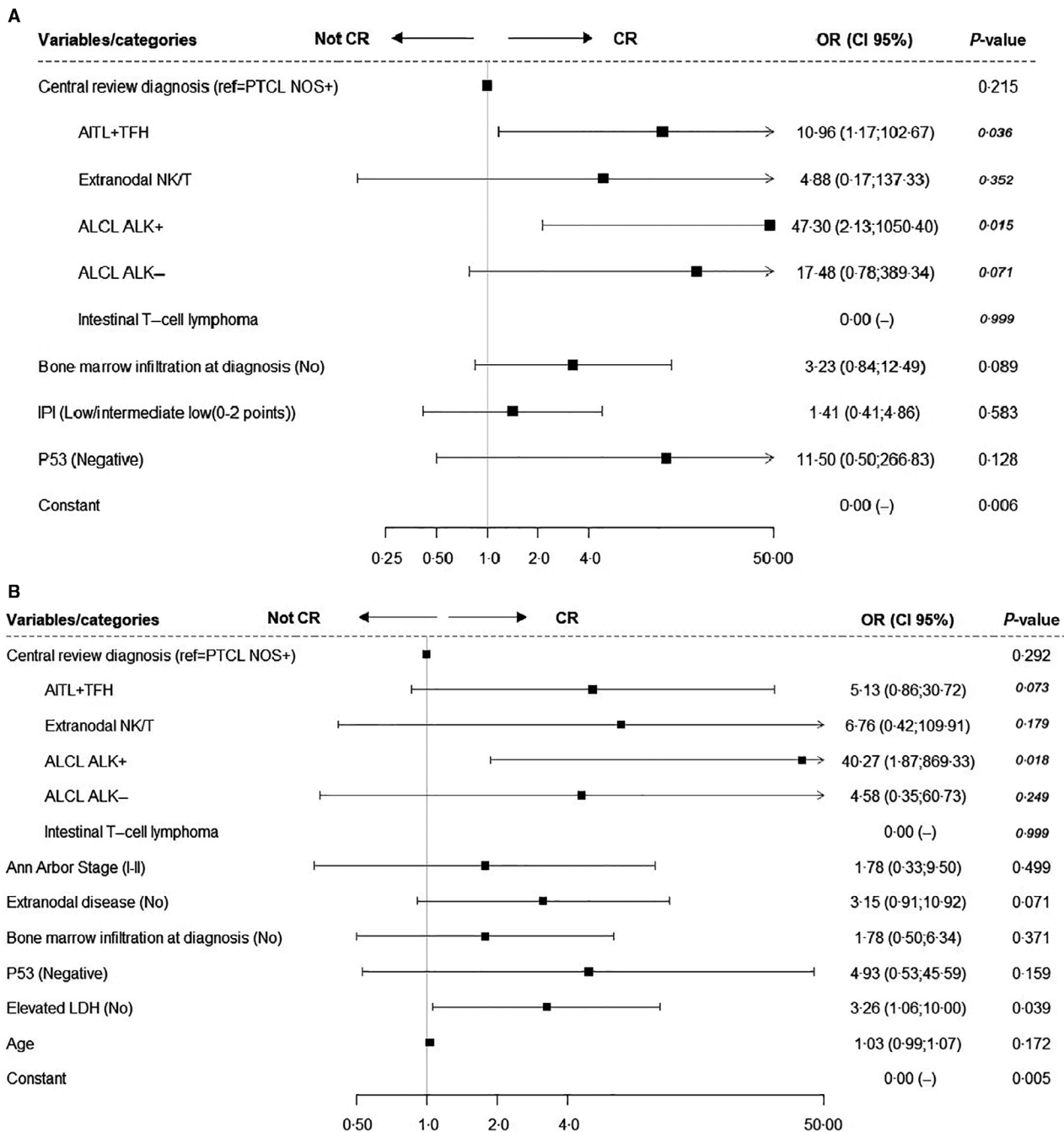


Fig 5. Multivariate logistic regression model for complete response (CR) to first-line treatment. (A) Multivariate logistic regression model on the probability of reaching CR to first-line treatment considering all factors with $P < 0.1$ in the univariate analysis, and excluding factors already included in the IPI calculation. (B) Probability of reaching a CR factors used in the IPI calculation (excluding IPI). **Reference factor. OR, odds ratio; CI, confidence interval; AITL, angioimmunoblastic T-cell Lymphoma; ALK+ ALCL, anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphoma; ALK- ALCL, ALK-negative ALCL; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, International prognostic index; PIT, Prognostic Index for T-Cell Lymphoma.

treatment emerged as the strongest (and probably the only modifiable) prognostic factor, considering that the IPI and PIT scores derived from the results of combinations of patient characteristics during therapeutic decisions.

The frontline management in all these centres followed international recommendations^{26,27} as in a previous report,²³ where 41.8% of patients were treated with doxorubicin-containing regimens (compared to CHOP and CHOP-like

treatments in 69.7% of our patients, irrespective of the PTCL subtype). Outcome is the most relevant issue in relation to treatment choice, in terms of response to treatment, only 34.9% of the patients reached CR after first-line treatment in our present investigation. There is evidently a need for new agents to improve the response after first-line treatment and positively affect the prognosis of these patients, even in those who initially attain remission.²⁶

Finally, one of the most relevant findings in the present study has been that CD30 was expressed across all subtypes, even though higher median values (>15% of cells) were reported for ALCL (ALK+ and ALK-) and extranodal NK/T PTCL groups; CD30 could also be explored as a potential marker for effectively differentiate PTCL-NOS from its morphological variant,^{28,29} the ALK- ALCL. Further, CD30 expression was lower among the higher-risk groups (based on the IPI or PIT scores), although the differences were not significant. Additional prospective studies with larger cohorts are needed to examine the role of this biomarker and to determine whether its expression can be clearly correlated with PTCL subtypes. Despite CD30 expression providing evidence to allow for targeting with specific therapies such as brentuximab vedotin that could be a potential first-line treatment for patients with PTCL,^{30,31} in terms of our present study results, CD30 expression could not be considered for prognosis, but remains relevant as a therapeutic target.

The present study provides information on a large number of patients with PTCL in Spain and provides insights into different epidemiological and clinical features that can characterise PTCL subtypes. Despite these strengths, the present study had some limitations. The numbers of patients in some parts of the analysis were low because of missing data, which reduced the number of events considerably in some subcategories. Furthermore, additional tools are needed to better define patient profiles, which would likely result in improved treatment selection and subsequent outcomes.

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Conflicts of interest

Socorro Maria Rodriguez-Pinilla, Fina Climent, Joaquin Sanchez, Carlos Perez Seoane, Monica Garcia-Cosio, Oscar Javier Blanco Muñoz, Josep Castellvi, Antonio Martinez Pozo,

Blanca Gonzalez Farre, Carlos Aliste, Ana Julia Gonzalez, Jose Gomez Codina, Empar Mayordomo-Aranda, Belen Navarro, Carmen Bellas, and Juan Jose Borrero have no conflicts of interest to declare. Eva Domingo-Domenech: consulting/advisory (C/A) role for Takeda. Research funding (RF) by Bristol-Myers Squibb (BMS) and Takeda. Travel, accommodations and expenses (TAE) by Takeda, Roche and Janssen. Javier Lopez Jimenez: RF by Gilead, Janssen, Abbvie and Roche. Speaker bureau (SB) for Gilead, Roche, Abbvie, Janssen, MSD and Takeda. Dolores Caballero: C/A for Gilead, Kire, Novartis, Celgene, Janssen; SB for Takeda and Jazz. Cecilia Carpio: SB for Takeda and Celgene; AB: SB for Roche. Sonia Gonzalez de Villambrosia: SB for Janssen and Roche. Miguel A. Piris: C/A for Celgene, Gilead, Janssen, Nanostring and Kyowa Kirin. RF by Gilead and Kura. Advisory board, lecture fees and RF for/by Millenium/Takeda. Guillermo Rodriguez: C/A for Roche, Janssen, Celgene and Takeda. Ana Ruiz-Zorrilla: Former employee of Takeda Farmacéutica España S.A at the time of study design, analyses of study results and manuscript writing. Marta Grande and Carmen Montoto are employees of Takeda Farmacéutica España S.A. Raul Cordoba: SB for Takeda.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of first-line treatment for PTCL.

Table S2. Cross-reference table comparing local diagnosis and central review diagnosis.

Table S3. Treatment characteristics for salvage therapy.

Table S4. Prognostic factors and CD30.

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