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Richter transformation in diffuse large B-cell lymphoma in patients with chronic lymphocytic leukemia receiving ibrutinib: risk factors and outcomes

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This study aimed to define the incidence and risk factors for diffuse large B cell lymphoma variant of RT (DLBCL-RT) in 976 patients with CLL who received ibrutinib therapy. DLBCL-RT was recorded in 83 (8.5%) patients, with a 7-year 15.6% rate. Most patients exhibited clinical signs of aggressive lymphoma, enlarged lymph nodes in 83%, cytopenia in 60%, and Suv_{max} values ≥ 5 at CT/PET in 98%. Among patients for whom the data was available, 83% had unmutated IGHV, 60% *TP*53 disruption, 26% mutated *NOTCH1*, 10% were categorized in subset #8 and 82% had a clonally-related lymphoma. Response to chemoimmunotherapy was achieved by 32% of patients. Median OS was 4.7 months, with cytopenia at DLBCL-RT diagnosis being the only significant factor for inferior survival (HR, 1.68). In multivariable analysis, factors predictive for increased risk of DLBCL-RT were age <70 years (HR: 1.98, $p = 0.019$), *TP*53 disruption (HR: 1.72, $p = 0.044$), with a trend to significance for prior treatment (HR: 1.91, $p = 0.065$). According to the number of these risk factors, DLBCL-RT rate varied from 4% to 22.6% ($p < 0.0001$). In conclusion, patients with CLL receiving ibrutinib with age <70 years, *TP*53 disruption and previously treated are at increased risk for developing DLBCL-RT and deserve close monitoring.

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INTRODUCTION

The Richter transformation (RT), also known as Richter syndrome, was first described by Dr. Maurice Richter in 1928 as an "aggressive reticular cell sarcoma of lymph nodes" occurring in a patient with chronic lymphocytic leukemia (CLL) [1].

RT can manifest as a diffuse large B-cell lymphoma (DLBCL RT) in 2-10% of CLL patients [2–4]. Less commonly, RT can present as Hodgkin lymphoma (HL RT) or, in rare cases, as other types of lymphoma [5, 6]. Overall, the transformation rate is estimated to be 0.5–1% per CLL patient per year [2, 7]. Histological evaluation, according to the World Health Organization diagnostic criteria [8], is essential for diagnosing RT.

Patients with DLBCL-RT typically experience rapidly progressing lymphoma with a poor response to standard chemotherapy and low survival rates. Clinically, individuals diagnosed with DLBCL-RT exhibit B symptoms, significantly enlarged lymph nodes, and frequent involvement of bone marrow and extra nodal areas [2]. A poor prognostic biologic profile is usually associated with RT,

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including unmutated IGHV, deletion (17p)/*TP*53 mutation, complex karyotype, and CD38 expression [9–11]. Other genetic abnormalities have been found enriched in patients with RT. These include MYC/MGA abnormalities, *NOTCH1* mutations, deletion of CDKN2A/B, and abnormalities in pathways regulating apoptosis, DNA repair, cell cycle, and epigenetic mechanisms [12–18]. Notably, biased usage of stereotyped immunoglobulin genes in subset #8, which is associated with trisomy 12 and *NOTCH1* mutation, identifies a subset of patients at high risk of RT [1–19]. Additionally, a clonal relationship between DLBCL-RT and CLL cells has been demonstrated through the immunoglobulin heavy chain variable region (IGHV) analysis, identifying clonally-related cases in 70–80% of patients [20]. Of note, clonally related forms of DLBCL-RT are associated with poorer survival and exhibit a distinct genetic profile compared to unrelated variants that can be considered de novo DLBCL [12, 16].

Since RT is a lymphoproliferative disorder that arises in the context of an indolent disease with low proliferative activity, positron emission tomography-CT (PET-CT) is helpful in guiding the site of biopsy to the involved tissues with the highest fluorodeoxyglucose (FDG) uptake [21–26].

Despite the significant improvement in outcomes following the introduction of targeted agents, some studies indicate that RT still occurs in patients with CLL receiving chemo-free regimens [27–32]. However, there is limited information on the incidence of RT and baseline factors predisposing to RT in patients treated with novel agents.

This real-world retrospective study aimed to systematically evaluate the incidence, characteristics, and outcomes of patients who develop DLBCL-RT in a large series of patients with CLL who received ibrutinib. Additionally, our analysis sought to identify baseline clinical and biological factors that might predict a higher risk of developing RT. The results from this study could help identify and improve monitoring for patients at increased risk of developing RT while undergoing therapy with BTKi.

PATIENTS AND METHODS

Patients

This multicenter, observational, retrospective study included consecutive patients diagnosed with CLL according to the iwCLL guidelines [33] from 22 Italian centers. Patients had received either front-line or advanced-line therapy with ibrutinib as per clinical practice for at least three months between October 2014 and October 2023.

Demographic, clinical, and biological data were extracted from medical records, including gender, age, previous treatments, beta2-microglobulin, CD38 expression, IGHV, *TP*53 mutation status, and cytogenetic profile by FISH. Data from the most recent exams conducted during the pre-treatment screening were required. Additionally, biological and molecular data needed to be made within six months before the treatment with ibrutinib.

We identified in this population patients who developed DLBCL-RT during ibrutinib treatment and analyzed their clinical and biological characteristics, treatment response, and survival. Patients diagnosed with DLBCL-RT after receiving other CLL-directed treatments following ibrutinib therapy were excluded from the study. A histologic diagnosis was required to define DLBCL-RT. Treating physicians reported the histologic characteristics of the biopsied tissue for each patient. When available, we collected further data from patients diagnosed with DLBCL-RT, including karyotype, *NOTCH1* mutational status, rates of Ki67, *cMYC*, and *BCL6* positive cells, clonal relationship with the pre-existing CLL.

Table 1. Characteristics of patients with CLL at the time of the start of ibrutinib.

	All patients $N = 976$ (%)	Patients without DLBCL-RT $N = 893$ (%)	Patients with DLBCL-RT $N = 83$ (%)	*p* value
Gender male	630 (64.5)	570 (63.8)	60 (72.3)	0.12
Gender female	346 (35.5)	323 (36.2)	23 (27.7)	
Median age, years (IQR, range)	70 (63–76) (37; 95)	70 (64–76) (37; 95)	67 (61–71) (39; 84)	<0.001
Age ≥70 years	515 (52.8)	488 (54.6)	27 (32.5)	<0.001
Age <70 years	461 (47.2)	405 (45.4)	56 (67.5)	
Median time from the start ibrutinib, months (IQR, range)	44 (25–61) (1;174)	45 (27–62) (3; 174)	19 (7–43) (1; 107)	<0.001
B2M ≥ 3.5 mg/L	454/682 (66.6)	417/625 (66.7)	37/57 (64.9)	0.78
B2M < 3.5 mg/L	228/682 (33.4)	208/625 (33.3)	20/57 (35.1)	
Median lymphocyte count x10^9/L (IQR, range)	47.5 (20.5–91.3) (5.2; 485.0)	47.8 (20.8–93.0) (5.2; 485.0)	41.3 (19.0–77.8) 6.0; 362.0)	0.24
Rai stage I-II	455/961 (47.3)	406/881 (46.1)	49/80 (61.3)	0.009
Rai stage III-IV	506/961 (52.7)	475/881 (53.9)	31/80 (38.8)	
*TP*53/del (17p) present	406/829 (49.0)	359/757 (47.4)	47/72 (65.3)	0.004
*TP*53/del (17p) absent	423/829 (51.0)	398/757 (52.6)	25/72 (34.7)	
Del (11q) present	152/911 (16.7)	142/833 (17.0)	10/78 (12.8)	0.34
Del (11q) absent	759/911 (83.3)	691/833 (83.0)	68/78 (87.2)	
Tris 12 present	106/911 (11.6)	97/833 (11.6)	9/78 (11.5)	0.98
Tris 12 absent	805/911 (88.4)	736/833 (88.4)	69/78 (88.5)	
Unmutated IGHV	592/800 (74.0)	540/737 (73.3)	52/63 (82.5)	0.11
Mutated IGHV	208/800 (26.0)	197/737 (26.7)	11/63 (17.5)	
Median number of prior treatments (IQR, range)	2 (1–2) (1; 10)	1 (1–2) (1; 10)	2 (1–3) (1; 7)	0.16
Prior treatments =0	269 (27.6)	257 (28.8)	12 (14.5)	0.005
Prior treatments ≥1	707 (72.4)	636 (71.2)	71 (85.5)	

CLL chronic lymphocytic leukemia, *DLBCL-RT* diffuse large B-cell lymphoma, *IQR* interquartile range, *B2M* Beta2-microglobulin, *TP53* disruption TP53 gene deletion and, or mutation, *Del* deletion, *Tris* trisomy, *IGHV* immunoglobulin heavy chain variable region genes.

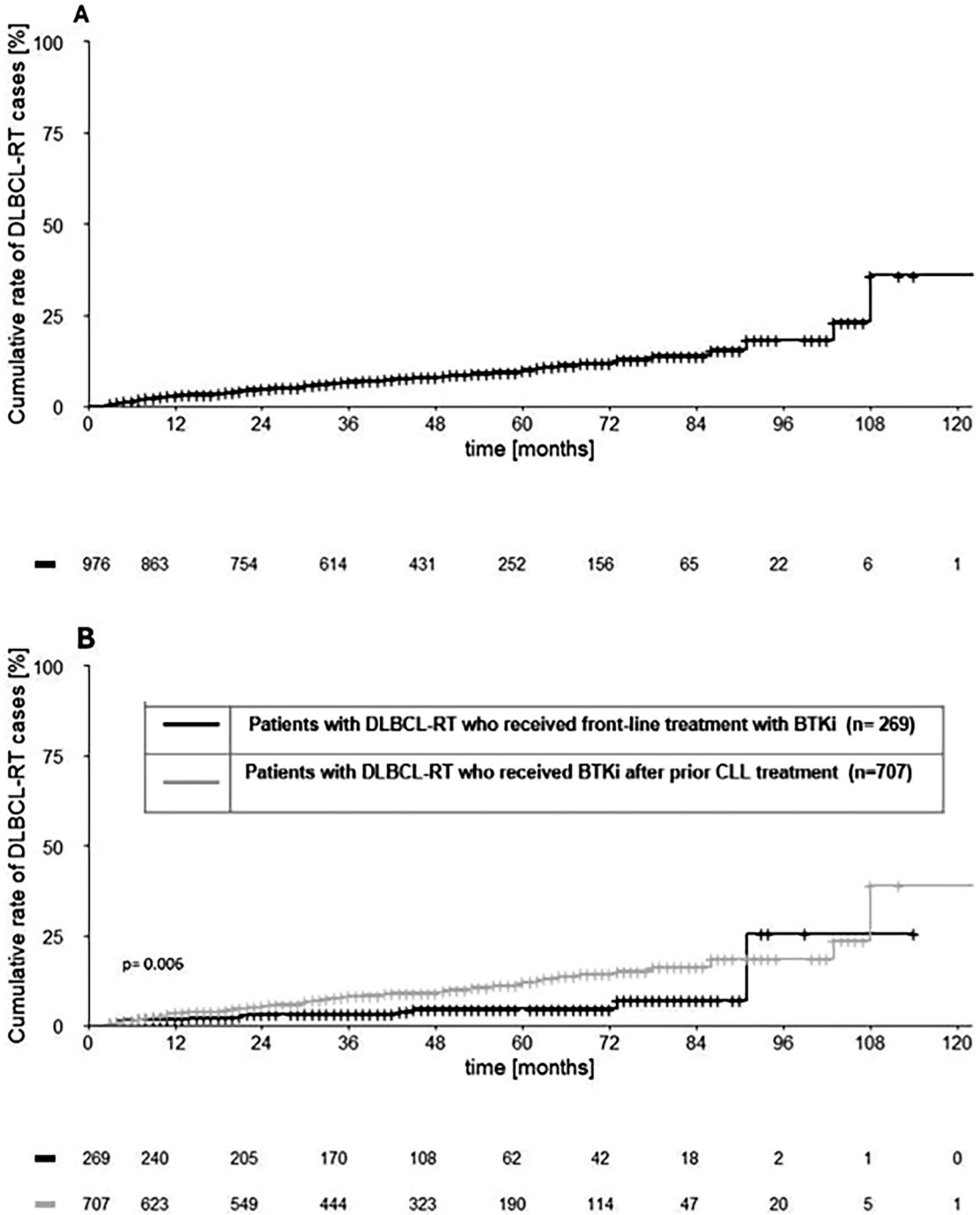

Fig. 1 Cumulative incidence of DLBCL-RT cases from the start of treatment with ibrutinib. A Cumulative incidence of DLBCL-RT cases for all patients included in the study. **B** Cumulative incidence of DLBCL-RT cases according to the treatment they received. Black line: patients who received front-line treatment ($N = 269$). Grey line: patients who received ibrutinib after prior treatment ($N = 707$).

Objectives

The primary objective of this study was to determine the rate of patients with CLL treated with ibrutinib who developed DLBCL-RT. Secondary objectives included: 1. the time between the start of ibrutinib therapy and the diagnosis of DLBCL-RT; 2. the clinical and biological characteristics of patients with DLBCL-RT; 3. DLBCL-RT-directed therapy and response; 4. survival from DLBCL-RT diagnosis;.5. factors associated with an increased risk of developing DLBCL-RT.

Statistical analysis

Survival rates were calculated from the date of DLBCL-RT diagnosis to the last follow-up or death. DLBC-RT-free survival was assessed from the start of treatment with ibrutinib to the date of DLBCL-RT diagnosis. Survival curves were generated using the Kaplan and Meier method. Differences in survival were analyzed using the Log-Rank test in univariate analysis and the Cox logistic regression model in multivariate analysis after assessing the proportionality of hazards. Factors included in the multivariate analysis were derived from the univariate analysis. Confidence intervals (CIs) were calculated at the 95% level, and all statistical tests were two-sided with a significance level set at $p < 0.05$. Risk factors for developing DLBCL-RT were analyzed according to patients' baseline clinical and biological characteristics, including: sex (male vs. female), age (<70 vs. ≥70 years), lymphocyte count ($<5 \times 10^9$/L vs. $\geq 5 \times 10^9$/L), beta2 microglobulin (<3.5 vs. ≥3.5 mg/dl), Rai stage (I-II vs. III-IV), *TP53* deletion/mutation (present vs. absent),

IGHV mutation status (unmutated vs mutated) and prior treatment (absent vs. present).To evaluate the impact of clinical and biologic factors measured at the time of RT diagnosis on overall survival (OS), we considered the following variables: sex (male vs. female), age (<70 years vs. ≥70 years), lymphocyte count ($<5 \times 10^9$/L vs. $\geq 5 \times 10^9$/L), LDH levels (normal vs. increased), presence of del (17p)/*TP53* mutation (absent vs. present), IGHV mutational status (unmutated vs. mutated), prior treatment before ibrutinib (no vs. yes), the presence of enlarged lymph nodes with or without lymphocytosis (lymphocyte count $\geq 5 \times 10^9$, present vs. absent), and the presence of cytopenia (hemoglobin ≤11 g/dL and/or platelets $<100 \times 10^9$/L: absent vs. present). The impact of the Ann Arbor stage was not analyzed because it was only assessable in the subset of patients who underwent the biopsy of bone marrow (BM) or extra-nodal involved tissues.

The statistical analysis was performed using SPSS Statistics for Windows, v.28., Armonk, NY, IBM Corp. and R statistical software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This study was conducted in compliance with local safety reporting requirements to Health Authorities and Independent Ethic Committee (Comitato Etico dell'Università Sapienza of Rome, -Prot. 0703/2020) with patients providing informed consent.

RESULTS

Incidence and time of DLBCL-RT diagnosis

We collected data on 1021 patients diagnosed with CLL and treated with ibrutinib. The incidence of RT cases was evaluated among 976 patients who had received ibrutinib for more than three months and excluded 45 patients with a lower follow-up, of whom 5 had been diagnosed with RT within 6 months from the start of treatment. Table 1 describes the patients' characteristics at the start of ibrutinib treatment. Briefly, the median age was 70 years, 269 (27.6%) patients had received front-line ibrutinib, and 707 (72.4%) had been previously treated with chemoimmunotherapy (median number of prior treatment, 2), unmutated IGHV was present in 74%, and *TP*53 deletion and, or mutation in 49%. With a median follow-up time of 44 months, 83 (8.5%) patients were diagnosed with DLBCL-RT. The 7-year cumulative incidence of RT was 15.6% with a 2.3% rate of RT cases per patient/year (Fig. 1A).

Table 2. Impact of baseline factors on the occurrence of DLBCL-RT.

	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Sex						
Male vs.	1.50	0.93–2.43	0.10			
female	Ref.					
Age, years					1.12–3.51	0.019
<70 vs.	2.01	1.27–3.19	0.003	1.98		
≥70	Ref.			Ref.		
Lymphocyte count, $\times 10^9$/L						
<5.00 vs.	Ref.	0.57–1.39	0.62			
≥ 5.00	0.89					
Beta-2 microglobulin, mg/dl						
<3.5 vs.	Ref.		0.87			
≥ 3.5	1.05	0.61–1.81				
Rai stage					0.84–2.48	0.18
I–II vs.	1.60	1.02–2.50	0.042	1.45		
III–IV	Ref.			Ref.		
Del17p/*TP*53 mutation				Ref	1.02–2.92	0.044
absent vs.	Ref.	1.23–3.26	0.005	1.72		
present	2.00					
Tris 12						
absent vs.	Ref.	0.47–1.91	0.89			
present	0.95					
Del11q						
absent vs.	Ref.					
present	0.77	0.40–1.50	0.44			
IGHV					0.77–2.93	0.23
unmutated vs.	1.92		0.050	1.50		
mutated	Ref.	1.00–3.69		Ref.		
Prior treatment					0.96–3.82	0.065
no vs.	Ref.			Ref.		
yes	2.17	1.18–4.01	0.013	1.91		

Cytopenia: Hb ≤11 g/dl and, or PLTS $< 100 \times 10^9$/L.
DLBCL-RT diffuse large B-cell lymphoma, *LDH* lactate dehydrogenase, *TP*53 TP53 gene, *Del* deletion, *Tris* trisomy, *IGHV* immunoglobulin heavy chain variable region genes.

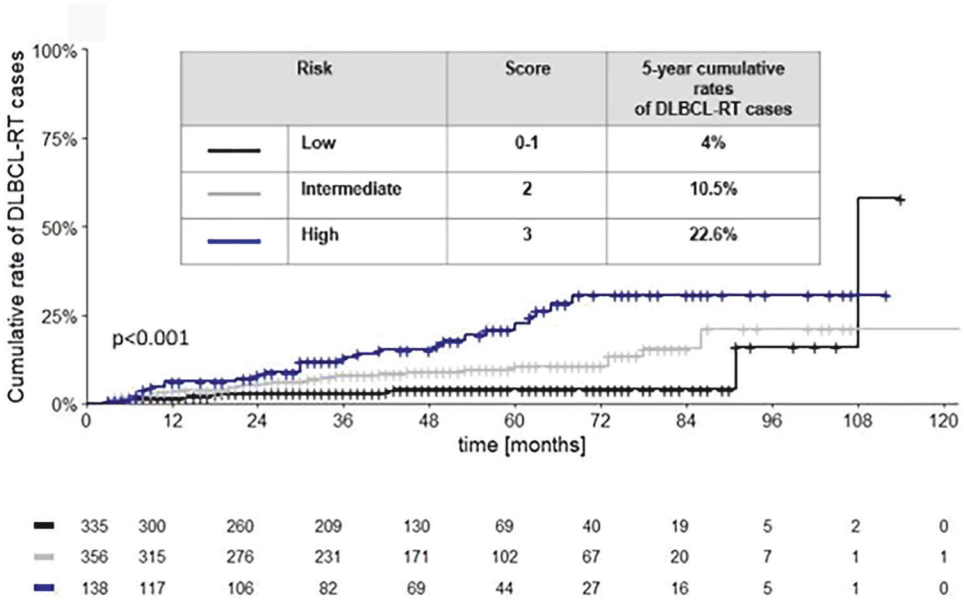

Fig. 2 Cumulative incidence of DLBCL-RT cases according to the number of risk factors. Black line: low risk patients with no/one risk factors ($N = 335$). Grey line: intermediate risk patients with two risk factors ($N = 356$). Blue line: high-risk patients with three risk factors ($N = 138$).

The 7-year cumulative incidence of RT cases was 18.6% in previously treated patients compared to 7.0% in front-line treated patients ($p = 0.006$) (Fig. 1B). Higher rates of DLBCL-RT cases were observed among patients younger than 70 years ($p < 0.001$), patients with Rai stage I-II ($p = 0.009$), *TP*53 disruption (del (17p), and, or *TP*53 mutation; $p = 0.004$), and those with prior treatment ($p = 0.005$) (Table 1).

Characteristics of patients diagnosed with RT

The characteristics of patients with DLBCL-RT diagnosis are described in the Supplementary Table S1. The median age was 70 years (IQR 63–73), and the median duration prior to treatment with ibrutinib 19 months (range, 7–43 months). Most patients exhibited typical signs of an aggressive lymphoma. Enlarged lymph nodes were present in 83% of the cases, and cytopenia (hemoglobin levels ≤11 g/dL and, or platelet count $<100 \times 10^9$/L) in 60%. Eleven percent of patients exhibited an extranodal localization of RT. Unmutated IGHV was present in 83% of tested patients, and deleted/mutated *TP*53 in 60%. *NOTCH1* mutation, the IGHV4-39 gene usage (subset #8) were detected in 26% and 10% of tested patients.

The diagnosis of RT was confirmed by the biopsy of the lymph-nodes, BM or involved tissue, except for four patients, in which a needle biopsy of an abdominal lymph node was made (Table S2). A clonal relationship between CLL and RT cells was demonstrated in 14/17 (82%) tested cases. Fifth-four (64%) patients performed total body CT/PET with SUV_{max} values ≥ 5 in 53 (98%) and >10 in 24 (44%).

Treatment

Fifteen (18%) patients received palliative treatment only due to older age and severe comorbidities. Treatment with curative intent was offered to 68 (82%) patients (Table S3). R-CHOP or R-CHOP-like schedules were the most frequently administered regimens (72%). A response to front-line treatment was recorded in 22 (32%) patients, and only two underwent a successful allogeneic stem cell transplant.

Baseline variables associated with an increased risk of developing RT

A significantly higher risk of developing RT was observed in patients with age <70 years (HR: 2.01 [95% CI: 1.27–3.19], $p = 0.003$), Rai stage I-II (HR: 1.60 [95% CI: 1.02–2,50], $p = 0.042$), unmutated IGHV, (HR: 1.92 [95% CI: 1.0–3.69; $p = 0.050$], *TP53* deletion/mutation (HR: 2.00 [95% CI: 1.23–3.26], $p = 0.005$), and prior treatment (HR: 2.17 [95% CI: 1.18–4.01], $p = 0.013$) (Table 2). However, in multivariable analysis, two baseline factors maintained independent significance: age <70 years (HR: 1.98 [1.12–3.51] $p = 0.019$) and *TP53* deletion/mutation (HR: 1.72 [1.02–2.92] $p = 0.044$) while prior treatment was associated with a trend to independent significance (HR, 1.91 [0.96–3.82] $p = 0.065$). The competing risk analysis accounting for death as competing risk demonstrated that the difference in DLBCL-RT rates based on age remains significant ($p < 0.001$) (Fig. S1). Taking into account the risk factors with a high HR value, age <70, *TP*53 disruption, and prior treatment, we stratified patients into three groups. The 5-year cumulative rate of RT cases for low-risk patients with one/no risk factors ($n = 335$) was 4%, for intermediate-risk patients with two risk factors ($n = 356$) it was 10.5%, and for high-risk patients with three risk factors ($n = 138$) it was 22.6% ($p < 0.001$) (Fig. 2). This scoring system exhibited the same predictive capability for assessing the risk of developing RT in another cohort of 486 Italian patients who received ibrutinib ($p < 0.001$; Table S4).

When we analyzed risk factors of developing RT in the cohort of 269 patients treated front-line, in multivariable analysis, Rai stage I-II showed independent significance (HR, 12.73 [95% CI: 1.6498.72]; $p = 0.015$) with a trend towards significance for *TP*53 deletion/mutation (HR, 4.07 [95% CI: 0.89–18.63]; $p = 0.071$) (Table 3).

Survival of patients diagnosed with RT

Seventy-three (88%) patients with RT have died. The most frequent cause of death was directly related to RT (59 patients, 81%), followed by severe infection (13 patients, 17%). The median OS from RT diagnosis was 4.7 months (Fig. 3A). The only baseline factor with a significant impact on OS of patients diagnosed with RT was cytopenia (hazard ratio: 1.68 [95% CI: 1.03–2.72]; $p = 0.036$) (Fig. 3A, B; Table S5).

DISCUSSION

In a large series of patients with CLL receiving ibrutinib, mainly after prior chemoimmunotherapy, we found a seven-year

Table 3. Impact of baseline variables on the risk of developing DLBCL-RT in patients receiving front-line ibrutinib.

	Previously untreated (*N* = 269)					
	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender						
male vs.	1.38	0.42–4.61		–	–	–
female	Ref.		0.59			
Age, years						
<70 vs.	1.37	0.43–4.31		–	–	–
≥70	Ref.		0.59			
Lymphocyte count x10^9/L						
<5.00 vs.	Ref.			–	–	–
≥ 5.00	0.83	0.27–2.57	0.74			
Beta-2 microglobulin mg/dl						
<3.5 vs.	Ref.			–	–	–
≥ 3.5	1.23	0.31–4.94	0.77			
Rai stage						
I-II vs.	12.46			12.73		
III-IV	Ref.	1.61–96.63	0.016	Ref.	1.64–98.72	0.015
Del17p and/or *TP*53 mutation						
absent vs.	Ref.			Ref.		
present	4.04	0.88–18.55	0.07	4.07	0.89–18.63	0.071
Tris 12						
absent vs.	Ref.			–	–	–
present	1.40	0.31–6.43	0.66			
Del11q						
absent vs.	Ref.			–	–	–
present	0.97	0.12–7.59	0.97			
IGHV						
unmutated vs.	2.11			–	–	–
mutated	Ref.	0.45–9.96	0.34			

CLL chronic lymphocytic leukemia, *IQR* interquartile range, *TP53TP53* gene, *Del* deletion, *Tris* trisomy, *IGHV* immunoglobulin heavy chain variable region genes.

cumulative incidence of DLBCL-RT cases of 15.6%, with a patient-year rate of 2.3%, showing no signs of plateauing.

A study by Al Sawaf et al. found a 12-year incidence of 8.2% in patients receiving front-line chemotherapy [34]. In another study by Hampel et al. including, about half of untreated patients the five-year incidence of RT was 1.7% [35]. Moreover, transformation rates varied widely, from 3% to 20%, in studies with novel agents, due to differences in follow-up duration and patient characteristics [36–38].

Patients diagnosed with DLBCL-RT displayed typical symptoms of an aggressive lymphoma with enlarged lymph nodes and cytopenia in 83% and 60% of the cases, respectively. Due to the suspicion of RT, 65% of patients underwent CT/PET, with 98% showing SUVmax values of ≥5, including 44% with values of ≥10. This finding underscores the importance of PET/CT in diagnosing RT and supports a PET-targeted biopsy for those with SUVmax ≥5 [24, 26, 39, 40]. As observed in other studies [27–32, 41, 42], patients who developed RT displayed unfavorable genetic alterations, with unmutated IGHV in 83% of patients and *TP*53 abnormalities in 60%. The clonal relationship between DLBCL-RT and original CLL cells has only been explored in a few cases highlighting the challenges in accessing biological assessments for treated patients in the real world.

Older age and severe comorbidities prompted palliative therapy to about 20% of patients with DLBCL-RT, a similar trend was also observed in another study [43]. Less than one-third of patients responded to chemotherapy. These findings, and the potential rise in RT cases due to the increased survival from targeted agents, indicate the urgent need for effective therapies. Preliminary results from studies investigating innovative treatments, including venetoclax [44, 45], covalent or non-covalent BTK inhibitors [46], immune checkpoint inhibitors [47–49], CD3/CD19 bispecific monoclonal antibodies [50–52], and the CAR (chimeric antigen receptor) T-cell therapy [53, 54] show promises.

This study also aimed to identify baseline clinical and biologic characteristics that could predict an increased risk of developing RT. Multivariate analysis revealed that younger age and *TP*53 disruption independently increased the risk of RT. Specifically, patients under 70 had a hazard ratio of 1.98 for DLBCL-RT risk. Interestingly, Davids et al. also found that patients who developed RT after receiving novel agents were younger than those typically diagnosed with CLL [29]. As the diagnosis of RT requires histological confirmation, it could be argued that younger, more likely than older patients, underwent diagnostic biopsy. This raises the concern that older patients with progressive disease may have missed a diagnosis of RT.

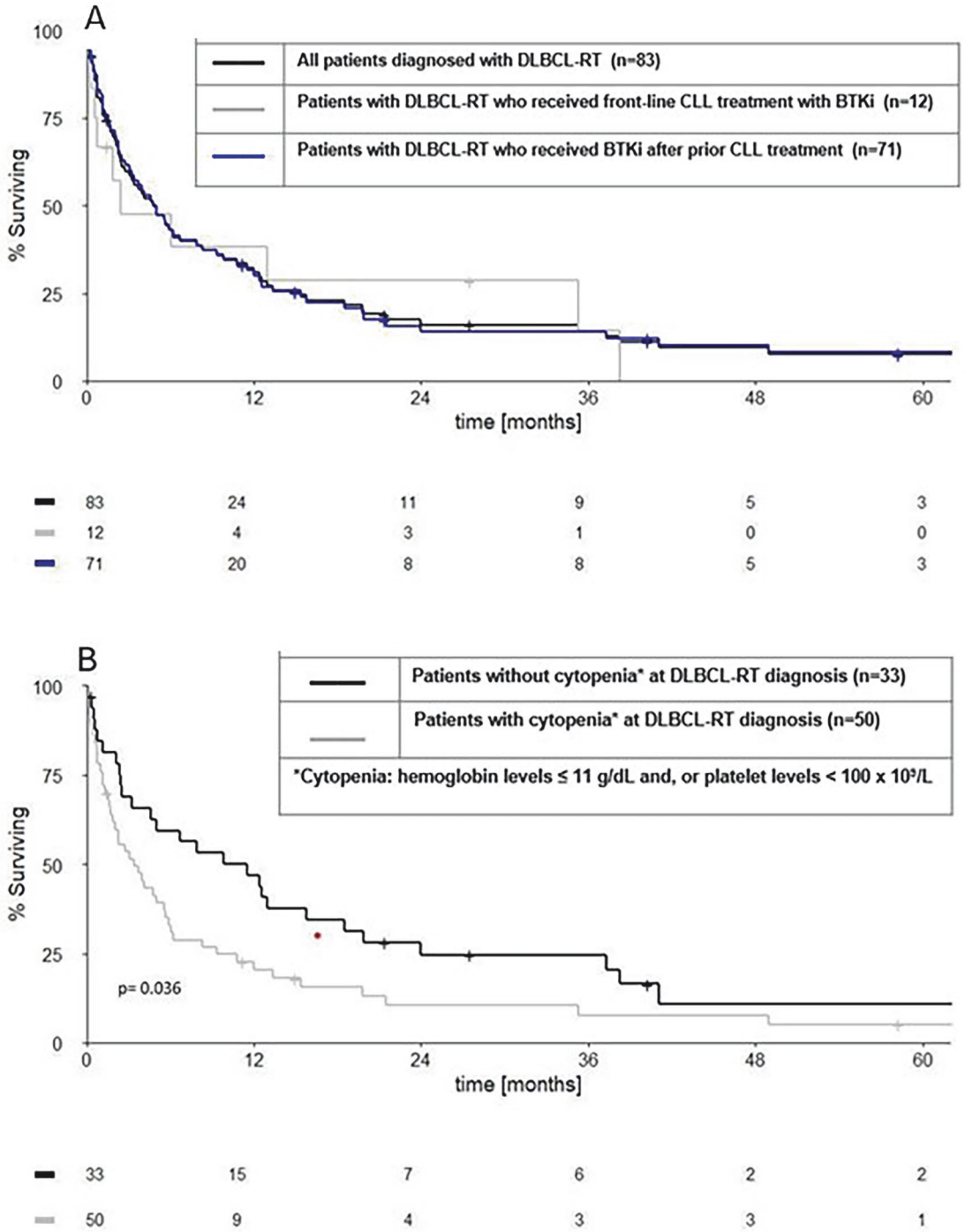

Fig. 3 Survival probability from diagnosis of Richter transformation. A Survival according to the treatment patients had previously received Black line: all patients with RT diagnosis ($N = 83$): Blue line: patients with RT diagnosis who received ≥1 lines of treatment before ibrutinib ($N = 71$). Grey line: patients with RT diagnosis who received front-line treatment with ibrutinib ($N = 12$). **B** Survival measured from the diagnosis of Richter transformation according to the presence or absence of cytopenia (hemoglobin ≤11 g/dL and/or platelets 100×10^9/L). Black line: cytopenia absent ($N = 33$). Grey line: cytopenia present ($N = 50$).

The 2024 ESMO guidelines recommend prioritizing continuous BTKi therapy for patients with *TP53* disruption due to extended PFS rates observed in these patients [55–59]. The increased risk of DLBCL-RT we found in these patients suggests close monitoring during treatment for the typical signs of RT.

The 7-year cumulative incidence of DBLCL-RT in previously treated patients was 18.6%, compared to 7.0% in those treated front-line. Although in multivariable analysis, prior treatment revealed only a trend toward independent significance, the hazard ratio for an increased risk of DLBCL-RT was 1.91. In line with this finding Hampel et al. found a lower incidence of RT in CLL patients during the targeted therapy than the pre-targeted era and noted higher risk of RT in patients who had received prior chemoimmunotherapy [35]. The reduced use of chemotherapy may reduce genetic pressure, preventing the emergence of preexisting cell clones associated with RT [18].

The increasing number of risk factors for developing DLBCL-RT (age, *TP*53 disruption, and previous treatment) was proportionally associated with a rise in the incidence of DLBCL-RT, from 4.0% to 22.6%. The predictive ability of the scoring system we designed has been confirmed in another series of 486 Italian patients with CLL who received ibrutinib and could help identify patients at an increased risk of developing RT.

When we analyzed patients who received front-line treatment, in addition to *TP*53 disruption, Rai stages, I-II emerged as a significant and independent risk factor for developing DLBCL-RT. This data is challenging to interpret. Patients with non-advanced Rai stages may require front-line treatment due to the rapid growth of their lymph nodes, which suggests a high proliferative pattern associated with an increased risk of transformation.

As previously described, the OS of patients with RT after receiving ibrutinib was dramatically low, not exceeding 4 months [29–32]. The only significant factor affecting OS was cytopenia at DLBCL-RT diagnosis. Notably, other factors from earlier prognostic scores [11, 12, 60], such as LDH levels, IGHV mutation status, *TP*53 disruption, and prior treatment, had no impact on OS.

We acknowledge the critical limits of this study. Our study was retrospective, and while RT cases were biopsy-confirmed, they were not centrally reviewed. Furthermore, we could not test the prognostic impact of some genetic variables, such as the clonal relationships of RT cells, due to the challenges of evaluating these characteristics in real-world settings.

Nonetheless, this study is the largest one that provides data on the incidence, characteristics, and risk factors for DLBCL-RT in well-characterized patients with CLL who received ibrutinib. Our findings indicate RT still occurs in in patients treated with ibrutinib, even among those treated front-line, adversely affecting survival rates. Significant predictors of a higher risk of DLBCL-RT included *TP*53 disruption, age under 70 years, and prior treatment. Our results highlight the need for closer monitoring of patients with these characteristics and emphasize the urgent need for innovative therapies for RT.

DATA AVAILABILITY

De-identified data will be shared upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

FRM, SP, and CV designed the study, collected clinical data, performed data analyses, and wrote the manuscript. DG provided guidance in the study design, performed data analyses, and wrote the manuscript. AV, AS, AMF, JO, FMQ, AG, PS, RM, II, GR, LP, LL, MP, FI, RM, MF, GMR, FC, FT, AC, MD, EM, LL, MC, AC, GG, and MG collected clinical data, reviewed data analyses and reviewed critically the manuscript. DR reviewed data analyses and reviewed critically the manuscript. All authors approved the final draft.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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