REAL-WORLD EVIDENCE IN ONCO-HEMATOLOGICAL PATIENTS

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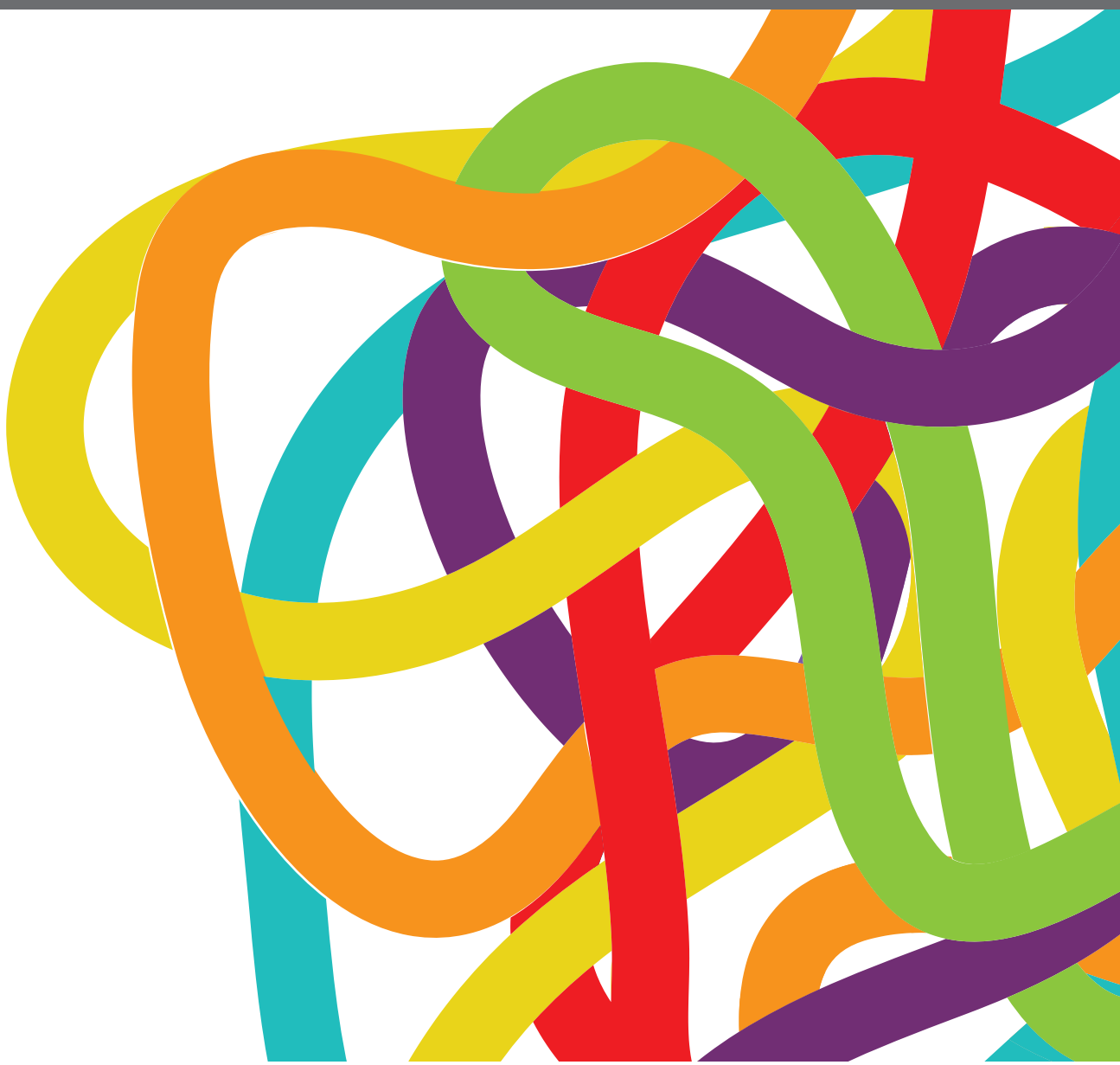

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REAL-WORLD EVIDENCE IN ONCO-HEMATOLOGICAL PATIENTS

Topic Editors:
Claudia Vener, University of Milan, Italy
Matteo Franchi, University of Milano-Bicocca, Italy
Annalisa Trama, National Cancer Institute Foundation (IRCCS), Italy

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Alessandro Isidori,
AORMN Hospital, Italy

*CORRESPONDENCE
Claudia Vener
claudia.vener@unimi.it

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Editorial: Real-World evidence in onco-hematological patients

Claudia Vener[1]*, Matteo Franchi[2,3] and Annalisa Trama[4]

[1]Department of Oncology and Haemato-Oncology, University of Milan, Milan, Italy, [2]National Centre for Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy, [3]Laboratory of Healthcare Research & Pharmacoepidemiology, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy, [4]Department of Research, Evaluative Epidemiology Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milan, Italy

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Editorial on the Research Topic
Real-world evidence in onco-hematological patients

Clinical practice, particularly in onco-haematological settings, relies on *randomised controlled trials* (RCTs), which provide rigorous scientific evidence under controlled experimental conditions. RCT results cannot be simply generalised to everyday clinical practice because of low overall trial accrual (<5% of all newly diagnosed cancer patients) and under-representation of patient frailties, as older age, advanced disease, concurrent disorders, lower socio-economic status, racial and ethnic minority membership, gender (females are less represented), and pregnancy. Conversely, *real-world studies* generate evidence on the actual benefits achieved in real-life settings, an essential requirement for public health research designed to assess and improve the impact of daily life treatment.

Our Research Topic confirms the importance of real-world studies by providing data on the pattern and quality of care and access to adequate healthcare, required to inform healthcare organisation. Interestingly, Pajiep et al. used administrative data from healthcare administrative databases in France, between 2011 and 2014, to build a specific algorithm to identify new cases of chronic myeloid leukaemia, describing patterns of tyrosine kinase inhibitor use and healthcare consumption. Daneels et al. adopted an innovative approach to describe patterns of care for diffuse large B-cell lymphomas based on Belgian health insurance data, underlining the importance of including old patients.

From a clinical viewpoint, *real-world studies* have permitted the study of therapy-related late effects. Trama et al. highlighted that survivors of adolescent and young adult haematological cancers face persistent long-lasting risk for many diseases, warranting careful consideration in cancer surveillance. Interestingly, Xiao et al. revealed substantial racial and ethnic differences associated with second malignant neoplasm subtype, risk, and mortality among Hodgkin lymphomas to be closely evaluated in cancer surveillance, and stressed the importance of including minorities in future studies. Originally, Efficace

et al. presented preliminary results, provided by treating haematologists, on the clinical utility of integrating electronic patient-reported outcomes into daily practice.

Moreover, *real-world studies* enable the study of advanced disease (Liu et al., Lecat et al.), comorbidities (Jia et al.), rare haematological cancers due to the huge amount of collected cases (Zhu et al., Liu et al.), prognoses (Vener et al., Daneels et al., Corley et al., Lecat et al.), and permit model prediction (Morabito et al., Jia et al.). *Real-world studies* also allow us to confirm in real-life what has been observed in other settings (Li et al.).

Despite the huge potential of real-world data in monitoring and evaluating healthcare patterns, including diagnosis, therapy, assistance, and rehabilitation in daily clinical practice, some methodological issues remain the subject of debate and are discussed in this Research Topic.

First, real-world studies are often based on small monocentric studies, limiting the representativeness of the patients included in the study cohort and the generalisability of the results. Second, as in all observational studies, when comparing individuals subject to two or more exposure levels, cohort patients are not randomised, making real-world studies susceptible to confounding. Indeed, exposed and unexposed patients differ for several measured or unmeasured characteristics outside the exposure of interest, which can bias the observed measures of association between exposure and outcome. This issue is particularly critical in studies using secondary data, collected for purposes other than clinical practice, which consequently do not include detailed clinical and behavioural information. Third, the criteria for defining the exposure or outcome of interest are not always objective. For example, the definition of progression-free survival is based on algorithms which have not been validated, generating unknown errors (i.e. false negative and false positive outcomes) associated with their use. Moreover, the frequent lack of detailed data on both administered therapies and clinical information may lead to misclassification of exposures and/or outcomes of interest.

Authors do not always take appropriate account of the aforementioned issues. These should instead be presented in the "Methods" section, where the criteria for defining exposures, outcomes, and covariates of interest are clearly described, and in the "Discussion" section, highlighting the study limitations, any potential associated bias, and the direction of the bias (for example, underestimation or overestimation of the association of interest). Articles should also adhere to RECORD reporting guidelines (1), used to describe studies adopting routinely collected, observational data. Furthermore, before being carried out, we believe that observational studies, particularly ones based on secondary data, should be examined and approved by an Ethics Committee, to guarantee that the study will be conducted according to best observational research practice.

Furthermore, issues of data accessibility and delays in data availability, intrinsic to retrospective data, do not always allow prompt evaluation of the clinical impact of new interventions.

Hence, what steps should, in our view, be taken to advance the development of real-world evidence?

1) Exploit real-world data by integrating the many heterogeneous datasets available (e.g. administrative datasets with population-based cancer registries and data collected in electronic medical records) to increase information potential and data representativeness. The knowledge that can be acquired from combined data could not be derived from any single source. However, heterogeneous environments also contain several biases that need to be addressed with new analytical tools (2).

2) Leverage novel artificial intelligence (AI) approaches to allow information extraction from unstructured data (e.g. electronic medical notes).

3) Ensure data exchange among multiple data sources and repositories by exploiting emerging common data models (CDM) (https://www.ohdsi.org/data-standardization/the-common-data-model/; https://build.fhir.org/ig/HL7/cdmh/). CDM enable information (e.g. encounters, patients, diagnoses, drugs, measurements, and procedures) to be captured uniformly across different data sources.

4) Facilitate data re-use and sharing by implementing data exchange and altruism concepts (i.e. voluntary data sharing for the benefit of citizens) aligned with both existing and emerging EU policies. Data sharing is still limited by a number of stumbling blocks (e.g. low trust in data sharing, issues with public sector data re-use, data collection for the common good, and technical obstacles).

5) Support communities of practice, internationally and nationally, to improve the use of real-world data (e.g. sharing of best practices, innovative tools for data exchange and harmonisation, AI-based analytics, etc.) through regular interaction.

6) Boost trust in real-world data by increasing the number and quality of studies and publications on real-world data; organising conferences focused on real-world data, and developing dedicated educational and training opportunities.

Author contributions

CV, MF, AT equally contributed to conception and design of the editorial. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Defining Unmet Need Following Lenalidomide Refractoriness: Real-World Evidence of Outcomes in Patients With Multiple Myeloma

Catherine S. Y. Lecat[1,2†], Jessica B. Taube[1†], William Wilson[3], Jonathan Carmichael[4,5], Christopher Parrish[4], Gabriel Wallis[1], Charalampia Kyriakou[1], Lydia Lee[2], Shameem Mahmood[1], Xenofon Papanikolaou[1], Neil K. Rabin[1], Jonathan Sive[1], Ashutosh D. Wechalekar[1], Kwee Yong[2], Gordon Cook[4,5] and Rakesh Popat[1]*

[1] Department of Haematology, University College London Hospitals NHS Foundation Trust, London, United Kingdom, [2] Department of Haematology, University College London Cancer Institute, London, United Kingdom, [3] Department of Oncology, Cancer Research UK & UCL Cancer Trials Centre, University College London, London, United Kingdom, [4] Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [5] Department of Oncology, The National Institute for Health Research Leeds In Vitro Diagnostics Co-operative (NIHR Leeds MIC), Leeds, United Kingdom

Background: The treatment paradigm for multiple myeloma (MM) continues to evolve with the development of novel therapies and the earlier adoption of continuous treatments into the treatment pathway. Lenalidomide-refractory patients now represent a challenge with inferior progression free survival (PFS) reported to subsequent treatments. We therefore sought to describe the natural history of MM patients following lenalidomide in the real world.

Methods: This was a retrospective cohort review of patients with relapsed MM who received lenalidomide-based treatments in the U.K. Data were collected for demographics, subsequent therapies, treatment responses, survival outcomes and clinical trial enrollment.

Results: 198 patients received lenalidomide-based treatments at a median of 2 prior lines of therapy at a median of 41 months (range 0.5-210) from diagnosis. 114 patients (72% of 158 evaluable) became refractory to lenalidomide. The overall survival (OS) after lenalidomide failure was 14.7 months having received between 0-6 subsequent lines of therapy. Few deep responses were observed with subsequent treatments and the PFS to each further line was < 7 months. There was a steep reduction in numbers of patients able to receive further treatment, with an associated increase in number of deaths. The OS of patients progressing on lenalidomide who did not enter a clinical trial incorporating novel agents was very poor (8.8 months versus 30 months, p 0.0002), although the trials group were a biologically fitter group.

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Matteo Franchi, University of Milano-Bicocca, Italy

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Stefan Knop, Julius Maximilian University of Würzburg, Germany
Alessandra Romano, University of Catania, Italy
Claudio Cerchione, Istituto Scientifico Romagnolo per lo Studio e il Trattamento dei Tumori (IRCCS), Italy

***Correspondence:**
Catherine S. Y. Lecat
catherine.lecat@nhs.net

†These authors have contributed equally to this work and share first authorship

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Conclusion: These data demonstrate the poor outcomes of patients failing lenalidomide-based treatments in the real world, the highlight need for more effective treatments.

Keywords: multiple myeloma, relapsed myeloma, lenalidomide, real-world data, Revlimid, survival outcomes

INTRODUCTION

Multiple myeloma (MM) is an incurable plasma cell malignancy of the bone marrow, characterized by multiple relapses and eventual development of resistant disease. The duration of treatment response typically reduces with each line of therapy, as does the depth of response. A large retrospective study of European real-world data demonstrated that the proportion of patients able to receive treatment reduces with each subsequent line of treatment, with only 15% of patients reaching 4th line treatment and beyond (1). This is likely due to resistant disease, toxicity burden from repeated therapies and age-related co-morbidities. However, recent novel therapy approvals and the development of more optimal drug combinations have translated into improved clinical outcomes, with an expected increase in number of patients receiving later lines of therapy.

Lenalidomide, an immunomodulatory drug (IMiD), is a key backbone agent in the treatment of MM and commonly used as frontline treatment for both transplant eligible and ineligible patients either in combination with proteasome inhibitors (PI), alkylators and/or CD38 monoclonal antibodies or as a doublet with corticosteroids according to performance status (2, 3). Additionally, it is used as maintenance following autologous stem cell transplant (4, 5). In some countries including the U.K., it continues to be used for relapsed MM (6–9) [**Supplementary Figure 1**, (10–13)].

As lenalidomide is typically continued until disease progression or intolerance, most patients become lenalidomide-refractory. Emerging data from sub-group analysis of clinical trials suggest that the treatment response and progression free survival (PFS) of lenalidomide-refractory patients are inferior to those that are sensitive (14–20). Real-world data from RRMM patients who were refractory to an IMiD also demonstrated poor outcomes [**Supplementary Figure 2**, (21–23)]. This highlights a subgroup of patients who are difficult to treat and the need for novel treatment options.

However, there may be discrepancies between clinical trial and real-world outcomes due to multiple patient-related, disease-related and treatment-related factors present between the two groups (24). The observed PFS in real-world data have been shown to be shorter than those reported in clinical trials (25), although there is a lack of clarity to the subsequent responses to treatments. Real-world data can be helpful in identifying outcomes in unselected patient groups, indeed the Connect MM registry suggested that 40% of patients would have been ineligible for inclusion in most randomized controlled trials (26). Whilst there are limitations in real-world datasets (27), they provide valuable insight into the natural history of patients that would otherwise not be known through individual clinical trials.

We therefore sought to understand the long-term outcomes of patients with relapsed or refractory MM (RRMM) following lenalidomide failure in the real-world setting by characterizing the response and PFS to each subsequent treatment and investigating the impact of access to novel agents through clinical trials.

MATERIALS AND METHODS

Study Design and Patient Selection

This was a retrospective, observational chart review study involving two large U.K. myeloma specialist centers (University College London Hospitals NHS Foundation Trust (UCLH) and Leeds Teaching Hospitals NHS Trust). RRMM patients who had previously received lenalidomide between August 2006 and September 2017 were identified using the hospitals' electronic health record systems. Patients were required to have at least one response assessment with a lenalidomide-based regimen in order to be included in the study. Baseline demographic details, disease characteristics and relevant laboratory blood results were recorded. International Staging System (ISS) at diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status at the time of lenalidomide use were noted. Lenalidomide-based treatment was defined as T0 and subsequent treatments were labelled as T1, T2, T3 etc. Treatment details were extracted, including clinical trial participation and treatment response based on the International Myeloma Working Group (IMWG) uniform response criteria (28).

The National Health Service Health Research Authority deemed that specific research ethical approval was not required due to the anonymous nature of the data collection (REF 704/60/88/81), and this study complied with information governance regulations at both hospitals.

Study Objectives

The primary objective was to estimate the duration of PFS at each subsequent line of therapy after lenalidomide-based treatment. Secondary objectives included describing overall response rate [ORR, defined as ≥ partial response (PR)] and response categories, overall survival (OS), and outcomes according to participation in clinical trials.

Statistical Analysis

Qualitative variables were presented as absolute percentage for each modality and quantitative variables were described in terms of mean, median, range and standard deviation. OS was measured from treatment start until death from any cause. PFS was measured from treatment start until whichever came first of disease progression or death from any cause. Patients with no

events were censored at the data-cut off of 1st November 2017. OS and PFS were calculated and presented as Kaplan-Meier curves. Differences in OS curves between groups were evaluated with the log-rank test. Cox regression analysis was used to examine the impact of different variables (univariate and multivariate) on OS post-lenalidomide. A p-value less than 0.05 was considered statistically significant. SPSS Statistics and GraphPad Prism were used to generate figures.

RESULTS

Patient Characteristics

198 RRMM patients were identified to have commenced lenalidomide-based treatment between August 2006 and September 2017 and had at least one evaluable response assessment. Of these, 159 were treated in UCLH and 39 in Leeds Teaching Hospitals NHS Trust. Patient demographics are shown in **Table 1**.

Outcomes With Lenalidomide and Overall Survival

The median age at the start of lenalidomide based therapy (T0) was 66 years (range 35-88). Patients received a median of 2 prior treatment lines before T0 (18%: 1 prior line, 82%: 2-3 prior lines). The majority of patients (n=146, 74%) received both a PI and thalidomide prior to lenalidomide therapy. Patients commenced lenalidomide at a median of 41 months from diagnosis (range 0.5-210), predominantly as doublet lenalidomide-dexamethasone regimen (n=138, 86% of 159 evaluable). Other regimens used include bortezomib-lenalidomide-dexamethasone (n=6, 4%), ixazomib-lenalidomide-dexamethasone (n=6, 4%), lenalidomide-dexamethasone-elotuzumab (n=2, 1.5%), daratumumab-lenalidomide-dexamethasone (n=5, 3%), cyclophosphamide-lenalidomide-dexamethasone (n=1, 0.6%), and lenalidomide-conditioned reduced intensity allogeneic stem cell transplant (n=1, 0.6%). Lenalidomide doses at disease progression were available in 98 patients (**Supplementary Figure 3A**).

The overall response rate to lenalidomide-based treatment was 67% (n=133) (**Figure 1A**): PR, 66 (33%); very good partial response (VGPR), 58 (29%); complete response (CR), 9(5%). The median PFS from T0 was 11.1 months (range 0.2-93.4) (**Figure 1B**) and median OS was 28.4 months with a median follow up of 33.8 months (**Figure 2A**). The median OS from IMWG defined disease progression on lenalidomide or change of therapy for another reason was 14.7 months. The median OS from T1 was 11.6 months as shown in **Figure 2B**. Those who achieved a response to lenalidomide had a superior OS than those who did not (38.6 months with VGPR/PR versus 12.3 months with MR/SD/PD, p<0.0001, see **Supplementary Figure 6A**). Those who became refractory to lenalidomide also had a shorter OS than those who did not (median OS 26.2 months *versus* not reached, p<0.0001, see **Supplementary Figure 6B**). In an exploratory analysis of the sub-group that had doses of lenalidomide recorded, there was no significant difference in PFS2 or OS for those progressing on lenalidomide 25mg *vs* <25mg (PFS2: 16 months *vs* 28.4 months respectively p=0.24; OS: 36.7months *vs* 22.0 months respectively p=0.055) (**Supplementary Figure 3B**).

As of data cut-off, 41 patients had not progressed on lenalidomide, of whom 31 were still alive and 10 had died. Lenalidomide was stopped due to toxicity in 11 (7%) patients.

TABLE 1 | Patient characteristics.

Patient characteristics (n = 198)		
Median age at diagnosis/years (range)		60 (33-86)
Median age at lenalidomide commencement/years (range)		66 (35-88)
Median age at progression on lenalidomide/years (range)		67 (36-92)
		Frequency (%)
ISS at diagnosis	I	42 (21)
	II	46 (23)
	III	32 (16)
	Unknown	78 (40)
Cytogenetics at diagnosis (High risk defined as t(4;14), del(17/17p), t(14;16), t(14;20), gain(1q))	High risk	28 (14)
	Standard risk	80 (40)
	Unknown	90 (45)
Isotype	IgG	83 (42)
	IgA	34 (17)
	IgD	1 (0.5)
	Light chain	38 (19)
	Non-secretory	2 (1)
	Unknown	40 (20)
Treatment line at which lenalidomide was commenced	2nd	36 (18)
	3rd	110 (56)
	4th	52 (26)
Prior PI/thalidomide exposure	Prior PI and thalidomide	146 (74)
	PI only	49 (25)
	Thalidomide only	2 (1)
	Neither	1 (0.5)

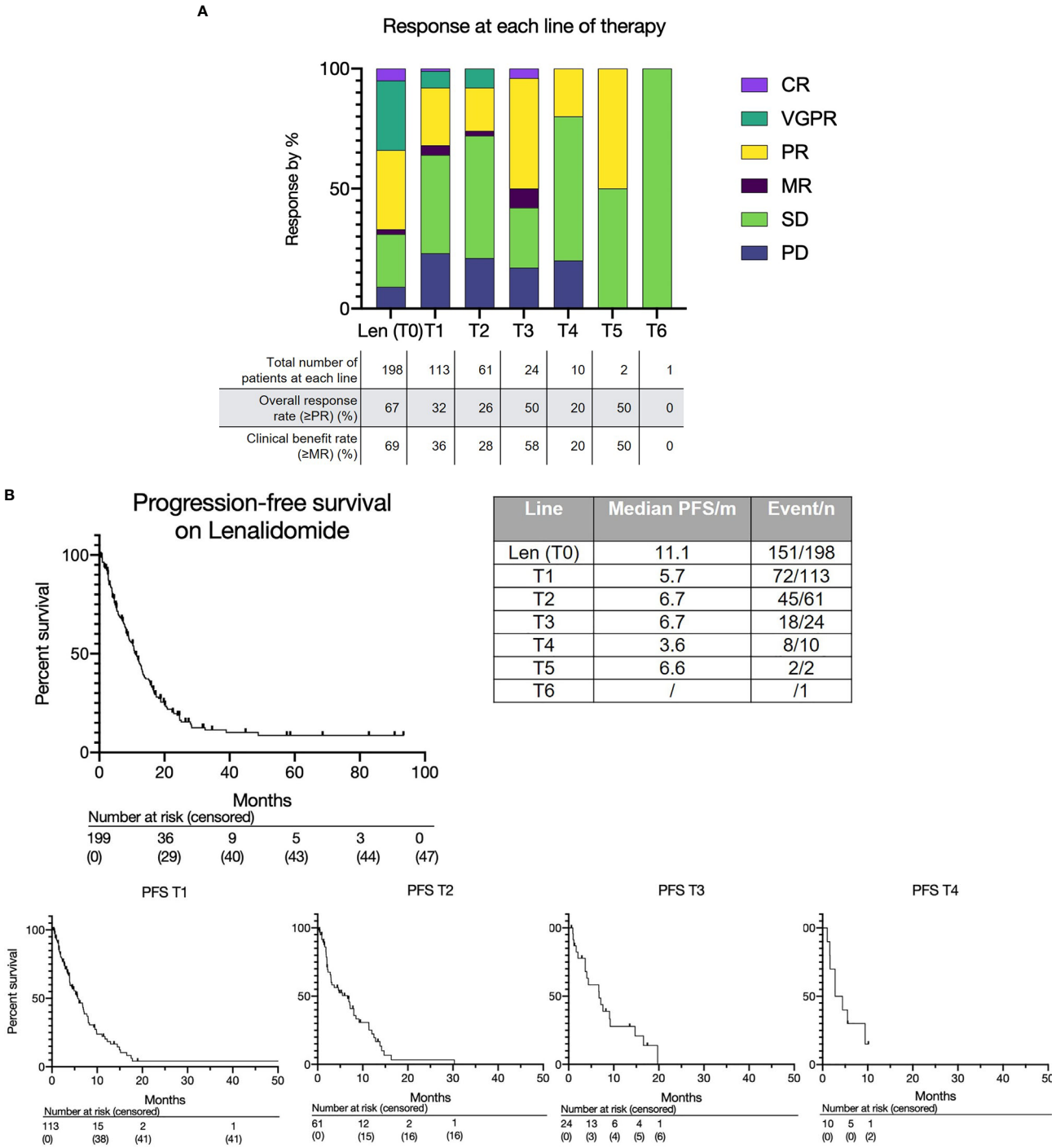

FIGURE 1 | **(A)** Treatment response to lenalidomide-based treatment and subsequent lines of therapy. **(B)** Progression free survival for lenalidomide-based therapy (T0) and each subsequent line (T1, T2, T3 etc.).

The majority of patients (n=112, 71% of 158 evaluable) became refractory to lenalidomide after an initial response. Despite this, 81 (51%) continued on lenalidomide for a median of 4.14 months (range 0.1-31.5) after evidence of progressive disease (PD). Out of these 81 patients, 24 continued on lenalidomide for more than 6 months. Overall, 31 (15.7% of 198 total population) patients progressed on lenalidomide and died without receiving any further treatment.

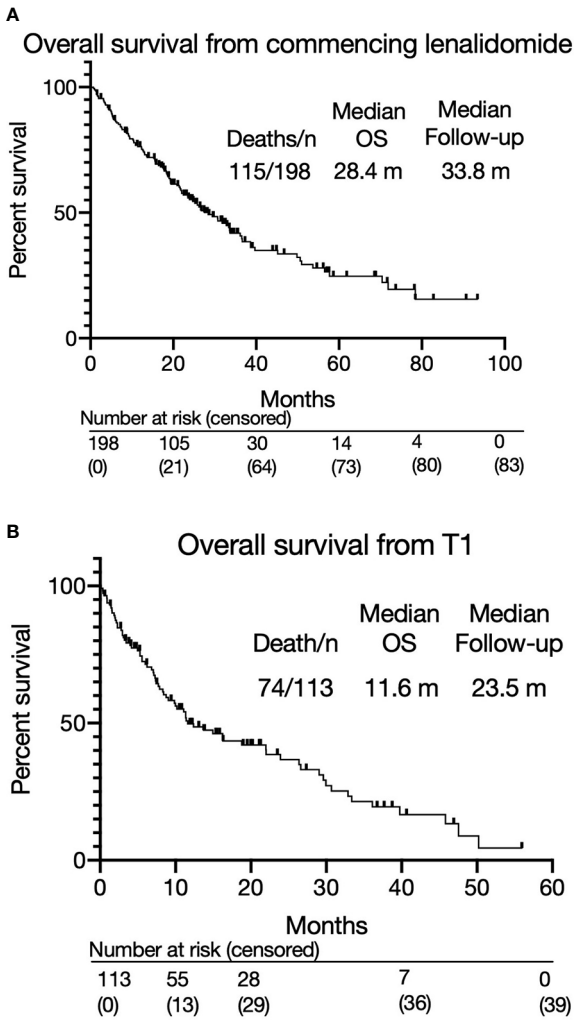

FIGURE 2 | **(A)** Overall survival from commencing lenalidomide-based therapy. **(B)** Overall survival from T1.

Subsequent Lines of Therapy Post-Lenalidomide

The absolute numbers of patients that were able to receive treatment diminished at each subsequent line after lenalidomide (**Figure 3A**): 113 patients (57%) received the next line of treatment after lenalidomide (T1), 61 (31%) received a further line (T2), 24 (12%) reached the subsequent line (T3) and 10 (5%) reached T4. Only two patients remained on treatment at T5 and beyond. The drop in patients able to receive subsequent lines of treatment was predominantly due to deaths during that line of treatment (**Figure 3B**). A smaller number had either PD but not yet changed treatment, or had not yet progressed. Approximately a third of subjects died at each line from T1 to T3.

A variety of other treatments were used immediately after lenalidomide. The most common was a pomalidomide containing regimen, although some were enrolled in clinical trials, or received alternative treatments including low dose palliative chemotherapy (for full list, see **Supplementary Figure 4**).

The overall and depth of response was limited at sequential lines of treatment (**Figure 1A** and **Supplementary Figure 5**). Overall response rates (≥PR) were as follows: T1 - 32% (36/113); T2 - 26% (16/61); T3 - 50% (12/24); T4 - 20% (2/10); T5 - 50% (1/2); T6 - 0% (0/1). Most patients achieved at least stable disease; deeper responses (≥VGPR) were rarely observed. The median PFS for each subsequent treatment was also short at 5.7 months at T1, 6.6 months at T2, 6.7 months at T3 and 3.6 months at T4 (**Figure 1B**).

As the majority (112/158, 71%) of patients were refractory to lenalidomide at the beginning of the next treatment (T1), PFS2 [from commencing lenalidomide to progression on next line of therapy (T1)] was assessed to review if there was an optimal salvage treatment for such patients, taking into consideration the duration of response to lenalidomide. The median PFS2 was similar irrespective of treatment choice (pomalidomide (n=28): 23 months, bortezomib and Panobinostat (n=12): 24 months, bendamustine (n=16): 25 months, with clinical trials (n=9):

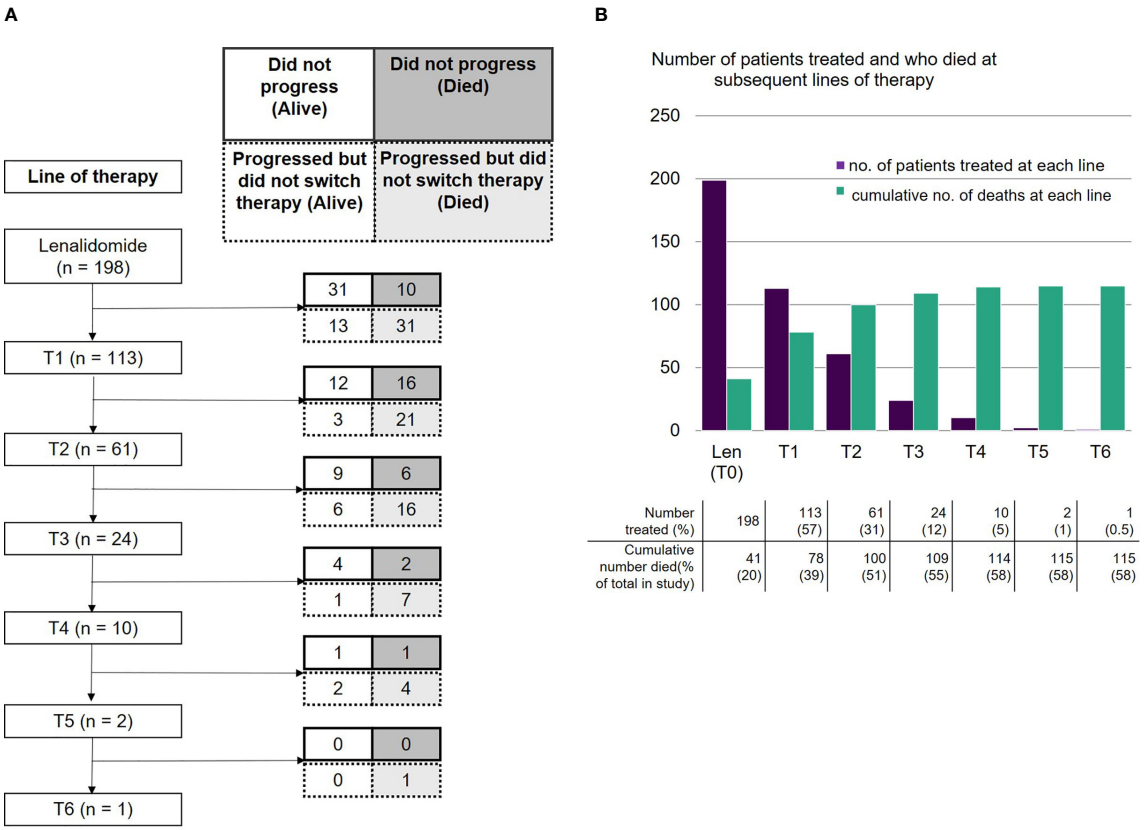

FIGURE 3 | **(A)** Number of patients receiving lenalidomide-based therapy and each subsequent line, including those who did not progress (alive or died) and those who progressed but did not switch therapy (alive or died). **(B)** Number of patients who were treated with lenalidomide-based therapy and each subsequent line, and cumulative number of deaths at each line.

19 months, other therapies (n=48): 25 months (p=0.89 (log rank)) (**Figure 4**). For those who received pomalidomide at T1, the PFS was significantly longer in those who achieved a longer (over 6 months) PFS with lenalidomide (7.04 months versus 2.78 months, p=0.038, see **Supplementary Figure 7**).

Clinical Trial Participation and Overall Survival

Overall, 37 patients (33%) enrolled in a clinical trial at any time after lenalidomide-based treatment. These patients had a superior median OS from T1 to those that did not (30.0 months versus 8.8 months, p=0.0002; HR 2.41, 95% CI 1.53 - 3.80, **Figure 5**). However, a high early mortality was noted in the non-trial group with a 6-month mortality of 91.9% (non-trial) versus 63.2% (trial) (p=0.0017, HR 3.2, 95% CI 1.5-6.7) from commencing T1. In univariate analysis of OS, C-reactive protein (CRP), platelet or neutrophil count, estimated glomerular filtration rate (eGFR, MDRD), high risk cytogenetics or patient age had no impact. However, subsequent trial enrollment, good performance status (ECOG 0-1), higher hemoglobin and higher albumin were all associated with significantly better overall survival. Significance was maintained in a multivariable model of these 4 variables, however some were excluded from this model as they did not have complete data (**Figure 6**).

DISCUSSION

The current treatment paradigm for MM involves continuous treatment until disease progression. Therefore, patients become refractory to treatments, which subsequently limit further options. Many patients become refractory to lenalidomide early on in their treatment pathway and this group have inferior outcomes compared to those who are not, as demonstrated in published studies as well as our dataset. Additionally, during the current COVID-19 pandemic some patients would have deferred ASCT and are continuing on lenalidomide instead. Understanding the natural history of patients following lenalidomide in the real world can therefore advise optimal management and help design future trials.

This study demonstrated that the survival after failing lenalidomide at 3rd line for relapsed MM was poor at 14.7 months, with fewer patients able to receive subsequent lines. Due to limited available data, a difference in outcomes for those

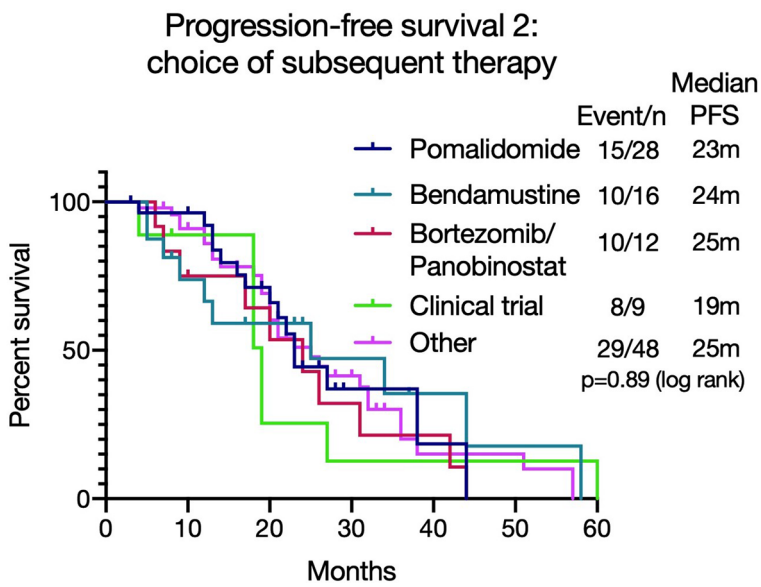

FIGURE 4 | Progression free survival 2 [PFS2 - from commencing lenalidomide to progression on next line of therapy (T1)] based on different treatment choices after lenalidomide-based therapy. The median PFS2 was similar irrespective of treatment choice (p=0.89).

progressing on full treatment dose lenalidomide versus a lower dose was not noted. This remains an area of interest. Subsequent response rates following lenalidomide were low with very few deep responses (≥VGPR) observed. Additionally, the median PFS for each subsequent line was less than 7 months and more patients died at each subsequent line. These observations suggest that patients should be treated with optimal treatment as early as possible, rather than reserving treatments for later lines, as not all patients will live to reach this point. As treatment advances continue, new and effective treatments are under evaluation. The advent of B-cell maturation antigen (BCMA) targeted treatments such as Belantamab Mafodotin, chimeric antigen reception

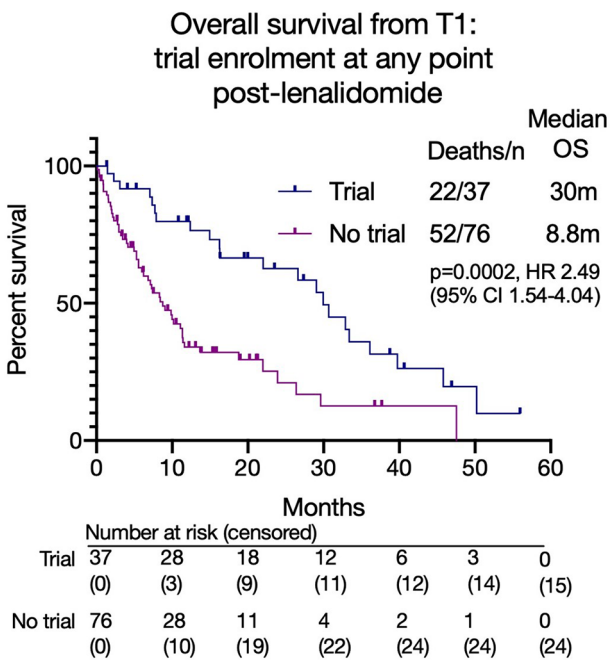

FIGURE 5 | Overall survival from T1 based on clinical trial enrolment at any time point after lenalidomide-based treatment.

Univariate analysis	N	HR	95% CI	P-value
Trial enrolment at any point post-Lenalidomide (*trial vs no trial*)	37 vs 76	0.369	0.22 - 0.63	**0.000**
ECOG pre-T1 (*ECOG 0-1 vs ECOG 2-4*)	45 vs 22	0.398	0.2 – 0.79	**0.008**
Age pre-T1	113	0.99	0.98 - 1.02	0.86
Cytogenetics at diagnosis (*standard vs high-risk*)	89 vs 24	1.15	0.66 - 1.99	0.63
Albumin pre-T1	87	0.91	0.86 - 0.96	**0.004**
Calcium pre-T1	93	1.31	0.33 - 5.16	0.69
eGFR pre-T1	93	0.99	0.99 - 1.01	0.18
CRP pre-T1	81	1.01	0.99 - 1.01	0.25
Haemoglobin pre-T1	94	0.97	0.96 - 0.99	**0.001**
Neutrophils pre-T1	94	0.89	0.76 - 1.06	0.2
Platelets pre-T1	113	0.99	0.99 - 1.01	0.28
Multivariate analysis	34 died vs 26 censored (53 incomplete data)			
Trial enrolment at any point post - Len (*trial vs no trial*)	23 vs 37	0.23	0.09 - 0.62	**0.004**
ECOG pre-T1 (*ECOG 0-1 vs ECOG 2-4*)	41 vs 19	0.26	0.12 - 0.6	**0.001**
Haemoglobin pre-T1	60	0.97	0.95 - 0.99	**0.006**
Albumin pre-T1	60	0.92	0.85 - 0.99	**0.03**

FIGURE 6 | Univariate and multivariate analyses showing impact of patient variables on overall survival from T1.

T-cells (CAR-T) and T-cell engagers as well as the incorporation of antibodies with standard to care regimens will lead to more effective salvage regimens for relapsed patients. Indeed, the ORR and durations of response to these treatments are already demonstrating improvements over historical data (29). However, these agents are not all yet routinely available and when they are licensed, they may be restricted in some countries. Therefore, it was of interest that patients enrolled into clinical trials had an improved survival to those that did not. This may be in part due to the effectiveness of the novel treatments; however, the early mortality of the non-trial patients as well as the difference in parameters such as hemoglobin and albumin suggests that the clinical trial group was potentially a biologically fitter group which is not surprising given the selection criteria for trials. Nevertheless, this data supports enrollment of patients into clinical trials to access novel treatments, although the impact could be greater if eligibility criteria were not so strict.

It is of interest that some patients continued on treatment with lenalidomide for over 6 months after IMWG defined disease progression due to lack of clinical relapse. This is relevant for treatment funders that may assume that treatments are stopped at the time of IMWG defined progression. Indeed, the clonal heterogeneity and patient variability observed in MM requires personalized decisions to be made based on the clinical phenotype of disease, genetic risk and patient preference, and as such some patients with indolent relapses continued on treatment for longer. There was no difference in PFS2 according to immediate next treatment, and so this dataset was unable to recommend an optimal treatment for lenalidomide-refractory patients, although those that had a PFS < 6 months had a shorter PFS with pomalidomide and should be considered for a class switch to a proteasome inhibitor-based combination. Ongoing clinical trials will be critical to guide this.

This study is limited by its retrospective nature, the heterogeneity of the lenalidomide-refractory cohort who received lenalidomide in line 1 to 3, and that newer agents and combination regimens have been approved or made available since the beginning of data collection in 2006. In addition, this data focuses on the use of lenalidomide in the relapsed setting whereas today it can be used at first line. However, this historical data allows longer follow-up and the ability to describe longitudinal outcomes according to each subsequent line. It also provides interesting data describing that natural plight of MM patients that switch from treatment to treatment across multiple lines at relapse.

Of note, one large U.S. real-world multi-sites myeloma dataset where 23.8% of patients were treated with lenalidomide upfront demonstrated a median PFS of 11.5 months (25), similar to our median lenalidomide PFS of 11.1 months. Furthermore, lenalidomide remains a treatment option only in relapsed settings for some countries across the world. Another

limitation is that the number of patients in later lines of treatment are small, but this represents the eventual incurable nature of the disease despite multiple lines of treatment. Further research examining quality of life in the real world would be of interest for these patients.

In conclusion, these data provide valuable insights into the real-world outcomes of patients with relapsed refractory MM that have failed lenalidomide and highlights an unmet need for the development of more effective treatment strategies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request, without undue reservation.

AUTHOR CONTRIBUTIONS

CL and JT are joint first authors. CL, JT, KY, GC, and RP designed the study. CP, GW, CK, LL, SM, XP, NR, JS, AW, KY, GC, and RP provided data. CL, JT, and JC collected the data. CL, JT, and WW analyzed the data. CL, JT, and RP wrote the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.703233/full#supplementary-material

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Lymphocyte Doubling Time As A Key Prognostic Factor To Predict Time To First Treatment In Early-Stage Chronic Lymphocytic Leukemia

Fortunato Morabito[1,2], Giovanni Tripepi[3], Riccardo Moia[4], Anna Grazia Recchia[1], Paola Boggione[4], Francesca Romana Mauro[5], Sabrina Bossio[1], Graziella D'Arrigo[3], Enrica Antonia Martino[6], Ernesto Vigna[6], Francesca Storino[1], Gilberto Fronza[7], Francesco Di Raimondo[8], Davide Rossi[9], Adalgisa Condoluci[9], Monica Colombo[10], Franco Fais[10,11], Sonia Fabris[12], Robin Foa[5], Giovanna Cutrona[10], Massimo Gentile[6], Emili Montserrat[13], Gianluca Gaidano[4], Manlio Ferrarini[11] and Antonino Neri[12,14]*

[1] Department of Onco-Hematology Azienda Ospedaliera (AO) Cosenza, Biotechnology Research Unit, Cosenza, Italy, [2] Department of Hematology and Bone Marrow Transplant Unit, Augusta Victoria Hospital, Jerusalem, Israel, [3] Centro Nazionale Ricerca Istituto di Fisiologia Clinica (CNR-IFC), Research Unit of Reggio Calabria, Reggio Calabria, Italy, [4] Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy, [5] Hematology, Department of Translational and Precision Medicine, 'Sapienza' University, Rome, Italy, [6] Department of Onco-Hematology AO Cosenza, Hematology Unit AO of Cosenza, Cosenza, Italy, [7] Mutagenesis and Cancer Prevention Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy, [8] Division of Hematology, Policlinico, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy, [9] Hematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [10] Molecular Pathology Unit, IRCCS Ospedale Policlinico San Martino, Genova, Italy, [11] Department of Experimental Medicine, University of Genoa, Genoa, Italy, [12] Hematology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy, [13] Department of Hematology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [14] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

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Edited by:
Annalisa Trama,
Istituto Nazionale dei Tumori (IRCCS), Italy

Reviewed by:
Federico Ambrogi,
University of Milan, Italy
John Seymour,
Peter MacCallum Cancer Centre, Australia

***Correspondence:**
Fortunato Morabito
f.morabito53@gmail.com

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The prognostic role of lymphocyte doubling time (LDT) in chronic lymphocytic leukemia (CLL) was recognized more than three decades ago when the neoplastic clone's biology was almost unknown. LDT was defined as the time needed for the peripheral blood lymphocyte count to double the of the initial observed value. Herein, the LDT prognostic value for time to first treatment (TTFT) was explored in our prospective O-CLL cohort and validated in in two additional CLL cohorts. Specifically, newly diagnosed Binet stage A CLL patients from 40 Italian Institutions, representative of the whole country, were prospectively enrolled into the O-CLL1-GISL protocol (clinicaltrial.gov identifier: NCT00917540). Two independent cohorts of newly diagnosed CLL patients recruited respectively at the Division of Hematology in Novara, Italy, and at the Hospital Clinic in Barcelona, Spain, were utilized as validation cohorts. In the training cohort, TTFT of patients with LDT >12 months was significantly longer related to those with a shorter LDT. At Cox multivariate regression model, LDT ≤ 12 months maintained a significant independent relationship with shorter TTFT along with *IGHV* unmutated (*IGHV*unmut) status, 11q and 17p deletions, elevated β2M, Rai stage I-II, and *NOTCH1* mutations. Based on these statistics, two regression models were constructed including the same

prognostic factors with or without the LDT. The model with the LTD provided a significantly better data fitting (χ^2 = 8.25, P=0.0041). The risk prediction developed including LDT had better prognostic accuracy than those without LDT. Moreover, the Harrell'C index for the scores including LDT were higher than those without LDT, although the accepted 0.70 threshold exceeded in both cases. These findings were also confirmed when the same analysis was carried out according to TTFT's explained variation. When data were further analyzed based on the combination between LDT and *IGHV* mutational status in the training and validation cohorts, *IGHV*unmut and LDT>12months group showed a predominant prognostic role over *IGHV*mut LTD ≤ 12 months (P=0.006) in the O-CLL validation cohort. However, this predominance was of borden-line significance (P=0.06) in the Barcelona group, while the significant prognostic impact was definitely lost in the Novara group. Overall, in this study, we demonstrated that LDT could be re-utilized together with the more sophisticated prognostic factors to manage the follow-up plans for Binet stage A CLL patients.

Keywords: CLL, prognosis, lymphocyte doubling time, TTFT, early stage

INTRODUCTION

The heterogeneous course and outcome of chronic lymphocytic leukemia (CLL) are associated with clinical and laboratory parameters as well as the molecular and cytogenetic complexity of the leukemic clone can contribute to setting a prognosis (1–31). In the past, attention was centered primarily on the predictors of general outcome, intended as overall survival. In contrast, more recently, the focus also has included the definition of time to first treatment (TTFT). According to the current guidelines (32, 33), CLL is treated at progression. Many patients and clinicians often see the start of therapy as a partition between a healthy and a disease condition. Besides, an accurate prediction of the TTFT permits setting the appropriate follow-up strategy. Several methodologies have been proposed to predict the patient's course and outcome, as well as the TTFT. Although the availability of a battery of cellular/molecular markers has opened the way to an always more refined prognostic stratification of patients, the current practice's reality indicates difficulties in carrying out several sophisticated features, often confined to a research setting (3). Thus, simplifications introducing inexpensive tests suitable for the clinical setting would be more than welcome, and such prognostic indexes would have a high likelihood of broad applicability.

The breakthrough of novel biologic variables has led to several prognostic indexes to weigh TTFT in early-stage (Binet A) CLL patients (1, 2, 34–52). Indeed, over the past few years, there has been a great effort to use novel molecular markers in prognostic modeling. Yet, questions about their usefulness to improve clinical prediction have been recently debated (53). On the other hand, as the concern for novel molecular markers detected by cutting-edge technologies has soared, performance measures for statistically quantifying their prognostic added value have risen accordingly (52).

The German study group (53) has recently established the independent prognostic value of lymphocyte doubling time (LDT) in Binet stage A patients after more than 50 years following the recognition of a correlation between the lymphocyte proliferation pattern and clinical outcome in CLL (54). LDT, defined as the period needed for the peripheral blood lymphocyte count to reach a double value of that corresponding to the initial observation, is a simple parameter that is useful in arriving at an accurate prognosis in CLL. Whereas a high LDT (greater than 12 months) identifies a population with an excellent prognosis, a low LDT (less than or equal to 12 months) LDT predicts rapid disease progression in patients in the early clinical stages (53, 55, 56). The raising question is whether the re-introduction of LDT among the last generation prognostic factors could help determine the follow-up strategies for an early-stage patient, possibly improving or maintaining the prediction power of more hi-tech markers such as the *IGHV* gene status (51, 57).

Herein, we investigated the LDT predictive value for TTFT in our prospective O-CLL cohort. The results of LDT prognostication power in the O-CLL training cohort were validated in two additional CLL cohorts.

MATERIALS AND METHODS

Lymphocyte Doubling Time

LDT was evaluated at diagnosis, also utilizing lymphocyte counts antecedent the enrollment, if available, and defined as the time needed for the peripheral blood lymphocyte count to reach a value double that of the initial observation (52, 55, 56). LDT was calculated as reported by Hoechstetter et al. (52) through a linear regression based on four blood lymphocyte measurements, each at an interval of a minimum of four weeks from the precedent one in no more than six months before enrollment.

O-CLL Training Cohort

Newly diagnosed CLL patients from 40 Italian Institutions were prospectively enrolled within 12 months of diagnosis into the

O-CLL1-GISL protocol (clinicaltrial.gov identifier: NCT00917540). The ethics committees from each participating center approved this study. Informed consent was obtained from all subjects. Recruitment began in January 2007 and terminated in January 2012. According to the guidelines (32, 33), treatment was decided uniformly for all participating centers based on documented progressive and symptomatic disease. The present analysis was carried out in 498 out of 523 accrued cases where LDT was available.

All patients from the O-CLL cohort were studied for CD38, and ZAP-70 expression, *IGHV* mutational status, FISH assays, and *NOTCH1* and *SF3B1* gene mutations as previously described (18, 28, 29, 58, 59).

The contribution of the single institutions of the training cohort is shown in **Supplementary Table 1**.

Validation Cohorts

An independent cohort of newly diagnosed and prospectively followed CLL patients recruited since 2001 at the Division of Hematology, Department of Translational Medicine, UPO, Novara, Italy, was utilized as a first validation cohort. The present analysis was restricted to 276, with LDT available, out of 283 cases included in a previous paper (5). All the prognostic factors required in this study (*IGHV* mutational status, Rai stage, β2M, 17(p) and 11(q) deletions, *NOTCH1* coding gene mutation, and LDT were available for 257 cases.

A further independent cohort of newly diagnosed and prospectively followed CLL patients recruited since 2001 at Hospital Clinic, Institute of Hematology and Oncology, University of Barcelona, Spain, was utilized as an additional validation cohort. The present analysis was performed in 414 cases; 355 were included in a recent paper (51). All the prognostic factors required in this study (*IGHV* mutational status, RAI stage, β2M, 17(p) and 11(q) deletions, *NOTCH1* coding gene mutation, and LDT) were available for 247 cases.

Statistical Analysis

TTFT analyses (including the identification of risk factors for this endpoint) were performed using the Kaplan-Meier method followed by log-rank test. The prognostic impact of specific risk factors on the outcome variable was investigated by univariate and multiple Cox regression analysis. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). The main prognostic factor in our study was the $_b$Score. It was calculated by deriving a weight corresponding to the regression coefficients of each prognostic factor (b) (60). The regression coefficients of the independent prognostic factors were preliminarily summed up. Then, they were divided by this sum and multiplied by 100, thus deriving a weight ranging from 0 to a given percentage, These weights were summed up on an individual basis, thus deriving a score interpretable in a prognostic scale ranging from 0 to 100% (for patients exposed to all risk factors) (60). The predictive accuracy of the prognostic models was quantified by calculating the Harrell C-index (HC-index), ranging from 0.5 to 1.0, the explained variation on the outcome (i.e., an index combining calibration and discrimination) (61), and the Akaike weights (AIC) (62). The integrated discrimination improvement (IDI) (53) was also calculated to assess the gain in prognostic accuracy provided by LDT. IDI is an index of risk re-classification that quantifies whether a new variable offers a clinically relevant improvement in prediction beyond and above provided by a model based on a previous risk prediction rule and not including the same variable.

The fittings between two nested prognostic models (including and not including LDT) were compared by the -2 log likelihood statistics (63). Data analysis was performed by STATA for Windows v.9 and SPSS Statistics v.21.

RESULTS

O-CLL Training Cohort

In the prospective O-CLL cohort, LDT was available in 498 Binet stage A CLL cases (median 72.4 months). Seventy-seven cases (15.5%) presented a LDT ≤ 12 months. Out of the 498 patients, 177 needed treatment, with a significantly higher percentage (P<0.0001) of cases requiring therapy detected among the group with LDT ≤ 12 months (54/77, 70.1%) as compared with that with LDT>12 months (123/431, 29.2%). TTFT of patients with LDT ≤12 months was significantly shorter (HR=2.9, 95% CI 2.1–4.0, *P*<0.0001) compared to those with a longer LDT (**Figure 1**). In the same cohort, when all the correlates of outcome determined by univariate analysis (**Table 1**) were introduced into the same multiple Cox regression model, only *IGHV* unmutated (*IGHV*umut) genes, 11q and 17p deletions, elevated β2M, Rai stage I-II, *NOTCH1* mutations and LDT ≤ 12 months maintained a significant independent relationship with shorter TTFT (**Figure 2**).

Starting from this analysis, two regression models were constructed, i.e., a Cox model including all significant and independent correlates of TTFT except LDT (Model 1, **Table 2**) and a Cox model including the same set of prognostic factors and LDT (Model 2, **Table 2**). Of note, Model 2 (including LDT) provided a significantly better data fitting (χ^2 = 8.25, P=0.0041) than Model 1 (not including LDT). Moreover, by IDI calculations, we demonstrated that LDT increased the estimated risk of +3.8%, a result of high statistical significance (P<0.001). These analyses were carried out in 334 cases in which all the variables were available.

Prediction Risk Scores in Training O-CLL Cohort

Based on Model 1 and Model 2, two risk prediction rules were developed, i.e. $_b$Score LDT and $_b$Score no LDT (**Figure 3**). $_b$Score which included LDT, had better prognostic accuracy than that without LDT (**Table 1**, training set). Moreover, the HC-index including LDT, was higher than those without LDT (75.4 *versus* 74.7), although the accepted 0.70 threshold (25) exceeded in both cases (**Table 3**). This was also true when the same analysis was carried out according to the explained variation in TTFT, which combines the discrimination and the calibration abilities of a risk prediction rule ($_b$Score LDT = 47.6% *versus* $_b$Score no LDT = 45.0%; **Table 3**).

Prediction Risk Scores in Validation Novara and Barcelona Cohorts

These analyses were carried out in two validation cohorts. LDT was available in 276 and in 414 Binet stage A cases respectively in Novara and Barcelona cohorts. Eighty-six and 148 patients

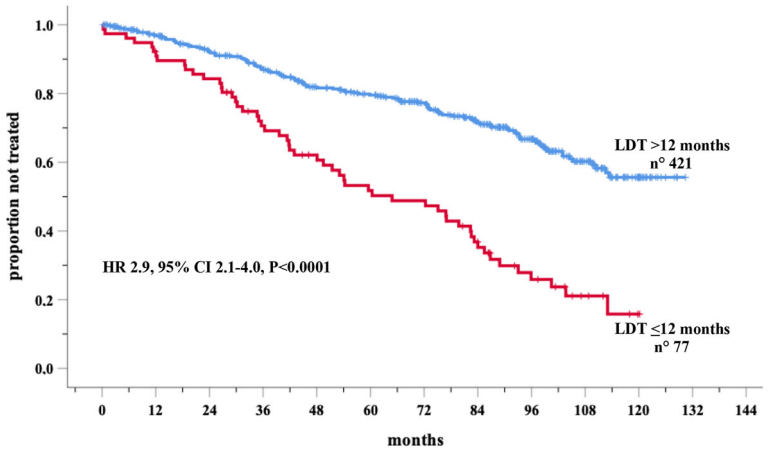

FIGURE 1 | Kaplan-Meir curves of time to first treatment (TTFT) of patients stratified by lymphocyte doubling time (LDT) in the O-CLL training cohort.

TABLE 1 | Cox univariate analyses of several variables that significantly predict TTFT in the training O-CLL cohort.

Variables	HR (95% CI)	P
Age, >65 years	0.9 (0.6-1.3)	0.5
Rai, I-II stage	1.9 (1.4-2.6)	<0.0001
MBL-CLL classification, CLL	2.3 (1.8-3.4)	<0.0001
SFB1, mutated	2.4 (1.2-4.8)	0.01
Notch1, mutated	2.4 (1.7-3.5)	<0.0001
β2-M, abnormal	2.2 (1.5-3.1)	<0.0001
ZAP-70, positive	2.8 (2.1-3.8)	<0.0001
CD38, positive	3.2 (2.3-4.3)	<0.0001
IGHV status, unmutated	5.4 (3.9-7.3)	<0.0001
BCR stereotypy, yes	1.7 (1.1-2.4)	0.002
Fish analysis, 11q deletion	5.3 (3.5-8.1)	<0.0001
Fish analysis, 17p deletion	5.2 (2.4-11.2)	<0.0001

TTFT, time to first treatment; HR, hazards ratio; 95% CI, 95% confidence interval; β2M, β2-microglobulin; ULN, upper limit of normal.

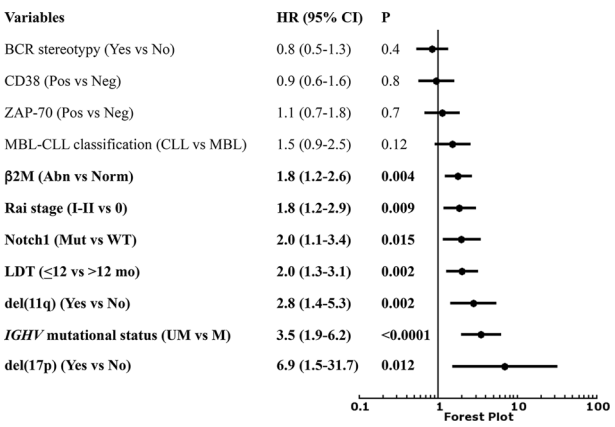

FIGURE 2 | Forest plot of Cox multivariate analysis for time to first treatment (TTFT) according to several variables.

required therapy in the Novara and Barcelona cohorts, respectively. A significantly higher percentage of treated cases were recorded among the group with LDT ≤ 12 months in both the Novara (LDT ≤ 12 70/121, 57.9% *versus* LDT>12 months (16/155, 10.3%) and the Barcelona (LDT ≤ 12 months 30/39, 76.9% *versus* LDT>12 months cohort 119/375, 31.7%). In the Novara cohort, Cox univariate analysis showed a significantly increased risk of treatment for patients with LDT ≤12 months (155 cases) (HR=6.1, 95% CI 3.6–10.6, *P*<0.0001) compared to those with a longer LDT (121 patients) (**Figure 4A**). Similar results were detected in the Barcelona validation set, in which the 39 cases with LDT ≤12 months showed a risk of being treated 7.4 times higher (95% CI 4.9–11.2, *P*<0.0001) than the 375 cases with a longer LDT (HR=1) (**Figure 4B**).

Table 4 reports the clinical and biological variables significantly associated with TTFT in the multivariate models of training as well as both validation cohorts. Remarkably, the higher prognostic value, provided by risk prediction rule including LDT, found in the training cohort was fully confirmed in the two validation cohorts (**Table 3**). The HC-indexes and the explained variations in TTFT were consistently higher for bScore including LDT than for that excluding this variable (**Table 3**) in both Novara cohort (HC-Indexes 80.4 *versus* 75.2; explained variations 49.6 *versus* 33.3) and Barcelona cohort (HC-Indexes 70.0 *versus* 68.1; explained variations 30.5 *versus* 25.8). Finally, the Akaike weights coherently indicated that the risk scores including LDT had a chance to provide the best prognostic estimates ranging from 98.1% to 100% in both the training and in the two validation cohorts (**Table 3**).

Relationship Between LDT and IGHV Mutational Status

Data were further analyzed based on the combination between LDT and *IGHV* mutational status in the training and validation cohorts, in cases with both variables available As expected, LDT ≤12 months significantly maintained its negative

TABLE 2 | Regression coefficients (b) derived from two multivariate models where lymphocyte doubling time (LDT) where excluded ($_{NO}$LDT MODEL) or included (LDT MODEL).

Variables	$_{NO}$LDT MODEL (Model 1)			LDT MODEL (Model 2)		
	b	HR (95% CI)	P	b	HR (95% CI)	P
del(17p) (Yes *vs* No)	2.225	9.3 (2.1-40.1)	0.003	1.921	6.8 (1.6-29.8)	0.011
IGHV mutational status (UM *vs* M)	1.279	3.6 (2.4-5.4)	<0.0001	1.271	3.6 (2.5-5.4)	<0.0001
del(11q) (Yes *vs* No)	1.025	2.8 (1.5-5.1)	0.001	0.988	2.7 (1.5-4.9)	0.002
β2M (Abn *vs* Norm)	0.662	1.9 (1.3-2.8)	<0.0001	0.668	1.9 (1.4-2.8)	<0.0001
Rai stage (I-II *vs* 0)	0.734	2.1 (1.4-3.1)	<0.0001	0.628	1.8 (1.3-2.8)	0.002
NOTCH1 gene (Mut vs WT)	0.576	1.8 (1.1-2.9)	0.023	0.551	1.7 (1.1-2.8)	0.03
LDT (≤12 *vs* >12 mo)	…	…	…	0.604	1.8 (1.4-2.8)	0.003

These analyses were carried out in 334 cases of the O-CLL training cohort in which all the variables were available.

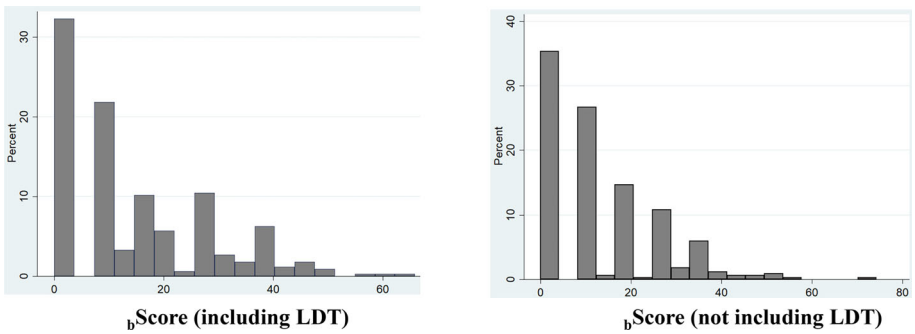

FIGURE 3 | Distribution of bScore with or without Lymphocyte Doubling Time (LDT).

TABLE 3 | Comparison between the $_{NO}$LDT score and the LDT score for the prediction of TTFT in the O-CLL, in the O-CLL, Novara, and Barcelona cohorts by regression coefficients ($_{B}$Score).

O-CLL cohort (training set)	$_{b}$SCORE	
	LDT	**$_{NO}$LDT**
HC index (%)	75.4	74.7
Explained variation (%)	47.6	45.0
Akaike weights (%)	98.1	1.9
Novara cohort (validation set)		
HC index (%)	80.4	75.2
Explained variation (%)	49.6	33.3
Akaike weights (%)	100%	0%
Barcelona cohort (validation set)		
HC index (%)	70.0	68.1
Explained variation (%)	30.5	25.8
Akaike weights (%)	98.2	0.8

prognostic power in both the *IGHV*mut and in the *IGHV*unmut patient groups in O-CLL (training) cohort (**Figure 5A**) as well as in both Novara (**Figure 5B**) and Barcelona (**Figure 5C**) validation cohorts, showing *IGHV*unmt & LDT ≤ 12 months and *IGHV*mut & LDT>12 months the shortest and the longest TTFT, respectively. Interestingly, the probability of remaining therapy-free at 6 years was 51% in the *IGHV*unmut and LDT>12months group and of 76% in the *IGHV*mut LTD ≤ 12 months, respectively (P=0.006) in the O-CLL validation cohort, confirming the predominant prognostic role of the *IGHV*umut status. However, this predominance was of borden-line significance (P=0.06) in the Barcelona group, while the significant prognostic impact was definitely lost in the Novara group. This discrepancy could be due to a different distribution of the above-mentioned subsets (*IGHV*unmut and LDT>12months and *IGHV*mut LTD ≤ 12 months) among Novara validation cohort (**Supplementary Figure 1**).

DISCUSSION

The clinical course of early-stage CLL is hugely heterogeneous. While some patients need treatment at the onset of the diagnosis, others remain therapy-free for many years or even do not receive any treatment livelong (1, 2).

Several prognostic algorithms derived from multivariable models, nomograms and score systems have been developed to predict clinical outcomes accurately in early-stage CLL (64). The *IGHV* gene configuration is one of the most important single factors predicting therapy need, and it is recurrently incorporated in all prognostic models (65).

In contrast, the prognostic role of LDT in CLL was acknowledged more than 35 years ago by Montserrat et al. (55) and soon after by Molica et al. (56), when disease biology of the neoplastic cell remained weakly recognized. The raising question is whether the re-introduction of LDT among the last generation

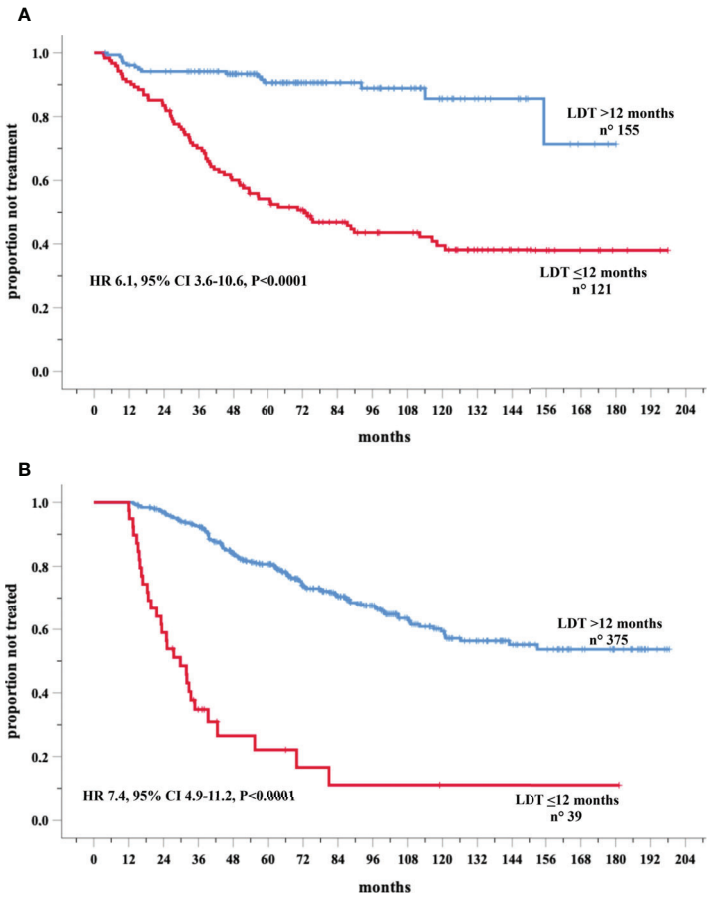

FIGURE 4 | Kaplan-Meir curves of time to first treatment (TTFT) of patients stratified by lymphocyte doubling time (LDT) in the Novara **(A)** and Barcelona **(B)** validation cohorts.

TABLE 4 | Comparison of the clinical and biological variables of O-CLL (training), Novara and Barcelona (validation) cohorts resulted significantly associated to time to first treatment in the multivariate models.

Variables	O-CLL cohort Number of cases (%)	Novara cohort Number of cases (%)	Barcelona cohort Number of cases (%)	Total (%) Number of cases (%)
LDT	**498 (41.9)**	**276 (23.2)**	**414 (34.8)**	**1188 (100)**
≤12months	77 (15.5)	121 (43.8)	39 (9.4)	237 (19.9)
>12 months	421 (84.5)	155 (56.2)	375 (90.6)	951 (80.1)
***IGHV* mutational status**	**482 (45.2)**	**265 (24.8)**	**320 (30)**	**1067 (100)**
UM	150 (31.1)	67 (25.3)	113 (35.3)	330 (30.9)
M	332 (68.9)	198 (74.7)	207 (64.7)	737 (69.1)
del(11q)	**477 (42.4)**	**274 (24.4)**	**373 (33.2)**	**1124 (100)**
Yes	30 (6.3)	15 (5.5)	28 (7.5)	73 (6.5)
No	447 (93.7)	259 (94.5)	345 (92.5)	1051 (93.5)
β2M	**343 (34.0)**	**268 (26.6)**	**397 (39.4)**	**1008 (100)**
Abnormal	127 (37.0)	126 (47.0)	158 (39.8)	411 (40.8)
Normal	216 (63.0)	142 (53.0)	239 (60.2)	597 (59.2)
Rai stage	**493 (41.7)**	**276 (23.3)**	**414 (35)**	**1183 (100)**
I-II	104 (21.1)	64 (23.2)	80 (19.3)	248 (21.0)
0	389 (78.9)	212 (76.8)	334 (80.7)	935 (79.0)
***NOTCH1* gene**	**487 (46.9)**	**276 (26.6)**	**275 (26.5)**	**1038 (100)**
Mut	63 (12.9)	21 (7.6)	28 (10.2)	112 (10.8)
WT	424 (87.1)	255 (92.4)	247 (89.8)	926 (89.2)
del(17p)	**477 (42.4)**	**274 (24.4)**	**373 (33.2)**	**1124 (100)**
Yes	10 (2.1)	9 (3.3)	14 (3.8)	33 (2.9)
No	467 (97.9)	265 (96.7)	359 (96.2)	1091 (97.1)

Cases with all available variables have been reported. All variables are in bold.

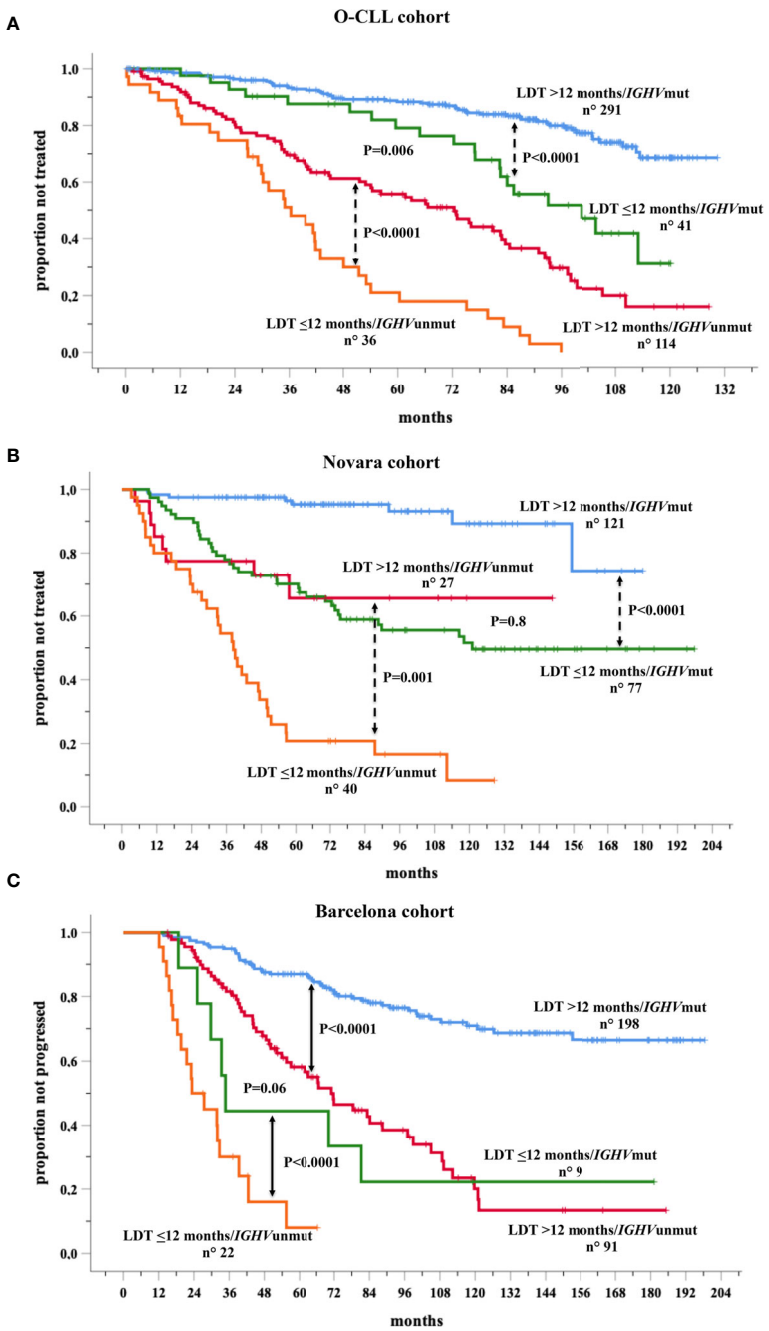

FIGURE 5 | Kaplan-Meir curves of time to first treatment (TTFT) of patients stratified by the combined analysis of lymphocyte doubling time (LDT) and *IGHV* mutational status in the O-CLL training cohort **(A)** and Novara **(B)** and Barcelona **(C)** validation cohorts for whom both variables were available.

prognostic factors could help determine the follow-up strategies for an early-stage patient, possibly improving the prediction power of more sophisticated markers such as *IGHV* gene status. In the prospective O-CLL training cohort, a Cox regression model indicated *IGHV*umut genes, 11q and 17p deletions, elevated β2M, Rai stage I-II, *NOTCH1* mutations and LDT ≤ 12 months as independently associated with shorter TTFT, thus confirmed the prognostic value of LDT in the era of new prognostic indicators. Our results fully agree with those of the German CLL Study Group, which endorses the prognostic benefit of determining LDT in the era of new markers (52). Specifically, the German prognostic model includes genetic features, i.e., 17p and 11q deletions, as well as *IGHV* mutational status. Similarly, the same prognostic indicators were demonstrated by our group to be independently associated with TTFT together with LDT. Unlike CLL1-PM, *NOTCH1* remained significant in our analysis, confirming previous results (3, 5, 18).

Remarkably, the higher prognostic value, provided by risk prediction score including LDT, found in the training cohort was fully confirmed in the two validation cohorts. Specifically, the indicators of performance, such as the HC-indexes and the explained variations, were consistently higher for bScore including LDT than for that excluding this variable in the training and both validation cohorts. Finally, the Akaike weights coherently indicated that the risk scores including LDT had a chance to provide the best prognostic estimates ranging from 98.1% to 100% in both the training and the two validation cohorts. More recently, the prognostic significance of LDT was demonstrated to be independent for TTFT from the CLL-IPI and the Barcelona/Brno prognostic models in a real-life cohort of 848 Binet stage A patients (66).

Thus, the question of whether the re-introduction of LDT among the more sophisticated prognostic factors could help to determine the follow-up strategies for an early-stage patient has an affirmative answer. However, several caveats have to be considered. Although simple, LDT determinations require a precise timing and relative frequent accesses of patients to the clinic, thus preventing the setting of a definite 'watch and wait' strategy in concomitance with the work-up at diagnosis. Alternatively, more precise and possibly more rapid methodologies to measure lymphocyte proliferating potential, such as labeling with deuterated water, are too complex to be used routinely (67). Moreover, when data were further analyzed based on the combination between LDT and *IGHV* mutational status in the training and validation cohorts, *IGHV*unmut and LDT>12 months group showed a predominant prognostic role over *IGHV*mut LTD ≤ 12 months (P=0.006) in the O-CLL validation cohort. However, this predominance was of borden-line significance (P=0.06) in the Barcelona group, while the significant prognostic impact was definitely lost in the Novara group, incongruity possibly due to a different distribution of the above-mentioned subsets among Novara validation cohort. Thus, the *IGHV* mutation status could offer some, likely marginal, sensitivity advantage over the LDT determination. Finally, no information on the LDT stability overtime is available. Therefore, LDT values may vary over time, particularly in concomitance with the progression of the CLL towards a more aggressive form. These changes are likely to relate to a minority of cases and may not influence an entire cohort's data but may have clinical relevance for the individual patients. These variations in time have been reported for cellular markers such as CD38 or ZAP-70 and have caused their subsequent obsolescence.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Regionale Liguria n° OMC07.002. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FMo, MG, MF, and AN designed the study. FMo, GT, MG, and GD'A performed statistical analysis. FMo, MG, GT, DR, GG, EMo, MF, GC, MC, FF, FS, SB, SF, and AN analyzed and interpreted data, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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For Each Institution, the Ethics Review Committee that approved the protocol is listed below. Unità di Ematologia e Trapianto di Cellule Staminali, Istituto di Oncologia "Giovanni Paolo II", Bari comitato etico Istituto di Oncologia "Giovanni Paolo II", di Bari, Italy; Dipartimento di Ematologia, Ospedale di Venere, Bari comitato etico Ospedale di Venere,Bari, Italy; U.O.C. Ematologia e Trapianto, Ospedale "Mons. R. Dimiccoli" -Barletta comitato etico Ospedale "Mons. R. Dimiccoli" -Barletta, Italy; Divisione di Ematologia, Presidio Ospedaliero "A. Perrino", Brindisi comitato etico Presidio Ospedaliero "A. Perrino", Brindisi, Italy; U.O.C. di Oncoematologia Ospedale "S. Anna e S. Sebastiano", Caserta comitato etico Ospedale "S. Anna e S. Sebastiano", Caserta, Italy; Divisione di Ematologia, Università di Catania Ospedale Ferrarotto, Catania comitato etico Ospedale Ferrarotto, Catania, Italy; U.O.S. di Emato-Oncologia, Ospedale Garibaldi-Nesima, Catania comitato etico Ospedale Garibaldi-Nesima, Catania, Italy, Dipartimento di Oncologia ed Ematologia, Pugliese-Ciaccio Hospital, Catanzaro comitato etico Pugliese-Ciaccio Hospital, Catanzaro, Italy; U.O.C di Ematologia, A.O. Cosenza comitato etico A.O. Cosenza, Italy; U.O.C. di Oncologia, Ospedale Giannettasio, Rossano Calabro, Cosenza comitato etico Ospedale Giannettasio, Rossano Calabro, Italy; Divisione di Ematologia, Ospedale Policlinico, Palermo, comitato etico Ospedale Policlinico, Palermo, Italy; Ematologia ospedale Goretti, Latina comitato etico ospedale Goretti, Latina, Italy; Clinica Ematologica, DIMI, Genova, comitato etico Ospedale San Martino, Genova, Italy; Oncologia medica C IRCCS Ospedale Policlinico San Martino, Genoa, Italy comitato etico IRCCS Ospedale Policlinico San Martino,Genova, Italy; Ospedale Villa Scassi Sampierdarena, Genova comitato etico Ospedale Villa Scassi, Genova, Italy; Ematologia, A.O. San Martino, Genova comitato etico A.O. San Martino, Genova, Italy; Unità di Ematologia, Ospedale Vito Fazzi, Lecce comitato etico Ospedale Vito Fazzi, Lecce, Italy; UOC di Ematologia Ospedale di Matera comitato etico Ospedale di Matera, Italy; Divisione di Ematologia, Ospedale Papardo, Messina, Italy. comitato etico Ospedale Papardo, Messina, Italy; Divisione di Ematologia, Università di Messina comitato etico Ospedale di Messina, Italy; Ematologia and CTMO, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano comitato etico Ospedale Maggiore Policlinico di Milano, Italy; Dipartimento di Oncologia, Ospedale Civile, Noale, Venezia comitato etico Ospedale Civile, Noale, Italy; Oncoematologia Policlinico di Modena comitato etico provinciale di Modena, Italy; Divisione di Ematologia, Ospedale Cardarelli, Napoli comitato etico Ospedale Cardarelli, Napoli, Italy; Ematologia, CTMO, Azienda Ospedaliera Universitaria di Parma comitato etico Azienda Ospedaliera Universitaria di Parma, Italy; Dipartimento di Ematologia, Ospedale Santo Spirito, Pescara comitato etico Ospedale Santo Spirito, Pescara, Italy; Unità di Ematologia, Dipartimento di Onco-Ematologia, Guglielmo da Saliceto Hospital, Piacenza comitato etico Guglielmo da Saliceto Hospital, Piacenza, Italy; Unità di Ematologia, A.O. of Reggio Calabria comitato etico A.O. of Reggio Calabria, Italy; Unità Operativa di Ematologia, A.O.S. Maria Nuova, Reggio Emilia comitato etico A.O.S. Maria Nuova, Reggio Emilia, Italy; S.C. di Ematologia e Trapianto di Cellule Staminali IRCCS-CROB di Rionero in Vulture, Potenza comitato etico IRCCS-CROB di Rionero in Vulture, Italy; Dipartimento di Ematologia, Ospedale Nuovo Regina Margherita, Roma comitato etico Ospedale Nuovo Regina Margherita, Roma, Italy; Ematologia, A.O. Sant'Andrea, Università La Sapienza, Roma comitato etico A.O. Sant'Andrea, Roma, Italy; Divisione di Ematologia, Università La Sapienza, Roma comitato etico Università La Sapienza, Roma, Italy; Unità di Ematologia e Trapianto di Cellule Staminali, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo comitato etico IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Unità di Ematologia, Ospedale San Vincenzo, Taormina, comitato etico Ospedale San Vincenzo, Taormina, Italy;Unità di Ematologia, Ospedale San Nicola Pellegrino, Trani comitato etico Ospedale San Nicola Pellegrino, Trani, Italy; Centro di Riferimento Ematologico-Seconda Medicina, Azienda Ospedaliero-Universitaria, Ospedali Riuniti, Trieste comitato etico Ospedali Riuniti, Trieste, Italy; U.O. Oncologia Medica, Ospedale di Circolo Fondazione Macchi, Varese comitato etico Ospedale di Circolo Fondazione Macchi, Varese, Italy; Unità Operativa di Ematologia, Ospedale dell'Angelo, Venezia-Mestre comitato etico Ospedale dell'Angelo, Venezia-Mestre, Italy; Istituto di Ricovero e Cura a Carattere Scientifico Cà Granda-Maggiore Policlinico, Milano comitato etico Policlinico, Milano, Italy.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.684621/full#supplementary-material

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A Real-World Observation of Eltrombopag and Recombinant Human Thrombopoietin (rhTPO) in Lymphoma Patients With Chemotherapy Induced Thrombocytopenia

*Qiuhua Zhu†, Shimei Yang†, Wenbin Zeng, Mingjie Li, Zebing Guan, Lanlan Zhou, Hong Wang, Yanan Liu, Yanmin Gao, Shiqiu Qiu, Chaolun Chen, Huan Li, Shanshan Zheng, Yuemei Yuan, Hanling Zhang and Xueyi Pan**

Department of Hematology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangdong, China

This real-world, observational study aimed to assess and compare the clinical efficacy and safety of eltrombopag with recombinant human thrombopoietin (rhTPO) in the treatment of chemotherapy induced thrombocytopenia (CIT) in patients with lymphoma. One hundred and fifty-three patients who experienced grade 3 or 4 thrombocytopenia after chemotherapy for lymphoma were enrolled, 51 of which were treated with eltrombopag, 50 with rhTPO, and 52 patients with no drug treatment were served as the control group. The lowest platelet level and mean platelet counts at Day 5, Day 7, and Day 10 were significantly higher in both the eltrombopag group (P=.041,.003,.000,.000) and rhTPO group (P=.005,.005,.000,.000) than the control, but there was no difference between treatment with eltrombopag and rhTPO. Similarly, days required for the recovery of platelet counts to $\geq 50\times10^9$/L and $\geq 75\times10^9$/L were not different between the two treatment groups but significantly higher than the control group (P <.05). Rates of bleeding and platelet transfusion were all significantly reduced in patients treated with eltrombopag (P=.031,.032) or rhTPO (P=.017,.009) when compared to the control. Treatment-related adverse events (AEs) were reported in 7 (13.7%) and 6 (12.0%) patients in the eltrombopag and rhTPO groups, respectively, all being mild and transient in nature. In conclusion, both eltrombopag and rhTPO were effective and safe in the treatment of thrombocytopenia after chemotherapy for lymphoma.

Keywords: eltrombopag, recombinant human thrombopoietin (rhTPO), lymphoma, chemotherapy, thrombocytopaenia

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***Correspondence:**
Xueyi Pan
xypan88@163.com

†*These authors have contributed equally to this work and share first authorship*

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INTRODUCTION

Lymphoma is a malignant tumor originating from lymph nodes and (or) extranodal lymphoid tissues. The main symptoms include painless lymphadenopathy, hepatosplenomegaly, accompanying whole-body and multi-organ reactions such as fever, drenching night sweat, wasting, and itching (1). Myelosuppression, presented as different degrees of leukopenia, thrombocytopenia and anemia, is prevalent in patients with lymphoma who are undergoing chemotherapy (2). Chemotherapy-induced thrombocytopenia (CIT) not only increases the risk of hemorrhage, but also causes chemotherapy dose delays, dose reductions, or even treatment discontinuation that may result in prolonged hospitalization, increased medical costs, and reduced progression-free and overall survival (3–5).

At present, the treatment of CIT for lymphoma is very limited, which mainly include platelet transfusion and recombinant human interleukin-11 (rhIL-11). Platelet transfusion is the fastest and most effective treatment for severe CIT; however, as a rescue therapy, it is associated with temporary effectiveness, adverse reactions, and loss of response with repeated administrations (3, 6). rhIL-11 is the only platelet growth factor approved by the United States (US) Food and Drug Administration (FDA) and China National Medical Products Administration (NMPA) for CIT, but its use is severely restricted by the narrow therapeutic index and significant side effects including edema and arrhythmia (7). Therefore, novel treatment options are needed to improve the efficacy and safety outcomes of thrombocytopenia after chemotherapy for lymphoma.

Thrombopoietic agents were designed to stimulate the c-mpl receptor that leads to megakaryocyte maturation and platelet production (7). The rhTPO is a full-length glycosylated thrombopoietin prepared from Chinese hamster by recombinant DNA technology, which has a pharmacological effect similar to endogenous thrombopoietin (TPO) (8). It is the only thrombopoietin receptor agonist (TPO-RA) that receives market approval in China for the treatment of CIT (9, 10). Eltrombopag, as a chemically synthesized, orally available, small molecule, nonpeptide TPO-RA, has been approved for the treatment of chronic immune thrombocytopenia, hepatitis C virusrelated thrombocytopenia, and (refractory) severe aplastic anemia. Recent studies showed that eltrombopag played an anti-proliferative effect in hematologic malignancies, raising the possibility of its use in CIT treatment (11).

It was reported in several randomized, placebo-controlled phase I and II clinical trials that eltrombopag has achieved objective curative effect on thrombocytopenia during chemotherapy cycles, especially in advanced solid tumor patients receiving gemcitabine –based chemotherapy and patients with acute leukemia (6, 12–14). Currently, there's no study that assessed TPO-RAs for treatment of CIT in patients with lymphoma, and it is unknown whether the two TPO-RAs, rhTPO and eltrombopag, are comparable with regard to the clinical effectiveness and tolerability in CIT treatment. Using the data from a tertiary clinical practice in China, this large sample, observational study innovatively reviewed and compared the efficacy and safety profiles of eltrombopag to the market-approved rhTPO in the treatment of thrombocytopenia after chemotherapy for lymphoma.

MATERIALS AND METHODS

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. Between April 2017 and September 2020, patients with histopathologically confirmed lymphoma who also experienced grade 3 or 4 thrombocytopenia (platelet counts $<30\times10^9$/L) after chemotherapy (15) at the Hematology Department of our institution were enrolled. For the same patient who met the above criteria in more than one chemotherapy cycles, data of the earliest occurrence of PLT $< 30\times10^9$/L that were treated either with eltrombopag, rhTPO, or no drug treatment were included in this study. Exclusion criteria included tumors secondary to lymphoma and concomitant hemophagocytic syndrome. Patients with documented treatment history of eltrombopag or rhTPO after chemotherapy for lymphoma in other hospitals, concurrent treatment with both eltrombopag and rhTPO, eltrombopag and rhIL-11, or rhTPO and rhIL-11, were also excluded. The need for informed consent was waived by the committee.

One hundred and fifty-three lymphoma patients (90 males, 63 females) with CIT were consecutively enrolled in this study. Among them, 51 patients were treated with eltrombopag, 50 patients were treated with rhTPO, and 52 patients without drug treatment were selected as controls. Eltrombopag or rhTPO was initiated when platelet counts fell below 30×10^9/L after chemotherapy. The starting dose of eltrombopag was 50 mg daily. The dose was adjusted to 75 mg/day when the platelet counts decreased to less than 10×10^9/L. For patients who received rhTPO, daily injection of 15,000 U was given subcutaneously. In all patients, platelet transfusion was initiated when the platelet level was less than 20×10^9/L. If platelets increased to more than 100×10^9/L, or 50×10^9/L more than the baseline, treatment of eltrombopag or rhTPO was stopped.

Demographic, socioeconomic, and clinical characteristics were obtained from patients. Efficacy variables, including platelet counts at baseline and on day 3, 5, 7, 10, and the lowest platelet counts after treatment, days required for the recovery of platelet counts to $\geq50\times10^9$/L and $\geq75\times10^9$/L, respectively, duration of platelet counts $<50\times10^9$/L, platelet transfusion frequency and volume, and the modified World Health Organization (WHO) bleeding grades (10), were assessed. Adverse events (AEs) were monitored and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (15). Increased transaminases were defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×the upper limit of normal (ULN), and hyperbilirubinemia as total bilirubin ≥1.5×ULN.

Statistical Analysis

All statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY). Continuous variables were summarized by mean, standard deviation (SD), median, and range, while categorical variables by number and frequencies (%). Comparisons of continuous variables among the three groups were carried out using one-way analysis of variance (ANOVA) test continued with *post hoc* analysis (LSD-t test) or non-parametric test when data did not follow normal distribution

or homogeneity of variance. Categorical variables were compared using chi-square tests. P-values <.05 (two-sided) were considered statistically significant.

RESULTS

Demographics, Socioeconomics, and Baseline Clinical Characteristics

Median time of treatment was 8 (range 5-14) days for eltrombopag and 7 (range 3-14) days for rhTPO. Patients in the control group were followed for a median of 12 (range 7-17) days.

Table 1 shows the demographic, socioeconomic, and clinical features by treatment cohorts. The three groups did not differ with regard to gender, age, and ethnicity. No significant difference was observed for socioeconomic variables including type of medical insurance, monthly household income, education level, and occupation (P>.05). Clinical characteristics that include BMI, ECOG score, type of lymphoma, disease duration, bone marrow (BM) invasion, chemotherapy regimen, radiation therapy, pre-chemotherapy platelets, leukocyte counts, hemoglobin, and previous bleeding were also similar among the three groups.

Treatment Efficacy

Platelet Response

Mean platelet counts at baseline (Day 0) were not different among the three groups [eltrombopag: (23.96 ± 14.15) $\times10^9$/L, rhTPO: (23.92 ± 12.45) $\times10^9$/L, control: (24.15 ± 7.47) $\times10^9$/L; P=.711]. At Day 5, Day 7, and Day 10, significantly higher platelet counts were observed in both the eltrombopag group [(44.24 ± 17.51) $\times10^9$/L, (67.30 ± 29.90) $\times10^9$/L, (130.73 ± 70.57) $\times10^9$/L; P=.003,.000,.000] and rhTPO group [(48.92 ± 32.46) $\times10^9$/L, (82.11 ± 33.37) $\times10^9$/L, (147.02 ± 68.47) $\times10^9$/L; P=.005,.000,.000] than the control group [(33.73 ± 24.62) $\times10^9$/L, (41.58 ± 21.27) $\times10^9$/L, (75.67 ± 40.40) $\times10^9$/L], but there was no difference between treatment with eltrombopag and rhTPO (P=1.000,.187,.598; **Table 2** and **Figure 1**). Similar trend was reflected in the lowest platelet count, which was significantly lower in the control group than the eltrombopag group and the rhTPO group [(11.37 ± 7.66) $\times10^9$/L *vs* (15.94 ± 9.09) $\times10^9$/L, (18.28 ± 15.59) $\times10^9$/L; P=.041,.005], but no difference was seen between the two treatment groups (P=1.000).

Platelet counts <50$\times10^9$/L lasted for 6.25 ± 2.61 days in the eltrombopag group and 5.48 ± 2.62 days in the rhTPO group (P=.599), both of which were significantly shorter than the control group [(8.33 ± 3.98) days; P=.036,.000]. Days required for the recovery of platelet counts to 50$\times10^9$/L or higher was comparable between patients treated with eltrombopag and those with rhTPO (P=.508) but significantly shorter than the control group [(6.33 ± 2.31) days, (5.44 ± 2.57) days *vs* (8.32 ± 2.53) days; P=.001,.000]. The findings were similar with regard to the days required for the recovery of platelet counts to ≥75$\times10^9$/L (**Table 3**).

Bleeding Outcomes

WHO grade 1 bleeding occurred in 3 patients (5.9%) treated with eltrombopag, 3 patients (6.0%) with rhTPO, and 8 (15.4%) patients in the control group, whereas grade 2 or 3 bleeding occurred in 3 (5.9%) patients treated with eltrombopag, 2 (4.0%) patients with rhTPO, and 6 (11.5%) patients in the control group (**Figure 2**). No cases of grade 4 bleeding occurred during study. Rates of overall bleeding (any grades 1-4) were significantly higher in the control group than eltrombopag and rhTPO groups (26.9% *vs* 11.8%, 10.0%; P=.031,.017), yet there was no statistical difference between treatment with eltrombopag and rhTPO (P=.776; **Table 4**).

Platelet Transfusion

A total of 28 (54.9%), 25 (50.0%), and 39 (75.0%) patients received one unit of platelet transfusion in the eltrombopag group, the rhTPO group, and the control group, respectively. Compared to the two treatment groups, a significantly higher proportion of cases required platelet transfusion in the control group (P<.05; **Table 4**). Platelet transfusion rates did not differ between eltrombopag and rhTPO treatment (P=.622).

Safety and Tolerability

Seven patients (13.7%) experienced AEs that may be related to eltrombopag treatment, including 3 cases of elevated transaminase (5.9%) and 1 case each (2.0%) of hyperbilirubinemia, fever, fatigue, and dizziness. Six patients (12.0%) experienced AEs that may be related to rhTPO treatment, including 2 cases of fever (4.0%) and 1 case each (2.0%) of fatigue, dizziness, diarrhea, and muscle aches. All these AEs were mild and transient in nature. The elevation of transaminase and blood bilirubin in the eltrombopag group were resolved after a short-term liver protection treatment, while the other AEs were relieved spontaneously without special treatment. No serious AEs were reported. Overall, eltrombopag and rhTPO were well tolerated in our study (**Table 5**).

DISCUSSION

In China, rhTPO was recommended for the treatment of severe CIT and as a prophylactic option in cancer patients with high risk of bleeding after chemotherapy (9, 10). The efficacy and safety of rhTPO to treat CIT in patients with solid tumor have been well demonstrated in previous studies (16, 17). Eltrombopag was reported as an effective agent to maintain platelet level, reduce bleeding episodes and transfusion requirements, and alleviate chemotherapy dose reductions and delays without compromising patient safety in a number of small-sample, early phase trials (6, 12–14, 18–21). Due to limited data available, eltrombopag has not been approved for the treatment of CIT; however, in view of the difficulties of CIT treatment and seriousness of bleeding consequences, it is considered as an alternative therapeutic option for use in patients with poor response to rhTPO (10). This is the first study to systematically evaluate and compare the effectiveness and safety of eltrombopag *versus* rhTPO for treatment of CIT in patients with lymphoma. Based on a large cohort of patients, our findings provide summarized experience in a real-world clinical practice.

Cytotoxic drugs used in chemotherapy can lead to increased platelet destruction, reduced platelet production, and abnormal platelet distribution that result in thrombocytopenia (22). TPO-

TABLE 1 | Demographic, socioeconomic, and baseline characteristics.

	Eltrombopag (N=51)	rhTPO (N=50)	Control (N=52)	P value[a]
Male, n (%)	29 (56.9)	30 (60.0)	31 (59.6)	.941
Age (years),				
Mean ± SD	49.1 ± 18.7	50.8 ± 15.3	48.3 ± 18.2	.865
Range	15-86	25-87	17-80	
Ethnic group, n (%)				1.000[b]
Han	51 (100.0)	50 (100.0)	51 (98.1)	
Others	0 (0.0)	0 (0.0)	1 (1.9)	
Medical insurance, n (%)				.863[b]
Urban employees' basic medical insurance	10 (19.6)	13 (26.0)	15 (28.8)	
Urban residents' basic medical insurance	17 (33.3)	19 (38.0)	12 (23.1)	
New rural cooperative medical system	7 (13.7)	5 (10.0)	9 (17.3)	
Mixed medical insurance[c]	4 (7.8)	2 (4.0)	2 (3.8)	
Full coverage[d]	2 (3.9)	4 (8.0)	3 (5.8)	
Others[e]	3 (5.9)	3 (6.0)	4 (7.7)	
Uninsured	8 (15.7)	4 (8.0)	7 (13.5)	
Household income (¥/month)[f], n (%)				.949[b]
<5000	18 (35.3)	14 (28.0)	19 (36.5)	
5000-10000	10 (19.6)	15 (30.0)	15 (28.8)	
10001-15000	6 (11.8)	8 (16.0)	5 (9.6)	
15001-20000	9 (17.6)	7 (14.0)	8 (15.4)	
>20000	5 (9.8)	3 (6.0)	3 (5.8)	
Unknown[g]	3 (5.9)	3 (6.0)	2 (3.8)	
Education level, n (%)				.606
Primary school or lower	17 (33.3)	15 (30.0)	22 (42.3)	
Middle school	14 (27.5)	13 (26.0)	10 (19.2)	
High school	12 (23.5)	15 (30.0)	9 (17.3)	
College or above	8 (15.7)	7 (14.0)	11 (21.2)	
Occupation, n (%)				.718
Manual workers	6 (11.8)	10 (20.0)	8 (15.4)	
Agricultural workers	9 (17.6)	6 (12.0)	10 (19.2)	
Self-employed	14 (27.5)	8 (16.0)	9 (17.3)	
Managers and professionals	10 (19.6)	11 (22.0)	14 (26.9)	
Unemployed	12 (23.5)	15 (30.0)	11 (21.2)	
BMI (kg/m^2), mean (range)	21.1 (17.5-26.6)	21.0 (17.1-26.1)	20.6 (15.4-27.9)	.521
ECOG score, mean (range)	2.9 (2-4)	2.7 (2-4)	2.9 (2-4)	.063
Time since diagnosis of lymphoma (months), mean (range)	16.0 (1-120)	18.0 (1-60)	14.0 (1-72)	.856
Type of lymphoma, n (%)				1.000[b]
DLBCL	28 (54.9)	26 (52.0)	28 (53.9)	
T or B lymphoblastic lymphoma	7 (13.7)	7 (14.0)	8 (15.4)	
NK/T-cell lymphoma	5 (9.8)	5 (10.0)	4 (7.7)	
PTCL	3 (5.9)	4 (8.0)	4 (7.7)	
Burkitt lymphoma	6 (11.8)	6 (12.0)	5 (9.6)	
Other types[h]	2 (3.9)	2 (4.0)	3 (5.8)	
Bone marrow invasion of lymphoma, n (%)	5 (9.8)	5 (10.0)	6 (11.5)	.952
Chemotherapy, n (%)				1.000[b]
CHOP or CDOP ± R	23 (45.1)	22 (44.0)	25 (48.1)	
R-EPOCH	3 (5.9)	3 (4.0)	3 (5.8)	
R-CODOX-M or R-IVAC	6 (11.8)	6 (14.0)	5 (7.7)	
CAM	3 (5.9)	4 (8.0)	4 (7.7)	
VDLP	4 (7.8)	3 (6.0)	4 (7.7)	
P-Gemox	5 (9.8)	5 (10.0)	4 (9.6)	
DICE	4 (7.8)	4 (8.0)	3 (5.8)	
Other chemotherapy[i]	3 (5.9)	3 (6.0)	4 (7.7)	
Prior chemotherapy regimens, mean (range)	6.1 (1-20)	6.6 (1-19)	6.9 (1-16)	.518
Radiation therapy, n (%)	3 (5.9)	3 (6.0)	2 (3.9)	.860
Platelet count before chemotherapy ($\times 10^9$/L)				
Mean ± SD	135.7 ± 129.1	130.3 ± 78.7	134.7 ± 87.1	.512
Range	5-625	7-309	8-370	
Leukocyte count ($\times 10^9$/L)				
Mean ± SD	2.5 ± 2.7	2.5 ± 2.5	2.6 ± 3.5	.469
Range	0.14-11.19	0.05-12.11	0.08-16.54	

(Continued)

TABLE 1 | Continued

	Eltrombopag (N=51)	rhTPO (N=50)	Control (N=52)	P value[a]
Hemoglobin (g/L)				
Mean ± SD	75.0 ± 18.0	78.7 ± 17.7	78.7 ± 22.7	.457
Range	44-138	45-115	40-149	
Previous bleeding[j], n (%)	2 (3.9)	3 (6.0)	2 (3.8)	.798

BMI, body mass index; CAM, cyclophosphamide, cytarabine, mercaptopurine; CDOP ± R, (cyclophosphamide, vincristin, prednisone, adriamycin/liposomal adriamycin) ± rituximab; DICE, dexamethasone, ifosfamide cisplatin etoposide; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; NK/T-cell lymphoma, Natural killer/T-cell lymphoma; P-Gemox, peaspartase, gemcitabine, oxaliplatin; PTCL, peripheral T-cell lymphoma; R-CODOX-M, tuximab, cyclophosphamide, vincristine, adriamycin, methotrexate; R-IVAC, tuximab, ifosfamide, etoposide, arabinoside glycoside; VDLP, prednisone, daunorubicin or liposomal adriamycin, vincristine, pegaspase.

[a]*P value compares baseline characteristics among three groups.*

[b]*Using Fisher's exact test in R*C table Chi-Square Test.*

[c]*Two or more insurances, normally indicating the basic insurance plus other supplementary insurances in China.*

[d]*Medical costs can be almost fully covered.*

[e]*Other single insurance.*

[f]*¥5000 equals to US$775, ¥5000-10000 equals to US$775-1550, ¥10001-15000 equals to US$1550-2325, ¥15001-20000 equals to US$2325-3100, ¥20000 equals to US$3100.*

[g]*Patients either refused to answer the question or did not know the answer.*

[h]*Other types of lymphoma include marginal area lymphoma, follicular lymphoma and mantle cell lymphoma.*

[i]*Other chemotherapy include GDP (gemcitabine, cisplatin, dexamethasone), BR (bendamustine, rituximab), and R+MTX (rituximab, methotrexate).*

[j]*WHO bleeding grades 1 or 2.*

RAs were designed as mimics to endogenous TPO that regulates the whole process of megakaryopoiesis and promotes platelet production (3, 23, 24). rhTPO, as the first generation TPO-RA, was shown to be effective in alleviating and shortening the duration of CIT at a daily dose of 15,000 U in our patients with lymphoma. Eltrombopag is the second generation, non-peptide TPO-RA that binds to the transmembrane domain of the thrombopoietin receptor and increases platelet counts by stimulating megakaryocytes proliferation from BM progenitor cells (25). Unlike rhTPO, eltrombopag does not compete with or elicit an antibody response to endogenous TPO (26). At a starting dose of 50 mg and adjustable daily dose during treatment, our results indicated that eltrombopag was comparable to rhTPO in terms of the efficacy to increase platelet counts and nadir platelet counts, and reduce the time required for platelet recovery.

In a study of rhTPO for the treatment of CIT in patients with solid tumor, time required for platelet levels recovered to $\geq 75\times10^9$/L and $\geq 100\times10^9$/L were 4.79 ± 3.67 and 6.93 ± 3.61 days, respectively, among 72 patients who had a post-chemotherapy platelet count of 55.9 ± 16.0 ($\times10^9$/L) (27). Another randomized, cross-over, self-controlled trial of rhTPO reported a mean of 2.5 ± 3.9, 10.3 ± 8.7, and 15.9 ± 10.5 days with respect to the duration of thrombocytopenia (platelet counts $<50\times10^9$/L), days required for the recovery of platelet counts to $\geq 75\times10^9$/L and $\geq 100\times10^9$/L, respectively (17). Our findings on the days

TABLE 2 | Platelet counts among the three groups.

	Eltrombopag (A)	rhTPO (B)	Control (C)	P value			
				Overall[a]	A *vs* C	B *vs* C	A *vs* B
Day 0, N	51	50	52				
Platelet count ($\times10^9$/L)	23.96 ± 14.15	23.92 ± 12.45	24.15 ± 7.47	.711	/	/	/
Day 3, N	51	50	52				
Platelet count ($\times10^9$/L)	25.24 ± 11.12	25.94 ± 10.08	25.21 ± 5.70	.613	/	/	/
Day 5, N	51	50	52				
Platelet count ($\times10^9$/L)	44.24 ± 17.51	48.92 ± 32.46	33.73 ± 24.62	.001	.003	.005	1.000
Day 7, N	46	45	50				
Platelet count ($\times10^9$/L)	67.30 ± 29.90	82.11 ± 33.37	41.58 ± 21.27	.000	.000	.000	.187
Day 10, N	44	44	45				
Platelet count ($\times10^9$/L)[b]	130.73 ± 70.57	147.02 ± 68.47	75.67 ± 40.40	.000	.000	.000	.598
The lowest platelet count ($\times10^9$/L)[b]	15.94 ± 9.09	18.28 ± 15.59	11.37 ± 7.66	.004	.041	.005	1.000
P1[c]	0.614	0.375	0.419				
P2[d]	0.000	0.000	0.113	/	/		/
P3[e]	0.000	0.000	0.000	/	/		/
P4[f]	0.000	0.000	0.000	/	/		/

Data are mean ± SD.

[a]*P value compares platelet counts among the three groups.*

[b]*Defined as the lowest platelet count observed after treatment initiation (or after enrolment for patients of the control group).*

[c]*P value compares platelet counts between Day 0 and Day 3.*

[d]*P value compares platelet counts between Day 0 and Day 5.*

[e]*P value compares platelet counts between Day 0 and Day 7.*

[f]*P value compares platelet counts between Day 0 and Day 10.*

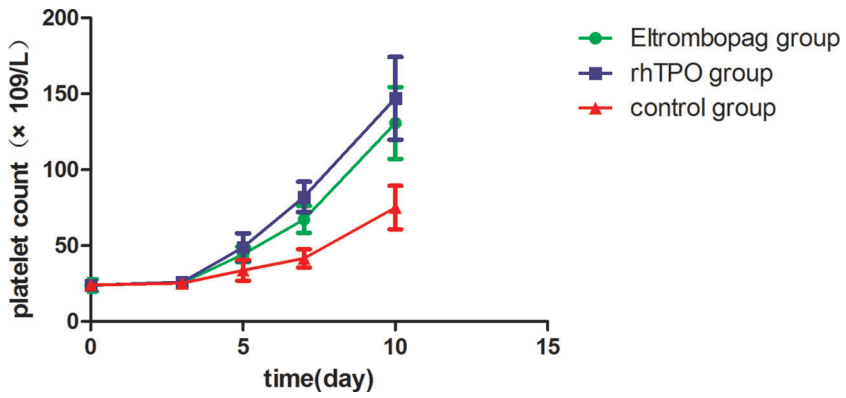

FIGURE 1 | Mean platelet counts during treatment period among the three groups. Error bars indicate 95% CI of the mean. CI, confidence interval.

TABLE 3 | Platelet response among the three groups.

	Eltrombopag (A)	rhTPO (B)	Control (C)	P value			
				Overall[a]	A *vs* C	B *vs* C	A *vs* B
Platelet count <50×10^9/L, N	51	50	52				
Lasting days	6.25 ± 2.61	5.48 ± 2.62	8.33 ± 3.98	.001	.036	.000	.599
Platelet count ≥50×10^9/L, N	48	48	50				
Required days	6.33 ± 2.31	5.44 ± 2.57	8.32 ± 2.53	.000	.001	.000	.508
Platelet count ≥75×10^9/L, N	46	46	47				
Required days	7.43 ± 2.54	6.56 ± 3.78	9.61 ± 2.55	.000	.004	.000	.451

Data are mean ± SD.

[a]*P value compares data among the three groups.*

required for the recovery of platelet counts to ≥75×10^9/L [eltrombopag (7.43 ± 2.54) days, rhTPO (6.56 ± 3.78) days; **Table 3**] were comparable to the aforementioned studies, yet the platelet counts <50×10^9/L lasting days were observed to be longer in either of our treatment groups [eltrombopag (6.25 ± 2.61) days, rhTPO (5.48 ± 2.62) days; **Table 3**]. This might be explained by the presence of more severe thrombocytopenia at baseline in our patient population, as subgroup analysis of severe CIT in the study of Bai et al. (16) reported longer duration of platelet counts <50×10^9/L (median 11 days) and that median time required for the recovery of platelet counts to ≥75×10^9/L and ≥100×10^9/L were 21 and 24 days, respectively. Due to the real-world nature of this

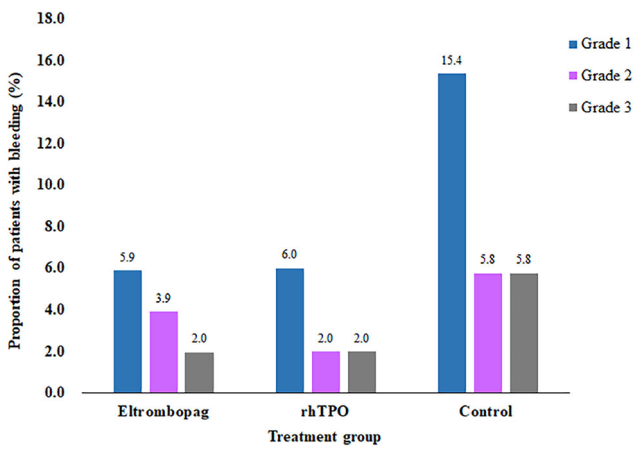

FIGURE 2 | Proportion of bleeding by WHO grades among the three groups.

TABLE 4 | Bleeding by WHO grades and platelet transfusion after treatment.

	Eltrombopag (A)	rhTPO (B)	Control (C)	P value			
	(N=51)	(N=50)	(N=52)	Overall[a]	A *vs* C	B *vs* C	A *vs* B
Any bleeding (Grades 1-4), n (%)	6 (11.8)	5 (10.0)	14 (26.9)	.019	.031	.017	.776
Platelet transfusion, n (%)	28 (54.9)	25 (50.0)	39 (75.0)	.023	.032	.009	.622

[a]*P value compares data among the three groups.*

study, some patients gave up the treatment due to financial burden such that we did not have adequate data to calculate days required for the recovery of platelet counts to ≥100×10^9/L. Well controlled, prospective studies will be conducted in the future to observe platelet response in a longer period with more comprehensive follow-up schedules.

CIT increases the risk of bleeding that may lead to dose adjustment and delayed treatment schedules with chemotherapy (22, 28). It was studied in cancer patients after chemotherapy that when platelet counts fell below 50×10^9/L, probability of any bleeding ranges between 0-9.6%; however, the risk doubles when platelet counts <20×10^9/L (10.1-17.7%) and continues to double when <10×10^9/L (18.4-40.1%) (7). Our study revealed that eltrombopag or rhTPO treatment was associated with significantly reduced rates of any bleeding and clinically significant bleeding (grade 2-4) when compared to the control group. In a study of patients with immune thrombocytopenia (ITP), regardless of platelet response, a reduced proportion of bleeding episodes were observed during eltrombopag treatment, which was considered to be correlated with the platelet adhesion effect enhanced by eltrombopag (29). Apart from a low baseline platelet count, a previous bleeding episode, BM metastasis, poor ECOG score (≥2), previous radiotherapy, and special chemotherapy regimen (cisplatin, carboplatin, gemcitabine, carmustine, or lomustine) were all related to elevated risk of bleeding in patients with CIT (30). Our findings showed no difference of bleeding rates between eltrombopag and rhTPO treatment groups; meanwhile, baseline predictors of bleeding were similar between the two groups, indicating that eltrombopag can be as effective as rhTPO with respect to reducing the risk and severity of bleeding events associated with CIT in patients with lymphoma.

Platelet transfusion is the elective procedure for prevention and treatment of bleeding in patients with hematological disorders, chemotherapy or hematopoietic stem cell transplantation. In case of an active bleeding, it is the first line of therapy if bleeding is considered associated with CIT (31). Prophylactic platelet transfusions are indicated when bleeding occurs or when platelet counts are <10×10^9/L (or <20×10^9/L if the patient is febrile) (3). However, repeated transfusions may lead to problems such as refractoriness, alloimmunization, febrile reactions, and transmission of infectious agents (7, 32, 33). Our study revealed significantly lower frequencies and volume of platelet transfusion in patients treated with eltrombopag or rhTPO when compared to the controls, but they were not different between eltrombopag and rhTPO treatment. When rhTPO was administered to patients with gynecologic cancer who developed severe thrombocytopenia after carboplatin chemotherapy, the need for platelet transfusion was reduced from the pre-treatment rate of 75% to 25% (P=.013) (34). Since it requires for about 5 days for platelet counts to rise after administering TPO-RAs, platelet transfusion, if indicated, should be used together with TPO-RAs (3). By stimulating platelet production that eventually leads to elevated platelet counts (24, 25), TPO-RAs such as eltrombopag and rhTPO can reduce the need for platelet transfusion due to bleeding or low platelet counts, thus lowering the overall risk of transfusion reactions and non-response.

TABLE 5 | Treatment-related adverse events.

	Eltrombopag (N=51)	rhTPO (N=50)
Any AE, n (%)	7 (13.7)	6 (12.0)
Elevated transaminase	3 (5.9)	0 (0.0)
Hyperbilirubinemia	1 (2.0)	0 (0.0)
Fever	1 (2.0)	2 (4.0)
Fatigue	1 (2.0)	1 (2.0)
Dizziness	1 (2.0)	1 (2.0)
Diarrhea	0 (0.0)	1 (2.0)
Muscle aches	0 (0.0)	1 (2.0)

In general, eltrombopag and rhTPO were well tolerated as all of the treatment-related AEs observed in our study were mild and in accordance with the safety profiles of previous reports (16, 19, 33, 35). Hepatobiliary toxicity is a major concern associated with eltrombopag use in patients of east Asian descent (20, 36). Elevated transaminase and hyperbilirubinemia occurred in 5.9% and 2.0% of our patients treated with eltrombopag, respectively. All these hepatobiliary abnormalities were mild and resolved after a short-term liver protection treatment. In a phase II study assessing the efficacy and safety of eltrombopag in patients receiving carboplatin/paclitaxel for treatment of advanced solid tumors, elevated aminotransferase ≥3 times the ULN and total bilirubin ≥1.5 times the ULN were 11% and 18% in the 50 mg group, 17% and 14% in the 75 mg group, and 13% and 23% in the 100 mg group (12). Hepatobiliary AEs were reported in 19% patients in a phase 1/2 trial assessing the safety and tolerability of eltrombopag for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukemia, including 8% with grade 3 or higher events (14). Our rates and severity of elevated hepatobiliary values were lower than these findings, suggesting that eltrombopag can be safely prescribed to treat CIT in patients with lymphoma.

Due to the good tolerability and efficacy to reduce the incidence and duration of thrombocytopenia, rhTPO was proposed as a second-line treatment option for CIT by the

Chinese Society of Clinical Oncology (9, 10). Our preliminary findings on a relatively large sample of patients with lymphoma suggested that eltrombopag had comparable efficacy and safety with rhTPO for treatment of CIT. Injection site reactions such as pain and ecchymosis are commonly expected in patients treated with rhTPO as the drug was approved for subcutaneous use. Eltrombopag, developed as an oral preparation, allows to avoid injection-related reactions and is considered more convenient for patients to administer. Well-designed medical cost research studies conducted in a wider geographic area of China are needed to further support if eltrombopag, when compared to rhTPO, is also a cost-effective treatment option to lymphoma patients with CIT.

There are several limitations in our study: first, because of retrospective and observational design, we are unable to evaluate how eltrombopag and rhTPO administration help to maintain scheduled dosing and treatment cycles of chemotherapy. Secondly, as this is a single-center study, generalizability of study results to other population should be made with caution. Thirdly, due to the inclusion of multiple chemotherapy regimens, it may not be possible to establish the impact of eltrombopag and rhTPO treatment on CIT after a specific regimen. Also, prognostic outcomes, such as progression-free and overall survival, cannot be explored owning to the relatively short duration of follow-up in the current study. Further prospective, interventional studies are needed to investigate the long-term effectiveness and safety of eltrombopag and rhTPO for treatment of CIT in patients with lymphoma that receive myelosuppressive chemotherapy, and to identify the optimal dose and dosing frequencies.

In conclusion, both eltrombopag and rhTPO were effective in the treatment of thrombocytopenia after chemotherapy for lymphoma with respect to the elevated platelet counts, prolonged periods of platelet response, reduced bleeding episodes and platelet transfusion requirements. Eltrombopag was well tolerated in real-world setting without raising additional concerns for hepatobiliary toxicity. Evidence from this large cohort study supports the use of eltrombopag as an alternative treatment option for CIT in lymphoma patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

QZ, SY, and XP conceptualized and designed the study. QZ and SY collected and analyzed data, and drafted the paper. LZ, WZ, and XP carried out the data analysis, and revised the paper. All authors contributed to the article and approved the submitted version.

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Patterns of Tyrosine Kinase Inhibitor Utilization in Newly Treated Patients With Chronic Myeloid Leukemia: An Exhaustive Population-Based Study in France

Marie Pajiep[1,2], *Cécile Conte*[1], *Françoise Huguet*[3], *Martin Gauthier*[3], *Fabien Despas*[1,2†] *and Maryse Lapeyre-Mestre*[1,2*†]

[1] Service de Pharmacologie Médicale et Clinique, Centre Hospitalier Universitaire de Toulouse, Toulouse, France, [2] Equipe PEPSS (Pharmacologie en Population, cohorteS, biobanqueS), Centre d'Investigation Clinique 1436, INSERM, Université de Toulouse 3, Toulouse, France, [3] Département d'Hématologie, Institut Universitaire du Cancer de Toulouse, Centre Hospitalier Universitaire (CHU) de Toulouse, Toulouse, France

We analyzed demographic characteristics, comorbidities and patterns of treatment with tyrosine kinase inhibitors (TKIs) in a cohort of 3,633 incident cases of chronic myeloid leukemia (CML) identified across France from 1 January 2011 to 31 December 2014. Patients were identified through a specific algorithm in the French Healthcare Data System and were followed up 12 months after inclusion in the cohort. The estimated incidence rate of CML for this period in France was 1.37 per 100,000 person-years (95% Confidence Interval 1.36-1.38) and was higher in men, with a peak at age 75-79 years. At baseline, the median age of the cohort was 60 years (Inter Quartile Range 47-71), the Male/Female ratio was 1.2, and 25% presented with another comorbidity. Imatinib was the first-line TKI for 77.6% of the patients, followed by nilotinib (18.3%) and dasatinib (4.1%). Twelve months after initiation, 86% of the patients remained on the same TKI, 13% switched to another TKI and 1% received subsequently three different TKIs. During the follow-up, 23% discontinued and 52% suspended the TKI. Patients received a mean of 16.7 (Standard Deviation (SD) 9.6) medications over the first year of follow-up, and a mean of 2.7 (SD 2.3) concomitant medications on the day of first TKI prescription: 24.4% of the patients received allopurinol, 6.4% proton pump inhibitors (PPI) and 6.5% antihypertensive agents. When treatment with TKI was initiated, incident CML patients presented with comorbidities and polypharmacy, which merits attention because of the persistent use of these concomitant drugs and the potential increased risk of drug-drug interactions.

Keywords: chronic myeloid leukemia, incidence, polypharmacy, comorbidities, first line treatment, tyrosine kinase inhibitors (TKI)

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Edited by:
Claudia Vener,
University of Milan, Italy

Reviewed by:
Ciprian Tomuleasa,
Iuliu Haţieganu University of Medicine and Pharmacy, Romania
Giovanni Martinelli,
University of Bologna, Italy
Gabriele Gugliotta,
University of Bologna, Italy

****Correspondence:***
Maryse Lapeyre-Mestre
maryse.lapeyre-mestre@univ-tlse3.fr

†These authors have contributed equally to this work and share last authorship

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the Philadelphia chromosome which is the source of a Bcr-Abl1 hybrid protein with constitutive tyrosine-kinase activity (1). Published data on the annual incidence of CML varies from as low as 0.4/100,000 persons in some non-Western countries to 1.75/100,000 in the USA (2–5). Reports from several European CML registries consistently show a crude annual incidence of 0.7–1.0/100,000 inhabitants, a median age at diagnosis of 57–60 years and a Male/Female (M/F) ratio of 1.2–1.7 (2, 6, 7). In France, some studies based on specific cancer registries for the period 1980-2009 estimate the CML incidence rate between 0.95 and 1.14 per 100,000 person-years with a mean age of 54,7 years and a M/F ratio of 1.22 to 1.36 (8, 9).

A more recent study based on a health insurance database estimated the prevalence of CML in France at 16.3 (95% Confidence Interval (95%CI): 16.0-16.6) per 100,000 inhabitants, with a median age of 63 years (Inter Quartile Range (IQR) 51-73) (10).

Since the 2000s, drugs specifically targeting the tyrosine-kinase activity of the BCR-ABL1 oncoprotein (Tyrosine Kinase Inhibitors: TKIs) have been on the market (11). The first to appear was imatinib, approved by the European Medicines Agency in November 2001 (12). Since then second (dasatinib in November 2006, nilotinib in November 2007, bosutinib in August 2013) and third generation (ponatinib in July 2013) TKIs have been approved. They were approved initially for imatinib-resistant or intolerant patients, and then dasatinib and nilotinib subsequently received approval as first-line treatments of chronic phase CML in 2010 (13). The prescription of TKI (all oral) is therefore systematic in any newly diagnosed case of CML (14, 15) and their advent has changed the prognosis of CML from hospital management in a life-threatening context to ambulatory management in patients whose average survival is now only slightly different from that of the general population (11, 15). Health insurance databases offer the opportunity to study real-life drug safety in general population (16–18). However, few studies describe the management of CML patients by TKI in the French general population since they have been available (19, 20). The SNDS (in French, "*Système National des Données de Santé*", French Healthcare Data System; https://www.snds.gouv.fr/SNDS/) was created in the early 2000s, and includes healthcare data from the entire French population (≈66 million inhabitants) (21–24). Based on these exhaustive national data, the aim of the study was to characterize the patterns of TKI utilization among incident CML patients, with a focus on the type of TKI in first-line therapy. The secondary objectives were to describe comorbidities and comedications at the time of TKI initiation.

MATERIALS AND METHODS

Data Source

The SNDS is an electronic healthcare database which centralizes the reimbursement data for over 98% of the French population (21, 24). Health insurance is mandatory in France with no exclusion according to professional activity or incomes. The SNDS contains individualized, anonymous comprehensive data on patient demographics, healthcare reimbursement and eligibility for full reimbursement of health care expenses related to long-term diseases (LTD) (in French "*Affections de Longue Durée*"). Available data include year of birth; gender; location; coverage by the CMU-c (in French "*Couverture Maladie Universelle*", a complementary universal health coverage system for people with low incomes); vital status and date of death. It also include reimbursed outpatient healthcare expenditures such as medical visits, laboratory tests, drugs dispensed with the date and quantity supplied identified with the Anatomic Therapeutic and Chemical (ATC) classification; hospital discharge summaries including all diagnoses (main, related and up to 10 associated diagnoses) coded with the International Classification of Diseases, 10th revision (ICD10) (25). There is a list of LTD, which includes 3448 ICD10 codes. Patients registered for these diseases benefit from full coverage for all medical expenses related to the disease for a period defined in the database. LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system. The SNDS has been widely used to conduct large epidemiologic studies and further information regarding the organization has already been described elsewhere (26–28). Access to the exhaustive database is done under permissions dependent on the type of data requested, with a particular attention to avoid any re-identification. For this study, data available at the time of extraction covered the period 2010-2015.

Study Design and Population Selection

We designed a retrospective national cohort study of all newly diagnosed patients for whom specific treatment was initiated with one of the TKIs approved in Europe for CML (imatinib, dasatinib, nilotinib, bosutinib and ponatinib). We selected all patients identified in the SNDS between 1 January 2010 and 31 December 2015 with at least one reimbursement for any of these TKIs and aged > 18 years old.

We used a specific algorithm to identify incident CML patients who were treated between 1 January 2011 (in order to have at least 12 months before TKI initiation for the identification of comorbidities) and 31 December 2014 (to have at least 12 months of follow-up for the last patients included, to investigate patterns of TKI utilization). The initial algorithm was previously used in a pilot study based on regional data extracted from the SNDS (27).

Patients were defined as incident CML patients with the following conditions:

- First reimbursement for a TKI between 01/01/2011 and 31/12/2014

AND

- First ICD10 codes for CML (C92.1 or C92) identified during a hospital stay or with LTD status between 01/01/2011 and 31/12/2014. Any mention of these codes before or after this period led to the patient's exclusion. For a patient with an ICD10 code of CML (hospital or LTD) before the first reimbursement of TKI, the date of CML incidence was the date of appearance of the ICD10 code.

AND

- At least two dispensations of TKI

Patients could be treated with TKI not for a CML, but for another indication (either approved, or off-label). These diseases were identified through a list of different diagnosis codes and specific drugs presented in detail in **Supplementary File 1**. Patients with at least one of these other conditions were excluded.

In order to validate the suitability of this algorithm, we extracted a randomly selected sample of 20 electronic files reviewed independently by two hematologists. For each selected patient, reviewers verified the standardized patient form with demographic characteristics and sequences of care (12 months before and 12 months after the use of a TKI for each patient). Inter-rater concordance between the classification obtained by the algorithm and the opinion of the two reviewers was estimated and considered as good if ≥ 80%.

Baseline Comorbidities and Care Consumption

Baseline comorbidities were those included in the Charlson's comorbidities index (CCI), and registered with ICD10 diagnosis codes in the 12 months before index date. Consumption of care was described by the characterization of drugs, hospital stays and LTD conditions in the 12 months preceding inclusion.

The comorbidities were evaluated by the CCI constructed from the SNDS data. A previous study based on the application of this index in the SNDS has shown its validity in predicting one-year mortality for the French population (29). As all patients in the cohort had incident CML by definition, the CML entity in the cancer class was not included in the index calculation. Baseline comorbidities were presented as the aggregate comorbidities measure (CCI), categorized as 0, 1, 2 or more than 2 comorbidities, and as individual comorbidities included in the CCI.

Consumption of care in the 12 months preceding inclusion was described by the characterization of drugs (at least one reimbursement of drugs categorized with the ATC classification) and by the number of hospital stays and LTD conditions.

Treatment Patterns During the First Year of Follow-Up

In order to describe treatment patterns we selected patients with at least two distinct dispensations of TKI within the first year of follow-up.

TKIs: Drugs of interest were exhaustively identified in the SNDS, as they are universally reimbursed. We described first-line TKI treatment (first TKI reimbursed) and classified them as first (imatinib), second (nilotinib, dasatinib, bosutinib) and third generation (ponatinib) (12). TKI sequences of treatment and switches between first and second generations within 12 months following the inclusion were also described.

Comedications: We described the number and distinct type of drugs prescribed to each patient (within 12 months after the inclusion).

Statistical Analyses

The analyses were performed with SAS V9.4® software. A descriptive analysis of the demographic and medical characteristics of the entire cohort was performed with the usual indicators: means and standard deviations (SDs) or medians and interquartile ranges (IQRs) depending on their normality, and absolute and relative frequencies. Eventually, patients who died after their inclusions were identified with their vital status and date of death (not cause of death, which was not available in the SNDS at the time of extraction). The overall survival probability was estimated through the mean of Kaplan Meier curves according to age and CCI. The overall cumulative incidence rate of newly treated CML patients and its 95%CI was estimated as a whole and by age group, gender and in the 22 main administrative regions of France.

For the cumulative incidence calculations, we use the following formula:

$$I_c = \frac{m[t, t+\Delta t]}{N_0[t, t+\Delta t]}$$

m = number of incident cases during all the period

N_0 = number of people not ill at the beginning of the period

Δ_t = Time period

We used as denominator the French population data provided by the INSEE (in French "*Institut National de la Statistique et des Etudes Economiques*", French Institute of Statistics and Economic Studies). A binary logistic regression was performed to assess relationship between interruption of treatment and switching with interruption as the dependent variable. In order to validate the descriptive results for the incident CML population that we constructed using our algorithm, we performed a sensitivity analysis by selecting only patients with an incident myeloid leukemia LTD code (C92) between 2011 and 2014.

Ethical Requirements

All ethical authorizations were obtained (*Institut des Données de Santé* approval, no. 165, November 24, 2015; *Commission Nationale de l'Informatique et des Libertés* authorization, no. DE-2015-119, December 24, 2015). The data recorded in this study were processed in accordance with French Data Protection Act No. 78-17 of 6 January 1978, amended by Act No. 2004-801 of 6 August 2004. Final data were extracted and made available for analysis in January 2018.

RESULTS

Population Selection and General Characteristics of the Cohort

Between 1 January 2010 and 31 December 2015, 20,592 patients had at least one TKI reimbursement for CML. After the selection process (**Figure 1**), we identified a cohort of 3,633 patients who started TKI treatment and were diagnosed with CML between 1 January 2011 and 31 December 2014 in France. At the index date, patients had a median age of 60 years [IQR: 47-71], with

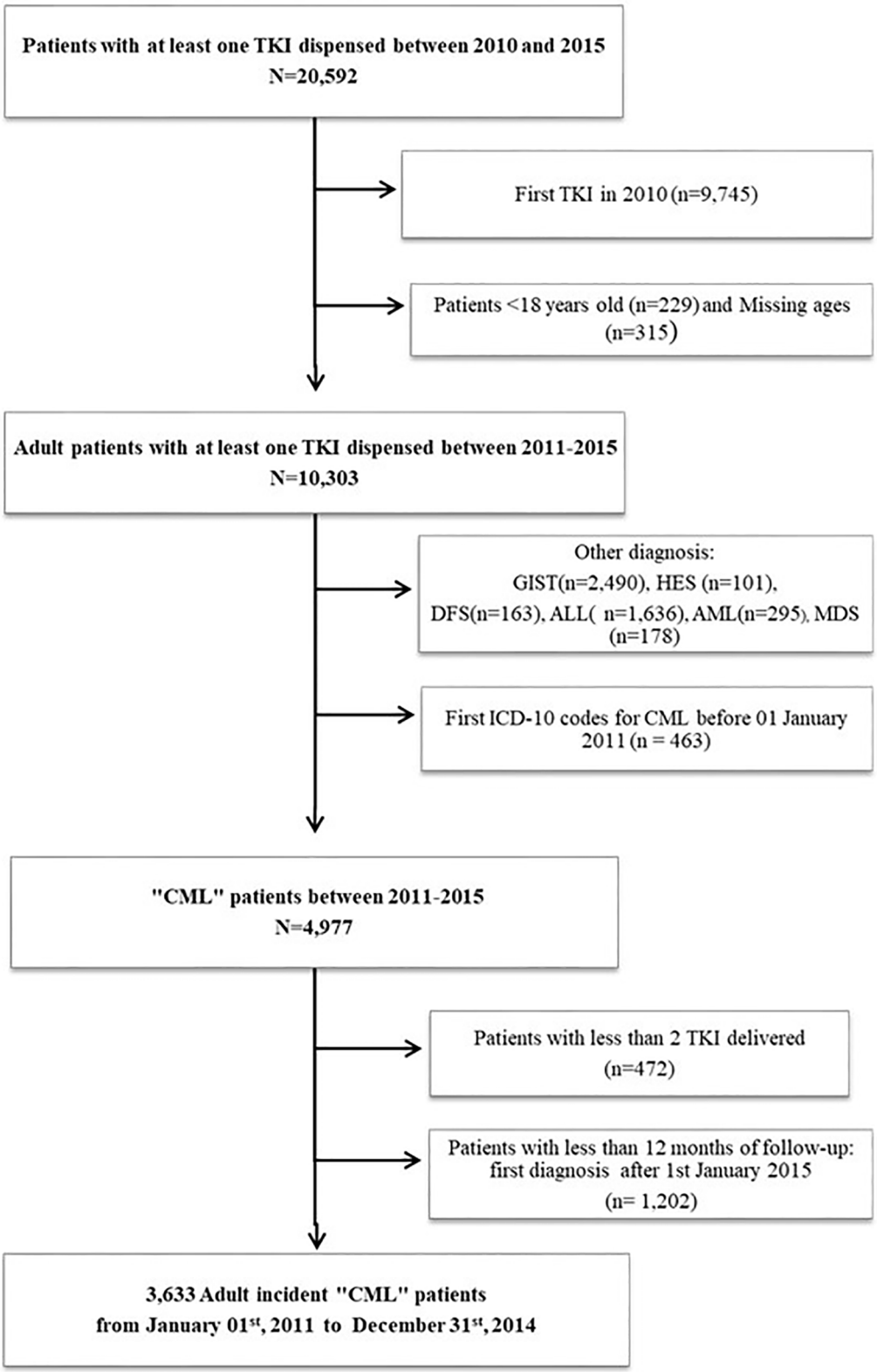

FIGURE 1 | Flowchart illustrating patients' selection. TKI, Tyrosin Kinase Inhibitor; CML, Chronic Myeloid Leukemia; GIST, Gastrointestinal Stromal Tumors; HES, Hypereosinophilic Syndromes; DFS, Dermatofibrosarcoma; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; MDS, Myelodysplastic Syndromes.

557 patients aged 18-39 years (15.3%), 1637 aged 40-64 (45.0%), 735 aged 65-74 (20.2%), and 704 patients over 75 years (19.4%). A majority was men (54.6%) with a M/F ratio of 1.2 **(Table 1).** The median duration of follow-up was 39 months (IQR: 27 – 48 months). At inclusion, only 1% (60) of patients was hospitalized for CML, increasing to 15% (536) during follow-up. We listed 2.6% (96 patients) deaths in the first year of follow-up, and overall 392 patients died during the study period, giving an overall survival probability of 89.21% (95%CI 88.20%-90.21%) at 5 years after inclusion (93.98% for patients 18-64 years old; 81.04% for patients over 65 years; p<0.05 according to the Log rank test) **(Figure 2).**

TABLE 1 | Description of population characteristics and comorbidities (in the 12 months preceding the index date) in incident "CML" subjects identified in the SNDS, 2011-2014, France.

Characteristics	N (%)
Number of subjects	3,633
Age, years - median (interquartile range)	60 (47-71)
Gender	
Men	1,984 (54,6)
Women	1,649 (45,4)
CMU-C status	
No	3,363 (92,6)
Yes	221 (6,1)
Comorbidities	
Subjects with at least one LTD in the 12months preceding the index date	342 (9.4)
Subjects with at least one hospitalization in the 12months preceding the index date	1,251 (34.4)
Charlson comorbidities index (CCI)	
0	2,738 (75.4)
1	338 (9.3)
2	305 (8.4)
>2	252 (6.9)
Individual comorbidities according to CCI	
Cancer (without CML)	402 (11.0)
Chronic lung disease	343 (9.4)
Diabetes without complications	313 (8.6)
Metastatic pathology	119 (3.6)
Peripheral vascular disease	95 (2.6)
Moderate to severe renal disease	87 (2.4)
Diabetes with complications	63 (1.7)
Myocardial infarction	61 (1.7)
Heart failure	56 (1.5)
Cerebrovascular pathology	47 (1.3)
Dementia	31 (0.8)
Mild liver disease	24 (0.7)
Connectivity	19 (0.5)
Hemiplegia	19 (0.5)
Ulcerative pathology	19 (0.5)
Moderate to severe liver disease	5 (0.1)
HIV-AIDS	6 (0.2)
Drug classes	
Subjects with at least one drug prescribed in the 12months preceding the index date	3,238 (89.1)
Paracetamol	2,253 (62.0)
Proton pump inhibitors	1,488 (40.9)
Antihypertensive agents	1,146 (31.5)
NSAIDS	1068 (29.3)
Intestinal motility stimulants	1,010 (27.8)
Opioid analgesics	977 (26.9)
Benzodiazepines	936 (25.7)
Glucocorticoids	956 (26.3)
Antithrombotic	868 (23.9)
Statins	772 (19.9)
Vitamin D	657 (18.1)
Antihistaminic	503 (13.8)
Allopurinol	402 (11.1)
Antidepressants (SSRI)	338 (9.3)
Levothyroxine	302 (8.3)

CMU-c, complementary universal healthcare coverage.
NSAIDs, Non-steroidal anti-inflammatory drugs; SSRI, Selective serotonin reuptake inhibitor.

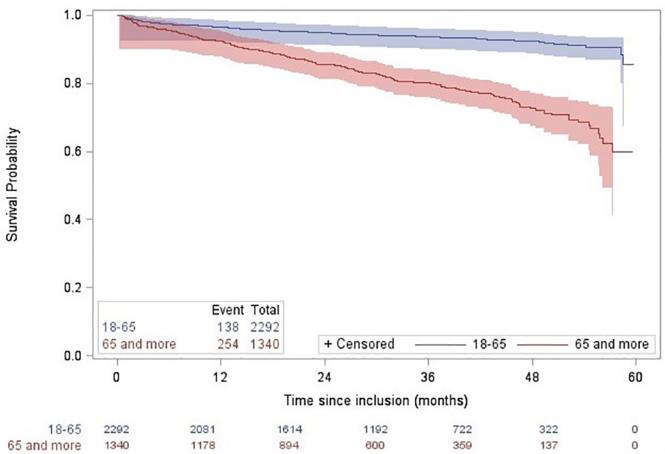

FIGURE 2 | Overall survival probability estimated through Kaplan-Meier curves according to age classes in incident Chronic Myeloid Leukemia (CML) patients identified in the SNDS between 2011 and 2014 in France. The overall survival rate was significantly different between age groups, according to the Log rank test.

Algorithm Validation to Identify CML Patients

The comparison of the algorithm with the opinion of hematologists indicated an observed 90% concordance rate. According to the hematologists, the algorithm correctly identified 10 true CML patients and correctly excluded 8 false CML patients. The two remaining patients with discordant results were defined as having CML before 2011, and therefore were not considered as incident CML case.

Incidence

In our study, the cumulative incidence rate of CML over the period 2011-2014 was estimated at 1.37/100,000 person-years (95%CI 1.36-1.38). It was higher in men (1.54/100,000 person-years, 95%CI 1.53-1.55) than in women (1.20/100,000 person-years, 95%CI 1.19-1.21) and increased with age, reaching a peak at 75-79 years, after which it decreased. There was a male preponderance of CML in men in the different age groups **(Figure 3).** This incidence was relatively stable over each calendar year between 2011 and 2014 with an average of 908 (±25) incident cases per year. The cumulative incidence varied from 1.07 to 1.69 per 100,000 inhabitants across France. We observed differences in incidence between regions with a higher frequency trend in the east compared to the west of the country **(Figure 4).**

Charlson's Comorbidities Index and Care Consumption at Baseline

The **Table 1** presents the main characteristics of patients at baseline: 75.4% of the patients did not present another comorbidity included in the CCI at baseline, the CML being excluded. For patients with a CCI ≥ 1, the most frequently reported was other cancer (including lymphoid leukemia, tumors of uncertain prognosis, melanoma, etc.). Except for paracetamol which was taken at least once by 62.0% of the patients in the year

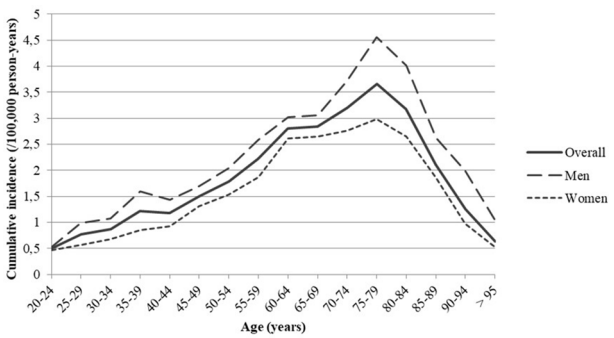

FIGURE 3 | Cumulative incidence of Chronic Myeloid Leukemia (CML) in France during the period 2011-2014 by age and gender.

before the index date, the main drugs used were proton pump inhibitors (PPI, 40.9% of patients), antihypertensive drugs (31.5%), non-steroidal anti-inflammatory drugs (NSAID, 29.3%), intestinal motility stimulants (27.8%) and opioid analgesics (26.9%) **(Table 1)**.

TKI Patterns

Among the 3,633 patients in the cohort, imatinib was the most frequently delivered as the first-line treatment for 77.6% of the patients (n = 2,821), followed by nilotinib (18.3%, n = 663) and dasatinib (4.1%, n = 148). Only one patient was initiated with bosutinib (in 2013). In 2011, imatinib represented 81.6% of first line TKIs versus 11.4% for nilotinib, and 7.0% for dasatinib, whereas from 2012 to 2014, nilotinib represented 19% to 21%. Imatinib was used as the first line for 64.4% of patients 18-39 years old and for 90.5% of those over 75 years old. The majority of prescriptions corresponded to a treatment duration of 30 days (packs of 30 tablets delivered). The initial prescriber was mainly a

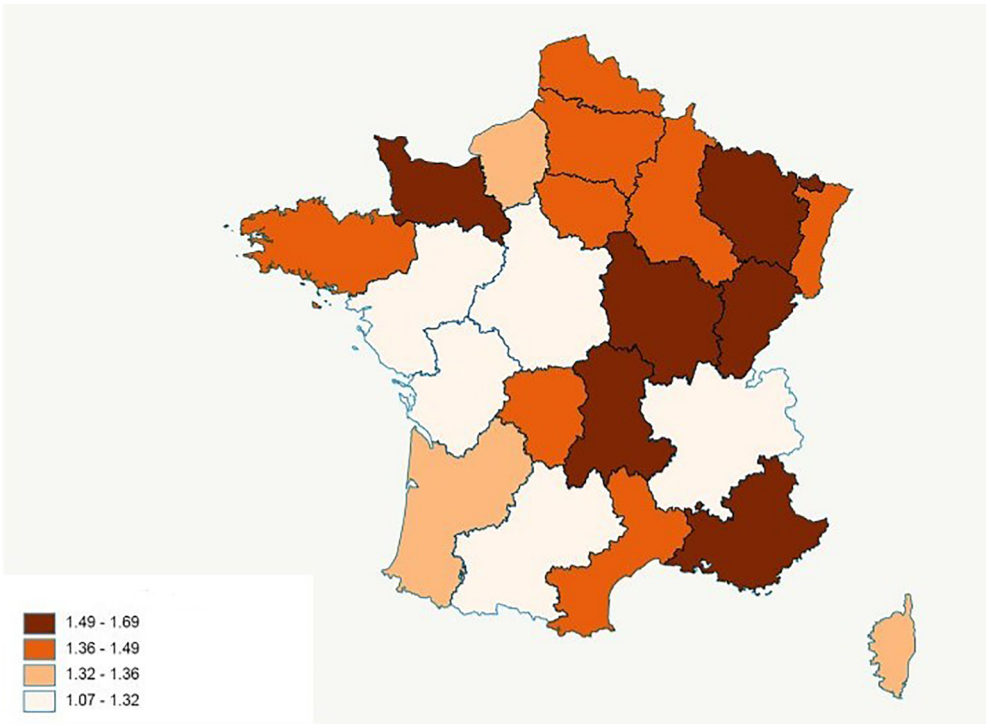

FIGURE 4 | Distribution of the population of incident Chronic Myeloid Leukemia (CML) patient identified in the SNDS between 2011 and 2014 by regions of France. These are estimates of CML incidence per 100,000 inhabitants. Regions are those in which incident CML patients lived in 2014.

hospital practitioner of the public sector (66%) and the median (IQR) time from first-line TKI to the end of follow-up was 36 months (26 – 47months).

In the year following the inclusion there were 3,480 patients with at least two distinct dispensations of TKI, on which we have performed the description of TKI and comedication patterns. Eighty-six percent of these patients received only one type of TKI during the first year of follow-up, 13% received two different TKIs and only 1% received subsequently 3 different TKIs. The median time (IQR) between two dispensations of TKI was 29 (26–34) days.

TKI Switch

68.5% of the patients (n = 2,384) were treated only by imatinib, 18.0% only had a second-generation TKI (with a predominance of nilotinib) and 13.6% received two different TKI (considered as a change in treatment during their care). Most of these switches (81%) occurred between imatinib and second-generation TKIs (either dasatinib or nilotinib). The median time (IQR) between the initiation of a CML TKI and a switch to another TKI was 5 (3-8) months. A higher proportion of patients (41%) had a TKI switch within 0-3 months after the start of treatment than in later periods.

TKI Interruption and Discontinuations

During this first year of follow-up, treatment discontinuations (defined as a cessation of TKI dispensation of more than 60 days before the end of following) were reported in 23% (n=818) of patients. Treatment interruptions (defined as temporary suspension of TKI dispensation, for more than 40 days) were observed in 52% (n=1,827) of the patients and approximately half of those patients (n=899) had more than one interruption. The median duration (IQR; min, max) of treatment interruption was 11 (4-22; 1, 319) days.

Of 473 patients who had a switch, 69% (n=328) also had an interruption of treatment and there was a significant relationship between switches and interruptions in treatment (Odds Ratio (OR) = 1.35; 95%CI 1.24-1.47). Most of the interruptions concerned patients with a TKI switch within 0-6 months after the start of treatment. Only 16% (n=76) of the patients who had a switch also had a discontinuation.

Comedications

Throughout their care, patients were exposed to other drugs in addition to TKI. The mean number (SD) of concomitant medications at the start of TKI treatment was 2.7 (2.3) and 16.7 (9.6) over the first year of follow-up. The main drugs dispensed were paracetamol, PPIs, and antihypertensive drugs. Of the 3,480 patients, 51.3% (n=1,863) had at least one prescription of another drug on the day of the prescription for the first-line TKI and 71.5% (n=2,487) had a concomitant prescription within the month following the first TKI prescription **(Tables 2**, **3)**.

TABLE 2 | Description of drug classes concomitant with TKI exposure (issued within the day of first TKI prescription) in the 3480 incident "CML" subjects with at least 2 dispensations of TKI, 2011-2014, France.

Drug classes	N (%)
Allopurinol	851 (24.4)
Intestinal motility stimulants	421 (12.1)
Antihypertensive agents	228 (6.5)
Proton pump inhibitors	223 (6.4)
Antithrombotic agents	211 (6.1)
Paracetamol	208 (6.0)
NSAIDS	185 (5.3)
Other neoplastic	155 (4.4)
Benzodiazepines	138 (3.9)
Opioid analgesics	135 (3.8)
Statins	75 (2.1)
Glucocorticoids	70 (2.0)
Antiemetics	66 (1.9)

NSAIDs, Non-steroidal anti-inflammatory drugs.

TABLE 3 | Description of drug classes concomitant with TKI exposure (issued within the month of first TKI prescription) in the 3480 incident "CML" subjects with at least 2 dispensations of TKI, 2011-2014, France.

Drug classes	N (%)
Antihypertensive agents	815 (23.4)
Proton pump inhibitors	779 (22.4)
Paracetamol	689 (19.8)
Allopurinol	621 (17.8)
Antithrombotic agents	589 (16.9)
Intestinal motility	499 (14.3)
Benzodiazepines	487 (14.0)
Statins	387 (11.1)
Opioid analgesics	360 (10.3)
NSAIDs	298 (8.5)
Thyroid hormones	242 (7.0)
Glucocorticoids	198 (5.7)
Antidepressants	188 (5.4)
Oral antidiabetics	183 (5.2)
Vitamin D	175 (5.0)

NSAIDs, Non-steroidal anti-inflammatory drugs.

Sensitivity Analysis

We selected patients who had at least one incident LTD record for myeloid leukemia (coded ICD-10 C92) between 1 January 2011 and 31 December 2014 from the 10,303 patients in the SNDS who had at least one incident reimbursement of TKI between 2011 and 2014. Three thousand one hundred and eighteen (3,118) patients were thereby identified, from whom all subjects with diagnostic codes for acute myeloid leukemia (AML: ICD-10 codes C920, C924, C925, C926 and C928) or acute lymphoblastic leukemia (ALL: ICD-10 code C910), either during hospitalization and/or in LTD, were excluded. With this method, we identified 2,812 patients who had an LTD with a potential incident "CML" between 01/01/2011 and 31/12/2014.

Characteristics of this population were similar to those of the CML population identified by the complete algorithm (**Supplementary File 2 Table S1**).

DISCUSSION

Main Results

The inclusion of 3,633 incident patients in 4 years makes this is one of the largest cohorts of incident patients with CML initially treated with TKI. This analysis of individual data from the French national health insurance databases provides original information on newly diagnosed CML patients in France at a nationwide scale. Median age at occurrence of CML was 60 years, and 52.2% of patients were 60 years or older with a M/F ratio of 1.2. Age and gender characteristics (aging population with increasing male preponderance) corroborate and update findings from previous studies on the incidence of CML in France (from a few cancer registries) and the prevalence at a regional and national level (8, 10). As reported in other studies, the overall survival rates in this population was similar to that of the general population (8, 30).

The incidence rate found in our study is within the range of population-based reports from Sweden, southeast England, the United Kingdom, Taiwan, and in a recently published study on CML patients in 20 European countries (**Table 4**). The incidence rates in these studies varied between 0.70 and 1.8/100,000 and the Surveillance, Epidemiology, and End Results (SEER) Program in the United States reported a remarkably high incidence of 1.75/100.000 (2, 3, 6, 7). Our incidence rate is higher than previous estimates of the incidence in France which are between 0.95 and 1.14 per 100,000 person-years **(Table 4)** (8, 9). These incidence rates were obtained from data of five to six French population-based cancer registries between 1980 and 2009. These registries cover approximately 8 million inhabitants in France, while we used individual data from the French national health insurance databases, which cover approximately 66 million inhabitants; we also covered a more recent period (2011-2014) than these studies. Therefore, the large size and aging of the French population in our study, may explain the increase in incidence.

In comparison with other studies performed outside France, the differences observed for the incidence estimates can be due to significant differences in the age distributions of the investigated populations and the geographical areas (e.g. Western vs several non-Western countries) (2, 6, 28). The differences may also be due to methodological issues (national extrapolation from regional registries, national exhaustive registries, single reference center, etc.) or differences in study periods. However, the difference between different geographical areas and/or ethnical sub-groups cannot be excluded to explain these incidence variations (7, 10, 31).

We observed variations in CML incidence across the different regions of the French territory but it should be taken with caution because these variations are based on crude incidence rates. To confirm it in our study, we should standardize the incidence rates in terms of age and gender. However, these geographic variations of CML incidence in France have also been described by Foulon et al. who studied the prevalence of CML in France using the SNDS (10). We agree with their assertion that this cannot be explained by a difference in the quality of data reporting across

TABLE 4 | Chronic Myeloid Leukemia incidence and prevalence rates estimated from different population-based registries or surveys.

First author (year of publication) [ref]	Geographical area	Years	Prevalence rate (/100,000)	Incidence rate (/100,000)	Data source
Chen et al. (Höglund et al.) (2013) (2)	USA	1975–2009		1.75	US (SEERS): 17 tumor registries covering approximately 25% of the US population
Gunnarsson (2016) (3)	Sweden	1970-2012	3.9 in 1985 11.9 in 2012		Swedish Cancer Register and Swedish Cause of Death Register
Delord et al. (2018) (9)	France	1960 to 2060	2.5 before the 1980s, to 6 by 2002. 18 and 24 in 2018 and 2030.	0.95	Cohort component-based model using projections of the French population. Six cancer registries for incidence from 1980-2009
Thielen N et al. (2015) (30)	Netherlands	1989-2011 and 2001-2012		0.9 and 0.8	Nationwide population based Netherlands Cancer Registry (NCR)
Visser et al. (2012) (28)	Europe	1995-2002	5.6 in 2008	1.2	Europe (RARECARE project) : 22 European cancer registries
Sant M et al. (2010) (6)	Europe	2000-2002		1.10	Europe (HAEMACARE project) : 44 European cancer registries
Penot et al. (2015) (8)	France	1980-2009		1.14	Five cancer registries
Höglund et al. (2015) (2)	Sweden	2002–2010		0.9	Swedish Cancer Register
Hoffman et al. (Höglund et al.) (2014) (2)	Europe	2008-2012		0.7-1.0	European Treatment and Outcome. Study (EUTOS) for CML in 27 European countries
Nguyen et al. (2018) (4)	Canada	2011- 2015		0.87	Calgary Laboratory Services (CLS) Cancer Cytogenetics Laboratory
Neves et al. (2018) (7)	Brazil	2004-2015		3.4	Reference center for diagnosis and treatment of adult leukemia patients in Pernambuco
Kuan JW et al. (2018) (31)	Malaysia	2011-2016	6.9 in 2016	0.8	Single but representative center in southern Sarawak
Foulon et al. (2019) (10)	France	2014	16.3		National Health Insurance database

the regions because information on reimbursement of TKI, on which the algorithm mainly based, is collected in the same manner across the French territory. The role of unknown environmental factors in the incidence of CML cannot be excluded. However, data regarding environmental exposures are not available in the National Health Insurance databases. This should be confirmed by other studies across Europe.

With the increase in the incidence of CML and particularly in the elderly patients (peak of incidence at >75 years in our study), precautions should be taken by physicians in order to adapt their practices, follow-up and informing of CML patients (32). Elderly patients may be more sensitive to side effects and interactions with TKIs.

Patterns of TKI Treatment and Healthcare Resources Consumption

This is the only recent study in France that examines patterns of TKI treatment among newly diagnosed CML patients in France between 2011 and 2014 (since the availability of second-generation TKI in 2006 and 2007 in France) (12, 33, 34). We observed that most of the patients were rarely or never hospitalized for CML on inclusion in the study or during the follow-up (15%). All the TKIs studied were delivered on an outpatient basis, on medical prescription and reimbursed by the health insurance, with one month's treatment provided. Imatinib remains the most widely used drug, both in first-line and throughout the study period. However, we noticed an increase in the use of second-generation TKIs in the first-line setting overtime (18% were nilotinib and 4% dasatinib), which is consistent with previously published data, and this trend is more marked in young patients (27.8% and 7.5% of patients 18-39 years old were exposed respectively to nilotinib and dasatinib as first line treatment in this study) (33). Only approximately 14% of the patients changed TKI in their first year of treatment but there were discontinuations in 23% of the cases and almost 52% of interruptions. These results are consistent with studies that investigate treatment patterns with protein kinase inhibitors among patients with CML (35–38). Reasons for switching or discontinuation could be adverse effects or intolerance to TKI (38, 39). In fact, most of the patients who switched from one TKI to another (41%) did so during the first three months of treatment, before the first milestone evaluation according to international guidelines (12). In addition, most of these patients who switched TKI (69%) also interrupted treatment.

Our study reveals that patients with CML have other co-morbidities during management of their hematological pathology, 11% of patients had a previous history of cancer, which is high for a population with a median age of 60 years. Similar results have been previously reported in a population based-study including CML patients in France using regional data, with a highest proportion (18%) of CML patients previously treated for one or more other cancers before the CML occurrence, including lymphomas or other lymphoid diseases, prostate, breast, or digestive cancers (27, 40). The proportion of patients with comorbidities was underestimated in this study by using only those included in the CCI (hypertension or dyslipidemia or not complicated diabetes being not included). This is underlined by the proportion of patients exposed to antihypertensive agents or statins in the year before inclusion.

At the same time, in most instances CML patients often chronically receive numerous medications. For example, nearly half are treated with proton pump inhibitors, one-third receive antihypertensive drugs, benzodiazepines, opioid analgesics (a category including tramadol and codeine), or anti-platelet agents, one-quarter are exposed to statins, and 10% are exposed to antidepressants. This level of use confirms the results observed in other recent studies (41, 42). The concomitant use of TKI and other drug is of significant concern because of its impact on survival and therapy discontinuation in older adults with CML (42). There is also a risk of potential drug-drug interaction that reduces the effectiveness of TKIs (e.g., concomitant use of TKI and PPI reduces TKI absorption) (43).

Identification of CML Cases in the SNDS

The use of the SNDS (a medico-administrative database) is the first and main strength of our study. It provides a representative and exhaustive sample of patients' pathway of care in real-life conditions (98.8% of the French population); data are collected prospectively and are readily available with a unique identifier for each patient (which helps to avoid selection and attrition bias) (24, 26). Therefore, the SNDS is a powerful tool to conduct observational studies especially for rare diseases such as CML. Cancer identification algorithms have been developed based on SNDS data and validated on cancer registry data in various cancer sites (44, 45). Building such algorithms requires expertise in both the disease studied and the administrative databases used. Yet, there is still no validated algorithm for CML, which is a limitation of our study.

The algorithm used to identify incident CML patients was developed through collaborative work involving hematologists and pharmacoepidemiologists. A one-year period before inclusion (1/1/2010 -1/1/2011) was applied to ensure that patients were not previously treated for CML. Actually, we choose this one year period because a molecular relapse leading to a subsequent TKI re-treatment often occurs within 6 months after a first TKI discontinuation (46, 47). Patients treated with TKIs for other conditions were excluded to ensure that only patients treated for CML were selected. The fact that we identify CML patients based on TKI reimbursement appears robust given the current management recommendations (CML does not require hospital management in most cases) (14). The efficacy of these drugs has led to a systematic prescription in all newly diagnosed patients. In order to ensure the relevance of this algorithm, we have taken two different approaches to protect its robustness.

The first approach was to ask two clinicians, who were blinded of the ranking provided by the selection algorithm, to analyze the sequence of care of a randomly selected sample of patients in the cohort and to categorize patients as probable cases of CML or excluded CML. Overall, 90% of the subjects were correctly classified (true positives and true negatives). The second approach was to perform a sensitivity analysis to describe the demographics and management characteristics of incident CML patients from a tighter identification based on the assignment of an LTD for CML (with an LTD start date to confirm the onset of disease) and excluding diagnoses of acute leukemia (identified by the corresponding LTD codes). The total number of this cohort is almost half the number of patients in our study (hospital clinical data had already shown that less than half of patients treated for CML had LTD in this indication). Overall, this approach confirmed same socio-demographic characteristics (**Supplementary File 2 Table S1**).

Our study also has limitations. The algorithm could not identify patients who had always received TKI in the setting of a clinical trial, in which case the TKI was provided by a sponsor and therefore not reimbursed by the National Health Insurance. In the EU Clinical Trials Register, there were 25 clinical trials on CML between 2004 and 2014 in France (48), which corresponds to an upper range of 628 prevalent patients that could have been missed by the algorithm (10). Among those patients, several discontinued the trials and were thus identifiable by the algorithm if treated by a TKI outside the trial. Therefore, the impact of these limitations on the estimation of the incidence of CML should be limited. Secondly, we were unable to validate CML patients' identification with our algorithm using medical records because data from the French national health insurance databases for research are anonymous. This difficulty was partially overcome through internal validation. However, for the same reasons of anonymity, we were unable to perform individual matching with the registries. The algorithm could have overestimated the number of incidents CML patients. Non-CML patients who received TKI for others diseases besides the differential diagnoses already excluded by the algorithm may have led to this slight overestimation.

Relevance and Limitations of the Use of SNDS in Measuring Drug Exposure

In pharmacoepidemiology, minimizing classification bias in the measurement of drug exposure is fundamental since the introduction of such bias can call into question the validity of the results obtained. In most studies, exposure can only be measured retrospectively and transversally with a risk of recall and non-response bias, while SNDS data collected continuously over time help avoiding those biases. Similarly, the qualitative aspect of drug consumption from these data sources may lack precision (dosage, duration of treatment, concomitant medications, etc.). Moreover, data on response rate to the TKI treatment and reasons for changes in treatment sequences were not available in the database.

CONCLUSION

In conclusion, we built an algorithm to identify CML patients in healthcare administrative databases and described patterns of use of TKI treatment and healthcare consumption in incident CML patients treated with TKI in France between 2011 and 2014. In 2014, the estimated cumulative CML incidence rate was 1.37 per 100,000 inhabitants in France. The data analysis revealed that CML patients are mostly old, have other co-morbidities at the time of management of their hematological pathology, and at the same time, in most

instances chronically receive numerous medications, but with little or no hospitalization for CML.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institut des données de Santé. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM and FD conceived the study. MP, CC, FH, and MG participated to study design, data management and statistical analysis plan. MP performed analysis and wrote the first draft. All the authors interpreted results and validated the manuscript's content. MM is the scientific guarantor for the study. All authors contributed to the article and approved the submitted version.

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National Cancer Institute, Colombia
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Shanghai JiaoTong University, China
Swami P. Iyer,
University of Texas MD Anderson Cancer Center, United States

***Correspondence:**
Jun Ma
majun0322@126.com
Zhixiang Shen
drshenzx@126.com
Jun Zhu
zhu-jun2017@outlook.com

†These authors have contributed equally to this work and share first authorship

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A Multi-Center, Real-World Study of Chidamide for Patients With Relapsed or Refractory Peripheral T-Cell Lymphomas in China

Weiping Liu[1†], Donglu Zhao[2†], Ting Liu[3], Ting Niu[3], Yongping Song[4], Wei Xu[5], Jie Jin[6], Qingqing Cai[7], Huiqiang Huang[7], Zhiming Li[7], Ming Hou[8], Huilai Zhang[9], Jianfeng Zhou[10], Jianda Hu[11], Jianzhen Shen[11], Yuankai Shi[12], Yu Yang[13], Liling Zhang[14], Weili Zhao[15], Kaiyang Ding[16], Lugui Qiu[17], Huo Tan[18], Zhihui Zhang[19], Lihong Liu[20], Jinghua Wang[21], Bing Xu[22], Hui Zhou[23], Guangxun Gao[24], Hongwei Xue[25], Ou Bai[26], Ru Feng[27], Xiaobing Huang[28], Haiyan Yang[29], Xiaojing Yan[30], Qingshu Zeng[31], Peng Liu[32], Wenyu Li[33], Min Mao[34], Hang Su[35], Xin Wang[36], Jingyan Xu[37], Daobin Zhou[38], Hongyu Zhang[39], Jun Ma[2]*, Zhixiang Shen[15]* and Jun Zhu[1]

[1] Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital and Institute, Beijing, China, [2] Department of Hematology and Oncology, Harbin Institute of Hematology and Oncology, Harbin, China, [3] Department of Hematology, West China Hospital Sichuan University, Chengdu, China, [4] Department of Hematology, Henan Cancer Hospital, Zhengzhou, China, [5] Department of Hematology, Jiangsu Province Hospital, Nanjing, China, [6] Department of Hematology, The First Affiliated Hospital of Zhejiang University, Hangzhou, China, [7] Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China, [8] Department of Hematology, Qilu Hospital Shandong University, Jinan, China, [9] Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China, [10] Department of Hematology, Tongji Hospital Huazhong University of Science and Technology, Wuhan, China, [11] Department of Hematology, The Affiliated Union Hospital of Fujian Medical University, Fuzhou, China, [12] Department of Medical Oncology, The Cancer Institute and Hospital Chinese Academy of Medical Sciences, Beijing, China, [13] Department of Lymphoma, Fujian Cancer Hospital, Fuzhou, China, [14] Department of Medical Oncology, Union Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, [15] Department of Hematology, Shanghai Rui Jin Hospital, Shanghai, China, [16] Department of Hematology, Anhui Provincial Cancer Hospital, Hefei, China, [17] Department of Hematology, The Hematology Institute and Hospital Chinese Academy of Medical Sciences, Tianjin, China, [18] Department of Hematology, The First Affiliated Hospital Guangzhou Medical University, Guangzhou, China, [19] Department of Medical Oncology, Sichuan Cancer Hospital, Chengdu, China, [20] Department of Hematology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China, [21] Department of Medical Oncology, Nanjing General Hospital of Nanjing Military Command, Nanjing, China, [22] Department of Hematology, The First Affiliated Hospital of Xiamen University, Xiamen, China, [23] Department of Lymphoma, Hunan Cancer Hospital, Changsha, China, [24] Department of Hematology, Xijing Hospital of Airforce Medical University, Xi'an, China, [25] Department of Lymphoma, The Affiliated Hospital of Qingdao University, Qingdao, China, [26] Department of Hematology, The First Bethune Hospital of Jilin University, Changchun, China, [27] Department of Hematology, Nanfang Hospital of Southern Medical University, Guangzhou, China, [28] Department of Hematology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, China, [29] Department of Lymphoma, Zhejiang Cancer Hospital, Hangzhou, China, [30] Department of Hematology, The First Hospital of China Medical University, Shenyang, China, [31] Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Anhui, China, [32] Department of Hematology, Zhongshan Hospital Fudan University, Shanghai, China, [33] Department of Lymphoma, Guangdong Provincial People's Hospital, Guangzhou, China, [34] Department of Hematology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumchi, China, [35] Department of Lymphoma, The Fifth Medical Center of the People's Liberation Army (PLA) General Hospital, Beijing, China, [36] Department of Hematology, Shandong First Medical University Affiliated Provincial Hospital, Jinan, China, [37] Department of Hematology, Nanjing Drum Tower Hospital of Nanjing University Medical School, Nanjing, China, [38] Department of Hematology, Peking Union Medical College Hospital, Beijing, China, [39] Department of Hematology, Peking University Shenzhen Hospital, Shenzhen, China

Chidamide has demonstrated significant clinical benefits for patients with relapsed/refractory (R/R) PTCL in previous studies. This multi-center observational study was aimed to evaluate the objective response rate (ORR), overall survival (OS), and safety of chidamide. From February 2015 to December 2017, 548 patients with R/R PTCL from 186 research centers in China were included in the study. Among the 261 patients treated with chidamide monotherapy, ORR was 58.6% and 55 patients (21.1%) achieved complete response (CR). Among the 287 patients receiving chidamide-containing combination therapies, ORR was 73.2% and 73 patients (25.4%) achieved CR. The median OS of all patients was 15.1 months. The median OS of patients receiving chidamide monotherapy and combination therapies was 433 and 463 days, respectively. These results demonstrate a significant survival advantage of chidamide treatments as compared with international historical records. Common adverse effects (AEs) were hematological toxicities. Most AEs in both monotherapy and combined treatments were grade 1–2. No unanticipated AEs occurred. In conclusion, chidamide-based therapy led to a favorable efficacy and survival benefit for R/R PTCL. Future studies should explore the potential advantage of chidamide treatment combined with chemotherapy.

Keywords: lymphoma, T-cell, peripheral, histone deacetylase inhibitors, efficiency, safety, survival

INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is a rare and heterogeneous group of clinically aggressive mature T- and natural killer (NK)-cell neoplasms associated with poor prognosis. Twenty-seven different types of PTCL are described in the 2016 revision of the World Health Organization classification of lymphoid neoplasms. PTCL represents 10–15% of non-Hodgkin lymphomas (NHLs) in Western countries and accounts for about 25–30% of NHLs in China (1, 2). Moreover, the subtype distribution of PTCL is different between China and Western countries. The most common subtype of PTCL in China is extranodal NK/T-cell lymphoma (NKTCL), nasal type, followed by PTCL-not otherwise specified (PTCL-NOS), anaplastic large-cell lymphoma (ALCL), and angioimmunoblastic T-cell lymphoma (AITL) (2, 3).

For relapsed or refractory PTCL, conventional chemotherapy without intensification is usually associated with high treatment failure and disease relapse rates (3–5). Novel agents that target various pathways, such as histone deacetylase (HDAC) inhibitors, have been intensively studied and developed. Epigenetic therapies is also supported by identifying mutations of epigenetic genes in different PTCL subtypes, including *TET2*, *IDH2*, *RHOA*, *DNMT3A*, *CD28*, and *FYN* (6–10). Chidamide, a novel benzamide class of HDAC inhibitors, has been demonstrated to block the catalytic pocket of class I HDACs and selectively inhibit the activity of HDAC1, 2, 3, and 10 (11–17). For relapsed/refractory (R/R) PTCL, chidamide led to an overall response rate (ORR) of 28% in a phase II study (18) and an ORR of 39% in a real-world study (19). This study was a single arm, open-label, retrospective, post-marketing observational study of chidamide. The primary objective was to evaluate the safety, efficacy, and survival benefit of chidamide-containing therapy for relapsed or refractory (R/R) PTCL.

METHODS

Patients and Study Design

The current study's protocol was approved by the Institutional Review Board of all of the participating centers and was in accordance with the Declaration of Helsinki. Written informed consent was waived owing to the use of a deidentified data set.

From February 2015 to December 2017, patients with R/R PTCL from 186 research centers in China were enrolled in the study. The main inclusion criteria were as follows: PTCL subtypes being relapsed or refractory disease as defined by histologic pathology, and receiving chidamide-containing therapy with a duration more than six weeks. When monotherapy was chosen, a dose of 30 mg chidamide was orally administered twice weekly. When combined with other regimens, chidamide with a dose of 20–30 mg twice a week was given consecutively or according to physicians' choices.

The response criteria was based on the Lugano classification recommendation for response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma (20). ORR was defined as the proportion of patients achieving complete remission (CR) and partial response (PR). OS was calculated from the initiation of chidamide until death or the final follow-up (June 2018). Safety assessment was graded according to the Common Toxicity Criteria for Adverse Events scale, v4.03 (CTCAEv4.03).

Statistics

Data analysis was conducted using IBM SPSS for Windows software (Version 25.0; IBM Corp). A chi-square test was used for comparison of categorical variables, and a *t* test was used for comparison of continuous variables. Kaplan-Meier method was employed for survival analysis. Multivariate analysis for OS was performed using the Cox proportional hazards model.

RESULTS

Patient Characteristics

A total of 548 patients with R/R PTCL were enrolled in the study. The baseline characteristics of the patients are summarized in **Table 1**. The median age was 57 years (range, 18–89 years), with a male/female ratio of 1.6:1. More than one half of the patients received chidamide-containing combination treatments, in which a cytotoxic drug was predominant (**Supplement Table 1**).

Efficacy

For the entire cohort, the ORR and CR rate were 66.2% and 23.4%, respectively. The best ORR was observed in AITL (75.1%), followed by ALCL (70.7%), PTCL-NOS (61.4%), and NKTCL (53.0%, **Table 2**). The CR rates varied from 20% to 30% according to different pathology, but was not statistically significant.

TABLE 1 | Baseline characteristics of 548 patients with relapsed or refractory PTCL.

Characteristic	Number of patients (%)
Total	548
Sex	
Male	341 (62.2)
Female	207 (37.8)
Age	
≤60 years	332 (60.6)
>60 years	216 (39.4)
ECOG PS	
0–1	336 (61.3)
2–4	212 (38.7)
Pathology type	
AITL	177 (32.3)
PTCL-NOS	220 (40.1)
ALCL	41 (7.5)
ALK-positive	12 (2.2)
ALK-negative	11 (2.0)
ALK-unknown	18 (3.3)
NKTCL	66 (12.0)
Others	44 (8.0)
IPI	
Low	124 (22.6)
Low-intermediate	173 (31.6)
High-intermediate	157 (28.6)
High	94 (17.2)
Treatment lines	
2nd line	224 (40.9)
3rd line	133 (24.3)
4th line or beyond	64 (11.7)
Data missing	127 (23.2)
Stage	
I–II	66 (12.1)
III- IV	471 (85.9)
Data missing	11 (2.0)
B symptoms	
With B symptoms	169 (30.8)
Without B symptoms	102 (18.6)
Data missing	277 (50.5)

PTCL, peripheral T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AITL, angioimmunoblastic T-cell; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; NKTCL, natural killer/T-cell lymphoma; IPI, International Prognostic Index.

Chidamide-containing combination therapies exhibited a better ORR (73.2% vs. 58.6%, $P < 0.001$) as compared with chidamide monotherapy, but had similar CR (25.4% vs. 21.1%) rates. Among the 261 patients treated with chidamide monotherapy, 55 (21.1%) patients achieved CR, 98 (37.5%) achieved PR, and 80 (30.7%) achieved SD. Of the 287 patients receiving chidamide-containing combination therapies, 73 (25.4%) patients achieved CR, 137 (47.8%) achieved PR, and 49 (17.0%) achieved SD. The differences in either the CR rate or ORR between different combination regimens were not statistically significant.

Safety

The most common adverse events (AEs) were neutropenia (46.7%) in patients treated with chidamide monotherapy, and fatigue (89.2%) in those treated with chidamide-containing combination therapies. Neutropenia was the most common grade 3-4 AE. The incidences and severity of AEs were significantly higher in patients receiving combination treatments than in those receiving the monotherapy (**Table 3**). There was no unanticipated AEs during the follow-up period.

Survival

A total of 260 patients died during the follow-up period. The median OS was 15.1 months (range, 12.9–17.4 months), and the anticipated 1- and 2-year OS rates were 57.9% and 35.8%, respectively, for the entire cohort. In terms of pathological subtypes, the anticipated 1- and 2-year OS rates were 64.2% and 45.4%, respectively, for AITL; 50.7% and 27.7%, respectively, for ALCL; 41.8% and 14.5%, respectively, for NKTCL; 54.2% and 32.0%, respectively, for PTCL-NOS; and 65.4% and 41.4%, respectively, for other types ($P < 0.001$, **Figure 1A**). The survival benefit varied according to treatment responses, with an anticipated 1- and 2-year OS rate of 90.4% and 69.4%, 58.1% and 36.1%, 39.7% and 8.7%, and 12.2% and 6.5% for patients achieving CR, PR, SD, and progression disease (PD), respectively ($P < 0.001$, **Figure 1B**).

The median follow-up was 4.9 months. Among patients treated with chidamide monotherapy, the expected 1- and 2-year OS rates were 58.0% and 36.5%, respectively, for all patients; 58.8% and 42.5%, respectively, for those with AITL; 46.0% and 23.0%, respectively, for those with ALCL; 48.5% and 27.0%, respectively, for those with NKTCL; 56.4% and 31.8%, respectively, for those with PTCL-NOS; and 67.2% and 56.0%, respectively, for those with other types ($P = 0.352$, **Figure 1C**). In terms of treatment responses, the expected 1- and 2-year OS rates were 95.3% and 77.5%, 53.8% and 34.9%, 47.7% and 10.1%, and 10.3% and 0 for patients achieving CR, PR, SD, and PD, respectively ($P < 0.001$, **Figure 1D**).

Among patients receiving chidamide-containing combination therapies, the expected 1- and 2-year OS rates were 57.3% and 35.2%, respectively, for all patients; 68.3% and 47.8%, respectively, for those with AITL; 43.2% and 28.8%, respectively, for those with ALCL; 32.2% and 7.4%, respectively, for those with NKTCL; 51.8% and 32.0%, respectively, for those with PTCL NOS; and 64.5% and 45.2%, respectively, for those with other types ($P = 0.001$, **Figure 1E**). In terms of treatment responses, the expected 1- and 2-year OS rates were 86.7% and 63.4%, 60.2% and 37.1%, 27.5% and 0, and 13.9% and 4.6% for patients achieving CR, PR, SD, and PD, respectively ($P < 0.001$, **Figure 1F**).

TABLE 2 | Efficacy of chidamide-based treatment stratified by baseline characteristics.

	CR		ORR	
	N (%)	*P*	N (%)	*P*
Age		0.031		0.842
≤60	88 (26.5)		221 (66.6)	
> 60	40 (18.5)		142 (65.7)	
Gender		0.892		0.47
Male	79 (23.2)		222 (65.1)	
Female	49 (23.7)		141 (68.1)	
ECOG PS		0.177		0.004
0–1	85 (25.3)		238 (70.8)	
2–5	43 (20.3)		125 (59.0)	
Stage	124 (23.1)	0.197	356 (66.3)	0.426
I–II	16 (24.2)		48 (72.7)	
III- IV	53 (22.9)		131 (65.4)	
Pathology		0.55		0.006
AITL	53 (29.9)		133 (75.1)	
PTCL-NOS	44 (20.0)		135 (61.4)	
ALCL	10 (24.4)		29 (70.7)	
NKTCL	16 (24.2)		35 (53.0)	
Others	5 (11.4)		31 (70.5)	
IPI score		0.391		0.115
Low risk			87 (70.2)	
Low-intermediate risk	39 (22.5)		123 (71.1)	
High-intermediate risk	33 (21.0)		97 (61.8)	
High risk	20 (21.3)		56 (59.6)	
Treatment line	90 (21.4)	0.672	276 (65.6)	0.212
2^{nd} line	51 (22.8)		155 (69.2)	
3^{rd} line	25 (18.8)		80 (60.2)	
≥ 4^{th} line	4 (21.9)		41 (64.1)	

CR, complete response; ORR, overall response rate; ECOG, Eastern Cooperative Oncology Group; PS, performance status; AITL, angioimmunoblastic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ALCL, anaplastic large-cell lymphoma; NKTCL, natural killer/T-cell lymphoma, IPI, International Prognostic Index.

DISCUSSION

The current large-scale, real-world study explored the safety, efficacy, and survival benefit of chidamide for R/R PTCL. Chidamide-containing therapy led to a satisfactory efficacy with a ORR of 73.2% and good tolerance without unanticipated AEs. Moreover, chidamide-containing therapy brought a survival advantage with a 2-year OS rate of 35.8%. Especially for those patients achieving CR, both chidamide monotherapy and combination therapy resulted in improved survival outcome with the 2-year OS of more than 60%.

Previous studies have shown that HDAC inhibitors have significant anticancer potential for R/R PTCL. In a phase II study involving 131 patients, romidepsin led to rapid response with a median time to objective response of 1.8 months, and resulted in an ORR of 25% and a CR rate of 15% (21). During the

TABLE 3 | Adverse events.

	Monotherapy		Combination therapy	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Neutropenia	81 (31.0)	41 (15.7)	80 (27.9)	106 (36.9)
Anemia	68 (26.1)	19 (7.3)	113 (39.4)	54 (18.8)
Thrombocytopenia	82 (31.4)	30 (11.5)	93 (32.4)	91 (31.7)
Fatigue	89 (34.1)	16 (6.1)	167 (58.2)	89 (31.0)
Fever	31 (11.9)	0 (0)	58 (20.2)	7 (2.4)
Nausea/vomiting	59 (22.6)	3 (1.1)	99 (34.5)	4 (1.4)
Diarrhea	35 (13.4)	2 (0.8)	44 (15.3)	3 (1.0)
Prolonged QTc period	6 (2.3)	1 (0.4)	8 (2.8)	0 (0)
Thromboembolism	2 (0.8)	0 (0)	14 (4.9)	0 (0)
Elevated ALT	16 (6.1)	4 (1.5)	40 (13.9)	2 (0.7)
Elevated AST	14 (5.4)	5 (1.9)	29 (10.1)	4 (1.4)
Elevated Creatinine	7 (2.7)	0 (0)	11 (3.8)	1 (0.3)
Proteinuria	8 (3.1)	0 (0)	13 (4.5)	0 (0)

ALT, alanine transaminase; AST, aspartate transaminase; QTc, QT interval corrected by heart rate.

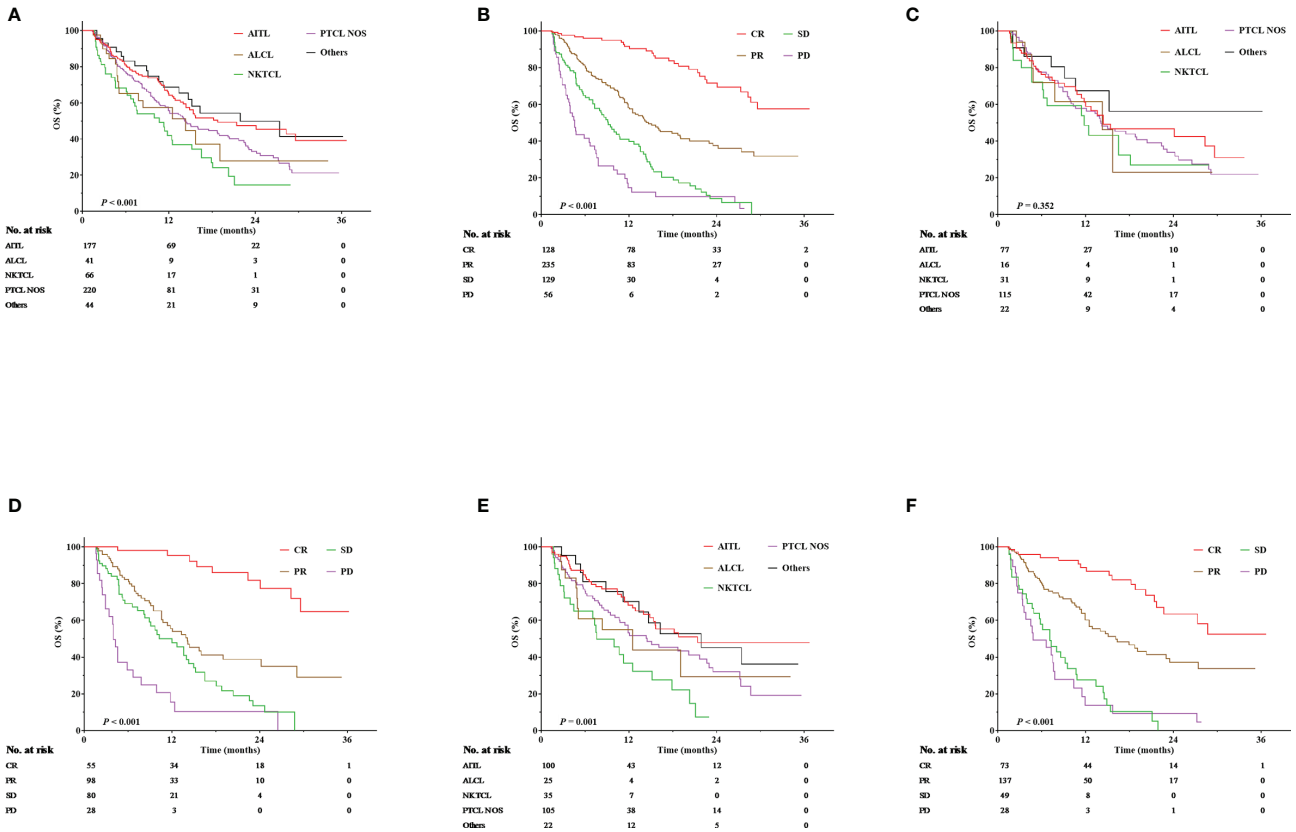

FIGURE 1 | Overall survival (OS) according to pathological subtypes and treatment responses. **(A)** OS according to pathological subtypes for the entire cohort. **(B)** OS according to treatment responses for the entire cohort. **(C)** OS according to pathological subtypes for those treated with chidamide monotherapy. **(D)** OS according to treatment responses for those treated with chidamide monotherapy. **(E)** OS according to pathological subtypes for those treated with chidamide-containing combined therapies. **(F)** OS according to treatment responses for those treated with chidamide-containing combined therapies.

long-term follow-up period, the median DOR for all responders was 28 months, and 32% of patients achieving CR had a DOR of more than 24 months (22). In a real-world study, romidepsin resulted in an ORR of 33%, a CR rate of 12.5%, and a median DOR of 13.4 months (23). Similarly, a pivotal phase II study showed the ORR of belinostat led to an ORR of 25.8% with a CR rate of 10.8% (24). In the current study, the ORR of chidamide-containing therapy was 66.2% for the entire cohort. Notably, a relatively higher response rate was observed in AITL with an ORR of 75.1% and a CR rate of 29.9%. AITL is characterized by high frequencies of mutations in epigenetic modifiers in neoplastic T cells (9), which can partly explain the significant clinical benefits of chidamide. In addition, the efficacy of chidamide seemed to be higher than that of pralatrexate which led to an ORR of 29% with a CR rate of 11% for relapsed or refractory PTCL (25), but it was lower than that of Brentuximab vedotin which led to an ORR of 86% with a CR rate of 57% for ALCL (26).Therefore, future studies focusing on the impact of HDAC inhibitors on the survival benefit of specific subtypes are needed.

Survival expectations for patients with R/R PTCL treated with salvage chemotherapy is very poor. A retrospective study demonstrated that patients with first-time relapsed PTCL treated with chemotherapy only had a median OS of 6.5 months (27). In contrast, HDAC inhibitors showed a better survival advantage. Romidepsin resulted in a median DOR of 28 months and a median PFS of 29 months, of which a better survival benefit was observed in those who achieved CR for ≥ 12 months (22). In the current study, the overall median OS for all patients was 15.1 months, and the 2-year OS rate was 69.4% for patients achieving CR, suggesting a significantly improved long-term survival benefit of chidamide to patients with R/R PTCL.

Chidamide was generally well-tolerated in the current study. Most of the AEs were hematological toxicities of grades 1–2, including thrombocytopenia, neutropenia, and anemia. The incidence of AEs slightly increased in patients receiving chidamide-containing combination treatments, but all AEs were manageable. Transient prolongation of QT interval corrected by heart rate (QTc) period was observed, which was not associated with concurrent cardiac symptoms. Therefore, this study further confirmed the safety of chidamide both in monotherapy and along with other chemotherapies.

There was several limitations in the current study. First, the time to response was taken into account when the inclusion

criteria was developed. The median time to objective response for romidepsin was 1.8 months (21), while chidamide led to a rapid response with 74% of all responses occurring within the first 6 weeks after treatment (18). Based on these reports, patients who received therapy with a duration more than six weeks were enrolled to explore the long-term survival benefit of chidamide in the current study. However, it resulted in a significant selection bias for the evaluation of efficacy, which led to a higher ORR (58.6%) than that reported in a previous real-world study (ORR was 51.2%) (19). Second, the optimal combined cytotoxic drugs were not determined due to the heterogeneous regimens during combined therapy, and data of salvage therapy after disease progression was not collected. Third, many baseline characteristics data including central pathology review, clinical manifestation, imaging examination methods for staging and response, and prognosis except international prognostic index was missing due to multicenter nature and enrollment, which made it difficult to select particular patient population who potentially benefitted from chidamide therapy.

In conclusion, the current large-scale study demonstrated that chidamide had a favorable efficacy and a tolerable safety profile for patients with R/R PTCL. In addition, the current study demonstrated the potential survival benefit of chidamide for patients with R/R PTCL when combined with chemotherapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of all of the participating centers. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

WpL conceived and designed the study, analyzed the data, and drafted and revised the paper. DLZ prepared and analyzed the data. JuZ, JM, and ZS conceptualized and designed the study. All authors provided critical comments to the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.750323/full#supplementary-material

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Racial/Ethnic Disparities on the Risk of Second Malignant Neoplasm Among Hodgkin Lymphoma Survivors

*Han Xiao[1], Jianghua He[2], Simin Liang[1], Duo Cai[1], Qiao Zhou[1], Lanxiang Liu[1], Xinyu Yan[1], Jianxiang Chi[3], Qing Xiao[1] and Li Wang[1]**

[1] Department of Hematology, The First Affiliated Hospital of Chongqing Medical University, Chongqing Medical University, Chongqing, China, [2] Department of Biostatistics and Data Science, University of Kansas Medical Center, Kansas City, KS, United States, [3] The Center for the Study of Hematological Malignancies, Karaiskakio Foundation, Nicosia, Cyprus

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***Correspondence:**
Li Wang
liwangls@yahoo.com

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Background: Hodgkin lymphoma survivors are at risk for second malignant neoplasm (SMN). How race/ethnicity affects the risk remains unclear.

Methods: This retrospective cohort study included 22,415 patients diagnosed with primary Hodgkin lymphoma from January 1992 to December 2015 in 13 Surveillance, Epidemiology, and End Results-based registries and divided patients into four groups: non-Hispanic whites, non-Hispanic blacks, Hispanics, and Asian/others. Taking non-Hispanic whites as a reference, both the proportional subdistribution hazard (PSH) and the cause-specific hazard (CSH) methods were used to calculate the SMN hazard ratio for other racial/ethnic groups with and without considering the competing mortality risk.

Results: 1,778 patients developed SMN with a median follow-up of 11.63 years. In the adjusted PSH model, Hispanic, Asian/others, and non-Hispanic black patients had 26% (PSH, 0.74; 95% CI, 0.63–0.87), 20% (PSH, 0.80; 95% CI, 0.64–1.01), and 12% (PSH, 0.88; 95% CI, 0.75–1.03) decreased overall SMN hazard, respectively. Moreover, the PSH method revealed the racial/ethnic difference in the SMN risk in the skin, the respiratory system, and the endocrine system. These hazards were slightly higher and different with the use of the CSH approach. In addition to the aforementioned overall SMN and subtypes, adjusted CSH analysis also revealed the racial/ethnic disparities in the risk of subsequent female breast cancer, digestive cancer, and non-Hodgkin lymphoma.

Conclusions: The subtype and SMN risk among Hodgkin lymphoma survivors varied by race/ethnicity. The use of CSH and PSH provides a dynamic view of racial/ethnic effects on SMN risk in Hodgkin lymphoma survivors.

Keywords: Hodgkin lymphoma, second malignant neoplasm, SEER database, racial/ethnic disparities, cancer surveillance

INTRODUCTION

Hodgkin lymphoma is a group of lymphoid neoplasms in which cancerous Reed–Sternberg cells are mixed with heterogeneous inflammatory cells, accounting for approximately 10% of all lymphomas, 0.6% of all cancers, and 0.2% of all cancer mortalities (1–3). Over the previous century, advances in treatment have drastically improved the survival of Hodgkin lymphoma patients wherein most patients will be cured (4, 5). However, growing long-term Hodgkin lymphoma survivors are at risk for late complications (e.g., second malignancies). Studies have demonstrated that Hodgkin lymphoma survivors have a higher risk of developing solid tumors and hematologic malignancies than the general population (6, 7). These second malignant neoplasms (SMNs) significantly impact the long-term survival of Hodgkin lymphoma patients (8, 9).

The risk of developing an SMN in Hodgkin lymphoma patients depends on factors related to the patient and the treatment, including age at treatment, family cancer history, smoking history, and the effect of treatment given (10–17). However, considerable racial/ethnic differences exist in these risk factors for SMN among Hodgkin lymphoma patients. The mean age of Hodgkin lymphoma diagnosis among whites was significantly older than all other races. The peak incidence of Hodgkin lymphoma was in young adulthood among non-Hispanics but was in the elderly among Hispanics (18). Moreover, whites were more likely to have family cancer information documented than non-whites (19, 20). The smoking prevalence also varied by race/ethnicity. Individuals of white and black descent have been reported to have a higher smoking prevalence than individuals of Asian and Hispanic/Latino descent (21). The study results about the association between treatment selection and race/ethnicity in Hodgkin lymphoma patients are not consistent. Rodday et al. showed that race/ethnicity was not associated with first-line treatment received using the SEER-Medicare database (22). However, Olszewski et al. reported that black and Hispanic patients received radiotherapy less frequently than white patients (23). Given this potential difference in clinical factors, SMN risk could also differ by race/ethnicity, which has important clinical implications on the long-term follow-up of Hodgkin lymphoma survivors.

The cause-specific hazard (CSH) is a classic method to ascertain the disease etiology and yields valid associations, which can be an ideal way to evaluate the direct association between race/ethnicity and SMN among Hodgkin lymphoma survivors without considering the effects of competing events. However, in the real world, mortality due to other causes can prevent from observing the SMN occurrence. A previous study showed that non-Hispanic black and Hispanic children had worse overall survival than non-Hispanic white patients (24). The difference in mortality may influence the actual racial-ethnic-specific SMN rate among Hodgkin lymphoma survivors. The proportional subdistribution hazard (PSH) is a more appropriate way to reveal how the probability of developing SMN differed by race/ethnicity in the actual situation (25, 26). With data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program, the present study would examine the effects of race/ethnicity on SMN risk in Hodgkin lymphoma survivors by PSH and CSH methods, with and without considering competing risks of mortality. As suggested by Latouche et al., the hazards of competing events (mortalities due to other causes) were also presented for complete understanding (27, 28).

MATERIALS AND METHODS

Data Source and Cohort Selection

A retrospective cohort study using data from 13 SEER cancer registries, Nov 2018 Submission, which covers approximately 13.4% of the US population, was conducted. This analysis included patients diagnosed with primary Hodgkin lymphoma from January 1992 to December 2015 (n = 23,906). Eligible patients were identified using the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes (Hodgkin lymphoma, 9,650–9,669). Patients diagnosed at autopsy or on a death certificate only (n = 101), had no data for Yost index (n = 14), without or unknown microscopic diagnostic confirmation (n = 122), and with unknown Ann Arbor stage were all excluded (n = 913). Moreover, patients who developed a second neoplasm within 2 months of the primary lesion were also excluded for the difficulty to identify which cancer was the first index cancer (n = 106). Patients who developed subsequent Hodgkin lymphoma were excluded for the difficulty to distinguish between second primary tumors and a recurrence (n = 235). The final sample size is 22,415 (**Figure 1**). The present study did not need ethics committee approval as the data are de-identified and publicly available.

The criteria for defining SMNs differ between studies (6, 7, 13, 14, 29). The definitions provided by the SEER project and the International Association of Cancer Registries and the International Agency for Research on Cancer (IACR/IARC) are widely used (30). Rules by SEER suggest the registration of synchronous tumors diagnosed in less than 2 months, which is used in the present study (31). However, IACR/IARC recommends using 6 months to distinguish between synchronous and metachronous multiple primaries (32). To test the overall impact of applying different definitions of SMN in the overall results of the present study, a sensitivity analysis was conducted with the rules developed by IACR/IARC.

Race or ethnicity is divided into non-Hispanic whites, non-Hispanic blacks, Hispanic, and Asian/others (which included non-Hispanic Asians, non-Hispanic Native American or Alaskans, non-Hispanic Native Hawaiians or other Pacific Islanders, and people of unknown racial or ethnic origin). Socioeconomic status was estimated using the Yost index, developed by Kathleen Yost, to evaluate the potential impact of socioeconomic gradients on cancer burden (33). Thus, a higher Yost score represents a higher socioeconomic status level.

Statistical Analysis

Patients were observed from the time of diagnosis with primary Hodgkin lymphoma until diagnosis with SMN, mortality, last

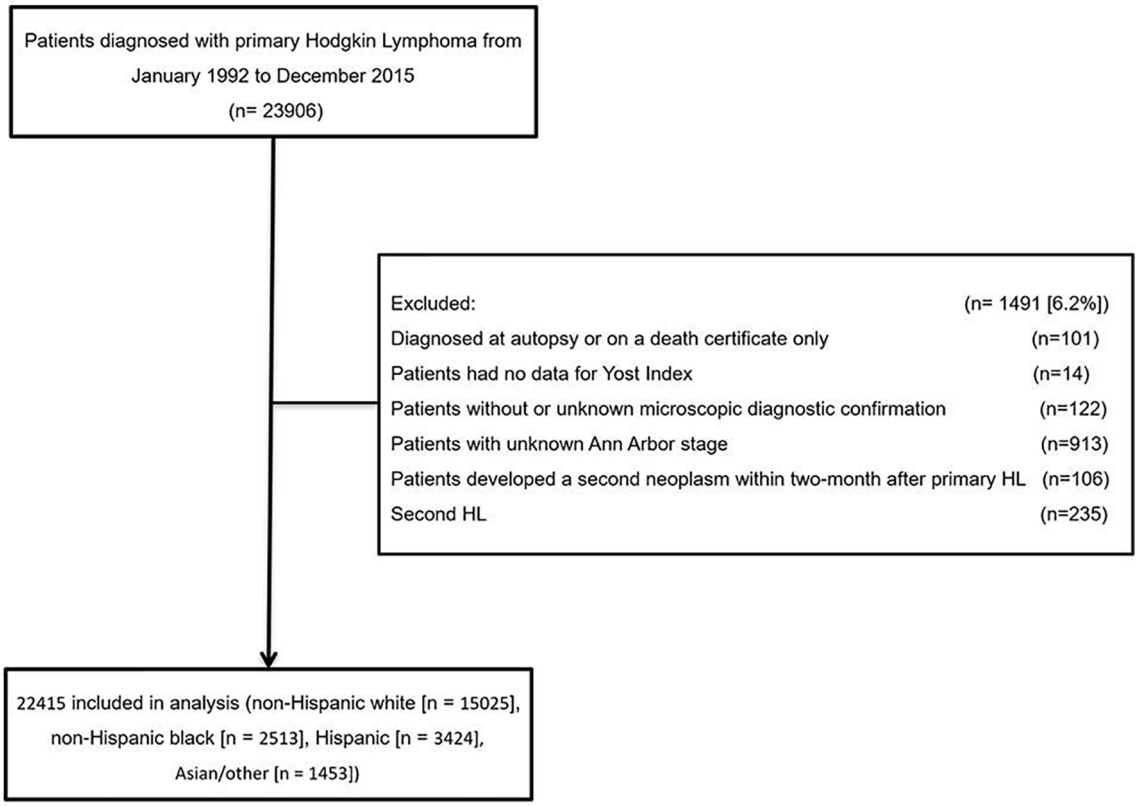

FIGURE 1 | Cohort selection. *HL*, Hodgkin lymphoma.

follow-up, or end of the study, whichever occurred first. The median follow-up time was calculated by the reverse Kaplan–Meier estimator (34). The cumulative SMN incidence was depicted using the PSH and CSH methods, respectively (35, 36). Both the CSH and PSH regression models were used to assess the effects of race/ethnicity on SMN risk on Hodgkin lymphoma survivors. Models were performed unadjusted (model 1); adjusted for age, gender, year of Hodgkin lymphoma diagnosis, Ann Arbor stage, and histology subtype (model 2); adjusted for age, gender, year of Hodgkin lymphoma diagnosis, Ann Arbor stage, histology subtype, and additionally Yost index (model 3); and adjusted for age, gender, year of Hodgkin lymphoma diagnosis, Ann Arbor stage, histology subtype, Yost index, and additionally treatment information (model 4). Baseline age (≤35 years, >35 years), sex (female, male), year of Hodgkin lymphoma diagnosis (1992–2003, 2004–2015), Ann Arbor Stage (I and II, III and IV), histology subtype of Hodgkin lymphoma (classic, non-classic), Yost Index (low, high), chemotherapy (yes, no/unknown), and radiotherapy (yes, no/unknown) were modeled categorically. The potential for multicollinearity was assessed using the variance inflation factor, with values between 1 and 5 considered acceptable (37, 38).

Among patients with SMN, the Cochran Armitage trend tests for trends was performed to evaluate trends in solid tumor proportions over time (39). SMNs in the present report are categorized on the basis of SEER site recode ICD-O-3/WHO 2008 definitions, which were recategorized into 12 different categories, as described in **Supplemental Table S1**. Both PSH and CSH methods were used to assess the racial/ethnic effects on the risk of categorized SMN subtypes. All reported p values were two-sided, and p values of <0.05 were considered statistically significant. All the analyses were conducted using R software version 4.03.

RESULTS

Study Population and Cohort Selection

Table 1 lists the baseline characteristics of included Hodgkin lymphoma patients. Among 22,415 patients, 67.03% of the cohort were non-Hispanic whites (n = 15,025), 11.21% were non-Hispanic blacks (n = 2,513), 15.28% were Hispanics (n = 3,424), and 6.48% were Asian/others (non-Hispanic Asians [n = 1,121], non-Hispanic Native American or Alaskans [n = 84], non-Hispanic Native Hawaiians or other Pacific Islanders [n = 119], and people of unknown racial or ethnic origin [n = 129]). The median age at primary Hodgkin lymphoma diagnosis was 35 years. Non-Hispanic white patients tended to be older than any other race/ethnicity ($p < 0.001$). Hispanic and non-Hispanic black patients had a lower Yost index than non-Hispanic white and Asian/other patients ($p < 0.001$).

TABLE 1 | Characteristics of patients with Hodgkin lymphoma in the SEER database by race and ethnicity (n = 22,415), diagnosed 1992–2015.

	Non-Hispanic White	Non-Hispanic Black	Hispanic	Asian/other	*p*
n	15,025	2,513	3,424	1,453	
Age, year (median [IQR])	36 [25, 52]	34 [25, 47]	32 [22, 50]	31 [23, 48]	<0.001
Gender = male, no. (%)	8,234 (54.8)	1,354 (53.9)	1,952 (57.0)	787 (54.2)	0.06
Diagnosis year = 2004–2015, no. (%)	7,386 (49.2)	1,425 (56.7)	1,998 (58.4)	925 (63.7)	<0.001
Yost index (median [IQR])	11,477 [11,045–11,604]	11,259 [10,936–11,556]	11,050 [10,964–11,551]	11,567 [11,050– 11,665]	<0.001
Histology, no. (%)					<0.001
cHL, NOS	2,377 (15.8)	529 (21.1)	684 (20.0)	276 (19.0)	
LD	149 (1.0)	25 (1.0)	68 (2.0)	20 (1.4)	
MC	1,885 (12.5)	318 (12.7)	584 (17.1)	167 (11.5)	
LR	432 (2.9)	88 (3.5)	98 (2.9)	50 (3.4)	
NS	9,515 (63.3)	1,308 (52.0)	1,874 (54.7)	874 (60.2)	
NLPHL	667 (4.4)	245 (9.7)	116 (3.4)	66 (4.5)	
Ann Arbor stage, no. (%)					<0.001
Stage I	3,114 (20.7)	515 (20.5)	581 (17.0)	242 (16.7)	
Stage II	6,457 (43.0)	868 (34.5)	1,279 (37.4)	661 (45.5)	
Stage III	3,027 (20.1)	559 (22.2)	743 (21.7)	269 (18.5)	
Stage IV	2,427(16.2)	571 (22.7)	821 (24.0)	281 (19.3)	
Radiotherapy, no. (%)					<0.001
Yes	6,172 (41.1)	749 (29.8)	1,043 (30.5)	616 (42.4)	
No/unknown	8,853(58.9)	1,764 (70.2)	2,381 (69.5)	837(57.6)	
Chemotherapy, no. (%)	15,025	2,513	3,424	1,453	<0.001
Yes	12,022 (80.0)	1,975 (78.6)	2,856 (83.4)	1,194 (82.2)	
No/unknown	3,003 (20.0)	538 (21.4)	568 (16.6)	259(17.8)	
Median person-years at risk [IQR]	12.55 [6.96, 18.71]	10.92 [5.80,17.05]	9.30 [4.38, 15.71]	9.38 [4.80;14.96]	<0.001

Categorical variables were compared using Pearson chi-square tests; continuous variables were compared using Kruskal–Wallis H tests.
cHL, classic Hodgkin lymphoma; NOS, not otherwise specified; LD, lymphocyte depleted; MC, mixed cellularity; LR, lymphocyte rich; NS, nodular sclerosing; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; IQR, interquartile range.

Moreover, the proportion of receiving radiotherapy and chemotherapy was the lowest in non-Hispanic black patients ($p < 0.001$). The proportion of nodular lymphocyte-predominant Hodgkin lymphoma subtype was the greatest for non-Hispanic black patients, followed by Asian/others, non-Hispanic whites, and then Hispanics ($p < 0.001$).

SMNs and Mortality in Hodgkin Lymphoma Survivors

The numbers of Hodgkin lymphoma patients experiencing SMN events and mortality without experiencing SMN are shown in **Supplemental Table 2**. With a median follow-up of 11.63 years, 1,778 and 4,774 patients developed second cancer and expired without experiencing an SMN, respectively. The 10-year cumulative incidence of SMNs was the highest for non-Hispanic white patients (6.58%; 95% CI, 5.91–7.25), followed by non-Hispanic black patients (5.35%; 95% CI, 4.35–6.35), Asian/others (5.12%; 95% CI, 3.78–6.45), and Hispanics (4.80%; 95% CI, 3.93–5.67). Moreover, the 10-year cumulative incidences of mortality without SMN were 19.17% (95% CI, 18.50–19.84), 20.44% (95% CI, 18.14–22.75), 24.53% (95% CI, 22.89–26.16), and 25.79% (95% CI, 23.91–27.67) in non-Hispanic whites, Asian/others, Hispanics, and non-Hispanic blacks, respectively. The gap between cumulative overall SMN incidence and mortality was the smallest among the non-Hispanic whites than any other racial/ethnic subgroups (**Supplemental Figure 1**).

As shown in **Figure 2**, the proportion of second solid tumors increased with time in non-Hispanic white ($Z = 6.68$, $p < 0.001$) and Asian/other patients ($Z = 2.268$, $p = 0.02$), but not in non-Hispanic black and Hispanic patients. Compared with other racial/ethnic groups, Asian/others had the highest proportion of subsequent hematologic malignancy (41.78%) and the lowest proportion of subsequent solid tumors (58.23%) among racial/ethnic subgroups, especially during the first 5 years after Hodgkin lymphoma diagnosis (hematologic malignancy, 52.63%; solid tumor, 47.37%). The composition of second solid tumors varied significantly between races/ethnicities ($p < 0.001$). The proportion of second skin cancer was the highest in non-Hispanic white patients (11.0%), followed by Asian/others (4.3%) and Hispanics (3.3%). Notably, no non-Hispanic black patient developed second skin cancer within the SEER cohort. Moreover, the proportion of SMN in the respiratory system was much higher in non-Hispanic white (16.0%) and non-Hispanic black (18.3%) patients than that in Hispanic (10.7%) and Asian/other patients (6.5%), as shown in **Supplemental Figure 2**.

Comparison of Risks of SMN and Mortalities Between Races/Ethnicities

The cumulative incidences of SMN were compared among races/ethnicities by PSH and CSH methods, with and without considering competing events. Both methods revealed the racial/ethnic disparities in the incidence of SMN overall (PSH method in **Figure 3A**, and CSH method in **Supplemental Figure 3A**) and specific SMN subtypes (PSH method in **Figure 4** and CSH method in **Supplemental Figure 4**). Both the CSH and PSH regression models were used to assess the effects of race/ethnicity on SMN risk and mortality due to other causes in Hodgkin lymphoma survivors. According to the multicollinearity diagnostic result, there is no multicollinearity between the variables in these regression models (**Supplementary Table 3**).

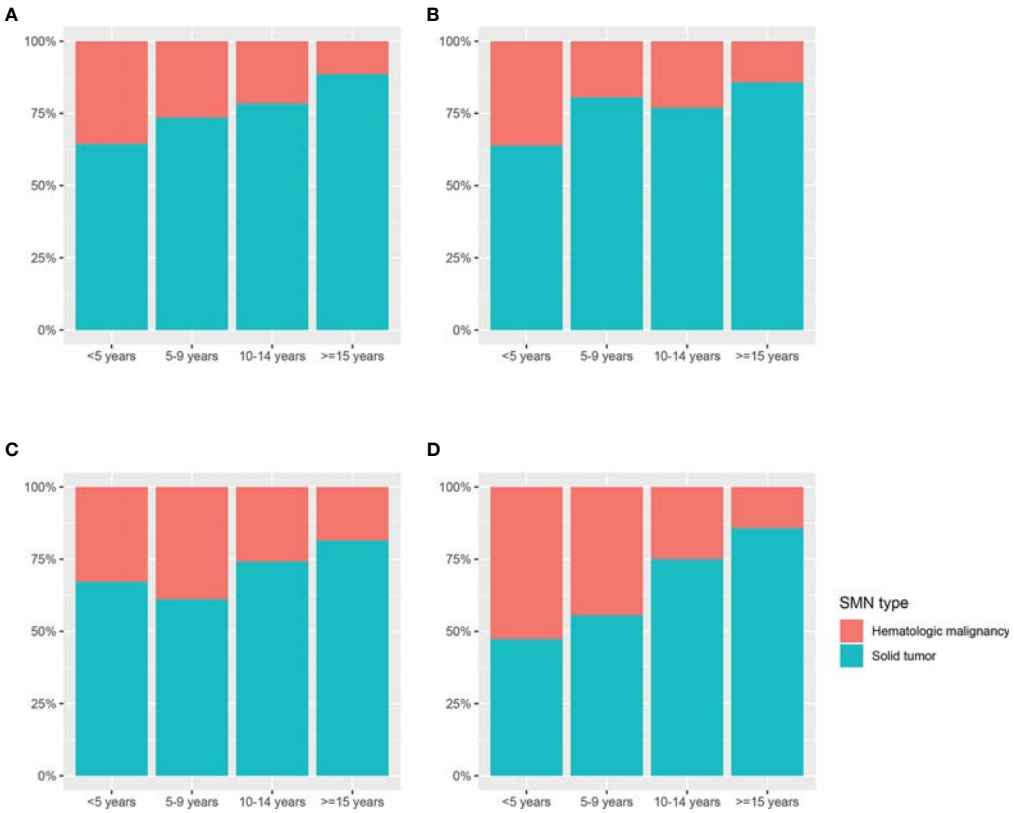

FIGURE 2 | The distribution of second hematologic malignancy and solid tumor in different racial/ethnic groups according to follow-up interval. **(A)** Non-Hispanic whites; **(B)** non-Hispanic blacks; **(C)** Hispanics; and **(D)** Asian/others. *SMN*, second malignant neoplasm.

As shown in **Table 2**, taking non-Hispanic white patients as a reference, non-Hispanic black patients had a 16% overall decreased SMN hazard (PSH, 0.84; 95% CI, 0.72–0.99; p = 0.03) in the unadjusted PSH model. After adjusting by age, gender, diagnosis year, stage, and histology subtype, the hazard attenuated statistical insignificance (PSH, 0.86; 95% CI, 0.73–1.01; p = 0.06). Additional stratification with the Yost index and treatment did not materially affect results. In the adjusted

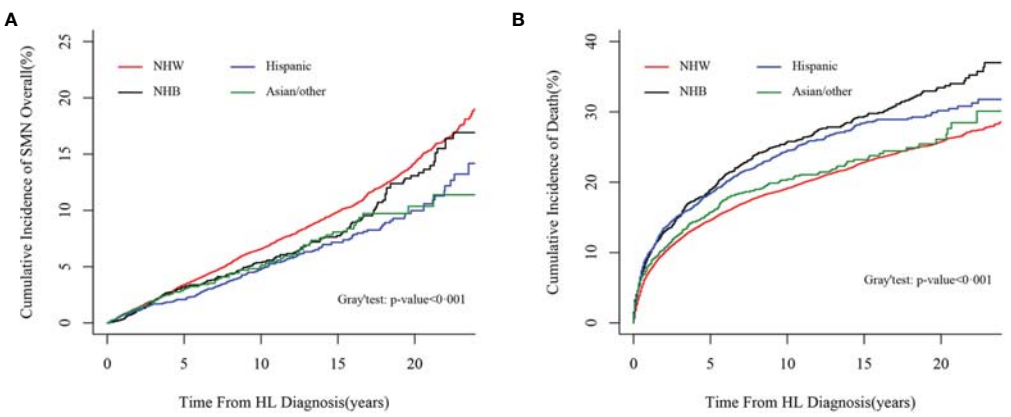

FIGURE 3 | Comparison of cumulative incidences of SMN overall and mortalities between races/ethnicities by the PSH method. **(A)** Comparison of cumulative incidences of SMN overall by the PSH method; **(B)** comparison of cumulative incidences of mortality without SMN by the PSH method. *SMN*, second malignant neoplasm; *PSH*, proportional subdistribution relative hazard.

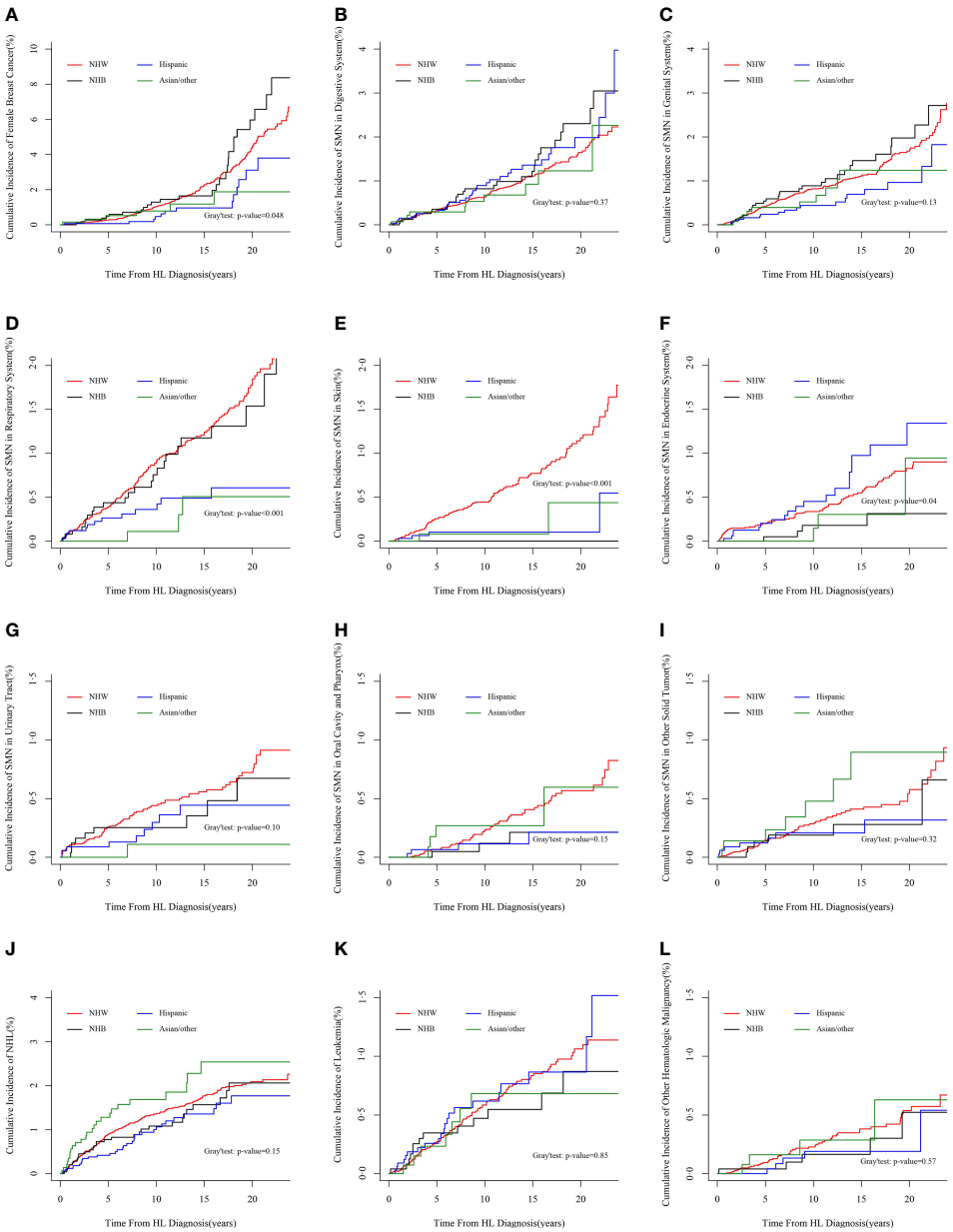

FIGURE 4 | Cumulative incidences of categorized SMN subtypes by PSH method. **(A)** Second female breast cancer, **(B)** SMN in the digestive system, **(C)** SMN in genital system, **(D)** SMN in the respiratory system, **(E)** SMN in the skin, **(F)** SMN in the endocrine system, **(G)** SMN in the urinary system, **(H)** SMN in the oral cavity and pharynx, **(I)** other second solid tumors, **(J)** second NHL, **(K)** second leukemia, and **(L)** other second hematologic malignancy. *SMN*, second malignant neoplasm; *PSH*, proportional subdistribution hazard; *NHL*, non-Hodgkin lymphoma.

analysis for SMN subtypes, non-Hispanic black patients demonstrated a 67% relative decreased SMN hazard in the endocrine system (PSH, 0.33; 95% CI, 0.12–0.91; $p = 0.03$). The adjusted hazard ratios for non-Hispanic black patients compared with non-Hispanic white patients for SMN were similar and somewhat greater in the CSH model. Non-Hispanic black female patients had a higher risk for second breast cancer than non-Hispanic white female patients with the use of the CSH method (CSH, 1.56; 95% CI, 1.03–2.36; $p = 0.04$). However, this risk was lower and non-significant with the use of the PSH method (PSH, 1.43; 95% CI, 0.95–2.17; $p = 0.09$) as shown in **Table 3**.

Hispanic patients had a 32% decreased SMN hazard overall (PSH, 0.68; 95% CI, 0.58–0.79; $p < 0.001$) than non-Hispanic white patients in the unadjusted PSH analysis. After adjusting by age, gender, diagnosis year, stage, and histology, the hazard increased to 0.73 (95% CI, 0.63–0.86; $p < 0.001$). Additional stratification with the Yost index yields a similar result. After

TABLE 2 | Cause-specific hazard and proportional subdistribution hazard among Hodgkin lymphoma patients for overall SMN and mortality due to other causes, taking SEER rules for the SMN definition.

	Non-Hispanic Black vs. Non-Hispanic white		Hispanic vs. Non-Hispanic white		Asian/other vs. Non-Hispanic white	
	CSH (95% CI)	PSH (95% CI)	CSH (95% CI)	PSH (95% CI)	CSH (95% CI)	PSH (95% CI)
Model 1: unadjusted						
Death	1.36 (1.25 to 1.48)*	1.36 (1.25 to 1.48)*	1.26 (1.17 to 1.37)*	1.27 (1.17 to 1.37)*	1.06 (0.94 to 1.20)*	1.06 (0.94 to 1.20)*
SMN	0.92 (0.79 to 1.08)	0.84 (0.72 to 0.99)*	0.74 (0.64 to 0.87)*	0.68 (0.58 to 0.79)*	0.77 (0.62 to 0.97)*	0.73 (0.58 to 0.92)*
Model 2: adjusted for age, gender, diagnosis year, stage, and subtype of HL						
Death	1.44 (1.32 to 1.57)*	1.45 (1.33 to 1.58)*	1.35 (1.25 to 1.46)*	1.36 (1.25 to 1.47)*	1.28 (1.13 to 1.44)*	1.26 (1.12 to 1.43)*
SMN	0.94 (0.80 to 1.10)	0.86 (0.73 to 1.01)	0.84 (0.71 to 0.98)*	0.73 (0.63 to 0.86)*	0.89 (0.71 to 1.11)	0.80 (0.64 to 1.01)
Model 3: additionally adjusted for Yost index						
Mortality	1.43 (1.31 to 1.46)*	1.44 (1.31 to 1.57)*	1.34 (1.24 to 1.45)*	1.34 (1.24 to 1.46)*	1.29 (1.14 to 1.46)*	1.28 (1.13 to 1.45)*
SMN	0.93 (0.79 to 1.09)	0.86 (0.73 to 1.01)	0.83 (0.71 to 0.97)*	0.73 (0.62 to 0.86)*	0.89 (0.71 to 1.12)	0.80 (0.64 to 1.01)
Model 4: additionally adjusted for chemotherapy and radiotherapy						
Mortality	1.35 (1.24 to 1.47)*	1.36 (1.24 to 1.49)*	1.30 (1.20 to 1.40)*	1.30 (1.20 to 1.41)*	1.29 (1.15 to 1.46)*	1.28 (1.13 to 1.46)*
SMN	0.93 (0.79 to 1.09)	0.88 (0.75 to 1.03)	0.83 (0.71 to 0.98)*	0.74 (0.63 to 0.87)*	0.89 (0.71 to 1.12)	0.80 (0.64 to 1.01)

*$p < 0.05$.

An SMN diagnosis was assigned to patients who developed a malignancy at least 2 months after the index Hodgkin lymphoma diagnosis according to the criteria for multiple primary cancers developed by the SEER program.

SMN, second malignant neoplasm; SEER, Surveillance, Epidemiology, and End Results.

additional treatment adjustment, the hazard increased further to 0.74 (95% CI, 0.63–0.87; $p < 0.001$). In the adjusted analysis for SMN subtypes, Hispanic patients demonstrated a 78% relative decreased hazard of subsequent skin cancer (PSH, 0.22; 95% CI, 0.08–0.59; $p = 0.02$) and a 55% decreased SMN hazard in the respiratory system (PSH, 0.45; 95% CI, 0.26–0.79; $p = 0.04$). Again, the CSH method yields similar but somewhat higher hazards. Hispanic patients had a higher SMN risk in the digestive system than non-Hispanic white patients with the use of the CSH method (CSH, 1.51; 95% CI, 1.04–2.21; $p = 0.03$). This risk was

TABLE 3 | Cause-specific hazard and proportional subdistribution hazard among Hodgkin lymphoma patients for categorized SMN subtypes, taking SEER rules for the SMN definition.

	Non-Hispanic Black vs. Non-Hispanic white		Hispanic vs. Non-Hispanic white		Asian/other vs. Non-Hispanic white	
	CSH (95% CI)	PSH (95% CI)	CSH (95% CI)	PSH (95% CI)	CSH (95% CI)	PSH (95% CI)
Skin excluding basal and squamous	NA	NA	0.24 (0.09 to 0.65)*	0.22 (0.08 to 0.59)*	0.26 (0.06 to 1.04)	0.23 (0.06 to 0.93)*
Oral cavity and pharynx	0.43 (0.13 to 1.39)	0.40 (0.12 to 1.29)	0.49 (0.18 to 1.35)	0.43 (0.15 to 1.20)	1.21 (0.44 to 3.36)	1.07 (0.38 to 2.98)
Digestive system	1.45 (0.97 to 2.17)	1.38 (0.92 to 2.08)	1.51 (1.04 to 2.21)*	1.34 (0.91 to 1.96)	1.10 (0.58 to 2.09)	0.97 (0.51 to 1.86)
Female breast	1.56 (1.03 to 2.36)*	1.43 (0.95 to 2.17)	0.62 (0.35 to 1.10)	0.55 (0.31 to 0.98)*	0.62 (0.27 to 1.40)	0.55 (0.25 to 1.24)
Respiratory system	1.09 (0.71 to 1.69)	1.04 (0.67 to 1.62)	0.52 (0.29 to 0.91)*	0.45 (0.26 to 0.79)*	0.30 (0.09 to 0.93)*	0.26 (0.08 to 0.82)*
Genital system	1.33 (0.89 to 1.99)	1.26 (0.85 to 1.88)	0.73 (0.45 to 1.19)	0.65 (0.40 to 1.07)	0.97 (0.51 to 1.85)	0.87 (0.46 to 1.64)
Urinary system	0.83 (0.41 to 1.66)	0.80 (0.39 to 1.62)	0.74 (0.37 to 1.49)	0.68 (0.34 to 1.38)	0.20 (0.03 to 1.43)	0.18 (0.03 to 1.30)
Endocrine system	0.35 (0.13 to 0.95)*	0.33 (0.12 to 0.91)*	1.31 (0.78 to 2.17)	1.24 (0.75 to 2.07)	0.50 (0.16 to 1.59)	0.47 (0.15 to 1.53)
Other solid tumor	0.79 (0.34 to 1.86)	0.74 (0.32 to 1.71)	0.78 (0.35 to 1.73)	0.72 (0.33 to 1.61)	1.86 (0.84 to 4.10)	1.75 (0.81 to 3.78)
NHL	0.81 (0.55 to 1.19)	0.78 (0.54 to 1.14)	0.84 (0.58 to 1.22)	0.77 (0.53 to 1.12)	1.59 (1.05 to 2.41)*	1.48 (0.98 to 2.25)
Leukemia	0.93 (0.52 to 1.66)	0.89 (0.50 to 1.59)	1.21 (0.75 to 1.94)	1.10 (0.67 to 1.78)	0.98 (0.45 to 2.11)	0.90 (0.42 to 1.92)
Other hematologic malignancy	0.75 (0.29 to 1.90)	0.72 (0.28 to 1.83)	0.70 (0.28 to 1.76)	0.62 (0.25 to 1.55)	1.30 (0.47 to 3.62)	1.15 (0.42 to 3.19)

*$p < 0.05$.

An SMN diagnosis was assigned to patients who developed a malignancy at least 2 months after the index Hodgkin lymphoma diagnosis according to the criteria for multiple primary cancers developed by SEER program. All these hazards were adjusted by age, gender, diagnosis year of Hodgkin lymphoma, Ann Arbor stage, histology, Yost index, and treatment as appropriate.

SMN, second malignant neoplasm; NHL, non-Hodgkin lymphoma; SEER, Surveillance, Epidemiology, and End Results. NA, not available.

lower and non-significant with the use of the PSH method (PSH, 1.34; 95% CI, 0.91–1.96; $p = 0.13$), as shown in **Table 3**.

Asian/other patients had a 27% decreased overall SMN hazard (PSH, 0.73; 95% CI, 0.58–0.92; $p < 0.001$) than non-Hispanic white patients in the unadjusted PSH analysis. After adjusting by age, gender, diagnosis year, stage, and histology subtype, the hazard increased to 0.80 (95% CI, 0.64–1.01; $p = 0.06$). Additional stratification with the Yost index and treatment yields similar results. In the adjusted analysis for SMN subtypes, Asian/other patients demonstrated a 74% relative decreased PSH of SMN in the respiratory system (PSH, 0.26; 95% CI, 0.08–0.82; $p = 0.02$) and a 77% relative decreased PSH of subsequent skin cancer (PSH, 0.23; 95% CI, 0.06–0.93, $p = 0.04$). The CSH method yields results that differed somewhat from the PSH method. Asian/other patients had a higher risk for subsequent non-Hodgkin lymphoma (NHL) than non-Hispanic white patients with the use of the CSH method (CSH, 1.59; 95% CI, 1.05–2.41; $p = 0.03$). However, this risk was lower and non-significant with the use of the PSH method (PSH, 1.48; 95% CI, 0.98–2.25; $p = 0.06$), as shown in **Table 3**.

The cumulative incidences of mortality before experiencing a second cancer were compared among different racial/ethnic groups by the PSH and CSH methods (PSH method in **Figure 3B** and CSH method in **Supplemental Figure 3B**). Non-Hispanic white patients were less likely to experience a mortality event before developing SMN than the other three groups. In the fully adjusted model, taking non-Hispanic whites as a reference, the PSH for NHB, Hispanic, and Asian/other patients was 1.36 (95% CI, 1.24–1.49; $p < 0.001$), 1.30 (95% CI, 1.20–1.41; $p < 0.001$), and 1.28 (95% CI, 1.13–1.46; $p < 0.001$), respectively. The results from the CSH model were similar (**Table 2**).

Sensitivity Analyses

These findings above were similar in the sensitivity analyses of the present study to exclude SMN diagnosed within 6 months of the primary Hodgkin lymphoma (**Supplemental Tables 4** and **5**). Indeed, the most significant difference observed was the SMN risk in the endocrine system. With the SEER criteria, both PSH and CSH methods showed that non-Hispanic black patients had a significantly lower SMN hazard in the endocrine system when compared with non-Hispanic white patients (**Table 3**). However, the hazard was higher and attenuated statistical insignificance by both methods using the IACR/IARC criteria.

DISCUSSION

To obtain a dynamic understanding of the racial/ethnic effects on SMN among Hodgkin lymphoma survivors, the PSH and the CSH methods were used in the present study. Both methods showed that, compared with non-Hispanic white patients, non-Hispanic patients had a lower SMN risk in the endocrine system; Hispanic patients had a lower risk for SMN overall, SMN in the respiratory system, and SMN in the skin; and Asian/others had a lower risk for SMNs in the respiratory system. Some differences were also found between the PSH and the CSH results. For instance, CSH analysis showed that Asian/other patients had no significantly lower risk for subsequent skin cancer, but the risk decreased further and became statistically significant with the PSH method. The differences observed between the two methods highlight the differing interpretations of both utilities for understanding the racial/ethnic effects on SMN in Hodgkin lymphoma survivors. CSH shows whether race/ethnicity is directly associated with SMN risk in Hodgkin lymphoma survivors without considering the competing events. However, the PSH method shows whether race/ethnicity affects the actual probability of experiencing second cancer regardless of the direct association.

In the competing risk analysis of the present study, the cumulative mortality due to other causes was found to be lower in non-Hispanic white and Asian/other patients and higher in Hispanic and non-Hispanic black patients. Consistent with existing literature, non-Hispanic black and Hispanic patients with Hodgkin lymphoma tend to have a worse outcome. A population-based analysis has shown that the 5-year overall survival rates for non-Hispanic black (76%) and Hispanic (75%) patients were lower compared with non-Hispanic whites (82%) and non-Hispanic Asians (81%) (18). Among children with Hodgkin lymphoma, Hispanic and non-Hispanic black children demonstrated a higher hazard of post-relapse mortality than non-Hispanic black children (24). Moreover, the adjusted hazard from both methods in the present study suggested that Asian/other patients also had a higher risk of mortality due to other causes than non-Hispanic patients.

Previous studies have shown an increased SMN risk among Hodgkin lymphoma survivors (7, 13, 14, 29, 40, 41). However, these studies were mainly based on white cohorts, and information on other races was limited. Lisa et al. recently noted that the Asian race was associated with SMN risk (42). However, in the present population-based cohort, Asian/other patients were shown to increase the risk of subsequent NHL, but not SMN overall. The different observation with the prior study may be caused by different inclusion criteria and conception of race.

This study is believed to be the first study to comprehensively evaluate the association between race/ethnicity and SMN among Hodgkin lymphoma survivors. This report suggested that SMN rate is lowest in Hispanic patients, and mortality due to other causes is lowest in non-Hispanic white patients. For non-Hispanic black patients, both SMN rate and mortality due to other causes are relatively high. Asian/other patients have a relatively low cumulative SMN incidence and mortality due to other causes and show a different SMN distribution when compared with other racial/ethnic groups. Asian/others have the highest proportion of subsequent hematologic malignancy and seem to more likely develop NHL than other groups. All the aforementioned suggested that race/ethnicity should be considered when developing strategies for survivorship care among Hodgkin lymphoma survivors. It is worth noting that the racial/ethnic impact pattern on SMN risk could differs between Hodgkin lymphoma and all cancer survivors. A large cohort study that included young patients diagnosed with

invasive cancer between 1990 and 2012 has revealed that, compared with non-Hispanic white patients, Asian/Pacific Islanders were associated with a lower risk for SMN overall, but Hispanics were not (43).

Parsing out the underlying cause for the association between race/ethnicity and SMN in the present study is challenging. The proposed hypotheses for cancer health disparities often relate to racial/ethnic differences in host biology or differences in socioeconomic status and healthcare access (44). In the present study, differences in SMN risk may not entirely be explained by socioeconomic status and treatment because the adjustment for Yost index and treatment type did not change the results. Genetic or biological attributes in each race/ethnicity group may explain the observed distribution of SMN risk in the present study. However, no relevant research was noted on racial differences in genetic factors associated with Hodgkin lymphoma. Besides genetic factors, differences in lifestyles may be a possible explanation for this observation. Lung cancers, as first or second neoplasm, are well-known to be influenced by smoking histories (45, 46). Interestingly, previous studies have reported that individuals of white and black descent have a higher smoking prevalence than Asians and Hispanics (21), which may take partial part in the higher second lung cancer incidence in non-Hispanic white and non-Hispanic black patients with Hodgkin lymphoma. Physical inactivity, excess body weight, and some aspects of the Western diet are known risk factors for colon cancer (47–49). Previous studies had reported that Hispanics were engaged in less healthy exercise and dietary behaviors than non-Hispanic whites (50–52). In the present study, we also identified that Hispanics had a higher risk for subsequent colon cancer when compared with non-Hispanic whites. Interventions focused on these factors may reduce racial/ethnic differences in certain second cancer incidence.

The present study includes a large number of Hodgkin lymphoma survivors from a population-based setting, which eliminated biases in hospital-based series. The present study also has some limitations. Some variables that would also potentially influence the risk of SMNs in Hodgkin lymphoma survivors (e.g., family history, genetic information, and lifestyle characteristics) were unavailable. Some information about treatment is missing out, and the SEER dataset only collects the initial treatment type; the detailed drugs, doses, radiation fields, and subsequent therapy patients received are unknown, potentially biasing the results. Moreover, there were no uniform criteria for SMN. The criteria for defining SMN differ between studies; analysis with different definitions may yield different results. However, the impact seems not large, based on the sensitivity analysis. An additional limitation is the multiple comparisons without correction that we undertook, given the exploratory nature of this study. Further research to validate the association between race/ethnicity and SMN among Hodgkin lymphoma survivors is needed.

CONCLUSIONS

In summary, the findings of the present study revealed substantial racial/ethnic differences in the SMN risk and mortality among Hodgkin lymphoma patients. The dual analysis with CSH and PSH methods provides a comprehensive view of racial/ethnic effects on SMN risk among Hodgkin lymphoma survivors. These findings suggest that race/ethnicity needs to be considered in future cancer surveillance for patients with Hodgkin lymphoma.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. These data can be found here: researchers interested in the SEER database may submit an inquiry online, at https://seer.cancer.gov/data/access.html.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LW, QX, and HX contributed to the conception and design of the study. LW, HX, JH, and SL contributed to data curation. LW, HX, JH, DC, and QZ performed the statistical analysis. HX, LL, XY and JC wrote the first draft of the manuscript. HX wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Late Mortality, Subsequent Malignant Neoplasms and Hospitalisations in Long-Term Survivors of Adolescent and Young Adult Hematological Cancers

Annalisa Trama[1], *Claudia Vener*[2], *Paolo Lasalvia*[1†], *Alice Bernasconi*[1*†] *and the Ada Working Group*

[1] Evaluative Epidemiology Unit, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, [2] Oncology and Haemato-Oncology Department, University of Milan, Milan, Italy

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Roberto Crocchiolo,
Niguarda Ca' Granda Hospital, Italy

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Guoqiao Zheng,
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Kristin Schroeder,
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***Correspondence:**
Alice Bernasconi
alice.bernasconi@istitutotumori.mi.it

[†]These authors have contributed equally to this work and share last authorship

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Background: Increased success in the treatment of hematological cancers contributed to the increase of 5-year survival for most adolescent and young adults (AYAs) with these tumours. However, as 5-year survival increased, it became clear that AYA long-term survivors were at increased risk for severe late effects. Moreover, limited information on long-term cancer impact is available for AYAs, since most studies focused on children and adolescents. We aimed to assess various long-term outcomes on AYA survivors of hematological cancers.

Methods: We selected patients diagnosed with a first primary hematological cancer between 1997 and 2006, in the Italian nationwide population-based cohort of AYA cancer survivors (i.e. alive at least 5 years after cancer diagnosis). Long-term outcomes of interest were: second malignant neoplasms (SMNs), hospitalizations and overall mortality. We calculated standardized incidence ratios (SIRs), standardized hospitalization rate ratios (SHRs) and standardized mortality rate ratios (SMRs). To study morbidity patterns over time, we modeled observed incidence rates by fitting flexible parametric models for nonlinear patterns and we used linear regression for linear patterns.

Results: The study cohort included 5,042 AYA hematological cancer survivors of which 1,237 and 3,805 had a leukaemia and lymphoma diagnosis, respectively. AYA survivors were at substantially increased risk for SMN (SIR=2.1; 95%CI=1.7; 2.6), hospitalisation (SHR=1.5; 95%CI=1.5; 1.6), and mortality (SMR=1.4; 95%CI=1.2; 1.6) with differences between leukaemia and lymphoma survivors. The highest excess risks of hospitalisations were for infectious diseases, respiratory diseases, and diseases of blood and blood-forming organs. The morbidity pattern differs over time by morbidity type.

Conclusions: Our results support the need for strict follow-up plans for survivors, and call for further study to better personalised follow-up plans for AYA cancer survivors.

Keywords: long-term outcomes, adolescents and young adults (AYAs), hematological cancers, cancer survivors, population-based cohort

INTRODUCTION

Hematological tumours are common cancers in adolescents and young adults (15-39 years at cancer diagnosis; AYAs), especially in males and younger AYAs (1). Survival for hematological cancers (acute lymphoid leukemias, acute myeloid leukemias, Hodgkin's lymphomas, non-Hodgkin lymphomas), is significantly worse in AYAs than in children but it is good and continuously improving (2), thus an increasing number of young people are becoming long-term cancer survivors.

Long-term outcomes in AYA cancer survivors are not well understood and are largely extrapolated from survivors of childhood cancer. However, AYAs have different cancer types from children and adults, and the biology of AYA cancers is distinct. AYAs may handle treatment differently and have different late effects. Furthermore, adolescence and young adulthood is a challenging developmental phase. The problem is that studies have focused mainly on childhood cancer survivors' late effects. Because cancer in AYAs is so different to cancer in children, findings derived from childhood studies cannot be extrapolated to AYA cancer survivors (3). Furthermore, the available studies on the long-term impact of cancer on AYAs have focused mainly on a single long-term outcome (4–8) or a single tumour (9–12).

Considering the dearth of information on AYAs, it is becoming very important to study late effects in AYA cancer survivors to optimize management that will reduce number and impact of adverse effects.

Against this background, we aim to provide a comprehensive assessment of diverse long-term health outcomes (i.e. subsequent malignant neoplasms (SMNs), all-cause mortality, and hospitalisations) on survivors of all and recently diagnosed hematological cancers. Taking advantage of the Italian nationwide cohort of AYA cancer survivors, we will consider the AYA cancer patient population as a whole (15-39 years). This is the first Italian nation-wide cohort of AYA cancer survivors which takes advantage of large population-based cancer registries (CRs) and, through large-scale record linkage techniques, with health database, death registries, and hospital registries, provides accurate follow-up information on AYA cancer survivors (13).

MATERIALS AND METHODS

The AYA cancer survivor cohort has been described elsewhere (13). Briefly, it is a retrospective incident-based cohort derived from CRs. Each CR identified patients with a first cancer diagnosis between the ages of 15 and 39 years during the entire incidence period covered, linking them to all their SMNs, hospital discharge records (HDRs), and mortality data. AYA cancer survivors were subsequently defined as those patients alive at least 5 years after the first cancer diagnosis. CRs contributed to the cohort with different incidence periods, depending on the year of establishment. As of September 2021, about 30 CRs contributed to the cohort with 67,692 AYA cancer survivors diagnosed between 1976 and 2013.

This paper focuses on AYA hematological cancer survivors. Hematological tumours were defined according to the International Classification of Childhood Cancer, Third Edition ICCC-3 (14): Group I "Leukaemia, myeloproliferative diseases, and Myelodysplastic diseases" and Group II "Lymphomas and reticuloendothelial neoplasms". We divided lymphomas into Hodgkin lymphomas (HLs) and non-Hodgkin lymphomas (NHLs) (except Burkitt lymphoma), as ICCC-3 Group IIa and Group IIb, respectively, and other lymphomas (**Supplementary Table 1**). Furthermore, leukemias were divided according to the histology codes of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), into acute leukemias (ALs), chronic leukemias (CLs), and other leukemias (**Supplementary Table 1**). Only tumours with malignant behaviour were included in the analysis (ICD-O-3 behaviour=3).

Outcomes of interest were: SMNs, hospitalisations (used as a proxy of chronic comorbid conditions), and overall mortality. An SMN was defined as a malignant neoplasm of any site with different morphology from the first primary tumour, according to recommended multiple primary cancer coding (15). The aim of these rules is to distinguish recurrences or progressive disease from multiple primary cancers. SMNs were provided by CRs. Hospital admissions were grouped into 10 main diagnostic groups, converting ICD-8 and ICD-10 codes to ICD-9 CM codes, as in Rubjerg et al. (16): Infectious and parasitic diseases (001–139), Endocrine diseases and other related diseases (240-279), Diseases of blood and blood-forming organs (280-289), Diseases of nervous system and sense organs (320-389), Diseases of circulatory system (390-459), Diseases of respiratory system (460-519), Diseases of digestive organs (520-579), Diseases of urinary system and genital organs (580-629), Diseases of the skin and subcutaneous tissue (680-709), and Diseases of bone, joint, and soft tissue (710-739). Hospitalisations were retrieved from HDRs. Mortality was retrieved from the regional mortality registries.

To maximise both the representativeness of the CRs and the follow-up time for each outcome of interest, we selected AYAs diagnosed with a first primary hematological cancer between 1997 and 2006 (**Figure 1**, cohort recruitment window). Of the 31 CRs included in the cohort, 6 CRs were excluded because cancer registration started outside the selected cohort window (i.e. from 2007 onwards) and 1 CR was excluded because the HDRs were missing. Ultimately, 24 CRs (**Figure 1**, red box) contributed to these analyses. The 24 included CRs covered about 34% of the Italian population from different geographical areas. Follow-up for cancer incidence was available for most CRs until 2012, while HDR and mortality files were available until 2016 (**Figure 1**, dotted lines).

Statistical Analyses

The three outcomes of interest (SMNs, all-cause mortality, and hospitalisations) were analysed separately. To avoid inclusion of most acute, sub-acute, non-persistent, or treatment-induced conditions, follow-up began 5 years after the date of cancer diagnosis. For each outcome, the follow-up ended on the date of emigration, last known vital status, specific outcome of interest occurrence (SMN, cause-specific first hospitalization or death), last availability of the linked data source (incidence date entered by the CRs, HDRs or mortality registry) or the closing date (31

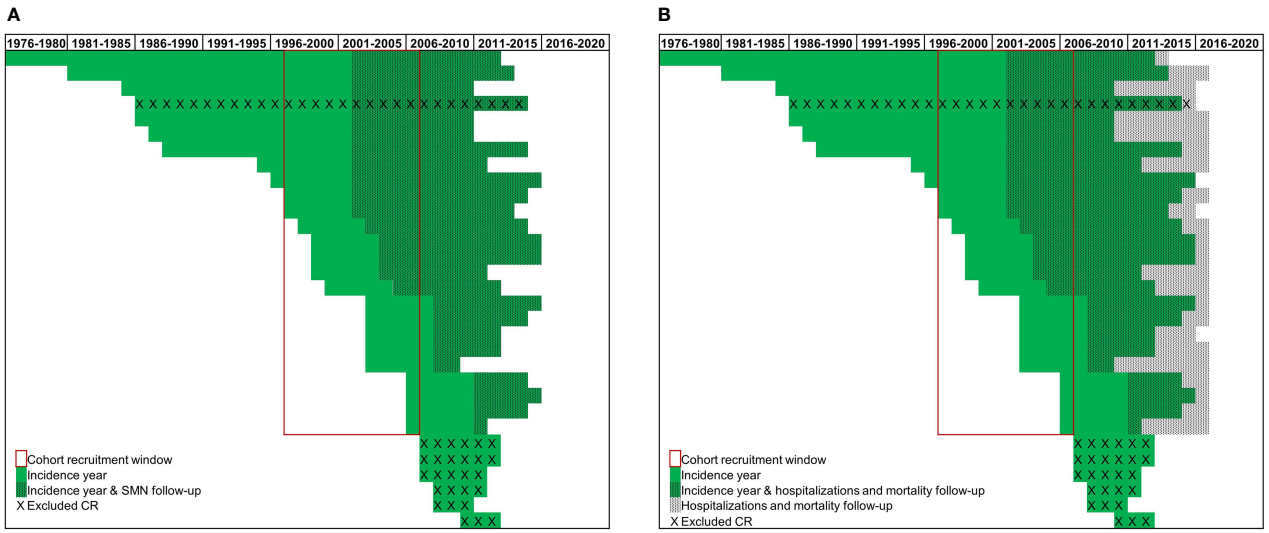

FIGURE 1 | Incidence and available follow-up **(A)** for Second Malignant Neoplasms (SMNs) and **(B)** for hospitalizations and mortality, over time by cancer registries (CR) (green lines).

December 2012 for SMNs or 31 December 2016 for mortality and hospitalisations). Only the first event (SMN and specific hospital admission) was considered in the analyses.

We estimated the excess risk of SMNs, hospitalizations, and all-cause mortality in AYA hematological cancer survivors by standardized incidence ratios (SIRs), standardized hospitalization rate ratios (SHRs), and standardized mortality rate ratios (SMRs), respectively. SIRs, SHRs, and SMRs were all calculated as the ratio between observed and expected events. Observed events refer to events experienced by the cohort during the follow-up period. Expected events are events the AYA cohort would have experienced had their risk been the same as the general population. Expected events were calculated by multiplying the incidence rates of the general population, matched by gender, area of residence, attained age (5-year band), and calendar year (1-year band), with the person-year at risk accrued by the AYA survivor cohort. Expected general population rates for SMNs, hospitalizations, and mortality were calculated using complete cancer incidence data provided by the CRs, Italian nationwide HDRs (13), and ISTAT (the Italian National Institute of Statistics) mortality tables (17), respectively. We calculated 95% confidence intervals (CI) assuming a Poisson distribution.

We identified non-linear hospitalization rates over time, modelling observed incidence rates by fitting flexible parametric models (18). We used linear regression to describe linear hospital admissions over time. To visualize the excess risk over time, we graphically present observed and expected hospitalization rates over time. We calculated expected events by multiplying the incidence rates of the general population, thus precluding formal assessment of the variability of the expected rates. This is why we have simply described the differences between the curves without comparing them statistically. All analyses were performed using Stata 17.

RESULTS

The cohort of 5,042, 5-year AYA hematological cancer survivors had a median follow-up time of 10 years (interquartile range 8-12) for SMNs and of 13 years (interquartile range 11-15) for hospitalisations and mortality. Most 5-year AYA survivors were males (54%) and were diagnosed during adulthood (30-39 years, 55%) (**Table 1**). Leukemias were reported in 25% of AYA survivors and most leukaemia survivors had CL (60%). Among leukaemia patients, as expected, AL was more common in adolescents while CL was more common in young adults. Lymphomas were described in 75% of AYA survivors of whom 54% were HL and 40% were NHL. Among patients with lymphoma, HL were more frequent in 15-19 and 20-29 years olds whereas NHL was more frequent in young adults (30-39 years).

Table 2 shows SIRs, SHRs, and SMRs overall, by sex and type of first hematological cancer. AYA hematological cancer survivors were at substantially increased risk for SMN (SIR=2.1; 95%CI=1.7; 2.6), hospitalisation (SHR=1.5; 95% CI=1.5; 1.6), and mortality (SMR=1.4; 95%CI=1.2; 1.6). SIR, SHR, and SMR were 2.4 (95%CI=1.7;3.3) and 1.9 (95%CI=1.4; 2.5); 1.7 (95%CI=1.6; 1.8) and 1.4 (95%CI=1.3; 1.5); 1.3 (95% CI=1.1; 1.5) and 1.7 (95%CI=1.4; 2.0) in males and females, respectively. Lymphoma survivors were at greatest risk of developing SMN, being more than two-fold higher (SIR=2.2; 95%CI=1.7; 2.8) than the age-specific and gender-specific rates. NHLs and HLs had equal SIR values, but NHLs showed higher SHRs and SMRs than HL survivors. The highest risk for leukaemia survivors was hospitalisation (SHR=1.8; 95%CI=1.6; 1.9). However, CL survivors had an 80% excess risk of developing any SMN (SIR=1.8; 95%CI=1.0; 3.2). For AL survivors, the number of observed events was too small to draw conclusions on the excess risk of SMN. No major differences in terms of SMR

TABLE 1 | Characteristics of adolescent and young adult hematological cancer survivor cohort, overall and by type of hematological cancer, by sex and age at diagnosis.

	Total	Sex				Age at diagnosis					
		Male	%	Female	%	15-19	%	20-29	%	30-39	%
Overall	5042	2702	54%	2340	46%	584	12%	1681	33%	2777	55%
Leukaemias	1237	674	25%	563	24%	117	20%	346	21%	774	28%
-Acute Leukaemias	427	229	9%	198	8%	81	14%	132	8%	214	8%
-Chronic Leukaemias	745	418	15%	327	14%	32	5%	202	12%	511	18%
-Other Leukaemias	65	27	1%	38	2%	4	1%	12	1%	49	2%
Lymphomas	3805	2028	75%	1777	76%	467	80%	1335	79%	2003	72%
-Hodgkin Lymphomas	2,048	1002	37%	1046	45%	358	61%	875	52%	815	29%
-Non-Hodgkin Lymphomas	1,533	894	33%	639	27%	84	15%	385	23%	1064	38%
-Other Lymphomas	224	132	5%	92	4%	25	4%	75	4%	124	5%

Percentages (%) are calculated as column totals except for overall (total for the row).

were observed between AYA survivors of lymphoma and leukaemia.

AYA cured from their hematological cancer were at high risk for solid (SIR=2.1; 95%CI=1.7; 2.7) and for hematological SMNs (SIR=1.8; 95%CI=0.9; 3.4) (**Figure 2A**). It should, however, be underlined that the hematological SIR was not statistically significant. SIRs for subsequent primary soft tissue sarcoma, melanoma, and cancers of the head and neck, lung, digestive tract, and thyroid rose significantly, but the increase did not achieve statistical significance for urinary tract and breast cancer. The highest excess risks of hospitalisation (four-fold compared to the general population not affected by a primary cancer during young adulthood) were for infectious diseases (SHR=4.5; 95% CI=4.0; 5.0), respiratory diseases (SHR=4.2; 95%CI=3.8; 4.6), and diseases of blood and blood-forming organs (SHR=4.1; 95% CI=3.7; 4.6), followed by diseases of the endocrine system, skin, circulatory system, and digestive organs (**Figure 2B**). SHRs for infectious and respiratory diseases, and diseases of blood and blood-forming organs were higher for leukaemia than for lymphoma survivors.

Figure 3 shows hospitalisation rates over time from 5 years after cancer diagnosis, by main diagnostic group (only hospital admissions with a non-linear trend are reported; those with a linear trend are in **Supplementary Table 1**). The incidence of infectious, endocrine, and blood and blood-forming organ diseases was highest close to the time of cancer diagnosis, declining over time, while the incidence of circulatory and respiratory system diseases was highest close to the time of cancer diagnosis, but then decreased and increased again at year 9. The SHR of AYA hematological cancer survivors remained higher (compared to general population who did not have a primary cancer during young adulthood) up to 20 years from cancer diagnosis. For central nervous and urinary system, skin, digestive organ, and bone diseases, hospitalisation rates did not differ over time from those of the general population (**Supplementary Figure 1**).

DISCUSSION

AYA hematological cancer survivors were at substantially increased risk of SMNs, hospitalizations, and mortality. Previous studies have focused on late effects that are most likely to increase the risk of death. We report all the different types of late effects showing that AYA cancer survivors will face several health problems that will impact their quality of life as well as increase their risk of dying. Notably, survivors not only had an increased risk of chronic diseases but also experienced several such diseases (on average 3). This is important to properly inform AYA survivors and personalize their follow-up.

TABLE 2 | Observed and expected numbers of events (O/E), Standardized Incidence Ratios (SIRs) of Second Malignant Neoplasms, Standardized Hospitalisation rate Ratios (SHRs) and Standardized Mortality rate Ratios (SMRs) with 95% confidence intervals (95% CI): overall and stratified by sex and primary hematological tumor.

	Subsequent Malignant Neoplasms			Hospitalisations			Mortality		
	O/E	SIR	95% CI	O/E	SHR	95% CI	O/E	SMR	95% CI
Overall	86/41	2.1	[1.7; 2.6]	3226/2092	1.5	[1.5; 1.6]	291/209	1.4	[1.2; 1.6]
Sex									
Male	39/16	2.4	[1.7; 3.3]	1786/1053	1.7	[1.6; 1.8]	179/142	1.3	[1.1; 1.5]
Female	47/25	1.9	[1.4; 2.5]	1440/1038	1.4	[1.3; 1.5]	112/67	1.7	[1.4; 2.0]
First primary hematological tumour									
Leukaemias (including other leukaemias)	18/11	1.7	[1.1; 2.7]	895/510	1.8	[1.6; 1.9]	78/54	1.4	[1.2; 1.8]
-Acute Leukaemias	5/3	1.5	[0.6; 3.7]	299/163	1.8	[1.6; 2.1]	31/16	2.0	[1.4; 2.8]
-Chronic Leukaemias	12/7	1.8	[1.0; 3.2]	521/322	1.6	[1.5; 1.8]	38/36	1.1	[0.8; 1.5]
Lymphomas (including other lymphomas)	68/31	2.2	[1.7; 2.8]	2331/1582	1.5	[1.4; 1.5]	213/155	1.4	[1.2; 1.6]
-Hodgkin Lymphomas	32/14	2.2	[1.6; 3.1]	1025/806	1.3	[1.2; 1.4]	82/70	1.2	[0.9; 1.4]
-Non-Hodgkin Lymphomas	32/15	2.2	[1.5; 3.1]	1167/683	1.7	[1.6; 1.8]	122/75	1.6	[1.4; 1.9]

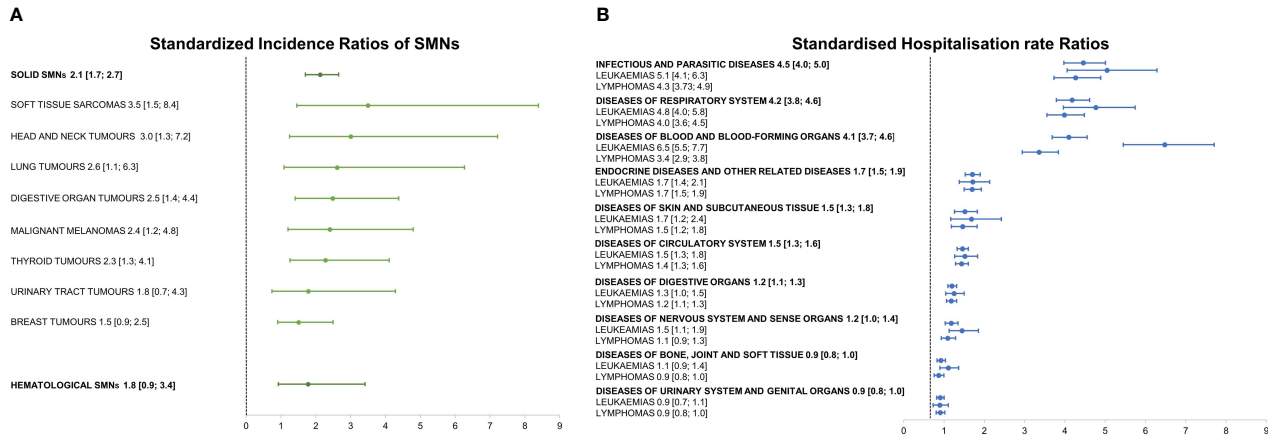

FIGURE 2 | **(A)** Standardized Incidence Ratios of Second Malignant Neoplasms (SMNs) stratified as hematological and solid and by subsequent solid malignant tumor type; **(B)** Standardized Hospitalisation rate Ratios stratified by cause of hospitalisation and hematological first primary cancer, with 95% confidence intervals in brackets.

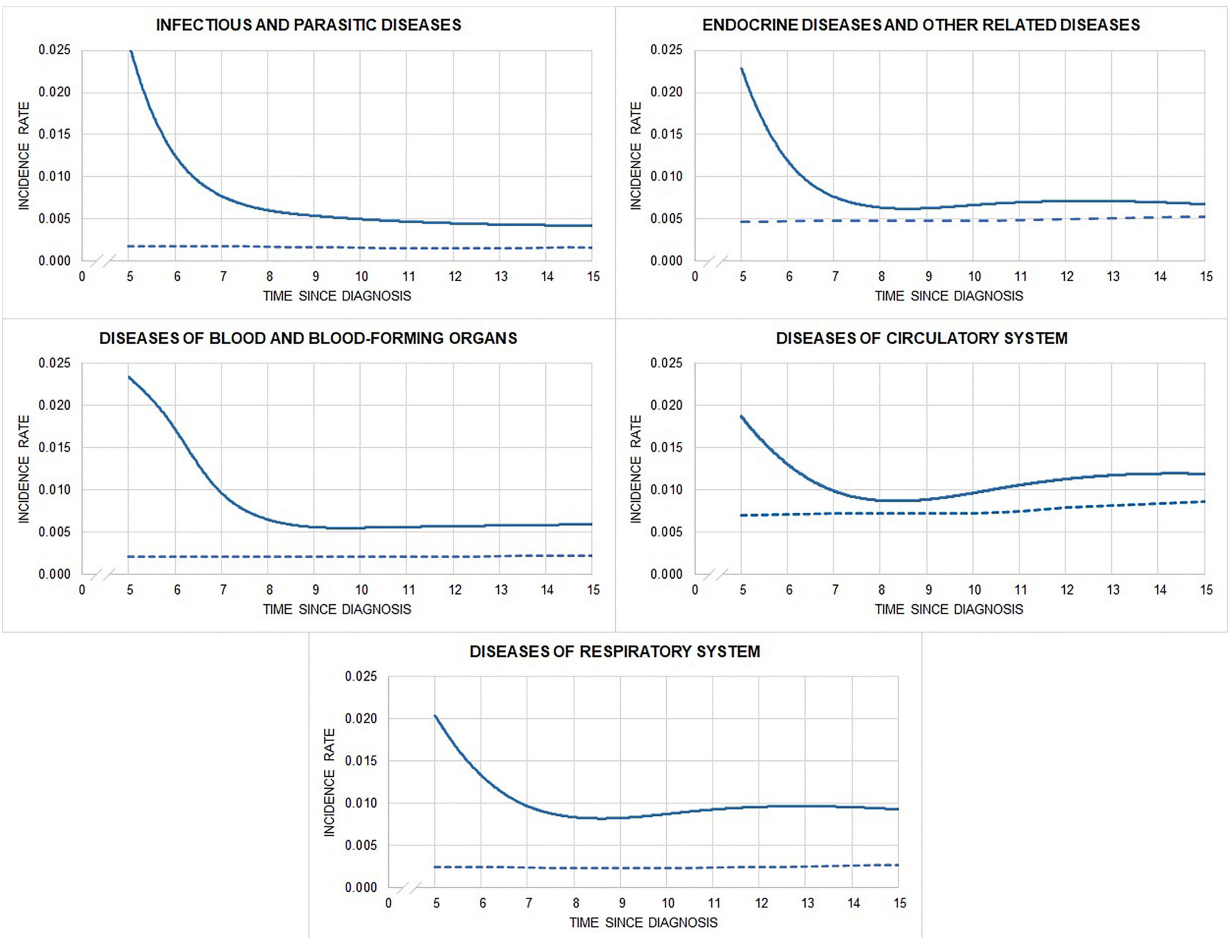

FIGURE 3 | Observed (solid) and expected (dashed) hospitalisation rates by time since diagnosis and main diagnostic groups of hospitalization.

Available studies are difficult to compare due to varying methods for defining risk, age groups (e.g. 15-24; 15-29 years), and primary cancer, in addition to differences in study period, follow-up, and comparison groups. In any event, our results support previous evidence of an excess risk of death (8, 9), SMNs (7, 19), and hospitalizations (16, 20–22) for AYA hematological cancer survivors compared to the general population. We report about the AYA cancer patient population as a whole (15-39 years).

Furthermore, we focused on a recent diagnosis period (1997-2006) during which improved cancer treatment, including targeted and precision therapies, should have reduced the therapeutic burden used. Our results confirmed that SMRs, SMNs, and SHRs are lower in more recent periods of diagnosis. Bhuller et al. (9) reported increased late morbidity (SIR=7.8) and mortality risk (SMR=8.8) for 442 teenage and young adult 5-year survivors of HL, diagnosed at 15–24 years of age, between 1970 and 1999. However, SMRs and SIRs were lower for survivors diagnosed in 1990-1999 compared to 1970-1979. Anderson et al. (8) observed a substantial decrease in 5-year all-cause mortality and primary cancer-specific mortality between the earliest (1975-1984) and most recent (2005-2011) diagnosis periods for several cancer types, including leukaemia, NHL, and HL. Kumar (23) reported that HL patients diagnosed between 1973 and 1986 had a 12% greater risk of developing secondary cancers (HR=1.12; 95%CI, 1.03-1.23; P = 0.01) compared with patients diagnosed between 1987 and 2000.

Our results have shown that solid tumors are the most common SMNs. We also observed that the risk of developing any SMN was higher for NHL and HL than for leukaemia survivors. Moreover, among leukaemia survivors, CLs showed higher SIRs than did ALs. These differences may be related to the natural course of the diseases, especially to the longer treatment burden for some lymphomas and CLs compared to ALs, in which treatment tends to be concentrated over a shorter time. The elevated risk of subsequent solid cancers (lung, breast, stomach, and pancreas) has been largely attributed to radiation therapy and particularly to high radiation doses. For lung cancer, the increased relative risk from smoking appeared to multiply the elevated risks from radiotherapy. We do not have data on smoking habits in our cohort. However, previous studies showed that compared with controls, survivors reported smoking tobacco at the same rate or higher rate (24–27); based on the *Behavioural Risk Factor Surveillance* Italian (*Progressi delle Aziende Sanitarie per la Salute in Italia [PASSI]*) among 18-24 and 25-34 years old, smoking prevalence was 30% and 33%, respectively (28). Furthermore, not only radiotherapy but also alkylating chemotherapy can substantially increase the risk of solid malignancies, particularly of lung, stomach, and pancreatic cancer (12), while anthracycline exposure can heighten the risk of breast cancer and other solid malignancies, including sarcoma (29). Immunosuppression, exposure to ultraviolet radiation, and genetic factors have been purported to generate a host environment conducive to the development of malignant melanoma, NHL or chronic lymphatic leukaemia (CLL) (30). Finally, chemotherapy and radiation therapy have been most closely explored as possible risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukaemia (31). Unfortunately, we do not have data on treatment details.

The pattern of hospitalization is similar among hematological cancer survivors, with the highest SHRs for infectious, respiratory, and blood and blood-forming organ diseases. However, the SHR was higher for leukaemia than for lymphoma survivors. This is likely the result of intensive treatments with immunosuppressive agents more commonly used in leukemias than in other hematological disorders, for which targeted and precision therapies have been available for many years (32–36). Unfortunately, we lack data on treatment details to support and discuss our hypothesis in detail. Note should also be taken of the high SHRs for endocrine and circulatory system diseases. Treatment for HL includes irradiation to the thyroid region, which increases the risk of thyroid diseases. In addition, evidence has shown that total body irradiation performed in preparation for bone marrow transplantation results in high risks for gonadal dysfunction, thyroid dysfunction, and adrenal abnormalities (5, 37). In our cohort, the most common dysfunctions observed in the endocrine diagnostic group were thyroid diseases and diabetes. A high incidence of cardiovascular disease among patients with leukaemia and NHL has previously been found and attributed to several cancer therapies (4, 21, 38, 39). The occurrence of cardiovascular disease events has also been associated with a substantially heightened risk of death (21), suggesting that the identification and mitigation of cardiovascular disease risk factors in these high-risk populations may improve long-term patient outcomes. While we observed a high SHR for disease of the circulatory system, we were unable to assess the cause of death. However, we did find that AYA survivors who died tended to have several chronic comorbid conditions, including cardiovascular diseases.

Our study has several strengths, including the unbiased population-based approach, the reliability of Italian CR data, the longitudinal nature of the data, and cohort coverage. Our cohort covers 34% of the Italian population and includes CRs from different geographical areas of northern, central, and southern Italy. It is thus reasonably representative of areas characterized by different lifestyles, which may have a relevant impact on the chronic comorbid conditions observed. This is also the first study to systematically characterize the development of chronic comorbidities, including SMNs, among survivors of AYA cancer in Italy. Nonetheless, our study does also have some limitations. CRs do not collect data on cancer stage, treatment, or genetic information. Our outcomes are time-dependent measures hence our results directly depend on observed follow-up time. We intentionally selected CRs to maximize the follow-up, but since we are focusing on a recent period of diagnosis, follow-up of our cohort may not be sufficient to provide a comprehensive burden of long-term comorbid conditions.

To conclude, AYA hematological cancer survivors face many life transitions in terms of education, employment, social relations, relocations, and family formation. Late effects could thus have far more physical and social consequences for AYAs

than for older adults. Our study, assessing multiple types of morbidities, has highlighted that survivors of adolescent and young adult hematological cancers face persistent risks (at least 20 years from diagnosis) for a broad range of diseases underscoring the need for strict evidence-based follow-up plans for survivors, designed to increase the likelihood of early detection and ultimately prevent chronic treatment-induced conditions. Our findings have also shown that the morbidity pattern differs over time by morbidity type. The incidence of some diseases (infectious, endocrine, and blood and blood-forming organ diseases) was highest close to the time of cancer diagnosis and declined over time, while the incidence of others (circulatory and respiratory system diseases) was highest close to the time of cancer diagnosis, but then decreased and increased again at year 9. Having information on when patients are at greatest risk is very important in defining personalized follow-up strategies that minimize the burden of follow-up exams.

ADA WORKING GROUP

Manuel Zorzi, Anita Andreano, Paolo Contiero, Gianfranco Manneschi, Fabio Falcini, Marine Castaing, Rosa Angela Filiberti, Cinzia Gasparotti, Claudia Cirilli, Rosalba Amodio, Isabella Bisceglia, Silvia Iacovacci, Maria Francesca Vitale, Fabrizio Stracci, Maria Adalgisa Gentilini, Rosario Tumino, Simona Carone, Giuseppe Sampietro, Anna Melcarne, Luciana Gatti, Lorenza Boschetti, Mariangela Corti, Magda Rognoni, Enzo Coviello, Maria Teresa Pesce, Giancarlo D'Orsi, Anna Clara Fanetti, Lucia De Lorenzis, Giuseppa Candela, Fabio Savoia, Cristiana Pascucci, Maurizio Castelli, Cinzia Storchi.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AT, CV, PL, and AB contributed to writing-original draft and writing-review and editing. AB and PL contributed also to formal analysis, investigation, software and methodology. AT contributed also to conceptualization, project administration and methodology. Ada working group contributed to data collection. All authors approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.823115/full#supplementary-material

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Real-World Estimation of First- and Second-Line Treatments for Diffuse Large B-Cell Lymphoma Using Health Insurance Data: A Belgian Population-Based Study

Willem Daneels[1,2,3*], *Michael Rosskamp*[4], *Gilles Macq*[4], *Estabraq Ismael Saadoon*[2], *Anke De Geyndt*[4], *Fritz Offner*[1,2,3†] *and Hélène A. Poirel*[4†]

[1] Department of Hematology, Ghent University Hospital, Ghent, Belgium, [2] Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium, [3] Cancer Research Institute, Ghent University, Ghent, Belgium, [4] Belgian Cancer Registry, Brussels, Belgium

We determined first- and second-line regimens, including hematopoietic stem cell transplantations, in all diffuse large B cell lymphoma (DLBCL) patients aged ≥20 yr (n = 1,888), registered at the Belgian Cancer Registry (2013–2015). Treatments were inferred from reimbursed drugs, and procedures registered in national health insurance databases. This real-world population-based study allows to assess patients usually excluded from clinical trials such as those with comorbidities, other malignancies (12%), and advanced age (28% are ≥80 yr old). Our data show that the majority of older patients are still started on first-line regimens with curative intent and a substantial proportion of them benefit from this approach. First-line treatments included full R-CHOP (44%), "incomplete" (R-)CHOP (18%), other anthracycline (14%), non-anthracycline (9%), only radiotherapy (3%), and no chemo-/radiotherapy (13%), with significant variation between age groups. The 5-year overall survival (OS) of all patients was 56% with a clear influence of age (78% [20–59 yr] versus 16% [≥85 yr]) and of the type of first-line treatments: full R-CHOP (72%), other anthracycline (58%), "incomplete" (R-)CHOP (47%), non-anthracycline (30%), only radiotherapy (30%), and no chemo-/radiotherapy (9%). Second-line therapy, presumed for refractory (7%) or relapsed disease (9%), was initiated in 252 patients (16%) and was predominantly (71%) platinum-based. The 5-year OS after second-line treatment without autologous stem cell transplantation (ASCT) was generally poor (11% in ≥70 yr versus 17% in <70 yr). An ASCT was performed in 5% of treated patients (n = 82). The 5-year OS after first- or second-line ASCT was similar (69% versus 66%). After adjustment, multivariable OS analyses indicated a significant hazard ratio (HR) for, among others, age (HR 1.81 to 5.95 for increasing age), performance status (PS) (HR 4.56 for PS >1 within 3 months from

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***Correspondence:**
Willem Daneels
willem.daneels@ugent.be

†These authors have contributed equally to this work and share last authorship

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incidence), subsequent malignancies (HR 2.50), prior malignancies (HR 1.34), respiratory and diabetic comorbidity (HR 1.41 and 1.24), gender (HR 1.25 for males), and first-line treatment with full R-CHOP (HR 0.41) or other anthracycline-containing regimens (HR 0.72). Despite inherent limitations, patterns of care in DLBCL could be determined using an innovative approach based on Belgian health insurance data.

Keywords: DLBCL - diffuse large B cell lymphoma, population-based cancer registry, health insurance database, first- and second-line therapy, R-CHOP, hematopoietic stem cell transplantation, comorbidities, real-world studies (RWS)

1 INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common mature B-cell lymphoma, making up about 25%–30% of all lymphoma subtypes in developed countries. For the Belgian population, a median age at diagnosis of 71 years with a crude incidence of 7.8 and age-standardized incidence rate using the European (2013) standard population (ESR2013) of 7.5/100.000 per year was reported in 2018 and 2019, respectively (1–4). Risk stratifications have been developed such as the International Prognostic Index (IPI) and several adaptations (R-IPI, age adjusted-IPI, National Comprehensive Cancer Network (NCCN)-IPI) incorporating tumor stage, lactate dehydrogenase (LDH) level, extranodal involvement, WHO performance status (PS), and age (1, 5, 6).

By gene expression profiling, the cell of origin (COO) can be distinguished as being of germinal center (germinal center B-cell, GCB), activated B-cell subtype (ABC), or non-classifiable. The ABC subtype is generally associated with a worse prognosis (1, 7). However, in routine practice, the cell of origin (COO) is usually determined by immunohistochemistry (IHC) as a proxy (GCB versus non-GCB) due to the unavailability of gene expression profiling. Unfortunately, this approach comes with several disadvantages such as a lower specificity (8). Cytogenetics allow for the identification of "high-grade B-cell lymphoma (HGBCL), with rearrangements of *MYC* and *BCL2* and/or *BCL6*," which is a subgroup with a worse prognosis (8). Overexpression of BCL2 has been identified as a negative prognostic marker (9). In about 30% of cases, both MYC and BCL2 are overexpressed without concomitant translocations in so-called double-expressing lymphomas (DEL), another high-risk group (10). More recently, several genetically defined subtypes of DLBCL have been proposed, based on the combination of various molecular aberrations, which might lead to more individualized treatments upon validation (11–13).

The current standard of care for DLBCL is still immuno-chemotherapy with R-CHOP (rituximab [R], cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone) followed by involved field radiotherapy (IFRT) in certain risk groups. A remission can be achieved in about 80% of patients, which is durable in 70% of cases, resulting in a 5-year overall survival (OS) of 65% in the R-CHOP era (1, 14). Attempts to improve on R-CHOP by adding novel agents have mostly been disappointing (14–16). Patients who experience primary refractory or relapsed disease have a poor prognosis with limited therapeutic options at that point (1, 17). Whenever possible, these patients should be included in clinical trials. Outside of clinical trials, fit patients are generally offered salvage regimens containing rituximab and platinum derivatives, followed by high-dose chemotherapy (HDC), and autologous stem cell transplantation (ASCT). Unfit patients will be offered either similar/less toxic salvage regimens without ASCT or alternatively palliative regimens. Some patients relapsing after ASCT can currently be offered CAR-T cell therapy (chimeric antigen receptor T cells), allogeneic hematopoietic stem cell transplantation (AlloSCT), or novel therapies such as tafasitamab, polatuzumab vedotin, or selinexor (6, 18–20).

However, a significant proportion of patients are unfit for these predominantly intensive treatments because of advanced age and/or comorbidities (21). In real life, the majority of DLBCL patients are older than 65 years of age at diagnosis and a significant proportion have a prior history of other malignancies and/or other comorbidities (2, 22–29). These groups are usually excluded from clinical trials resulting in uncertainty about their optimal clinical management. This underscores the growing interest for real-world population-based studies, to compare the results of randomized clinical trials, with a more representative and unselected population.

With this study, we describe the real-world pattern of care in adult (≥20 yr) DLBCL patients, diagnosed in Belgium between 2013 and 2015, with a specific focus on patients aged ≥60 yr, using the Belgian Cancer Registry (BCR) and health insurance databases, to infer treatment modalities as well as comorbidities.

2 MATERIALS AND METHODS

2.1 The Belgian Cancer Registry and Accessible Databases

The Belgian Cancer Registry (BCR) collects, processes, and analyzes data on all new cancers diagnosed in Belgian residents, by independent collection of double input: oncological care programs and pathology reports. Near-complete coverage is presumed due to combined reporting in nearly 90% of DLBCL cases (4). The BCR is authorized by law to use the National Social Security Identification Number, making it possible to link these data to national administrative health insurance data from the Intermutualistic Agency (IMA). The IMA centralizes details on all healthcare reimbursements of all Belgian citizens (30). Vital status was available until April 2021

through linkage with the national Crossroads Bank for Social Security, providing a follow-up of 5–8 years for all patients. All health records were pseudonymized prior to analysis.

2.2 In- and Exclusion Criteria

Using the diagnostic code 9680/3 from the third edition of the International Classification of Diseases for Oncology (ICD-O-3) (32), we included all new diagnoses of adult (≥20 yr) DLBCL (including B-cell lymphoma unclassifiable), with features intermediate between DLBCL and Burkitt lymphoma (31) and high-grade B-cell lymphoma (HGBCL) [NOS/with *MYC* and *BCL2* and/or *BCL6* rearrangements) (14)] in Belgium between January 1, 2013, and December 31, 2015 (n = 2,139). The final cohort included 1,888 patients after step-wise exclusion of 251 cases due to no available survival data (n = 17), non-Belgian residents (n = 2), no IMA records (n = 38), suspicion of posttransplant lymphoproliferative disorder after prior solid organ/stem cell transplantation (PTLD; n = 33), primary central nervous system lymphoma (PCNSL; n = 158), acute lymphoblastic leukemia (ALL; n = 1), mantle cell lymphoma (MCL; n = 0), or primary mediastinal B-cell lymphoma (PMBCL; n = 2).

2.3 Extraction of Biomarkers

Besides structured files from pathology laboratories, the BCR also receives free-text pathology reports. The latter were used to extract the status of ten main biomarkers (obtained by manual annotations and verified by natural language processing (NLP) automatic extraction). These included expression levels of immunohistochemistry (IHC) markers (CD10, BCL6, IRF4, BCL2, BCL6, MYC, KI-67), cell of origin (COO) classification as determined by the Hans algorithm (33), and gene rearrangements (*MYC*, *BCL2*, *BCL6*) by fluorescence *in situ* hybridization (FISH). Expression of IHC markers was defined positive or negative as described in the pathology report or, when available, using cutoff values for the individual IHC markers according to international guidelines (e.g., ≥40% MYC-positive nuclei and ≥50% for BCL2 expression) (10, 14).

2.4 Extraction of Clinical Data

The ECOG/WHO performance status (PS) and Ann Arbor stage were retrieved from the records of oncological care programs and were available in 85% and 66% of cases, respectively. Information regarding B-symptoms and extra-nodular involvement was only poorly available and not considered for analysis.

2.5 Extraction of Data on Comorbidities

Because the modified Charlson Comorbidity Index (CCI) could not be calculated for 2015, respiratory, cardiovascular, and diabetic comorbidities were assessed for each patient using health insurance data of reimbursed drugs as previously published (34). The BCR gathers information on all new cancer diagnoses in Belgium; hence, we could identify patients having multiple malignancies. Patients were considered to have another tumor if a diagnosis of another malignancy (excluding non-melanoma skin cancer), with an incidence date within 5 years prior to DLBCL diagnosis or thereafter, was registered at the BCR. Additionally, patients without another cancer diagnosis but who received other non-lymphoma-specific chemotherapy within the study period were also identified and considered for outcome analyses.

2.6 Identification of Treatment Regimens

Health insurance data provided a timestamped list of all reimbursed drugs and (medical) procedures per patient. We considered all drugs and procedures within the timeframe of 30 days prior to and 2 years after diagnosis. This window was determined based on the assumption that some drugs might be administered before a definitive diagnosis was made, potential small deviations between the billing and administration date, and that most relapses in DLBCL occur within 2 years (35–38).

For chemotherapy, we included all drugs with the ATC code 'L01' ("Antineoplastic and immunomodulating agents" from the Anatomical Therapeutic Chemical (ATC) Classification System) (39). These drugs are further classified according to specific Belgian CNK codes (Code Nationa(a)l Kode), which allowed us to identify the specific brand, dose, and distribution form (40). An in-house algorithm was set up to define the treatment regimens based on the timed combination of different drugs and administration route. For example, registration of rituximab, cyclophosphamide, and vincristine within a 12-day period was considered as 1 cycle of R-CVP. The addition of doxorubicin within the same timeframe would be considered as R-CHOP. The number of cycles and cycle duration was based on the interval between these drug administrations. Modifications to the initial regimen during treatment could be identified, and the first-line regimen was reclassified based on the predominant regimen.

By selecting for nomenclature codes (a coded list of all medical performances that are entitled for (partial) reimbursement by the mandatory national health insurance), we identified autologous and allogeneic hematopoietic stem cell transplantations (HSCTs) and all forms of external beam radiotherapy (RT). Data on transplantations were available until December 2019 and have been cross-validated and completed with data from the Belgian Transplant Registry (BTR), which is hosted by the BCR. Data on HSCT performed for presumed acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), or myelodysplastic syndrome (MDS) were excluded from our analyses.

We defined refractory and relapsed disease as initiation of any second-line regimen within or beyond 12 weeks from the end of the last first-line treatment administration, respectively. Consolidation regimens, such as in the LNH03-2B protocol (16), and central nervous system (CNS) prophylaxis [e.g., high-dose methotrexate (HD MTX)] within 6 weeks after the end of first-line treatment were still considered to be part of the first-line regimen. Intrathecal (IT) and intravenous (IV) administration of MTX could be distinguished based on the CNK codes.

During our study period, the standard-of-care regimen recommended by ESMO/NCCN/BHS (6, 18, 35) for all DLBCL patients was R-CHOP for 6–8 cycles but based on more recent findings from the FLYER (41), SWOG S0014 (42), and LNH09-1B (43) trials, excellent results can be achieved in patients with

low-risk limited stage disease with only 4 cycles (or even 3 with IFRT). We therefore considered full R-CHOP as ≥6 cycles (n = 793) or ≥4 for Ann Arbor stage I (n = 33). For statistical analyses, treatments were hierarchically grouped into 6 main categories according to their most important components: full R-CHOP (≥6 or ≥4 cycles if Ann Arbor = I, including R-miniCHOP); incomplete (R-)CHOP (<6 cycles or <4 if Ann Arbor = I, and CHOP without R); other anthracycline-containing regimens (e.g., (R-)ACVBP, (R-)CHOP-like, intensified regimens); non-anthracycline-containing regimens (e.g., R-CVP, bendamustine-containing regimens, palliative treatments); only radiotherapy; and no chemo/radiotherapy. Second-line treatments were regrouped into 4 main categories: platinum-containing; non-platinum-containing; bendamustine-containing; and palliative regimens. An in-depth manual revision of more than 400 cases was performed to fine-tune the algorithm.

2.7 Statistical Analyses

Analyses were performed using the SAS 9.4 software package (SAS institute, Cary, NC). Uni- and multivariable survival analyses were based on Cox models. For the multivariable model, we have included all our variables of interest without interaction between them. To avoid a problem of collinearity, we decided to include PS and not Ann Arbor stage in the final multivariable model, as the former had proportionally fewer missing values. For Ann Arbor stage, PS, center volume, BCL2 overexpression on IHC, and COO, we have considered an interaction with a timepoint binary variable (equal to 0 before the considered timepoint and 1 after it) because the proportional hazard assumption (44) was not fulfilled for the whole study period. Consequently, for these variables, hazard ratios were estimated for two distinct periods following the incidence. Because treatments (and likewise the diagnosis of subsequent tumors) occurred after the DLBCL incidence date, the starting point of our study, the different treatments (and subsequent tumors) were considered as time-dependent variables to avoid an immortal time bias (45). The hazard ratio of each treatment compares the group of patients who received the treatment with all other patients (including patients with other treatments). Tests for statistical significance were 2-sided at an alpha = 0.05 level of significance and 95% confidence intervals [95% CI]. Relative survival is calculated as the ratio of the observed survival in a group of patients to the expected survival (obtained with Ederer II method) (4) in a comparable group of individuals from the general Belgian population matched on age, sex, region, and calendar period.

3 RESULTS

3.1 Population Characteristics

We analyzed 1,888 newly diagnosed DLBCL patients with a male/female ratio of 1.2. The median age was 72 years (interquartile range 61–80 yr [IQR]) with 28% of patients aged 80 years or older. Patient characteristics and prognostics markers by age category are detailed in **Supplementary Table 1**. Information on PS was missing in 15% of cases but, when available, was generally deemed good (0 or 1) in 82% of all, and in 72% of patients ≥85 yr. In 12% of cases, another malignancy was registered at the BCR (**Supplementary Figure 1** shows the exact distribution and timing with regard to the DLBCL diagnosis). In 20 patients, 2 or more malignancies (excluding the DLBCL) were registered within the considered timeframe. We did not find an increased standardized incidence ratio (SIR) of prior malignancies compared to the general population when stratified by gender, region, 5-year age category, and incidence year. Respiratory, diabetic, and cardiovascular comorbidities increased with age. Ann Arbor stage was distributed similarly across all age groups, when corrected for the increased number of missing data with advancing age. Information on the cell of origin (COO) was available in 63% of cases with an even distribution of GCB and non-GCB subtypes (32 and 31%). The distribution of COO was similar across all age categories, Ann Arbor stages, PS, comorbidities, and first-line treatments. BCL2 was overexpressed in 79% of evaluable cases. Of only 16% evaluable cases, 49% were double-expressor lymphomas (DEL). Information on *MYC*, *BCL2*, and *BCL6* rearrangements was available in only 11%, 11%, and 8% of cases, respectively. These limited cases demonstrated 20% of isolated *MYC* rearrangements, and 8.7% of "HGBCL, with rearrangements of *MYC* and *BCL2* and/or *BCL6*" according to the latest WHO classification (14).

3.2 Overall Survival Stratified by Age Groups

The 5-year OS of all patients was 56% with a clear influence of age (from 78% [20–59 yr] to 16% [≥85 yr]). Survival curves for the age categories below 55 years closely overlap. Beyond 55 years of age, survival probability decreases with age as demonstrated in **Supplementary Figure 2**. In contrast to the International Prognostic Index (IPI), which uses 60 yr as the only age cutoff, survival changed more markedly after the age of 70. We have regrouped our cohort into 5 clinically relevant categories which are of adequate size for statistical comparisons and demonstrate a different overall survival. These groups are [20–59 yr; n = 432], [60–69 yr; n = 393], [70–79 yr; n = 535], [80–84 yr; n = 289], and [≥85 yr; n = 239]. The 5-year OS (%[95% CI]) was 78 [74.0–81.8], 64 [59.4–68.9], 52 [47.6–56.1], 32 [26.5–37.2], and 16 [11.2–20.4], respectively, and longer follow-up is shown in **Figure 1**.

To correct for competing causes of death in this predominantly older population, we determined the 2- and 5-year relative survival of the whole cohort, 69% and 63%, respectively. Similar to OS, relative survival decreased with age. Relative survival according to the major patient and treatment characteristics are shown in **Supplementary Table 2**.

3.3 First-Line Treatments

Systemic first-line treatment was started in 85% of cases, varying from 95% in <60 yr to only 46% in ≥85 yr. These treatments contained rituximab in most cases (96%) and were predominantly (90%) anthracycline-containing regimens (considered as curative intent), even in 51% of patients ≥85 yr. The exact frequency of all

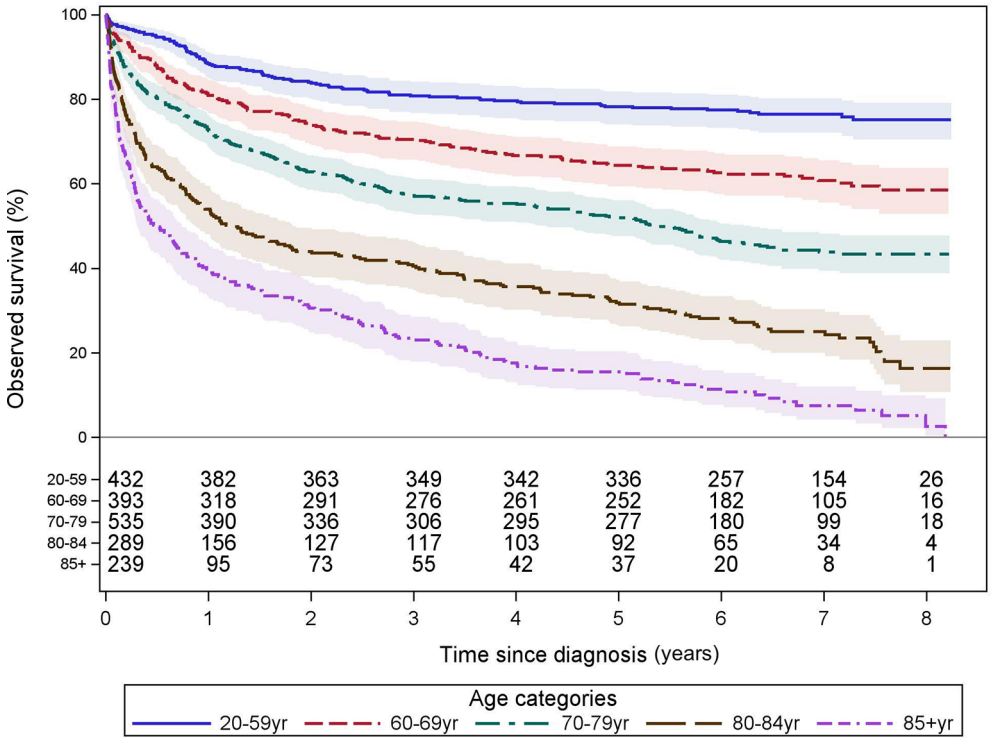

FIGURE 1 | Observed survival by age categories. These Kaplan–Meier curves show the observed survival from time of diagnosis, of all 1,888 patients, grouped into 5 clinically relevant age categories associated with a significantly different overall survival from time of diagnosis. The numbers of patients at risk are tabled below the curves. Colored areas represent the 95% confidence intervals.

first-line regimens, including concomitant use of rituximab, is shown in **Supplementary Table 3**. Treatments were regrouped into full R-CHOP (44%), "incomplete" (R-)CHOP (18%), other anthracycline (14%), non-anthracycline (9%), only RT (3%), and no chemo/RT (13%). As detailed in **Table 1**, treatments varied between age groups: younger patients were more frequently treated with anthracycline-containing regimens other than R-CHOP (e.g., R-ACVBP), in contrast to older patients, who were more frequently treated with non-anthracycline-containing regimens (e.g., R-CVP), radiotherapy alone, and no systemic treatment at all. The median [IQR] delay from diagnosis to the start of systemic treatment or radiotherapy was 21 [13–34] days, consistent across age groups.

The 2- and 5-year overall survivals (%[95% CI]) vary across the first-line treatments: full R-CHOP 85 [81.9–86.8] and 72 [69.1–75.2], other anthracycline 66 [60.5–71.7] and 58 [51.8–63.5], "incomplete" R-CHOP 55 [49.4–60.0] and 47 [41.7–52.4], non-anthracycline 44 [36.1–51.3] and 30 [23.4–37.4], only radiotherapy 45 [30.2–58.1] and 30 [17.6–43.0], and no chemo/radiotherapy groups 14 [10.2–19.0] and 9.0 [5.8–13.0]. Observed survival by first-line treatment and age group is visualized in **Figure 2**.

3.3.1 R-CHOP Regimens

R-CHOP was started in 1,163/1,596 (73%) of treated patients. The median [IQR] cycle interval was 21 [21–22] days, consistent across age groups. The median [IQR] number of cycles was 6 [4–8]. In 62% of R-CHOP-treated patients aged 85–89 yr, and 2 patients aged ≥90 yr, ≥6 cycles were given. However, our methodology could not discriminate R-CHOP from R-miniCHOP, the preferred regimen in patients ≥80 years old (46, 47).

In 337/1,163 cases (29%), we classified treatment as "incomplete" R-CHOP (<4 cycles (n = 178), 4–5 cycles (n = 142) if Ann Arbor stage >I, and CHOP without rituximab (n=17)).

In 40/337, a second-line regimen was started within 12 weeks, indicating primary refractory patients. Radiotherapy was applied after <4 and 4–5 R-CHOP cycles in 43/178 and 36/142 patients, respectively. Detailed patient characteristics of these different incomplete R-CHOP subgroups are shown in **Supplementary Table 4**. Importantly, when compared to the full R-CHOP cohort, patients receiving radiotherapy after incomplete R-CHOP had a similar PS (0–1 in 80%) but a higher proportion of Ann Arbor stage I–II disease (29% versus 49%).

The 5-year OS with incomplete R-CHOP ranged between 23% and 77% with primary refractory cases and radiotherapy groups associated with the lowest and highest OS, respectively (**Figure 3**).

3.3.2 Other Anthracycline-Containing Regimens

In our cohort, 271 patients were treated in first line with anthracycline-containing regimens different from the standard R-CHOP or with platinum-based regimens (frequencies summarized in **Table 2**). Anthracycline subtypes used were

TABLE 1 | Grouped first- and second-line treatments, including HSCT, by age group.

Age categories	N (%)	20–59 years	60–69 years	70–79 years	80–84 years	85+ years
First-line regimens	**N = 1,888**	**N = 432 (22.9%)**	**N = 393 (20.8%)**	**N = 535 (28.3%)**	**N = 289 (15.3%)**	**N = 239 (12.7%)**
Full R-CHOP[a]	826 (44)	210 (49)	238 (61)	261 (49)	90 (31)	27 (11)
Incomplete R-CHOP[b]	337 (18)	78 (18)	70 (18)	110 (21)	62 (21)	17 (7)
Other anthracycline[c]	271 (14)	115 (27)	45 (11)	68 (13)	30 (10)	13 (5)
Non-anthracycline[d]	162 (9)	8 (2)	16 (4)	39 (7)	46 (16)	53 (22)
Only radiotherapy[e]	47 (2)	2 (0.5)	3 (0.8)	6 (1)	12 (4)	24 (10)
No chemo/radiotherapy	245 (13)	19 (4)	21 (5)	51 (10)	49 (17)	105 (44)
Second-line regimens	**N = 252**	**N = 82**	**N = 71**	**N = 71**	**N = 24**	**N = 4**
Platinum-based	178 (71)	64 (78)	56 (79)	45 (63)	12 (50)	1 (25)
Cytarabine-based[f]	8 (3)	4 (5)	3 (4)	1 (1)	0 (0)	0 (0)
Anthracycline-based	17 (7)	8 (10)	2 (3)	6 (8)	1 (4)	0 (0)
Bendamustine-based	8 (3)	0 (0)	0 (0)	1 (1)	5 (21)	2 (50)
Palliative	19 (8)	1 (1)	4 (6)	11 (15)	3 (13)	0 (0)
Other[g]	22 (9)	5 (6)	6 (8)	7 (10)	3 (13)	1 (25)
% of start first line	16%	20%	19%	15%	11%	4%
% of diagnosed	13%	19%	18%	13%	8%	2%
Refractory[h] (%first line)	111 (7)	34 (8)	35 (9)	32 (7)	8 (4)	2 (2)
Relapsed[h] (%first line)	142 (9)	49 (12)	36 (10)	39 (8)	16 (7)	2 (2)
HSCT[i]	**N = 92**	**N = 66**	**N = 24**	**N = 2**	**N = 0**	**N = 0**
Autologous	82	56	24	2	0	0
Allogeneic	10	8	2	0	0	0

[a]≥ 6 cycles (≥ 4 if Ann Arbor stage = I).
[b]Incomplete if < 6 cycles or < 4 if Ann Arbor stage = I or if CHOP without R.
[c]R-ACVBP, RA-CHOP, CHOEP, COEP, CODOX-M, HyperCVAD, CHOP-like, DHAP, DHAP-like, ICE, platinum-containing, R-MAD.
[d]R-monotherapy, R-CVP, bendamustine-containing, experimental and palliative regimens.
[e]Within 12 weeks from diagnosis, 6 additional patients received only RT > 12 weeks from diagnosis.
[f]Not containing platinum, anthracyclines, or bendamustine.
[g]Includes CNS-directed therapy, only gemcitabine-containing, experimental therapies.
[h]Presumed refractory of relapsed when starting the 2nd line of therapy < or >12 weeks from last administration of the first-line treatment.
[i]Hematopoietic stem cell transplantation, after 1st, 2nd, or further lines of therapy.

doxorubicin (88%), followed by epirubicin (10%) and mitoxantrone (2%). This was a younger population compared to R-CHOP-treated patients (42% versus 25% are <60 yr). Other patient characteristics were similar and are shown in **Supplementary Table 5**. The reasons for attribution to this group are however unknown and could potentially be for DLBCL with high-risk features. The latter, combined with the younger age, could potentially explain the intermediate 5-year OS when compared to all R-CHOP-treated patients (58% versus 65%).

3.3.3 Non-Anthracycline-Containing Regimens

This group mainly consists of 93/162 patients treated with (R-) CVP, 20/162 with rituximab in monotherapy, and 23/162 with palliative regimens (**Supplementary Table 3**). Compared to full R-CHOP, this group is enriched with patients ≥80 yr (14% versus 61%) and cardiovascular comorbidities (52% versus 81%), potentially explaining, at least in part, the inferior 5-year OS of 30% (**Figure 2**).

3.3.4 Radiotherapy

During our study period, 379/1,888 (20%) patients received radiotherapy of which 336/379 (89%) within 12 months from diagnosis. For 53 patients, this was the only registered treatment. We discriminated between "Early" and "Late" radiotherapy (within 12 weeks from diagnosis or thereafter). In short, 30% fell into the "early" category with 47/101 not receiving any further systemic treatment. The "early" group was enriched with older patients when compared to the "late" group, and "late" radiotherapy was performed less frequently with advancing age (26% in 20–59 yr, 20% in 60–69 yr, 30% in 70–79 yr, 17% in 80–84 yr, and 6% in ≥85 yr). When available, the Ann Arbor stage in each group was predominantly stages I–II (60%–64%) or stage IV (29–33%). The exact indications for radiotherapy are unknown but presumably include urgent decompression/pain, primary radiotherapy, or palliation in the "early" group and consolidation after first-line treatment or treatment of relapsed/refractory disease in the "late" group.

Survival of patients treated with only primary radiotherapy is poor compared to the whole cohort but nonetheless is equal to 30% at 5 years compared to only 9% for those receiving neither radiotherapy nor systemic treatment (**Figure 2**).

3.3.5 No Systemic Treatment

Overall, 292 patients (15%) did not receive any lymphoma-directed systemic treatment with 53 of them receiving radiotherapy alone (see previous section). This frequency increased with age, and 65% of patients in this subgroup were ≥80 years old. Compared to the other treatment groups, information on prognostic factors like Ann Arbor stage, PS, COO, and BCL2 overexpression on IHC was more frequently missing (**Supplementary Table 5**). As expected, the survival of these patients was very poor with most patients deceased within 4 months (**Figure 2**).

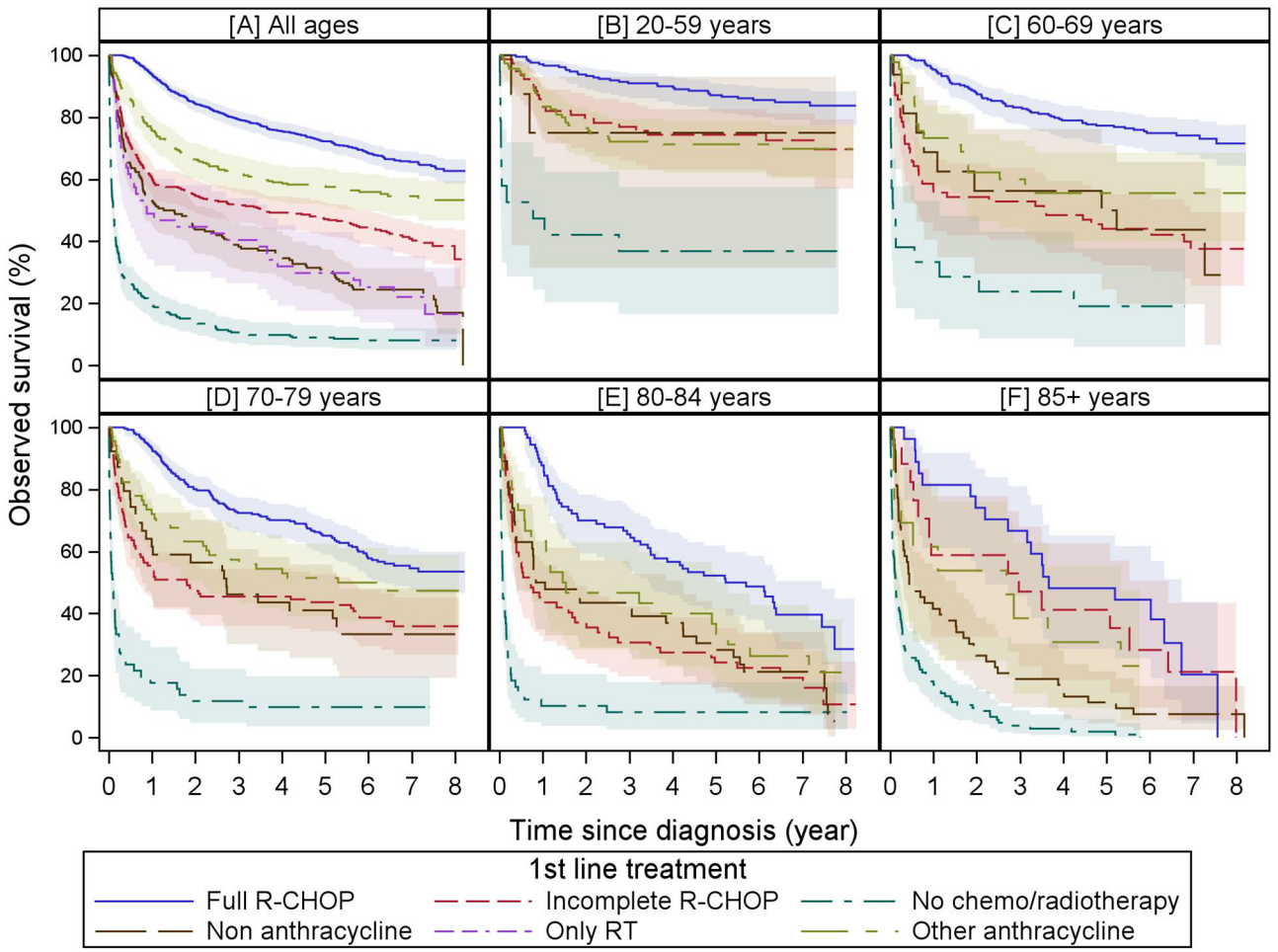

FIGURE 2 | Observed survival by first-line treatment by age group. These Kaplan–Meier curves show the observed survival from diagnosis stratified by first-line treatment of all patients **(A)** and stratified by age group (20–59, 60–69, 70–79, 80–85, and 85 years+ in (**B–F**, respectively). For all age groups, full R-CHOP and "no chemo/radiotherapy" are consistently associated with the best and worst overall survivals, respectively. Immortal time bias is not taken into account as survival is presented from diagnosis and patients have to survive until the end of a treatment to be categorized as having received this treatment. While observed survival in the whole cohort for incomplete R-CHOP, other anthracycline, and non-anthracycline groups are significantly different, this is largely lost when stratified by age except in the oldest age category. Due to low numbers, overall survival for radiotherapy alone is only displayed for the whole cohort. Colored areas represent the 95% confidence intervals.

3.3.6 CNS-Directed Therapy

We considered any CNS-directed therapy, administered between diagnosis and 6 weeks from the end of first-line treatment, to be prophylactic. In our cohort of R-CHOP(-like)-treated patients, CNS-directed prophylaxis was administered in 19% of cases. This proportion increased with advancing Ann Arbor stage and worsening PS but decreased with advancing age (**Supplementary Table 6**). Overall survival was not significantly different. However, enrichment of younger patients in the CNS prophylaxis group is a major confounder (<70 yr in 70% versus 45%). The administration of MTX was predominantly IT (IT; n = 176; 77% versus IV; n = 55; 23%). This is in contrast to the current ESMO guidelines preferring IV MTX over IT MTX for efficacy (18). In 70/229 (31%) of cases, CNS prophylaxis was administered after completion of systemic therapy. It was impossible to determine the efficacy of CNS prophylaxis in our cohort, since we had neither information on CNS relapse nor initial CNS involvement.

3.4 Second-Line Treatments

A second-line therapy was initiated in 252 patients, or 16% of those starting any first-line therapy (20 to 4% decreasing with age), and was predominantly platinum-based. A summary by age, including subsequent HSCT, is shown in **Table 1**, and a more detailed analysis of the different second-line regimens by age category is shown in **Supplementary Table 7**.

For survival analyses, all second-line regimens were regrouped into "platinum-containing," "non-platinum-containing," "bendamustine-containing," and "palliative" regimens. Grouped OS curves from the start of the second-line treatment are shown in **Figure 4** and demonstrate a 5-year OS of 26%–36% for relapsed or refractory patients deemed fit for non-palliative regimens.

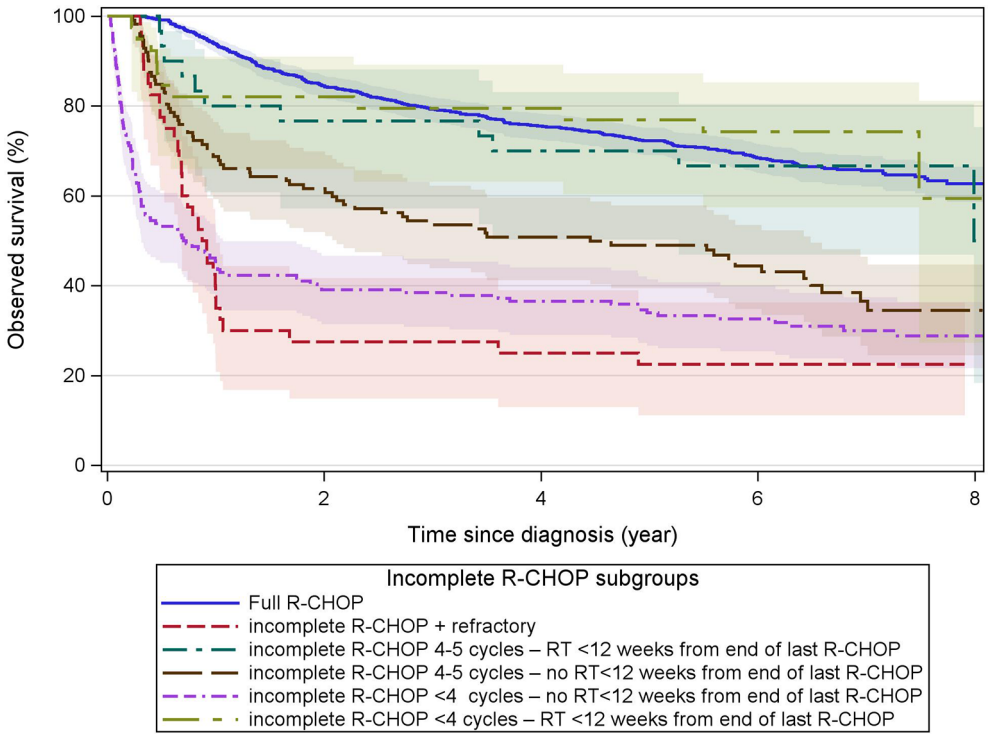

FIGURE 3 | Observed survival after incomplete R-CHOP. These Kaplan–Meier curves show the observed survival from diagnosis of patients receiving first-line treatment with incomplete R-CHOP (< 6 cycles or < 4 cycles if Ann Arbor stage = I, or CHOP without R) grouped by refractory status (start of any second-line treatment within 12 weeks from the end of first-line therapy), number of R-CHOP cycles, and radiotherapy within 12 weeks from the end of the last R-CHOP cycle. Primary refractory cases had the worst survival. The overall survival of incomplete R-CHOP followed by radiotherapy (green curves) was similar to that of full-R-CHOP. Immortal time bias is not taken into account as survival is presented from diagnosis and patients have to survive until the end of a treatment to be categorized as having received this treatment. Colored areas represent the 95% confidence intervals.

We presumed treatment to be for refractory (7% of all treated patients) or relapsed disease (9% of all treated patients), as defined in the methods section above. No major difference between relapsed or refractory patients in the choice of second-line regimen could be observed.

Figure 5 shows the observed survival of patients receiving a platinum-based second-line regimen without ASCT, compared to recipients of an ASCT with a BEAM-like conditioning after any preceding line. The ASCT group had a relatively good 5-year OS of 66% [54.1, 75.7]. This is in sharp contrast to those receiving salvage therapy without subsequent ASCT, with a 5-year OS of only 17% [10.0, 26.2] and 11% [4.3, 20.0] in patients aged <70 yr (n = 81) or ≥70 yr (n = 57) respectively.

In an effort to approach the definition of refractory DLBCL according to the SCHOLAR-1 study (17), we analyzed 3 subgroups: first, patients starting any second-line regimen <12 weeks after the end of ≥4 cycles of any first-line regimen (n = 75); second, patients starting a third-line regimen <12 weeks after ≥2 cycles of any second-line regimen (n = 29); and third, patients starting any therapy (radiotherapy, chemotherapy, or HSCT) <12 months after the start of ASCT (only ASCT within 2 years after incidence were included) (n = 23). Overall survival is shown in **Figure 6** and **Table 3**. To be cautiously interpreted because of the selection bias due to inherent exclusion of untreated refractory patients.

TABLE 2 | Breakdown of other anthracycline-containing first-line regimens.

Other anthracycline-containing regimens[a]	Frequency	Percent
(R-) CHOP-like	86	32%
(R-) ACVBP	59	22%
(R-) CODOX-M/HyperCVAD	43	16%
(R-) CHOEP	43	16%
(R-) CEOP	26	10%
(R-) DHAOX	1	0.4%
(R-) DHAP	2	0.7%
(R-) ICE	1	0.4%
(R-) MAD	6	2%
Other platinum-containing regimens	4	1%

[a]*This group also includes platinum-based regimens used in first-line.*

3.5 Hematopoietic Stem Cell Transplantation

3.5.1 Autologous Stem Cell Transplantation

We could capture information on ASCT for 4–7 years after diagnosis for the whole cohort. In total, 82 ASCT were registered of which 67/82 within the first 2 years from diagnosis. A BEAM-like conditioning regimen was used in 91%. The ASCT was performed as part of first-line in 35/82 (43%), second-line in 44/82 (54%), and further-line in 3/82 (4%). The treatment regimen

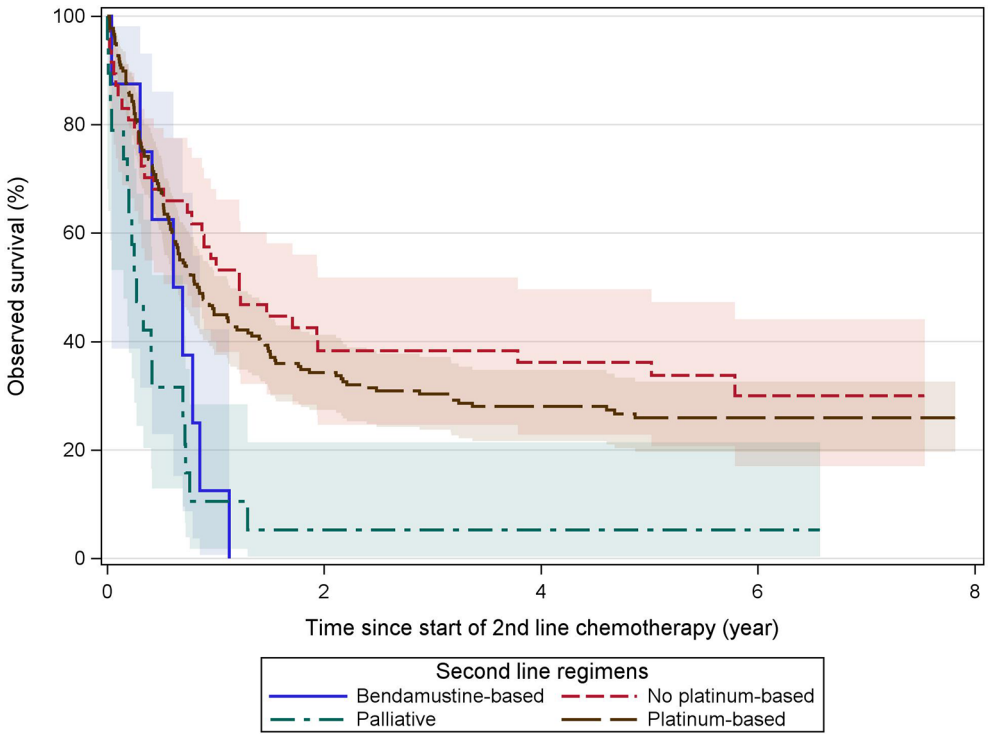

FIGURE 4 | Observed survival after second-line treatment. These Kaplan–Meier curves show the observed survival from the start of second-line treatment grouped by treatment categories. Patients receiving subsequent ASCT and/or AlloSCT are included. Both platinum and non-platinum-containing regimens are associated with a similar but limited long-term overall survival. Palliative and bendamustine-containing regimens provided (nearly) no survival beyond the 1-year mark. Colored areas represent the 95% confidence intervals.

preceding the ASCT in first-line was R-CHOP(-like) in 59%, R-ACVBP in 27%, and platinum-containing in 9% of cases. In second-line, this was nearly exclusively platinum-containing (88%). The 5-year OS of 69% and 66% was similar in first- and second-line ASCT.

3.5.2 Allogeneic Stem Cell Transplantation

Ten AlloSCTs for relapsed/refractory DLBCL were identified during the follow-up. They were performed after multiple lines of therapy without prior ASCT (n = 6) or at second relapse after prior ASCT (n = 4).

3.6 Outcome Analyses (Univariable and Multivariable Models)

The prognostic markers identified from univariable survival models with a significant HR are age category, language of the pathology report, PS, Ann Arbor stage, non-GCB COO, BCL2 overexpression, Ki-67, any considered comorbidity, prior malignancies, subsequent malignancies, center volume, and all first-line treatment categories except "other anthracycline" (**Supplementary Table 8**). Double expressions of BCL2&MYC and/or *MYC* rearrangements were associated with an inferior overall survival, but we could not include these variables in our models because of the high proportion of missing data. Having no information on Ann Arbor stage, COO, BCL2, or MYC was associated with a worse or an equivalent overall survival compared to the other subgroups of these variables.

The multivariable survival analysis (**Supplementary Table 9**) included all 1,888 patients, age category, language of the pathology report, gender, PS, cell of origin, BCL2 overexpression, Ki-67, respiratory comorbidity, cardiovascular comorbidity, diabetic comorbidity, prior malignancies, subsequent malignancies, and the different first-line treatments. After adjustment, several variables seem to be linked to overall survival with a significant type 3 test: gender (HR 1.25 for males), age (HR 1.81 to 5.95 for increasing age with the youngest age group as reference), PS (poorer prognosis of all categories compared to 0–1 category, especially for the period of time following diagnosis), cell of origin (non-GCB associated with a poorer prognosis compared to GCB, only for the period beyond 1 year after incidence), respiratory and diabetic comorbidity (HR 1.41 and 1.24), prior malignancies (HR 1.34), subsequent malignancies (HR 2.50), and first-line treatment with ≥6 cycles R-CHOP (HR 0.41) or other anthracycline-containing regimens (HR 0.72) (**Table 4**).

4 DISCUSSION

This comprehensive description of real-world first- and second-line treatments is the first of its kind for any hematological

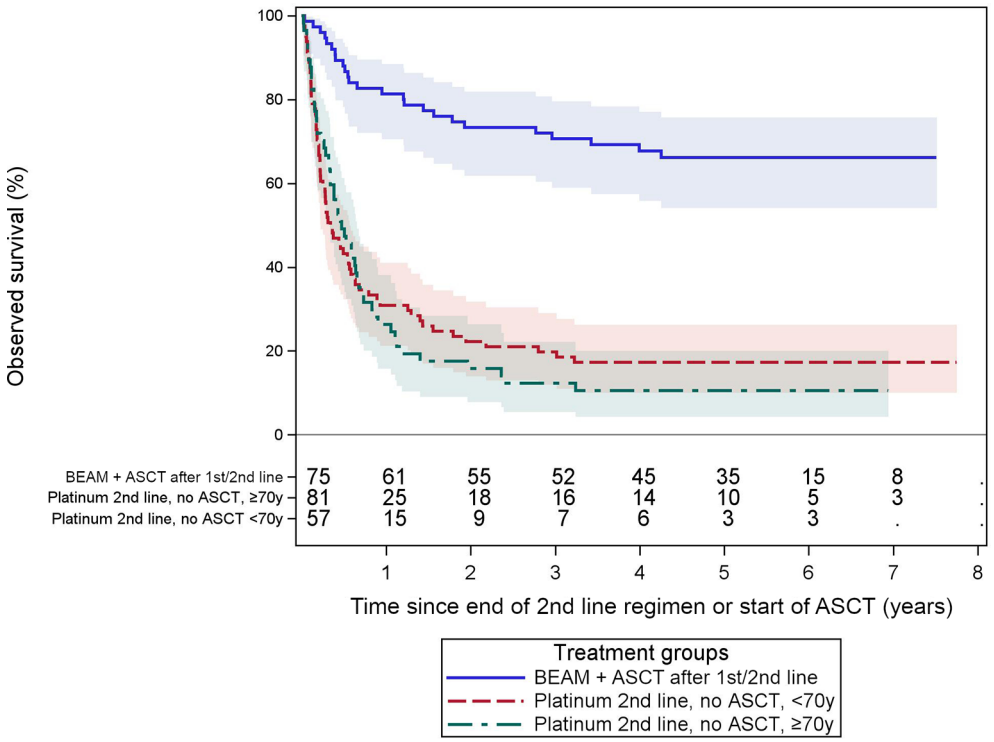

FIGURE 5 | Observed survival after ASCT or platinum-containing second-line treatment without ASCT. These Kaplan–Meier curves show the observed survival from the start of ASCT or end of second-line therapy in patients either receiving an ASCT after a BEAM-like conditioning or patients receiving platinum-based salvage regimens without ASCT. The latter stratified by age (< or ≥70 years old). Observed survival in the groups without ASCT is poor compared to the ASCT group. The numbers of patients at risk are tabled below the curves. Colored areas represent the 95% confidence intervals.

malignancy in Belgium. To our knowledge, such methodology has not been published in other registry-based studies so far, with the exception of a recent study by Huang et al. in the Taiwanese population, but limited to first-line treatments only (28).

4.1 Advantages and Limitations of Our Methodology

A major strength of our study is the near complete coverage of all adult DLBCL patients through the obligatory national registration at the BCR, and registration of all drugs through the national mandatory health insurance. Inclusion was done regardless of insurance status, hospital, department, or received treatment. At the BCR, nearly 90% of all Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, and Burkitt lymphoma are recorded separately by both a pathologist and an oncological care program, suggestive of near complete coverage of all cases (4). This eliminates a potential selection bias present in single- or multicenter studies, or in registries covering only part of the population, such as the SEER-Medicare database or United Kingdom's Clinical Practice Research Datalink (25). A similarly high coverage is also present in other registries such as the Netherlands Cancer Registry (NCR — 95%), Danish Cancer Register (LYFO — 98%) and Swedish Lymphoma Registry (SLR — 95%) (23, 24, 48).

The use of raw health insurance data eliminates the need for trained registrars to extract treatment regimens from medical records, as currently performed by most registries (23, 24, 48–50). This comes with some major advantages. First, since our algorithm is based on the raw data of the individual components instead of recoded variables, additional analysis of new components or combinations can be added without the need to recode all cases. Second, registering the individual components at individual timepoints allows to evaluate certain dose reductions, incomplete regimens, or switches between them. In essence, we capture the administered regimens instead of the intention-to-treat regimens, an important difference in a predominantly older population. Third, by combining two national databases (BCR and IMA) with obligatory registration for all patients in Belgium, we cover patients from large and small centers alike, including those diagnosed at non-hematological wards and receiving treatments outside of the original hospital.

However, our methodology does have some intrinsic limitations. First, there are limitations related to missing data. No information regarding remission status is available, neither the exact timing of relapse nor remission status at death. In Belgium, causes of death are classified according to the ICD-10 classification which does not include a lymphoma-specific code. We did not have information on all the components of established prognostic markers like the IPI.

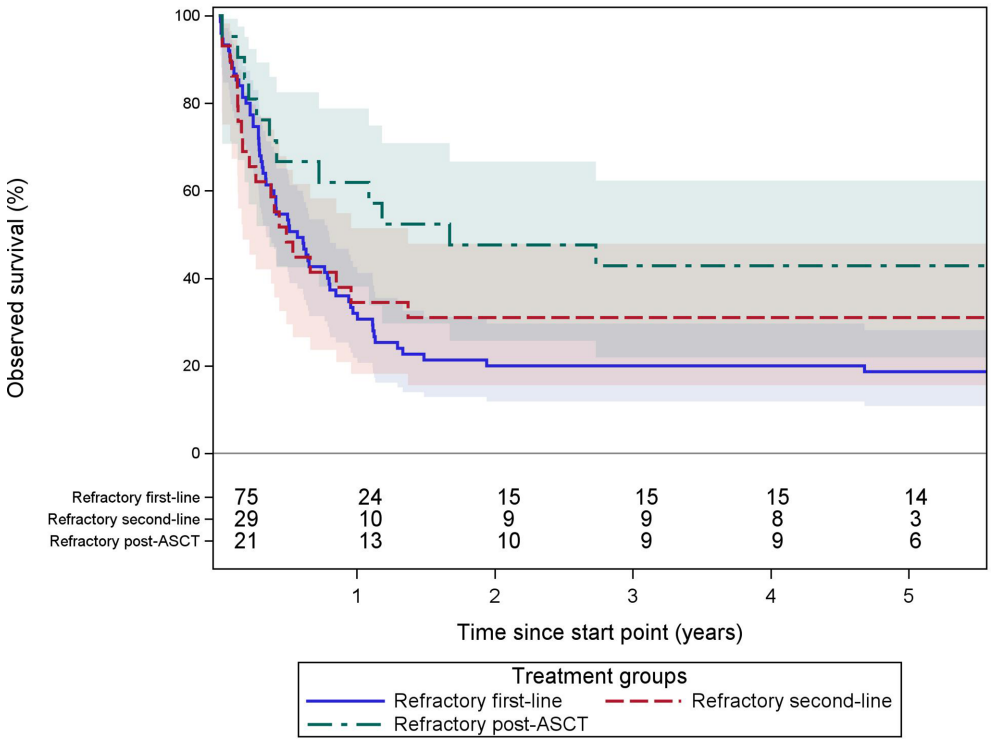

FIGURE 6 | Observed survival of refractory DLBCL patients. These Kaplan–Meier curves show the observed survival from the start of second- or further-line of therapy stratified in 3 groups. In blue, patients starting any second-line regimen <12 weeks after the end of ≥4 cycles of any first line regimen (n = 75). In red, patients starting a third line regimen <12 weeks after ≥2 cycles of any second-line regimen (n = 29). In green, patients starting any therapy (radiotherapy, chemotherapy, or HSCT) <12 months after start of ASCT (ASCT within 2 years from incidence) (n = 23). The starting point for each group is different and defined as the start of the first (salvage) therapy after becoming refractory. Treatments were only considered during the 2 years of follow-up after for diagnosis. The numbers of patients at risk are tabled below the curves. Colored areas represent the 95% confidence intervals.

A significant proportion of other prognostic criteria like Ann Arbor stage, PS, or biomarkers from pathology reports was missing (37%–92% depending on marker). Due to the initial design of the study, no information on drugs administered more than 2 years from diagnosis was registered, leading to the underestimation of late relapses. This is illustrated by the facts that 18 out of 82 ASCT were added after selective extension of our study period from 2 to 5 years after diagnosis.

Second, limitations related to the inference of treatment regimens. We performed a deduction of the intended treatments based on IMA data and thus captured only the administered treatments and not the "intention-to-treat" regimens, in contrast to results from clinical trials. The missing information on the intent of treatment is illustrated by the different survival rates within the "incomplete" R-CHOP subgroups. Identifying refractory patients according to exact definitions used in the SCHOLAR-1 study (17)

TABLE 3 | Observed survival of refractory DLBCL according to approximations of the SCHOLAR-1 (17) definitions.

	At 2 years		At 5 years		Median OS (years)
	Estimate	95% CI	Estimate	95% CI	
All refractory DLBCL cases	28.57	[20.5, 37.1]	26.61	[18.8, 35.1]	0.7
Refractory per SCHOLAR-1 def.	.		.		
Refractory at first-line	20.00	[11.9, 29.7]	18.67	[10.8, 28.2]	0.6
Refractory at second-line	31.03	[15.6, 47.9]	31.03	[15.6, 47.9]	0.5
Refractory at post-ASCT	47.62	[25.7, 66.7]	42.86	[21.9, 62.3]	1.7

The starting point for each group is different and defined as the start of the first (salvage) therapy after becoming refractory. Refractory at first-line: patients starting any second-line regimen < 12 weeks after the end of ≥ 4 cycles of any first line regimen (n = 75). Refractory at second-line: patients starting a third line regimen < 12 weeks after ≥ 2 cycles of any second-line regimen (n = 29). Refractory at post-ASCT: patients starting any therapy (radiotherapy, chemotherapy, or HSCT) < 12 months after start of ASCT (ASCT within 2 years from incidence) (n = 23). Treatments were only considered during the 2 years of follow-up after for diagnosis.

CI, confidence interval.

TABLE 4 | Adjusted hazard ratios (HR) from a multivariable analysis based on Cox models including age category, gender, PS, cell of origin, respiratory comorbidity, diabetes, other malignancies, and first-line treatments.

Variable	Category	Hazard ratio	95% Confidence interval	p value
Age category	60–69 years	1.81	1.40–2.35	<0.0001
(Ref: 20–59 years)	70–79 years	2.62	2.05–3.34	<0.0001
	80–84 years	4.13	3.18–5.35	<0.0001
	85+ years	5.95	4.53–7.82	<0.0001
Gender	Male	1.25	1.10–1.42	0.0008
Performance status early[a]	>1	4.56	3.43–6.06	<0.0001
Performance status late[a]	>1	1.88	1.53–2.30	<0.0001
BCL2 overexpression[b]	Yes	1.51	1.08–2.12	0.0159
Cell of origin[b]	Non-GCB	1.45	1.14–1.84	0.0022
Comorbidity[c]	Respiratory	1.41	1.15–1.73	0.0009
	Diabetes	1.24	1.05–1.46	0.0119
Other malignancies[d]	Before	1.34	1.07–1.68	0.0117
	After	2.50	1.96–3.20	<0.0001
First-line treatment[e]	Full R-CHOP[f]	0.41	0.33–0.52	<0.0001
	Other anthracycline	0.72	0.55–0.94	0.0143

Only those with a significant HR are shown, results on all evaluated variables can be found in ***Supplementary Table 9****.*

[a]*Impact on OS during time period ≤0.25 (early) versus >0.25 (late) years from incidence.*

[b]*Impact on OS during time period >1 year from incidence. Not significant at ≤1 year.*

[c]*Based on reimbursed drugs in same time period.*

[d]*Other malignancies before or after the diagnosis of DLBCL.*

[e]*Each treatment has been included in the model as time dependent variable to overcome immortal time bias.*

[f]*R-(mini)CHOP for ≥ 6 cycles (≥ 4 if Ann Arbor stage = I).*

non-GCB, non germinal center B-cell; OS, overall survival; BCL2, B-cell lymphoma 2; DLBCL, diffuse large B-cell lymphoma; PS, performance status; R-(mini)CHOP, Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone; Ref, reference.

was not possible because of 2 reasons. First, we defined relapsed or refractory cases based on the initiation of another therapy, thus excluding relapsed/refractory patients unable, unfit, or refusing further treatment. This is illustrated by the decrease of relapsed and refractory cases with advancing age; we presume in part due to not starting salvage therapy in elderly unfit patients. Second, we did not have information on non-reimbursed drugs such as experimental therapies in clinical trials, the preferred option in this setting, both highlighting the underestimation of the real number of cases with our methodology. We analyzed different subgroups of patients and compared them, but it is not possible to assess the efficiency of the different types of treatments due to the retrospective nature of this research. Additionally, it is not possible to compare the efficacy of 2nd lines and 3rd lines of treatment without the information of the clinical status after the previous line (complete remission, relapsed or refractory). Reasons for altering or stopping treatments could not be identified and could be progression, intolerance, or per-protocol guidance.

Despite its inherent limitations, this real-world population-based study is the first of its kind for DLBCL in Belgium. Specifically, it assesses patients usually excluded from clinical trials [advanced age, comorbidities, and other malignancies (12%)]. It provides us with a multicentered view of all patients in Belgium with little selection bias.

4.2 Age Appears to Remain an Important Prognostic Factor for DLBCL Patients, and We Should Consider Changing the IPI

With an HR of 1.8 to 5.9 for increasing age (with the youngest age group as reference), it remains an important discriminating factor related to survival. Decreasing with age, 5-year OS ranged from 78% to 16%, warranting the need to compare clinical trials according to the age category of the participants. When evaluating relative survival, and thus correcting for an increase in competing risks of death due to age itself, this detrimental effect of advancing age is still observed (**Supplementary Table 2**). An interesting observation is the more pronounced drop in OS around the age of 70 instead of 60, as incorporated in the IPI. This finding has already been suggested by Advani et al. in 2010 with the introduction, and later validation of the Elderly International Prognostic Index (E-IPI) (51–54). Currently, the E-IPI is not frequently used in routine practice, and only the commonly used NCCN-IPI incorporates additional age cutoffs other than 60 years of age (6). Gang et al., from the Danish Lymphoma registry, suggested the development of the DLBCL-IPI, equally adapting the age cutoff to 70 (55). Additionally, in our cohort, overall survival worsened for each age category beyond 55 years, suggesting that the incorporation of age in risk stratifications should perhaps not be dichotomous.

4.3 In 12% of DLCBL Patients, a Second Primary Malignancy Is Diagnosed With a Negative Impact on Prognosis: A Group Systematically Left Out of Clinical Trials

Our data suggest an age-consistent incidence of prior malignancies, but a 5%–7% of registered malignancies within 5 years after the diagnosis of DLBCL regardless of age group. This is consistent with 5.4% secondary primary malignancies beyond 1 year after DLBCL diagnosis in 25,089 patients from the Californian Cancer Registry (56). Others have found a similar or higher incidence of 13% (before) in the Swedish population, 10.9% (after) in the US population, and 15.2% (before and after) in the Japanese population (22, 24, 57). In our cohort, the malignancies after treatment for DLBCL had the biggest impact on prognosis.

Those registered were quite heterogeneous with the most prevalent being prostate, lung, colorectal, and head-and-neck cancers, and acute leukemias.

4.4 The Majority of Patients Were Treated With R-CHOP, and Completing It Had the Best OS

The use of R-CHOP is recommended in fit patients up to 80 years of age, R-miniCHOP in patients older than 80, and modification of the anthracycline component in frail or unfit patients (6, 18, 35). Our methodology did not allow for the discrimination of R-miniCHOP. However, Hounsome et al. recently described a similar 3-year OS for patients ≥80 yr treated with R-CHOP versus R-miniCHOP in England (58). Rituximab was included in 96% of first-line treatments, and an R-CHOP-like regimen was used in 85% of all treated patients. The latter is consistent with data in the Swedish (86%) and English populations (81%) (24, 58). The remaining first-line treatments consisted of intensified regimens like R-ACVBP or platinum-containing regimens in younger patients, in contrast to the less intensive R-CVP and rituximab monotherapy in older patients. After exclusion of all untreated patients, the 5-year OS ranged between 30% and 72% according to first-line treatments. Patients completing at least 6 cycles of R-(mini)CHOP had the best prognosis. However, immortal time bias needs to be considered for this group due to inherent exclusion of unfit patients, early treatment deaths, and primary refractory cases. A similar conclusion was found by Hamlin et al. in the US population (26). Additionally, a recent Dutch registry study showed no difference in OS between 6 and 8 R-CHOP cycles (59). The reasons for not completing ≥6 R-CHOP cycles could not be determined but may include early death, treatment-related toxicities, refractory disease, limited stage disease, and part of extended and/or non-reimbursed regimens. Overall survival of "incomplete" (R-)CHOP was worse than "full" R-CHOP, but very heterogeneous when consolidative radiotherapy was taken into account (**Figure 3**). For those patients treated with radiotherapy after incomplete R-CHOP, OS is markedly better and even similar to "full" R-CHOP. These findings further support the current evidence for the curative potential of fewer cycles of R-CHOP followed by consolidative radiotherapy in selected patients. Our findings also suggest a potential role for radiotherapy alone in selected cases. Patients without registered treatments had a very poor 5-year OS of 9%. These few long-term survivors might be explained by either complete chirurgical resection of a solitary lesion or, and most likely, unsuccessful capturing of effectively administered treatments (e.g., within clinical trials) inherent to our methodology. The (lack of) success of salvage strategies in primary refractory cases is indicated by the 5-year OS of 23%.

4.5 Up to 16% Receive a 2nd-Line Treatment Within 2 Years; Those Not Advancing to ASCT Have a Poor Prognosis

In our cohort, 16% of patients treated with curative intent in first-line received some form of second-line therapy. This is consistent with the 11% identified in a SEER-Medicare analysis for patients ≥66 years old (60). To no surprise, this proportion decreased with advancing age. The majority of second-line regimens contained rituximab, platinum derivatives, and cytarabine. Second-line treatment was presumed to be for relapsed disease in 9% and for primary refractory disease in 7%. The reported incidence of relapsed/refractory DLBCL patients ranges between 17% and 30%, with up to 10% after EFS24 (15, 18, 38, 61, 62). This discrepancy with our cohort probably relies on 2 main factors. Firstly, we only capture patients that relapsed within 2 years from diagnosis due to our study design. Secondly, we only capture patients actually receiving second-line regimens, and not those who relapsed but were unfit for salvage therapy. The importance of the latter is demonstrated by a Danish registry study, with 66% of relapsed or refractory patients receiving no or palliative treatments (63). Overall survival of refractory patients at first- or second-line is poor and seems similar, with a median OS of 0.6 and 0.5 years, respectively (**Table 3**). These results are comparable with results from the SCHOLAR-1 study (17). For refractory patients <12 months post-ASCT, OS seems to decrease less rapidly to reach a higher plateau than the group of refractory DLBCL in first- of second-line (**Figure 6**). However, interpretations should be done with caution due to inherent exclusion of untreated refractory patients resulting in a selection bias. Additionally, treatments were only considered during the first 2 years from incidence, limiting the real number of cases in the post-ASCT group.

Survival from the end of second-line treatment of patients not able to proceed to ASCT after platinum-based second-line regimens is still very poor (5-year OS 11%–17%). This finding is consistent with most of the available literature in the post-rituximab era (15, 63, 64).

In our cohort, only a minority of those starting platinum-based salvage regimens proceeded to ASCT. This proportion was lower than the 46% reported in a Danish registry study or the 52% in the CORAL trial (63, 65). Unfortunately, the reasons for withholding ASCT are unknown but could include patients unfit for transplantation, patients not obtaining a remission after salvage therapy, and death before ASCT due to progression or toxicities of the salvage regimen. Therefore, immortal time bias needs to be taken into account when discussing survival of ASCT recipients. Together, these findings suggest that patients not able to proceed to ASCT at first relapse or for primary refractory disease, either due to refractoriness or due to fitness, most urgently need novel therapies.

4.6 ASCT Is Performed in 5% of DLBCL, Frequently in First-Line, With a Good 5-Year OS

In our cohort, ASCT was performed within 0.3–3.3 years from diagnosis in 5% of patients receiving any first-line treatment. This is higher than 1.3% and 1.8% as reported in the SEER-Medicare database and 1.6% reported in the Danish Cancer Registry (3, 63, 66). Moreover, ASCT was performed in 67/82 cases within 2 years from diagnosis and in 15/82 beyond 2 years in our series. Most guidelines consider ASCT in first-line to be experimental and only to be proposed for selected high-risk

patients or slow-responders (18). In our study, 43% (n = 35/82) of all ASCTs were performed in first line, mostly after R-CHOP or R-ACVBP regimens. Unfortunately, we do not have information on the exact reasons for this allocation. ASCT was performed as part of a second-line in 54% (n = 44) of cases, nearly exclusively after platinum-containing salvage regimens. Somewhat surprisingly, the 5-year OS from ASCT did not seem to differ between first- and second-line and was relatively good at 69% and 66%, respectively. This is higher than the reported 3-year OS of 53%–56% or 5-year OS of 46% from other studies (38, 63, 65, 67). Within our follow-up period, 10 allogeneic HSCT specific for DLBCL were performed, all for relapsed/refractory disease of which 4 after prior ASCT.

4.7 With Advancing Age, Overall Survival Worsens, and Systemic Treatment Is More Often Omitted; However, Most Older Patients Are Successfully Treated With Anthracycline-Containing Regimens

In Belgium, 56% of patients were ≥70 years old and 28% ≥80 years old. Subsequently, treatment options are impeded by comorbidities and increased frailty. Based on the prognostic markers we examined in this cohort, disease characteristics did not seem to differ by age, except that they were more frequently not reported in the older population. Therefore, prognosis appears to be mainly determined by patient- and treatment-related factors. Overall, 15% of patients did not receive any systemic lymphoma treatment ranging between 5% and 54% in young versus older patients resulting in a dismal prognosis. These findings are similar to those reported in the SEER-Medicare database for patients aged ≥66 yr, with 20%–35% of patients receiving no systemic treatments with 50% of them being >80 years old (3, 26). Additionally, in our cohort, older patients were more frequently (0.5% in 20–59 yr versus 10% in ≥85 yr) treated with radiotherapy alone.

However, our results suggest that a substantial fraction of this older population still qualifies for standard R-(mini)CHOP treatment, and more importantly, still benefits from it.

Firstly, the majority of older patients (64% in ≥70 yr and 46% in ≥80 yr) are started on anthracycline-containing first-line treatments with potentially curative intent. A study from the Netherlands Cancer Registry described the proportion of anthracycline-containing regimens to be 46% in patients ≥75 yr and 34% in those ≥80 yr (49). A study from the Danish National Lymphoma Registry showed "standard treatment" to be initiated in 64% of patients, ranging from 83% among patients aged 75–79 yr to 32% among patient aged ≥85 yr (23). Secondly, the median number of R-(mini)CHOP cycles remains 6, with a median 21-day cycle length in this older population. Finally, older patients who complete R-CHOP still have a good 5-year OS relative to their age-matched peers. Several registry studies in the US, Danish, Swedish, Dutch, English, and Taiwanese populations have also demonstrated the increased overall survival in older patients receiving R-CHOP(like) first-line therapies (23–28, 58).

Except for the ≥85-yr age category, patients treated with non-anthracycline-containing regimens demonstrated a similar overall survival compared to "incomplete" R-CHOP and other anthracycline-containing regimen. Williams et al. described a similar OS for older patients treated with R-CVP versus CHOP without rituximab in the SEER-Medicare database (25). Maguire et al. demonstrated a survival benefit for R-CVP in older patients from the Californian Cancer Registry (27). Additionally, in our cohort, treatment with radiotherapy alone, or with a limited number of cycles of R-CHOP, demonstrated curative potential for a selection of patients with limited stage disease.

Second-line therapy was started in 8% of those aged ≥80 yr who had started first-line treatment, and no one received a HSCT. Their prognosis was very dismal compared to the younger patients still fit for ASCT. These second-line regimens were still predominantly platinum-based up to the age of 84. Bendamustine-containing regimens were infrequently but exclusively used in those >75 years of age but without any long-term survival.

Therefore, this specific population has two large clinical needs: firstly, the availability of less toxic, but still effective first-line regimens for those unfit for R-miniCHOP, and secondly, potent salvage options that do not necessitate consolidation with an ASCT, a treatment too toxic for the majority of DLBCL patients.

4.8 A Unique View on the Patterns of Care in the Belgian Adult DLBCL Population

Despite its inherent limitations, this real-world population-based study provides useful information on the pattern of care of DLBCL in Belgium. Specifically, it assesses the clinical management of patients usually excluded from clinical trials [those with advanced age (56% ≥70 yr; 28% ≥80 yr), comorbidities, and other malignancies (12%)]. It provides a multicentered view of all patients in Belgium with little selection bias. We were able to validate, retrospectively, several known prognostic markers and map the patterns of care within the Belgian population. Some known prognostic markers such as cell of origin had a less important impact on prognosis while others like other malignancies were somewhat more important than expected (22). Currently, the French multicenter real-world cohort study (REALYSA) is evaluating some of these prognostic markers in a prospective matter (68).

During our study period, most patients received the standard of care as defined by different guidelines, albeit with some differences regarding the use of radiotherapy and ASCT in first-line. The majority of DLBCL patients are aged ≥70, addressing significant challenges with regard to treatment decisions. Nonetheless, the majority still receives adequate treatment in Belgium and a significant proportion will be cured from its DLBCL.

4.9 Future Directions

Using our now established methodology, we will explore the patterns of care for DLBCL in more recent incidence years to determine if clinical practice has changed. Secondly, we plan to incorporate the impact of socioeconomic factors into our analyses, as they are known to have an important influence on survival (69). Finally, we will extend this methodology to other

hematological malignancies, such as follicular lymphoma, and solid tumors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WD, FO, and HA contributed to the conception and design of the study. WD wrote the first draft of the manuscript. WD, MR, ES, AD, and HA performed the data extraction from the pathology reports or linked databases. MR, WD, and HA set up the in-house algorithm to infer the treatment regimens from the health insurance database. MR organized the database and performed the data curation. GM performed the statistical analyses. All authors contributed to the manuscript revision and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.824704/full#supplementary-material

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GLOSSARY

ABC	activated B-cell
ALL	acute lymphoblastic leukemia
AlloSCT	allogeneic hematopoietic stem cell transplantation
ASCT	autologous stem cell transplantation
ATC	anatomical therapeutic chemical
BCL2	B-cell lymphoma 2
BCL6	B-cell lymphoma 6
BCR	Belgian Cancer Registry
BEAM	bendamustine–etoposide–AraC–methotrexate
BHS	Belgian Haematological Society
BTR	Belgian Transplant Registry
CAR-T	chimeric antigen receptor T cells
CD10	cluster of differentiation 10, neprilysin
CHOP	cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone
CNK	Code Nationa(a)l Kode
CNS	central nervous system
COO	cell of origin
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EFS24	event-free survival at 24 months
ESR2013	age-standardized incidence rate using the European standard population of 2013
FISH	fluorescence *in situ* hybridization
GCB	germinal center B-cell
HD MTX	high-dose methotrexate
HDC	high-dose chemotherapy
HGBCL	high-grade B-cell lymphoma
HR	hazard ratio
IFRT	involved field radiotherapy
IHC	immunohistochemistry
IMA	Intermutualistic Agency
IPI	International Prognostic Index
IRF4	interferon regulatory factor 4
IT	intrathecal
IV	intravenous
KI-67	marker of proliferation Ki-67
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MYC	MYC proto-oncogene, bHLH transcription factor
NCCN	National Comprehensive Cancer Network
NOS	not otherwise specified
OS	overall survival
PCNSL	primary central nervous system lymphoma
PMBCL	primary mediastinal B-cell lymphoma
PS	performance status
PTLD	post-transplant lymphoproliferative disease
R	rituximab
R-ACVBP	rituximab, adriamycine, cyclophosphamide, vincristine, bleomycine, prednisolone
R-CHOP	rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone
R-CVP	rituximab, cyclophosphamide, oncovin, prednisolone
R-DHAP	rituximab, dexamethasone, high-dose Ara-C, platinum
RT	radiotherapy
SEER	Surveillance, Epidemiology and End Results
SIR	standardized incidence ratio
WHO	World Health Organization
WSR	world standard rate
YR	years
IQR	interquartile range

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Development and Validation of a Novel Prognostic Model for Overall Survival in Newly Diagnosed Multiple Myeloma Integrating Tumor Burden and Comorbidities

Shuangshuang Jia†, Lei Bi†, Yuping Chu, Xiao Liu, Juan Feng, Li Xu, Tao Zhang, Hongtao Gu, Lan Yang, Qingxian Bai, Rong Liang, Biao Tian, Yaya Gao, Hailong Tang and Guangxun Gao**

Department of Hematology, Xijing Hospital, Air Force Medical University, Xi'an, China

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***Correspondence:**
Guangxun Gao
gaoguangxun@fmmu.edu.cn
Hailong Tang
tanghailong@fmmu.edu.cn

†*These authors have contributed equally to this work*

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Background: Multiple myeloma (MM) is a highly heterogeneous disease with enormously variable outcomes. It remains to be a major challenge to conduct a more precise estimation of the survival of MM patients. The existing stratifications attached less importance to the prognostic significance of comorbidities. In the present study, we aimed to develop and validate a novel and simple prognostic stratification integrating tumor burden and comorbidities measured by HCT-CI.

Method: We retrospectively enrolled 385 consecutive newly diagnosed multiple myeloma (NDMM) patients in Xijing Hospital from January 2013 to December 2020. The cohort between January 2016 and December 2020 was selected as development cohort (N = 233), and the cohort between January 2013 and December 2015 was determined as validation cohort (N = 152). By using LASSO analysis and univariate and multivariable Cox regression analyses, we developed the MM-BHAP model in the way of nomogram composed of β2-MG, HCT-CI, ALB, and PBPC. We internally and externally validated the MM-BHAP model and compared it with ISS stage and R-ISS stage.

Results: The MM-BHAP model was superior to the ISS stage and partially better than the R-ISS stage according to time-dependent AUC, time-dependent C-index, DCA, IDI, and continuous NRI analyses. In predicting OS, only the MM-BHAP stratification clearly divided patients into three groups while both the ISS stage and R-ISS stage had poor classifications in patients with stage I and stage II. Moreover, the MM-BHAP stratification and the R-ISS stage performed well in predicting PFS, but not for the ISS stage.

Besides, the MM-BHAP model was also applied to the patients with age ≤65 or age >65 and with or without HRCA and could enhance R-ISS or ISS classifications.

Conclusions: Our study offered a novel simple MM-BHAP stratification containing tumor burden and comorbidities to predict outcomes in the real-world unselected NDMM population.

Keywords: prognostic model, risk stratification, HCT-CI, comorbidity, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy characterized by hyperproliferation of clonal plasma cells within the bone marrow (1). Despite its incurability, the median overall survival (OS) in MM patients has obtained a significant improvement over the years due to the introduction of novel therapies, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMIDs), monoclonal antibodies, and immunotherapy. However, even among the patients with the same genetic background currently known, the high heterogeneity of the outcome still exists, with the survival varying from a few months to more than 10 years (2–4). Therefore, it remains to be a major challenge to conduct precise estimation of the survival in MM patients.

The current International Staging System (ISS) (5) and Revised International Staging System (R-ISS) (6) were widely used in clinical practices. The R-ISS stage combined the ISS stage, lactate dehydrogenase (LDH), and high-risk chromosomal abnormalities (HRCA), which achieved an improvement in estimating prognosis compared to the ISS stage. However, the R-ISS was composed of disease-related factors, which mainly reflected the inherent biological characteristics of myeloma but reckoned without the patient-related factors like comorbidities and performance status. Moreover, there was a large portion of patients distributed into R-ISS stage II (6), indicating that it was necessary to conduct a more precise estimation of prognosis for better differentiation in these patients. Besides, the R-ISS stage was based on the data derived from clinical trials and might result in some limitations for the application in the real-world unselected patients.

Based on the abovementioned reasons, efforts were always underway to explore new risk stratifications for the prediction of survival in the patients with newly diagnosed multiple myeloma (NDMM). Some studies established prognostic tools with biological parameters, such as gene expression (7–14) and lncRNA (15), followed by the limitations of the complexity and non-standardization. A few of new prognostic models predicting survival were based on new integration of chromosomal abnormalities and clinical indicators, whereas these only focused on disease-related factors (2, 16–18). Therefore, a more comprehensive assessment, orchestrating the genetic landscape of myeloma and host characteristics, may be more appropriate to distinguish the benefits from existing treatments in an unselected community setting. For example, the UK Myeloma Research Alliance Risk Profile (MRP) taking account of WHO performance status and age, together with ISS stage and C-reactive protein, could help to predict the prognosis and therapy delivery in patients who are not candidates for transplantation (19). Furthermore, a survival matrix was created using the factors of age, del (17p), triplet therapy use, EQ-5D mobility, ISS stage, solitary plasmacytoma, history of diabetes, platelet count, Eastern Cooperative Oncology Group performance status, and serum creatinine for predicting the outcomes of NDMM patients (20). Moreover, a pleural effusion-based nomogram including factors of pleural effusion, plasma cell proportion in the bone marrow, ISS stage, Charlson Comorbidity Index (CCI), 1q21 gain, and autologous hematopoietic stem cell transplantation (HSCT) (21) was also performed to evaluate the prognosis in unselected MM population.

It is obvious that there is still a lack of comprehensive studies for the prognostic significance of comorbidities which are usually excluded from the clinical trials but maybe partially determine the treatment options, treatment intensity, and time to next treatment (3, 4). Both the CCI and hematopoietic cell transplantation-comorbidity index (HCT-CI) were ways of evaluating the impact of comorbidities. However, the HCT-CI could have clearer definitions of comorbidities than the CCI (22) and also considered recent infections which usually led to less intensive therapies and associated with worse OS (23). Moreover, HCT-CI was widely used to predict the survival probabilities of patients after HSCT (24–27), while little attention was paid to its prognostic value in the outcome of NDMM patients.

Hence, we explored the possibility of predicting the survival of MM patients with the HCT-CI evaluated at the time of diagnosis. Using routinely available clinical factors that integrated comorbidities and tumor burden, we developed and validated a new prognostic model and risk stratification for predicting the probability of 6-month, 1-year, 2-year, and 4-year OS of patients with NDMM. Our study offered a novel simple tool to predict outcomes in NDMM patients, as a supplement for a better stratification on the basis of current risk classifications.

METHODS

Cohort Selection

We retrospectively enrolled 385 consecutive newly diagnosed MM patients in our institution from January 2013 to December 2020. All patients were aged at least 18 years, diagnosed

according to International Myeloma Working Group (IMWG) criteria (28) and followed up for the available treatment and survival information until June 1, 2021. The cohort between January 2016 and December 2020 was selected as development cohort (N = 233), and the cohort between January 2013 and December 2015 was determined as validation cohort (N = 152).

Data Collection

The baseline characteristics, such as patient/disease-specific data at diagnosis and treatment information, were collected. The patient-specific data included age, sex, body mass index (BMI, kg/m^2), history of hypertension, history of thrombosis, and HCT-CI. The disease-specific data contained white blood cell (WBC, $\times10^9$/L), neutrophil granulocyte (NEU, $\times10^9$/L), lymphocyte (LYM, $\times10^9$/L), monocyte (MONO, $\times10^9$/L), hemoglobin (HGB, g/L), platelet (PLT, $\times10^9$/L), β2-microglobulin (β2-MG, mg/L), albumin (ALB, g/L), serum calcium (Ca^{2+}, mmol/L), lactate dehydrogenase (LDH, IU/L), high-risk chromosomal abnormalities (HRCA), bone marrow plasma cells (BMPC), peripheral blood plasma cells (PBPC), DS stage, ISS stage, and R-ISS stage. The treatment information involved novel therapies and autologous stem-cell transplantation (ASCT).

Definition of Some Variables and Survival Outcomes

The condition of infection in HCT-CI was assessed at the time before induction therapy and other comorbidities that were measured at diagnosis in our study. The HRCA was defined as the presence of t (4;14) and/or t (14;16) and/or del(17p), detected by fluorescence *in situ* hybridization (FISH) (6). The thresholds were set at 10% for t (4;14) and t (14;16) and at 20% for del(17p), recommended by the European Myeloma Network (29). The BMPC was referred to as the proportion of clonal plasma cells on a bone marrow smear. The PBPC meant the proportion of clonal plasma cells on a peripheral blood smear.

The time of last follow-up was on June 1, 2021. The primary end point was OS defined as the time from the start of diagnosis until all-cause death or until the last follow-up time the patient was known to be alive. The secondary end point was progression-free survival (PFS) defined as the time from the start of diagnosis until progression or all-cause death or until the last follow-up time the patient was known to be progression-free.

Development of the New Prognostic Model

Before variable selection, we examined the non-linear association between continuous variables with OS *via* restricted cubic splines based on Cox regression (**Supplemental Figure S1**), then transformed the variable into categorical variable according to the cutoff points when the p value for non-linearity <0.05. We handled missing data on candidate prognostic variables using multivariate imputation by chained equation (MICE) and created five imputed datasets. Then, we evaluated the potential prognostic value of candidate variables by using univariate Cox regression analysis in all the five imputed datasets and the coefficients were combined with R package "mice." The variables with p value < 0.10 were subjected to the least absolute shrinkage and selection operator (LASSO) analysis to prevent overfitting (30), and we finally picked up four predictors of them taking account of clinical importance and prediction of the model (**Supplemental Methods**).

Validation of the New Prognostic Model

We internally and externally validated the predictive power of the model respectively in the development cohort and validation cohort *via* the following analyses: (1) discrimination: assessed by time-dependent area under the curve (AUC) of the receiver operator characteristic (ROC) and time-dependent Harrell's concordance index (C-index) analyses; (2) calibration: examined by calibration curve with 1,000 bootstrap resamples, which indicated a good fit of the predicted probabilities with actual outcome frequencies when the curve had a good agreement with the 45° diagonal line; (3) clinical usefulness: estimated by decision curve analysis (DCA), which showed that the model was the best choice for all patients that had the highest net benefits among all the range of risk thresholds (31); and (4) improvement in prediction: tested by integrated discrimination improvement (IDI) and continuous net reclassification index (NRI), which suggested that the new model had an improvement in predictive capacity compared with the old model when they were greater than zero. In particular, we would like to compare the performance of the new prognostic model with that of the R-ISS stage which showed missing data in the development cohort. To reduce the influence of data deficiency, we carried out the abovementioned analyses in each imputed dataset.

Statistical Methods

All the statistical analyses were carried out using R version 4.1.0 and SPSS version 26.0, and a two-sided p < 0.05 suggested a statistical significance. The chi-square test or Fisher's exact test was used to analyze qualitative variables, and the Mann–Whitney U test was used to analyze quantitative variables. Survival was analyzed by Kaplan–Meier curves and log-rank tests. Uni- and multivariable Cox proportional hazard models were used to assess the prognostic factors and calculated hazard ratios (HR) with 95% confidence intervals (CI). The R packages used in the abovementioned analyses were shown in **Supplemental Methods**.

RESULTS

Patients' Characteristics

We presented the baseline characteristics of the development cohort (N = 233) and validation cohort (N = 152) in the **Supplemental Table S1**. Moreover, the median age was respectively 59 (35–88) and 58.5 (18–89) years. In the development cohort, the vast majority (99.6%) of the patients received anti-myeloma treatment and most (98.3%) patients underwent novel therapy in their induction treatment. Similarly, 98.7% of the patients were treated with anti-myeloma therapy and 98.0% of the patients received novel therapy in the validation cohort. As of the end of June 1, 2021,

the median time of follow-up was 24.0 (range from 0.1 to 61.8) and 28.8 (range from 0.4 to 101.9) months in the development cohort and validation cohort, respectively.

Development and Evaluation of the MM-BHAP Model

In the development cohort, we evaluated the correlation of candidate variables with OS using univariate Cox regression analysis (**Table 1**), and the variables with p value < 0.10 were subjected to the LASSO analysis. Finally, we picked up four variables to construct a new prognostic model in the way of nomogram (**Figure 1** and **Supplemental Table S2**) by using the multivariate Cox proportional hazard model based on the β coefficients of predictive factors (**Table 2**). The nomogram consisted of β2-MG, HCT-CI, ALB, and PBPC, which comprised a new prognostic model called MM-BHAP model for predicting the probability of 6-month, 1-year, 2-year, and 4-year OS in NDMM patients. Also, we constructed two additional models individually including only ISS stage or R-ISS stage, comparing the predictivity of the MM-BHAP model with them in each imputed dataset (we just showed the results in one of the five imputed datasets in the text due to their similarity).

TABLE 1 | Univariate Cox regression analyses in the development cohort.

Characteristics	HR	95% CI	p
Age >65 vs. ≤65 years	1.64	0.91–2.95	0.098
Male (vs. female)	1.37	0.74–2.56	0.32
BMI (kg/m^2)			
>22.5 and ≤25.5 vs. ≤22.5	0.92	0.47–1.79	0.803
>25.5 vs. ≤22.5	0.69	0.28–1.71	0.410
History of hypertension			
Yes vs. no	0.91	0.45–1.83	0.788
History of thrombosis			
Yes vs. no	0.9	0.36–2.28	0.827
HCT-CI >1 vs. ≤1	2.46	1.39–4.33	0.002
WBC >8.85 vs. ≤8.85 ×10^9/l	2.28	1.07–4.88	0.034
Neu (×10^9/L)	1.18	1.05–1.34	0.008
LYM (×10^9/L)	1.35	1.07–1.72	0.013
MONO >0.9 vs. ≤0.9 ×10^9/L	4.25	1.68–10.75	0.002
HGB (g/L)			
>70 and ≤120 vs. ≤70	0.68	0.33–1.39	0.29
>120 vs. ≤70	0.41	0.16–1.09	0.074
PLT >228 vs. ≤228 ×10^9/L	0.69	0.31–1.54	0.369
β2-MG (mg/L)			
≥3.5 and <5.5 vs. <3.5	1.48	0.51–4.26	0.471
≥5.5 vs. <3.5	3.78	1.58–9.06	0.003
ALB (g/L)			
>24.5 and ≤35 vs. ≤24.5	0.60	0.24–1.47	0.263
>35 vs. ≤24.5	0.30	0.12–0.77	0.012
Serum calcium (mmol/L)	2.36	0.90–6.17	0.079
LDH >300 vs. ≤300 IU/L	1.57	0.52–4.67	0.391
HRCA: yes vs. no	1.98	0.89–4.43	0.089
BMPC >61.7% vs. ≤61.7%	1.54	0.78–3.04	0.211
PBPC			
>0 and <2.7% vs. 0	2.07	0.91–4.70	0.082
≥2.7% vs. 0	3.20	1.51–6.78	0.002
DS stage			
II vs. I	0.64	0.14–2.9	0.64
III vs. I	1.83	0.57–5.92	0.314
ISS stage			
II vs. I	0.73	0.24–2.27	0.589
III vs. I	3.33	1.40–7.93	00.007
R-ISS stage			
II vs. I	1.23	0.40–3.77	0.707
III vs. I	5.14	1.75–15.09	0.004
ASCT: yes vs. no	0.29	0.07–1.21	0.09

In the development cohort, the 50-sample bootstrapped calibration curve, with 1,000 bootstrap resamples, was used to examine the calibration of the MM-BHAP model. **Table 3** summarizes other evaluations of models. The predictive OS probabilities were basically in accordance with those observed in 2-year OS (**Figure 2A**). As for discrimination, both time-dependent AUC and C-index of MM-BHAP model were globally higher than that of ISS stage and R-ISS stage (**Figures 2B, C** and **Table 3**). We also assessed clinical effect by DCA for 2-year OS (**Figure 2D**). The MM-BHAP model could achieve positive net benefit over a wider range of risk threshold, with higher area under the decision curve analysis (AUDC) than ISS stage and R-ISS stage in most time-points (**Table 3**). Moreover, the results of calibration curve and DCA for 6-month, 1-year, and 4-year OS are shown in **Supplemental Figure S3**.

Besides, we evaluated the IDI and continuous NRI to test the improvement in the prediction efficiency of the MM-BHAP model (**Table 3**). Compared to ISS stage, the MM-BHAP model showed the statistical improvement of predicting 2-year OS (6.3%, $p = 0.046$, **Figure 2E**) and had a tendency to perform better for the prediction of 6-month and 1-year OS (p = 0.088 and 0.080, respectively, **Supplemental Figures S4A, C**), but it was not statistically different for predicting 4-year OS (**Supplemental Figure S4E**) according to the IDI values. Moreover, there was no statistical difference in the prediction of OS between the MM-BHAP model and ISS stage according to the continuous NRI values. Moreover, the prediction efficiency of the MM-BHAP model was comparable to R-ISS stage, with no statistical difference according to the values of IDI and continuous NRI (**Figure 2F** and **Supplemental Figures S4B, D, F**).

In addition, the MM-BHAP model had great calibration for predicting PFS (**Supplemental Figure S5A**). Moreover, it also had globally higher AUC and C-index (**Supplemental Figures S5B, C**), as well as clinical usefulness (**Supplemental Figure S5D**) than that of ISS stage and R-ISS stage in each imputed dataset. Also, there was no statistical difference between the MM-BHAP model and ISS stage/R-ISS stage according to IDI and continuous NRI analyses (**Supplemental Figures S5E, F**).

Construction of MM-BHAP Stratification

We calculated the total point for each patient according to the nomogram (**Figure 1** and **Table S2**) and divided the patients into low-, medium-, and high-risk subgroups according to the optimal cutoff points calculated by the X-Tile program (32). MM-BHAP stratification stage I was defined as the point ≤110; stage II was defined as the point from 110 to 248; stage III was defined as the point ≥248.

In the development cohort (N = 233), the patients were distributed across the three stages of the MM-BHAP stratification as follows (**Table 4** and **Figure 3A**): stage I (38.6%), stage II (45.5%), and stage III (15.9%), with median overall survivals that were not reached (NR), 50.1 months and 26.2 months, respectively. In

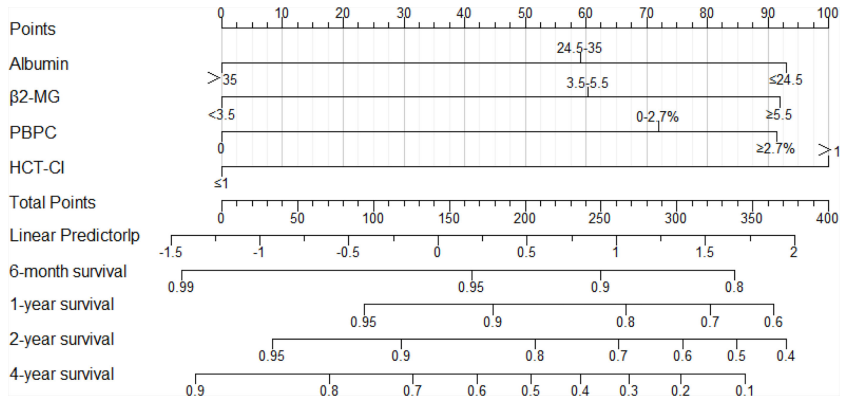

FIGURE 1 | The nomogram derived from the development cohort to predict OS of NDMM patients. The precise values of each variable are showed in **Supplemental Table S2**. Also, the likelihood of 6-month, 1-year, 2-year, or 4-year survival was predicted according to the total points which are located on the corresponding axes.

TABLE 2 | Multivariate Cox regression analysis of variables included in the MM-BHAP model in the development cohort.

Characteristics	Coefficient	HR	95% CI	*p*
ALB (g/L)				
>24.5 and ≤35 vs. ≤24.5	-0.29	0.75	0.29–1.91	0.546
>35 vs. ≤24.5	-0.79	0.45	0.17–1.23	0.121
β2-MG (mg/L)				
≥3.5 and <5.5 vs. <3.5	0.51	1.67	0.57–4.86	0.346
≥5.5 vs. <3.5	0.78	2.18	0.85–5.58	0.100
PBPC (%)				
>0 and <2.7 vs. 0	0.61	1.84	0.78–4.38	0.165
≥2.7 vs. 0	0.78	2.18	0.96–4.93	0.062
HCT-CI (points)				
>1 vs. ≤1	0.85	2.34	1.22–4.49	0.010
Statistical analysis of the prognostic model				
Likelihood ratio test				<0.001
Wald test				<0.001
Score (log-rank) test				<0.001

contrast, both ISS stage (**Figure 3B**) and R-ISS stage (**Figure 3C**) were not satisfactory in stratifying the patients between stages I and II in all the five imputed datasets. Previous studies also indicated the prognostic value of ISS stage II (33) and R-ISS stage II (34) required further improvement.

The median OS of stage III of the MM-BHAP stratification was shorter than that of ISS stage and R-ISS stage (26.2, 46.1, and 33.4 months, respectively), suggesting that the MM-BHAP stratification performed better in identifying a specific group of high-risk patients. We also assessed the stratification for PFS (**Table 4**), indicating that both the MM-BHAP stratification and R-ISS stage had good prognostic stratification (**Figures 3D, F**), while ISS stage was not satisfactory in stratifying patients between stage I and stage II (**Figure 3E**) in all the five imputed datasets.

Subgroup Analyses

Next, we explored the performance of MM-BHAP stratification in specific groups of patients with age ≤65 or age >65 years and patients with or without HRCA in predicting OS. Both age and HRCA were important prognostic factors, but the MM-BHAP stratification still applied to the four different subgroups (**Figures 4A–D**). Then we further analyzed the applicability of our model in the subgroup of patients with at least two HRCAs recommended by mSMART 3.0, and the result indicated the applicability of MM-BHAP stratification in the double-hit or triple-hit myeloma patients (**Figure 4E**).

We also examined the distribution and co-occurrence of the MM-BHAP stratification, R-ISS stage, and ISS stage in the development cohort (N = 233) (**Figure 5A**). There were 37 patients among MM-BHAP stage III, all of whom were distributed in ISS stage III simultaneously. Among them, 22 patients existed in R-ISS stage III and 15 patients had R-ISS stage II.

Notably, there was a substantial portion of the patients with R-ISS stage II or ISS stage III, indicating that the two groups of patients needed an accurate stratification. The patients with ISS stage III (**Figure 5B**) could be further divided into three groups by our MM-BHAP stratification. Moreover, in the patients with R-ISS stage II, our model identified a group of patients with favorable outcomes (**Figure 5C**).

External Validation of the MM-BHAP Model

We calculated the total point for each patient of the validation cohort according to the abovementioned nomogram, as a factor for subsequent analyses (35). In the validation cohort, the calibration curve indicated an optimal agreement between the prediction and actual observation for the probability of OS (**Figure 6A** and **Supplemental Figure S6**).

Table 5 presents other comprehensive evaluations of the MM-BHAP model and ISS stage. Both time-dependent AUC and C-index of the MM-BHAP model were higher than those of the ISS stage, showing a greater prediction performance compared to the ISS stage (**Figures 6B, C**). In the analysis of DCA, the MM-BHAP model had higher net benefits among wider risk thresholds than that of the ISS stage at all time-points (**Figure 6D** and **Supplemental Figure S7**). Surprisingly enough, the MM-BHAP model had a remarkable

TABLE 3 | Comprehensive evaluations of the different models in the development cohort.

OS	6 months	12 months	24 months	48 months
AUC, n (95% CI)				
MM-BHAP	0.793 (0.691–0.895)	0.781 (0.684–0.878)	0.789 (0.702–0.875)	0.721 (0.566–0.875)
ISS stage	0.720 (0.626–0.815)	0.749 (0.686–0.813)	0.724 (0.644–0.803)	0.771 (0.647–0.896)
R-ISS stage	0.730 (0.590–0.871)	0.755 (0.655–0.856)	0.791 (0.696–0.886)	0.636 (0.527–0.746)
C-index, n				
MM-BHAP	0.788	0.760	0.724	0.667
ISS stage	0.720	0.732	0.680	0.670
R-ISS stage	0.714	0.736	0.722	0.600
Range[a], n (%)				
MM-BHAP	1.25%–26.64%	2.28%–38.16%	3.78%–61.25%	11.51%–95.07%
ISS stage	2.05%–8.99%	3.69%–15.74%	5.88%–24.12%	16.42%–55.84%
R-ISS stage	2.68%–13.29%	4.84%–22.97%	8.01%–35.53%	25.23%–78.31%
AUDC, n				
MM-BHAP	0.0027	0.0094	0.0195	0.0757
ISS stage	0.0015	0.0052	0.0106	0.0472
R-ISS stage	0.0018	0.0058	0.0144	0.0922
IDI, n (95% CI), *p* value				
Vs. ISS stage	2.4% (-0.3%–14.8%) *p* = 0.088	3.9% (-0.4%–19.5%) *p* = 0.080	6.3% (1.0%–22.1%) *p* = 0.046	-1.8% (-23.1%–24.7%) *p* = 0.815
Vs. R-ISS stage	0.6% (-3.7%–11.3%) *p* = 0.547	1.1% (-5.4%–16.4%) *p* = 0.500	1.3% (-13.1%–15.3%) *p* = 0.659	0% (-26.9%–34.5%) *p* = 0.685
Continuous NRI, n (95% CI), *p* value				
Vs. ISS stage	1.2% (-14.9%–48.6%) *p* = 0.314	-2.1% (-16.1%–41.9%) *p* = 0.596	12.4% (-4.4%–50.2%) *p* = 0.114	-21.1% (-82.1%–70.9%) *p* = 0.839
Vs. R-ISS stage	5.9% (-29.7%–43.9%) *p* = 0.697	12.1% (-23.7%–44.2%) *p* = 0.436	3.3% (-34.8%–42.1%) *p* = 0.753	22.7% (-68.5%–89.4%) *p* = 0.545

[a]*Range: range of risk threshold to get a positive net benefit in the decision curve analysis (DCA).*

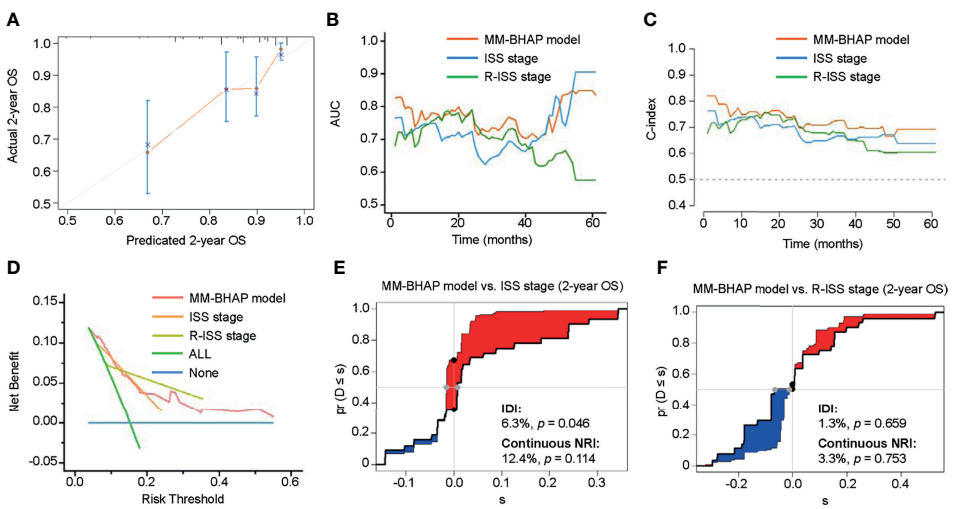

FIGURE 2 | The performance of the MM-BHAP model, ISS stage, and R-ISS stage for predicting OS in the development cohort. **(A)** The calibration curve of the MM-BHAP model for predicting 2-year OS. **(B)** The time-dependent AUC of the ROC in the three models. **(C)** The time-dependent Harrell's C-index in the three models. **(D)** The DCA was used to estimate clinical usefulness of the three models for predicting 2-year OS. The improvement in prediction of the MM-BHAP model was compared to the ISS stage **(E)** or R-ISS stage **(F)**. The IDI was the value of the difference in area between red and blue zones **(E, F)**. The continuous NRI was the value of the distance between two black dots **(E, F)**.

TABLE 4 | Comparison of OS and PFS duration by stage in the development cohort.

Stage	Median OS (months)	Median PFS (months)
MM-BHAP stratification		
I	NR	29.8
II	50.1	22.3
III	26.2	10.9
ISS stage		
I	NR	42.8
II	NR	29.9
III	46.1	14.0
R-ISS stage		
I	NR	35.8
II	NR	24.5
III	33.4	11.9

improvement compared to the ISS stage according to the IDI values (range from 4.8% to 11.8%) and continuous NRI values (range from 30.2% to 56.0%) in predicting OS at different time points (**Figure 6E**, **Supplemental Figure S8** and **Table 5**).

Also, the MM-BHAP model had great calibration for predicting PFS (**Supplemental Figure S9A**). At the same time, it performed better in all the analyses of time-dependent AUC and C-index, DCA, IDI, and continuous NRI compared to the ISS stage (**Supplemental Figures S9B–E**).

The MM-BHAP stratification also categorized patients into three groups well as follows (**Figure 7A**): stage I (38.8%), stage II (40.8%), and stage III (20.4%), with median overall survivals of 71, 44.9, and 22.8 months, respectively. Also, our MM-BHAP stratification had a good stratification for PFS (**Figure 7B**). However, the ISS stage did not perform well in stratifying patients between three stages whether to predict OS ($p = 0.18$) or PFS ($p = 0.11$) (**Figures 7C, D**). Actually, the curves of the ISS stage were superimposable when time was more than approximately 60 months for OS (**Figure 7C**) and when time was more than about 50 months for PFS (**Figure 7D**), which suggested it was not enough for predicting long-term survival to merely utilize the ISS stage.

In the validation cohort, we did not draw comparison of the predictive capacity between the MM-BHAP model and R-ISS stage. This is because the patients were diagnosed between January 2013 and December 2015 in which our center did not completely perform FISH analysis with CD138-purified plasma cells, resulting in the problem taking no unified thresholds to identify HRCA.

Distribution of Transplant-Eligible Patients

Given that the new stratification included the HCT-CI that was used to assess transplant eligibility, we exploringly analyzed the association between the MM-BHAP stratification at diagnosis

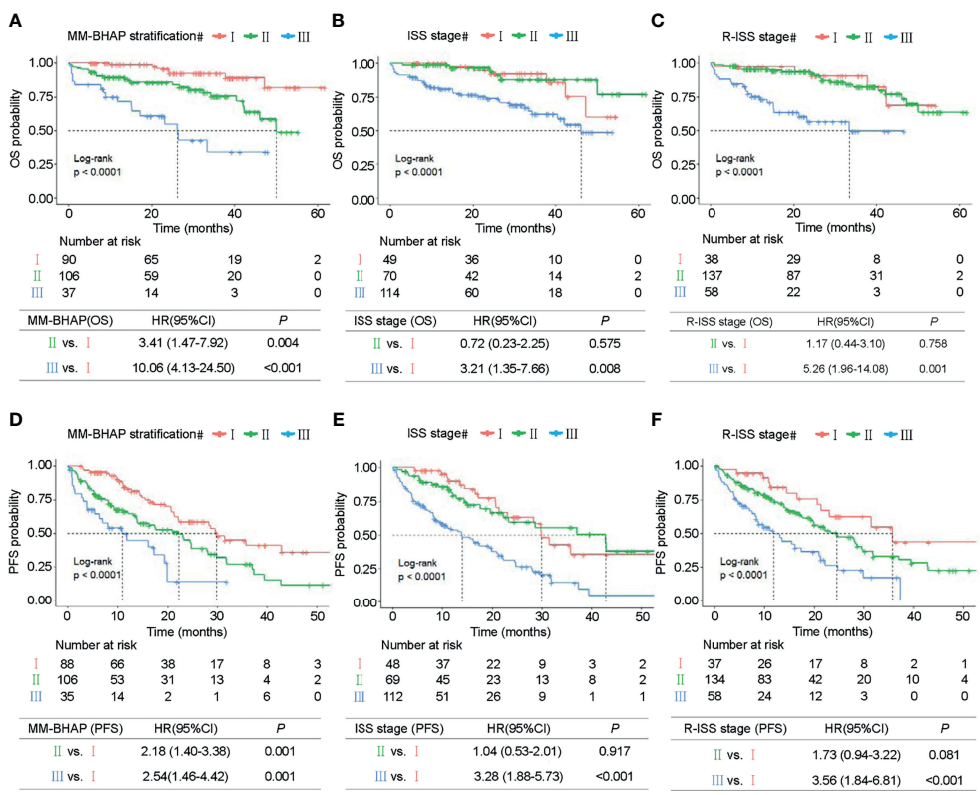

FIGURE 3 | Kaplan–Meier survival curves in the development cohort. OS of MM patients was stratified by the MM-BHAP stratification **(A)**, ISS stage **(B)**, and R-ISS stage **(C)**. PFS was also classified by the three risk stratifications **(D–F)**.

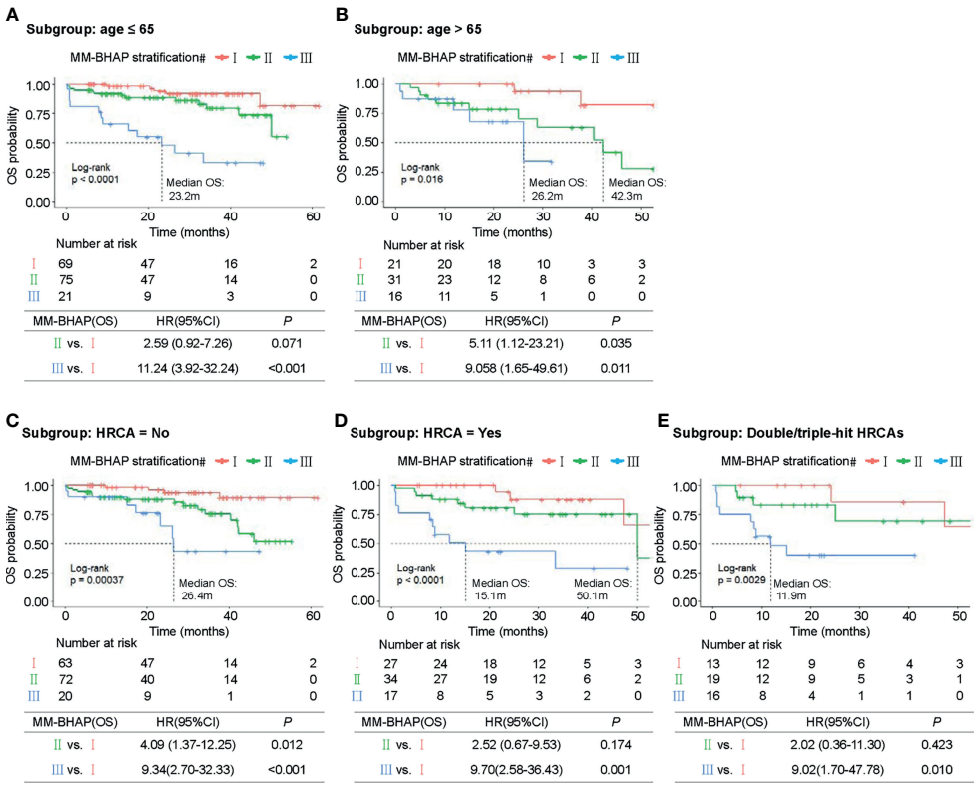

FIGURE 4 | Kaplan–Meier survival curves of specific subgroups stratified by the MM-BHAP stratification in the development cohort. OS curves in the subgroups with different characteristics of age **(A, B)** and HRCA **(C–E)** were shown.

with the probability of receiving ASCT afterward. In the whole cohort (N = 385), 47 (12.2%) patients underwent ASCT, which were distributed across three stages of the MM-BHAP stratification as follows: stage I (25/149; 16.8%), stage II (18/168; 10.7%), and stage III (4/68; 5.9%). With multiple-comparison analysis by using the Bonferroni method, we found that the proportions between stage I (16.8%) and stage III (5.9%) had statistical difference ($p < 0.05$), suggesting the patients with stage III had less probability to fulfill the eligibility for transplantation in the future compared to patients with stage I.

DISCUSSION

In this study, we developed and validated a new simple prognostic model (MM-BHAP) integrating comorbidities and tumor burden, for predicting the probability of 6-month, 1-year, 2-year, and 4-year OS of NDMM patients. The novel MM-BHAP model performed well in terms of calibration, discrimination, clinical usefulness, and improvement in prediction, suggesting a good prognostic value for OS and PFS of NDMM patients. Moreover, the performance of the MM-BHAP model was superior to the ISS stage in both development and validation cohorts, while it was partially better at least not worse than the R-ISS stage in the development cohort. Notably, the MM-BHAP stratification categorized patients into three subgroups with clearly different OS or PFS, which was superior to the ISS stage and partially better than the R-ISS stage. Also, it identified a group of high-risk patients with shorter median OS (26.2 months) than that of the ISS stage (46.1 months) and R-ISS stage (33.4 months), indicating an advantage of defining truly high-risk patients in the real-world population. Furthermore, it enhanced the differential power of the ISS stage and R-ISS stage, with reclassifications in patients with ISS stage III or R-ISS stage II.

The MM-BHAP model was composed of four widely accessible factors of β2-MG, HCT-CI, ALB, and PBPC. β2-MG and ALB were typically prognostic factors integrated into the ISS stage (5). In contrast, we divided the value of ALB into three levels (≤24.5; >24.5 and ≤35; >35 g/l), based on the restricted cubic splines. With regard to PBPC, its importance was second only to HCT-CI in the MM-BHAP model. Multiple studies demonstrated that high levels of circulating plasma cells (CPCs) in MM patients were associated with worse prognosis (36–40) and even the prognosis of the MM patients with ≥5% CPCs was equivalent to that of the patients with plasma cell leukemia (41). In addition, it was evidenced that HCT-CI was independently associated with poor OS of MM patients undergoing HSCT (26, 27). It was of concern that HCT-CI

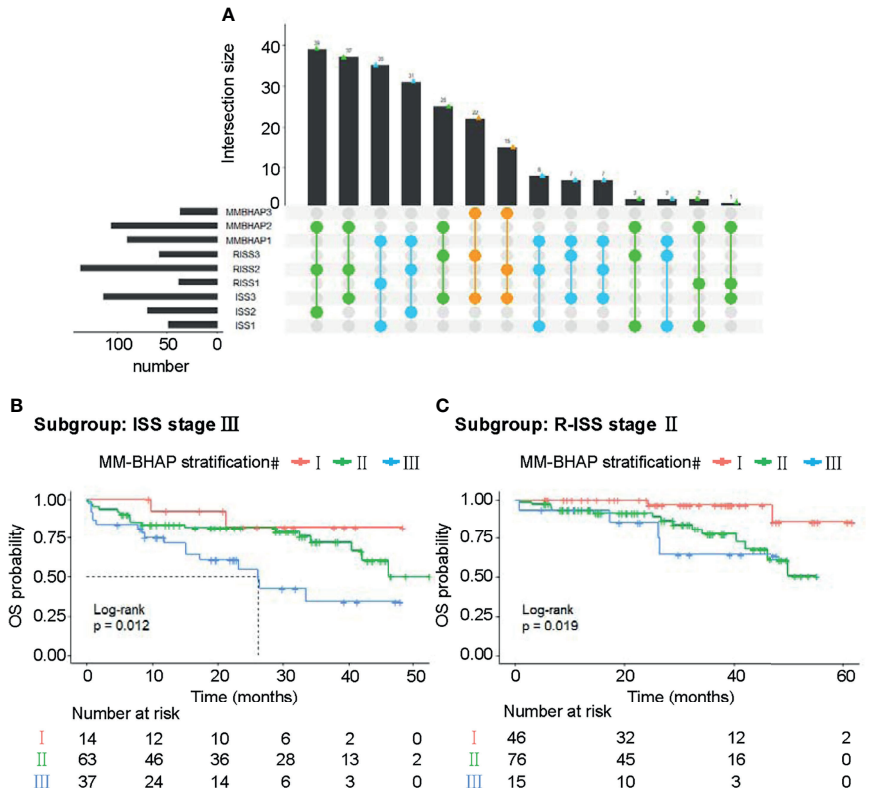

FIGURE 5 | Subgroup analyses about the three risk stratifications in the development cohort. **(A)** The distribution and co-occurrence of the patients respectively classified by the MM-BHAP stratification, R-ISS stage, and ISS stage in the development cohort were displayed. Dots with connected lines represented that the patients coexisted in corresponding different subgroups and the vertical bar graphs reflected the number of these patients. Also, the blue, green, and orange dots respectively represented the co-occurrence of the patients classified by stage I, stage II, and stage II of the MM-BHAP stratification with other subgroups. **(B)** OS curves in the subgroup with ISS stage III stratified by the MM-BHAP model. **(C)** OS curves in the subgroup with R-ISS stage II stratified by the MM-BHAP model.

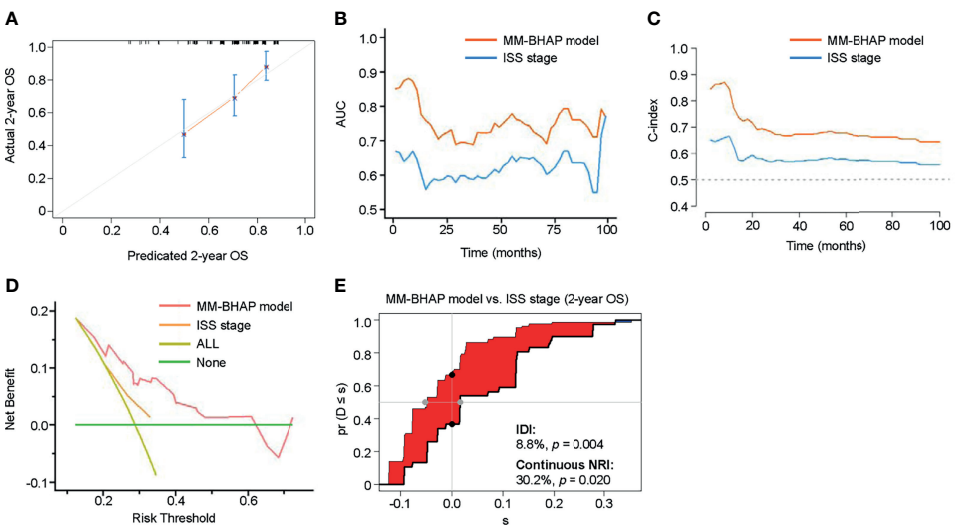

FIGURE 6 | The performance of the MM-BHAP model and ISS stage for predicting OS in the validation cohort. **(A)** The calibration curve of the MM-BHAP model for predicting 2-year OS. **(B)** The time-dependent AUC of the ROC in the two models. **(C)** The time-dependent Harrell's C-index in the two models. **(D)** The DCA for predicting 2-year OS. **(E)** The IDI and continuous NRI of the MM-BHAP model compared to the ISS stage.

TABLE 5 | Comprehensive evaluations of the different models in the validation cohort.

OS	6 months	12 months	24 months
AUC, n (95% CI)			
MM-BHAP	0.875 (0.816–0.934)	0.797 (0.683–0.912)	0.724 (0.627–0.820)
ISS stage	0.650 (0.540–0.761)	0.629 (0.518–0.741)	0.598 (0.503–0.692)
C-index, n			
MM-BHAP	0.867	0.774	0.692
ISS stage	0.649	0.618	0.576
Range[a], n (%)			
MM-BHAP	2.93%–18.97%	4.70%–23.67%	12.44%–60.88%
ISS stage	5.29%–9.24%	8.24%–14.21%	20.15%–33.04%
AUDC, n			
MM-BHAP	0.0051	0.0087	0.0347
ISS stage	0.0008	0.0017	0.0073
IDI, n (95% CI), *p* value			
Vs. ISS stage	4.8% (1.9%–11.8%)	5.4% (1.6%–11.4%)	8.8% (2.8%–15.9%)
	$p < 0.001$	$p = 0.004$	$p = 0.004$
Continuous NRI, n (95% CI), *p* value			
Vs. ISS stage	56.0% (30.4%–72.7%)	46.5% (9.7%–64.0%)	30.2% (7.0%–49.1%)
	$p < 0.001$	$p = 0.016$	$p = 0.020$
OS	**48 months**	**60 months**	**72 months**
AUC, n (95% CI)			
MM-BHAP	0.739 (0.649–0.829)	0.766 (0.675–0.856)	0.735 (0.623–0.847)
ISS stage	0.608 (0.512–0.703)	0.646 (0.546–0.748)	0.611 (0.477–0.744)
C-index, n			
MM-BHAP	0.674	0.677	0.661
ISS stage	0.569	0.574	0.565
Range[a], n (%)			
MM-BHAP	26.62%–95.14%	33.15%–98.04%	38.98%–99.20%
ISS stage	38.58%–58.06%	45.87%–66.52%	52.25%–73.23%
AUDC, n			
MM-BHAP	0.1070	0.1290	0.1202
ISS stage	0.0235	0.0308	0.0290
IDI, n (95% CI), *p* value			
Vs. ISS stage	11.7% (3.6%–18.7%)	11.8% (3.3%–18.7%)	10.6% (1.9%–16.9%)
	$p < 0.001$	$p = 0.008$	$p = 0.012$
Continuous NRI, n (95% CI), *p* value			
Vs. ISS stage	40.6% (6.5%–51.5%)	48.0% (6.4%–57.3%)	42.5% (0%–57.1%)
	$p = 0.020$	$p = 0.032$	$p = 0.052$

[a]*Range: range of risk threshold to get positive net benefit in the decision curve analysis (DCA) analysis.*

also had potential to predict outcomes of the patients with newly diagnosed hematologic malignancies, not merely the patients after HSCT. A multicenter study firstly developed and validated a prognostic model incorporating HCT-CI at diagnosis, to estimate risks of mortality in acute myeloid leukemia (42). Nevertheless, little is known about the prognostic impact of HCT-CI at the time of diagnosis on the outcomes of NDMM patients. Herein, we systematically examined the prognostic value of HCT-CI at diagnosis which contributed the most to our MM-BHAP model. To our knowledge, the present study is the first to develop and validate a novel prognostic model integrating comorbidities measured by HCT-CI and tumor burden reflected by β2-MG, ALB, and PBPC.

Although HRCA was not selected into our model, it had robust prognostic implications. However, the application of novel agents and ASCT seemed to improve the poor outcomes of the patients with certain HRCAs. For instance, the adverse impact of t(4;14) could be partly overcome by bortezomib (43) and the inferior outcome of del(17p) could be improved by maintenance therapy and ASCT especially in transplant eligible patients (44, 45), suggesting highly heterogeneous outcomes of the patients with HRCA. Therefore, there was an urgent need to further identify the ultra-high-risk subgroup within the patients harboring HRCA. In our cohort, the overall survival of the patients with HRCA or double/triple-hit HRCA could be further differentiated by our MM-BHAP stratification, maybe partially because of diverse therapy regimens and treatment intensity resulting from the burden of different comorbidities.

It was noteworthy that the R-ISS stage was inclined to present a better prognostic stratification for PFS compared to OS. As we all know, the R-ISS stage was completely composed of disease-related factors, which mainly reflected the inherent biological characteristics of myeloma (46–49). However, the overall survival of MM was dependent on not only the disease progression but also the host features such as comorbidities, performance status, treatment intention, and socioeconomic support, which were more likely to affect the drug accessibility and treatment integrity. Moreover, the R-ISS stage was developed

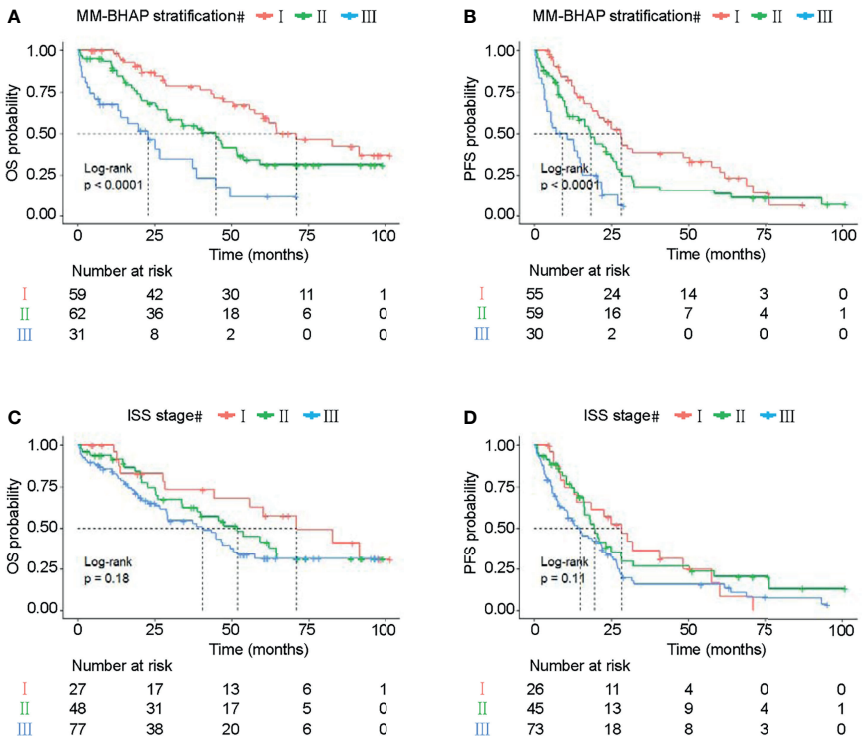

FIGURE 7 | The OS and PFS curves in the validation cohort stratified by the MM-BHAP stratification **(A, B)** and ISS stage **(C, D)**.

in the highly selected cohorts within clinical trials (6) in which the patients with comorbidities were not underrepresented. Therefore, the R-ISS stage might be more applicable to the patients defined as "fit," and it was essential to combine disease-related and patient-related prognostic factors in predicting overall survival in the real-world unselected population.

It was well known that the intermediate-risk group of the R-ISS stage was an exclusionary definition, which was an indication of the high heterogeneity of genetic background and outcomes. Further subdivision may redefine the outcomes of some patients, thereby achieving precise and personalized management. In our study, about 60% of the patients were among R-ISS stage II, which was similar to a previous R-ISS study (62%) (6). Moreover, among these patients, our model could identify a subgroup of patients with favorable outcomes. Furthermore, the MM-BHAP stratification could distinguish a group of patients with higher risk in the subgroup with ISS stage III, which further verified its applicability in some specific subsets.

Yet, there were still some limitations in our study. This study only included patients from a single center and needed further confirmations from larger multicenter cohorts. Moreover, this is a real-world retrospective cohort study, showing some missing data inevitably, but we handled missing data by using MICE to minimize the impact of data deficiency. HRCA was a known prognostic factor, and our subgroup analysis also suggested that patients with HRCA had poor median OS. However, it was finally not selected into our model, maybe because the impact was undervalued due to data deficiency, or it was knocked out since other variables contribute more in LASSO analysis. Besides, the comparison between MM-BHAP model and R-ISS stage was established only in the development cohort, requiring further validation. However, the effect of missing value on our model was minor because the finally selected variables included in the nomogram were all complete data in both development cohort and validation cohort. Moreover, the MM-BHAP stratification could definitely categorize patients into different groups with distinct outcomes.

In conclusion, our study was the first to use HCT-CI at diagnosis to predict the outcome of NDMM patients. Utilizing widely available prognostic factors, we constructed a novel simple MM-BHAP stratification combining tumor burden with comorbidities for better differentiation of real-world unselected patients with NDMM. It was expected to have a more accurate prediction for outcome uniting the MM-BHAP stratification and the current risk stratifications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The study was reviewed and approved by the Ethics Committee of Xijing Hospital of Air Force Medical University.

AUTHOR CONTRIBUTIONS

GG, HT, SJ, and LB designed and conducted the research. JF, LX, TZ, HG, LY, QB, and RL enrolled the patients. SJ, LB, YC, XL, BT, and YG collected the data. SJ and HT analyzed the data and wrote the paper. GG and HT reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.805702/full#supplementary-material

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Physicians' Perceptions of Clinical Utility of a Digital Health Tool for Electronic Patient-Reported Outcome Monitoring in Real-Life Hematology Practice. Evidence From the GIMEMA-ALLIANCE Platform

Fabio Efficace[1], Andrea Patriarca[2], Mario Luppi[3], Leonardo Potenza[3], Giovanni Caocci[4], Agostino Tafuri[5], Francesca Fazio[6], Claudio Cartoni[6], Maria Teresa Petrucci[6], Ida Carmosino[6], Riccardo Moia[2], Gloria Margiotta Casaluci[2], Paola Boggione[2], Elisabetta Colaci[3], Davide Giusti[3], Valeria Pioli[3], Francesco Sparano[1], Francesco Cottone[1], Paolo De Fabritiis[7], Nicolina Rita Ardu[7], Pasquale Niscola[7], Isabella Capodanno[8], Anna Paola Leporace[5], Sabrina Pelliccia[5], Elisabetta Lugli[8], Edoardo La Sala[1], Luigi Rigacci[9], Michelina Santopietro[9], Claudio Fozza[10], Sergio Siragusa[11], Massimo Breccia[6], Paola Fazi[1] and Marco Vignetti[1]*

[1] Data Center and Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA), Rome, Italy, [2] Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy, [3] Hematology Unit and Chair, Azienda Ospedaliera Universitaria di Modena, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy, [4] Department of Medical Sciences and Public Health, Businco Hospital, University of Cagliari, Cagliari, Italy, [5] Azienda Ospedaliera Sant'Andrea, Rome, Italy, [6] Hematology, Department of Translational and Precision Medicine, Azienda Ospedaliera Policlinico Umberto I, Sapienza University of Rome, Rome, Italy, [7] Hematology Unit, Sant'Eugenio Hospital, Rome, Italy, [8] Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [9] U.O. di Ematologia e Trapianti di cellule Staminali. A.O.S. S. Camillo-Forlanini, Rome, Italy, [10] Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy, [11] Policlinico Paolo Giaccone, Unit of Haematology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy*

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***Correspondence:**
Fabio Efficace
f.efficace@gimema.it

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Digital health tools are increasingly being used in cancer care and may include electronic patient-reported outcome (ePRO) monitoring systems. We examined physicians' perceptions of usability and clinical utility of a digital health tool (GIMEMA-ALLIANCE platform) for ePRO monitoring in the real-life practice of patients with hematologic malignancies. This tool allows for the collection and assessment of ePROs with real-time graphical presentation of results to medical staff. Based on a predefined algorithm, automated alerts are sent to medical staff. Participating hematologists completed an online survey on their experience with the platform. Of the 201 patients invited to participate between December 2020 and June 2021 (cut-off date for current analysis), 180 (90%) agreed to enter the platform and had a median age of 57 years. Twenty-three hematologists with a median age of 42 years and an average of 17 years of experience in clinical practice were surveyed. All hematologists agreed or strongly agreed that the platform was easy to use, and 87%, agreed or strongly agreed that ePROs data were

useful to enhance communication with their patients. The majority of physicians (78%) accessed the platform at least once per month to consult the symptom and health status profile of their patients. The frequency of access was independent of physician sex (p=0.393) and years of experience in clinical practice (p=0.404). In conclusion, our preliminary results support the clinical utility, from the perspective of the treating hematologist, of integrating ePROs into the routine cancer care of patients with hematologic malignancies.

Keywords: digital health, symptoms, quality of life, hematology, patient-reported outcomes (PROs), leukemia, multiple myeloma, lymphoma

INTRODUCTION

Patients with cancer typically experience disease- and treatment-related symptoms that affect their health-related quality of life (HRQoL). Therefore, it is critical to capture the patient experience *via* validated patient-reported outcome (PRO) measures that provide unique information, unobtainable by other sources of more traditional clinical and laboratory measures. For example, PROs, such as functional aspects or symptoms reported by patients themselves, provide independent prognostic information for survival (1, 2). Additionally, there is ample literature documenting that clinicians often underestimate the severity of their patients' symptoms (3–6).

The assessment of PROs has been historically confined to clinical research settings; however, in recent years, we have seen a greater interest in using PROs in clinical practice in an effort to improve the quality of patient care. Indeed, systematic evaluation of PROs in routine practice has been found to be associated with several benefits, including improved symptom control, HRQoL, patient satisfaction, as well as improved physician-patient communication and decreased hospitalizations and emergency department visits (7–10).

The inclusion of PROs in routine practice settings has been facilitated by advances in digital health technology, which now allows the implementation of PROs into electronic formats that can be administered remotely *via* online platforms (11). Two recent randomized controlled trials (RCTs), including patients with several types of cancer during chemotherapy, showed that remote symptom monitoring with electronic PROs (ePROs) was associated with reduced symptom burden and improved HRQoL outcomes (12, 13). Remarkably, the systematic monitoring of PROs *via* web-based platforms has also been found to be associated with improved overall survival in patients with advanced cancers (14–17).

The recent coronavirus disease pandemic has further boosted the adoption of digital health tools that could facilitate remote patient monitoring during emergencies, making ePROs even more critical in enhancing patient-centered care. However, implementation of ePRO monitoring in the routine care of patients with hematologic malignancies has been less documented in the literature (18), and only recently have we seen valuable evidence in this area (19, 20). In any case, there is a paucity of information about users' perceptions of the clinical utility of digital health tools in routine care.

Late in 2020, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) developed a digital health tool for adult patients with hematological malignancies (GIMEMA-ALLIANCE platform) (21) with the main goal of facilitating patient-centered care in routine practice.

We herein report a survey conducted to better understand the hematologists' perceptions of usability and clinical utility of this platform in real-life practice.

MATERIALS AND METHODS

Study Design and Participants

Adult patients with a diagnosis of any hematologic malignancies according to the 2016 World Health Organization classification (22), who signed a written informed consent form, were eligible for enrollment in the GIMEMA-ALLIANCE platform. For the purpose of this project, patients could be included regardless of their type of therapy or individual characteristics, including age, level of education, or presence of comorbidities. After registration, patients were given (by their treating hematologist) a personal password to access the patient portal and complete a PRO survey that assessed aspects related to HRQoL, symptoms, and medication adherence. PRO measures include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core (EORTC QLQ-C30) (23), four items from the EORTC Item Library (24), and the shortened 7-item Adherence to Refills and Medications Scale (ARMS-7) (25). These measures were selected based on their clinical relevance for the population under consideration. Indeed, the PRO questionnaires and items included in the platform, cover several aspects which are of importance across various hematological malignancies and have been widely used in previous studies. Each patient entering the platform has to be followed up for two years from the date of registration. As of January 2022, the platform includes 420 patients with hematologic malignancies, and 23 centers have obtained ethical approval to participate to this study. PRO results are available for both patients and physicians and are displayed graphically (in real time) with colored bars indicating the presence or absence of a clinically important problem or symptom. An example of the interfaces of the platform with the clinician with regard to display of functional aspects and symptoms is reported in the Appendix (**Supplementary**

Figures 1, 2). Treating hematologists were required to collect clinical and socio-demographic information at baseline (e.g., patients' and physicians' characteristics, disease status at study entry) and every 3 months at follow-up (e.g., disease progression and survival status). Given the real-life nature of this study, no specific time-points were preplanned for the completion of the PRO survey. However, the platform is currently designed to send automated reminders to patients for completing the Survey after one week from registration (if this has not been completed within the first week from study inclusion), and thereafter every two weeks from the first PRO survey completion. In addition, physicians are encouraged (by the GIMEMA-ALLIANCE management team) to emphasize to their patients the importance of possibly completing the survey on a regular basis and, in any case, just few days before a planned clinical visit. The rationale for this latter aspect is that of providing a basis (updated information on patient's HRQoL and symptoms) for further discussion during the clinical consultation. This study was registered at ClinicalTrials.gov (NCT04581187).

Overview of the GIMEMA-ALLIANCE Infrastructure

The GIMEMA-ALLIANCE platform is hosted in the Computer-based Health Evaluation System (CHES) infrastructure, a software used worldwide for the electronic collection, analysis, and presentation of ePROs (26). Full details of the development process and architecture of the GIMEMA-ALLIANCE platform, including the study rationale and the implementation of ePRO measures, as well as clinical data collected, have been described previously (21). Briefly, the platform consists of two dedicated secure portals, the patient (https://alliance.gimema.it) and physician (https://physician-alliance.gimema.it) portals. Based on a predefined algorithm, the treating hematologists and medical staff receive automated email alerts following the presence of clinically important problems, symptoms, or problems with adherence to therapy. The definition of clinically important problems and symptoms is based on previously defined evidence-based thresholds for the EORTC QLQ-C30 (27). Once the alert is received, and depending on the types and frequencies of the alerts received, the physician may decide to contact the patient by phone, schedule a face-to-face visit, or arrange a video-consultation within the GIMEMA-ALLIANCE platform. Indeed, the possibility of video consultations is an additional feature of this tool. A specific standard operating procedure (SOP) on "how to handle e-mail alerts" was not developed because the platform is open to patients with any hematologic malignancy, hence representing a wide range of patients with different clinical conditions and different needs. Therefore, the protocol stipulated that physicians are free to decide which action they feel most appropriate for their specific patients.

A brief schematic workflow of the data process is shown in **Figure 1**. After obtaining approval from the local ethics committee, and before being officially opened for recruitment, a start-up training session was organized by the GIMEMA-ALLIANCE management team. This session aimed to instruct the clinical staff of the participating hospital in using the platform and interpreting PRO data. SOPs developed for using the platform were illustrated during this online training session and also sent to the clinical staff just afterwards.

Survey Evaluating Physicians' Perception of Usability and Clinical Utility

For the purpose of this work, approximately after six months from the implementation of the platform, we asked the participating hematologists for structured feedback on their experience with its use, with a focus on their perception of its usability, clinical utility in their daily practice, and impact on quality of care. Only the hematologists who had registered at least one patient (also from the same center), were invited to complete the survey. Only one of the respondents was involved in the development process of the platform.

We developed an *ad hoc* web survey covering the following three broad domains: 1) usability and potential benefits; 2) monitoring of symptoms and health status; and 3) aspects related to physician-patient communication. Selection of items included in the Survey was based on consensus among the management Team and it was aimed at capturing the physicians' perception of the specific features of the Platform.

The survey was implemented and administered online to physicians *via* REDCap (28). Each treating hematologist received a personal link through which they could enter and complete the online survey. Every two days, automatic reminders were sent to hematologists who had not yet completed the survey. Once the hematologists completed their survey, REDCap automatically saved the answers into a secure online database. Of note, REDCap was only used for the purpose of capturing physicians' answers to the Survey and it had no role in the development or management of the GIMEMA-ALLIANCE Platform. The invited hematologists had two weeks to respond, and after this deadline, the survey was taken offline. The database with all the responses was closed and downloaded for statistical analyses. The characteristics of the enrolled patients and treating hematologists were summarized by proportions, mean, median, and range. Additionally, in order to check the possible association of the characteristics of hematologists with survey results, we performed a multivariable logistic regression analysis including the sex of the treating hematologists (male=1 vs. female=0) and the corresponding years of experience in dealing with hematologic patients as independent variables. The statistical tests we performed were bilateral, with α=0.05, set as the threshold for statistical significance. All analyses were performed using SAS software v.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between December 2020 and June 2021 (cut-off date for current analysis), 201 patients were invited to participate, and 180 (90%) accepted to enter the ALLIANCE platform. The median age of the patients was 57 years (range 21-91). The majority were diagnosed with chronic myeloid leukemia (n=32, 18%) or multiple myeloma (n=31, 17%). Overall, there were 89 (49%) of patients in stable disease. Twenty-three hematologists (44% males and 56% females) from 11 centers, with a median age of 42

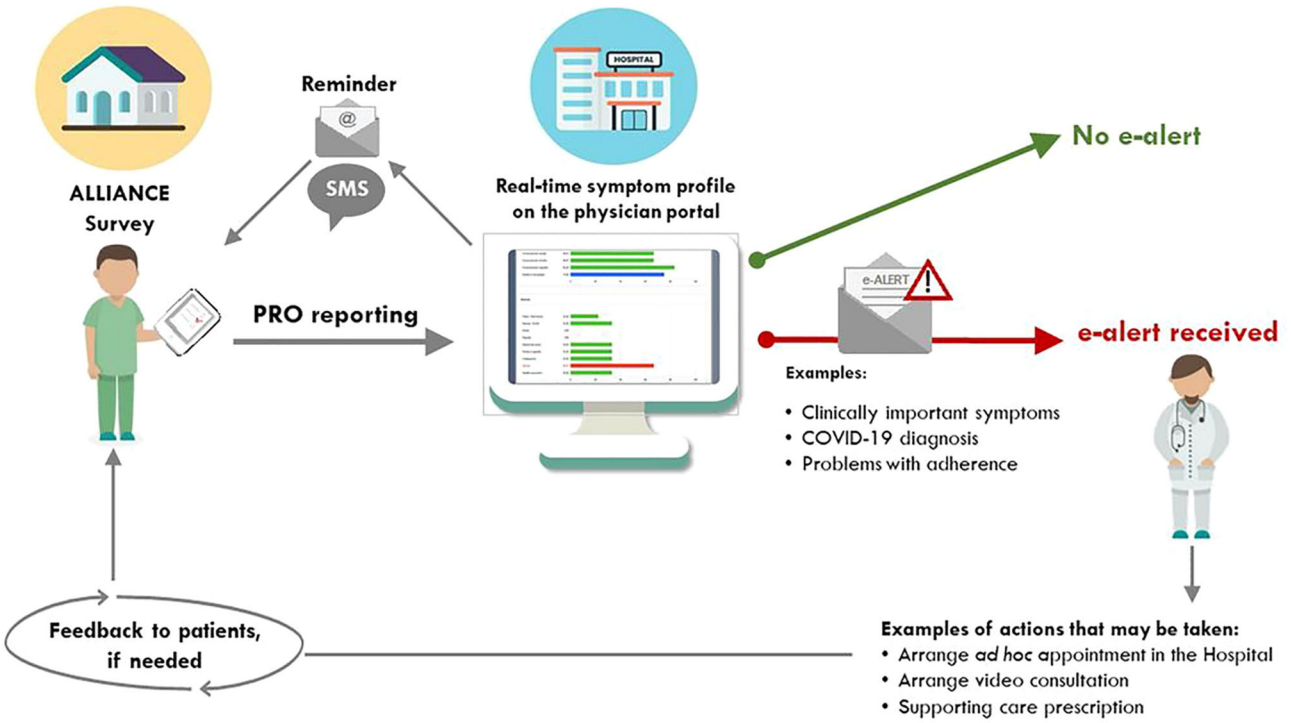

FIGURE 1 | Schematic workflow of the patient-generated alerts to the medical team. PRO, patient-reported outcomes. This Figure was first published under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/) in JMIR Research Protocols: Efficace F, Breccia M, Fazi P, Cottone F, Holzner B, Vignetti M. The GIMEMA-ALLIANCE Digital Health Platform for Patients With Hematologic Malignancies in the COVID-19 Pandemic and Postpandemic Era: Protocol for a Multicenter, Prospective, Observational Study JMIR Res Protoc 2021;10(6):e25271 (21). URL: https://www.researchprotocols.org/2021/6/e25271.

years (range 31-63) and an average of 17 years (range 5-34) of experience in clinical practice completed the online survey.

Usability and Potential Benefits of the Platform

All the treating hematologists agreed or strongly agreed that the platform was easy to use, and the majority agreed or strongly agreed (91.3%, n=21) that it is useful in the clinical management of their patients. Regardless of receiving the alerts when clinically important problems and symptoms occurred, 30.4% (n=7) of physicians entered the portal at least once a week to monitor their patients' health status, while 30.4% did so at least once every two weeks. Only 21.7% (n=5) entered the portal less than once per month. The frequency of access on a regular basis was also independent of physician sex (p=0.393) and years of experience in clinical practice (p=0.404). After receiving the alert, the majority of physicians entered the portal the same day (60.9%, n=14) and made a phone call to their patients (69.6%, n=16). The hematologists often (30.4%, n=7) or very often (26.1%, n=6) used the ePRO information from the platform for their discussion with the patients, but this was not the case within their team. The same information was sometimes (30.4%, n=7), rarely (34.8%, n=8), or never (17.4%, n=4) used for discussion with other colleagues. Further details are presented in **Table 1**.

Monitoring of Patients' Health Status and Symptoms Profile

Almost all the treating hematologists agreed or strongly agreed (95.6%, n=22) that the graphics about patients' health status displayed on the platform were easy to understand and interpret. Sixteen physicians (69.6%) agreed and 3 (13.0%) strongly agreed that the platform helped them to better understand the patients' general health status. Sixteen physicians (69.6%) agreed and 4 (17.4%) strongly agreed that the platform helped them to better understand the patients' symptoms. Overall, 91.3% of physicians (n=21) agreed or strongly agreed that ePRO is useful to more accurately document patients' symptomatic adverse events (AEs). In addition, 82.6% and 60.9% of physicians deemed ePRO information helpful to better identify low-grade and high-grade symptomatic adverse events, respectively. Further details are presented in **Table 2**.

Physician-Patient Communication

Overall, 91.3% of physicians (n=21) deemed ePRO information useful to favor shared decision-making, and all of them considered this information helpful in suggesting supportive care strategies. Twenty hematologists (87.0%) deemed the information reported in the GIMEMA-ALLIANCE platform helpful in setting up unplanned visits with their patients and

TABLE 1 | Usability and benefits of the platform.

Item	Categories	n (%)
The automatic alert functionality is useful	*No*	1 (4.35)
	Yes	22 (95.65)
Most frequently undertaken action after receiving e-mail alert	*Phone call to the patient*	16 (69.57)
	None	5 (21.74)
	Set up a visit in the hospital	1 (4.35)
	Other	1 (4.35)
After how long the physician enter to the portal, after receiving the e-mail alert	*Within one day*	14 (60.87)
	Within 2-7 days	8 (34.78)
	More than 15 days after	1 (4.35)
Frequency of the access to the portal, regardless the e-mail alert receipt	*At least once a week*	7 (30.43)
	At least once every two weeks	7 (30.43)
	At least once a month	4 (17.39)
	Less than once a month	5 (21.74)
Use of the ePRO information from the platform for the discussion with the patients during clinical visits	*Very often*	6 (26.09)
	Often	7 (30.43)
	Sometimes	4 (17.39)
	Rarely	4 (17.39)
	Never	2 (8.7)
Use of the ePRO information from the platform for the discussion with the colleagues	*Very often*	2 (8.7)
	Often	2 (8.7)
	Sometimes	7 (30.43)
	Rarely	8 (34.78)
	Never	4 (17.39)
The platform is easy to use	*Strongly agree*	12 (52.17)
	Agree	11 (47.83)
	Disagree	0 (0.0)
	Strongly disagree	0 (0.0)
The platform is useful for the clinical management of the patients	*Strongly agree*	6 (26.09)
	Agree	15 (65.22)
	Disagree	2 (8.7)
	Strongly disagree	0 (0.0)

PRO, patient-reported outcomes.

TABLE 2 | Evaluation of patients' health status and symptoms profile.

Item	Strongly disagree n (%)	Disagree n (%)	Agree n (%)	Strongly agree n (%)
The graphics about patients' health status are easy to understand and interpret	0 (0.0)	1 (4.35)	12 (52.17)	10 (43.48)
The platform was helpful to better understand patients' general health status	0 (0.0)	4 (17.39)	16 (69.57)	3 (13.04)
The platform was helpful to better understand patients' general symptom profile	0 (0.0)	3 (13.04)	16 (69.57)	4 (17.39)
The platform was used (at least once) for patients' clinical management	1 (4.35)	3 (13.04)	17 (73.91)	2 (8.7)
ePRO useful to more accurately document patients' symptomatic AEs	0 (0.0)	2 (8.7)	15 (65.22)	6 (26.09)
ePRO helpful to better identify low-grade symptomatic AEs	0 (0.0)	4 (17.39)	15 (65.22)	4 (17.39)
ePRO helpful to better identify high-grade symptomatic AEs	0 (0.0)	9 (39.13)	12 (52.17)	2 (8.7)

AE, adverse events; PRO, patient-reported outcomes.

to enhance physician-patient communication. Only 13% of the treating physicians (n=3) did not agree with these statements. The details are presented in **Table 3**.

DISCUSSION

In this study, we explored the physicians' perception of the usability and clinical utility of a digital health tool for ePRO monitoring in real-life hematology practice. While the clinical value of eHealth platforms has been well studied and documented in the context of solid tumors, less is known about their value in the context of hematologic malignancies.

Overall, our findings indicated a positive feedback from the hematologists interviewed, as most of them used the platform routinely, regardless of receiving automated alerts informing them about patients' clinically relevant problems or symptoms. Additionally, graphically displayed ePRO results were found to be useful in enhancing patient-physician communication and in improving the detection of low-grade symptomatic AEs, by a large majority of respondents. This latter aspect may be of special relevance in routine practice across several hematologic cancer populations, such as those receiving long-term oral anticancer therapies. Indeed, it was previously observed that in these settings, patient-reported symptoms are typically of low to mild intensity and are therefore most likely to be unrecognized

TABLE 3 | Physician-patient communication and intention to use the Platform in the future.

Item	Strongly disagree n (%)	Disagree n (%)	Agree n (%)	Strongly agree n (%)
ePRO useful to favor share-decision making	0 (0.0)	2 (8.7)	17 (73.91)	4 (17.39)
ePRO helpful to suggest supportive care strategies	0 (0.0)	0 (0.0)	17 (73.91)	6 (26.09)
ePRO helpful to set up unplanned visits with the patients	0 (0.0)	3 (13.04)	18 (78.26)	2 (8.7)
ePROs useful to enhance physician-patient communication	0 (0.0)	3 (13.04)	14 (60.87)	6 (26.09)
Would use the platform also in the future	0 (0.0)	1 (4.35)	14 (60.87)	8 (34.78)
Would recommend the platform to other colleagues	0 (0.0)	2 (8.7)	10 (43.48)	11 (47.83)

PRO, patient-reported outcomes.

by the treating hematologist (5). Therefore, a better understanding of these chronic low-to-mild symptomatic AEs experienced by patients may have important clinical implications, for example, the adoption of more timely supportive care interventions. Results from the survey suggest that our platform may play a role in this respect, as all the physicians found it helpful in suggesting supportive care strategies. However, it should also be observed that there were 39% of physicians who did not find it useful to detect high-grade symptomatic AEs.

Recently, two studies evaluated the clinical utility and patient and staff feedback of ePRO systems (29, 30) in routine cancer care. In a non-randomized prospective cohort feasibility study, Kennedy et al. (29) explored the acceptability of an electronic system for collecting patient-self-reported AEs and quality of life. Staff feedback was positive, and 64% emphasized the benefits of receiving regular symptom reporting. In the PRO-TECT trial (30), 91% of the oncologists who responded to the survey found ePRO information useful, and this finding is consistent with that observed in our survey, where 87% of hematologists declared to have better understood patients' symptoms by using the platform.

The clinical utility of ePRO systems is also linked to their ability to enhance patient-physician communication. In the PRO-TECT trial, 65% of the oncologists declared that they use PROs to often or sometimes guide discussions with patients (30), and this data is similar to our findings indicating that 74% of hematologists used (sometimes, often or very often) PRO information during clinical visits with their patients.

The active participation of clinicians is critical to enhance patients' involvement and facilitate patient-centered care in routine practice. A recent study showed that the more clinicians looked at ePRO information from an online eHealth system (i.e., the eRAPID) before or during an appointment, the higher the patient engagement was with this system (13). One of the main challenges in implementing ePRO systems is clinicians' reluctance to take on additional responsibility as well as perceived disruptions of the workflow (31). To minimize this risk, one solution may be to find physicians willing to engage their colleagues by demonstrating the flexibility of the tool, highlighting efficiencies in the overall work process, and convincing them of the value of the ePROs (31). It is also important to keep training physicians in the use of PROs with specialized training programs (32).

While we have documented a positive uptake of the use of this platform from the physicians' standpoint, we cannot speculate on the patients' perception of using this platform. However, a recent study that specifically examined the value of ePRO collection in the hematologic setting (including 102 patients with multiple myeloma and chronic lymphocytic leukemia) focused on the patients' perception of the use of the portal and provided some reassuring data (19). The authors found that the majority of patients (84%) were willing to use the portal; however, they also observed that the completion of ePROs decreased over time, mainly because of the patient's forgetfulness, and suggested ways to increase long-term participation rates (19). In another recent study, 227 lymphoma and chronic lymphocytic leukemia patients who completed web-based PRO questionnaires were randomized to care as usual (CAU), or to CAU plus return of PRO results (with or without a web-based self-management intervention) (20). No negative effects, for example in terms of psychological distress, were observed when individual PRO results were returned to patients, and authors concluded that this approach can be safely implemented in routine care practice (20).

The findings of our survey should be interpreted considering several limitations. It is possible that the positive results might be partly influenced by the characteristics of the sample, which consisted of physicians accepting to participate in the GIMEMA-ALLIANCE project. Hence, they are more likely to be enthusiastic about its use and reflect this positive perception in the rating of the survey. In addition, these findings should be regarded as preliminary, as the survey was performed approximately six months after the implementation of this tool and involved a small sample of hematologists. Additionally, our findings cannot be contextualized for a specific hematologic population or type of therapy. A key strength of our study is that it is one of very few reports documenting hematologists' perception of the use of ePROs in real-life practice. In addition, we were able to document the feasibility of using the platform across several different institutions, each with different IT infrastructures and logistic support.

In conclusion, our results support the clinical utility, from the perspective of the treating hematologist, of integrating ePROs into the routine cancer care of patients with hematologic malignancies. Efforts are currently being made to put in place further educational and training activities for the use of PROs for hematologists involved and to implement novel IT functionalities that can further enhance its use in daily busy clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available upon reasonable request to the corresponding author.

ETHICS STATEMENT

The study was reviewed and approved by Comitato Etico dell'Università "Sapienza". Also, each participating center obtained approval from its local ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FE and MV designed the study. FC and FE performed statistical analysis. FE and FS wrote the first draft. All the authors interpreted results and validated the manuscript's content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.826040/full#supplementary-material

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Impact of IDH1 c.315C>T SNP on Outcomes in Acute Myeloid Leukemia: A Propensity Score-Adjusted Cohort Study

Elizabeth M. Corley[1], Moaath K. Mustafa Ali[2,3†], Hanan Alharthy[3], Kathryn A. F. Kline[2,3], Danielle Sewell[4], Jennie Y. Law[2,3], Seung Tae Lee[2,3], Sandrine Niyongere[2,3], Vu H. Duong[2,3], Maria R. Baer[2,3] and Ashkan Emadi[2,3,4,5]*

[1] School of Medicine, University of Maryland, Baltimore, Baltimore, MD, United States, [2] Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, Baltimore, MD, United States, [3] Department of Medicine, School of Medicine, University of Maryland, Baltimore, Baltimore, MD, United States, [4] Translational Genomics Laboratory, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, Baltimore, MD, United States, [5] Department of Pharmacology, School of Medicine, University of Maryland, Baltimore, Baltimore, MD, United States

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Edited by:
Annalisa Trama,
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Benjamin Kent Nagy Tomlinson, University Hospitals Cleveland Medical Center, United States
Nicola Stefano Fracchiolla, Ca 'Granda Foundation Maggiore Policlinico Hospital (IRCCS), Italy

***Correspondence:**
Ashkan Emadi
aemadi@umm.edu

†ORCID:
Moaath K. Mustafa Ali
orcid.org/0000-0003-3289-2333

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Acute myeloid leukemia (AML) is the common type of acute leukemia in adults. Definitive prognostic significance of variants of unknown significance lacks for many commonly mutated genes, including the isocitrate dehydrogenase 1 (IDH1) synonymous single nucleotide polymorphism (SNP) variant c.315C>T. In this retrospective cohort study of 248 AML patients at the University of Maryland Greenebaum Comprehensive Cancer Center, we show that the IDH1 c.315C>T SNP, previously reported to be associated with poor prognosis by other studies with conflicting data, does not confer worse prognosis, with a median overall survival (OS) of 17.1 months compared to 15.1 months for patients without this SNP (P=0.57). The lack of negative effect on prognosis by IDH1 SNP c.315C>T is consistent with the absence of amino acid alteration (p.Gly105Gly).

Keywords: AML, IDH1 c.315C>T SNP, prognosis, survival, Myeloid mutations

INTRODUCTION

It is estimated that 20,050 new cases of acute myeloid leukemia (AML) will be diagnosed in the United States in 2022 (1). AML-related mortality remains high, with an estimated 11,540 deaths expected in 2022 (1). Over the last decade, there have been significant advances in understanding the genetic landscape and pathophysiology of AML, leading to the approval of nine new medications for AML treatment (2). Targeted therapies are now available against the Fms-like tyrosine kinase 3 gene (FLT3) and isocitrate dehydrogenase (IDH) 1 and 2 gene mutations in AML (3).

The detection of genetic variants has become essential in determining risk stratification of AML and may guide treatment. However, definitive information on prognostic significance of various well-characterized mutations is still lacking. Although *FLT3*-ITD, Nucleophosmin-1 gene *(NPM1)* and CCAT/enhancer binding protein a gene (*CEBPA)* mutations have become established as prognostic markers in cytogenetically normal AML (CN-AML), there is a large group of patients without these mutations (4). Thus, there is a need for additional markers that may predict the

differential outcomes of these patients. One potential source for expanding prognostication of AML is variants of unknown significance (VUS), such as common single nucleotide polymorphisms (SNPs) found in the population. A VUS becomes classified as pathogenic or benign once its impact is better understood. Therefore, studying VUS in commonly mutated genes may improve risk stratification and prognostication for AML patients.

Pathogenic variants within *IDH1* or *IDH2* occur in approximately 20% of AML (5). These mutations include R132 (in IDH1) and R140/R172 (in IDH2), which lead to the production of the oncometabolite 2-hydroxyglutarate and are targeted with selective oral inhibitors (6, 7). Currently, the VUS SNP in codon 105 in exon 4 of the *IDH1* gene (8), (c.315C>T (p.Gly105=), rs11554137), which occurs in approximately 5-10% of AML cases, is poorly understood. In two studies, the *IDH1* c.315C>T SNP was associated with an inferior outcome in cytogenetically normal AML (9, 10). In a third study, outcomes were also inferior, but this was attributable to association with *FLT3*-ITD (11). These studies proposed that the "silent" SNP may affect gene function by way of decreasing mRNA stability and thereby changing rates of protein translation, folding, and ultimately, function. However, these proposed ideas have never been demonstrated *in vitro* or in clinic. To date, the *IDH1* c.315C>T SNP is not commonly screened for in myeloid mutation panels. In this study, we hypothesized that presence of *IDH1* c.315C>T SNP does not impact clinical outcome of AML patients because of the lack of amino acid (glycine, Gly) change in position 105.

METHODS

Study Design

We conducted a single-site retrospective cohort study to compare overall survival (OS), event-free survival (EFS) and complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) rates in adults with AML with and without the *IDH1* c.315C>T (p.Gly105=) SNP from 2013 through 2020. OS was defined as the time from diagnosis to death from any cause. EFS was defined as the time from treatment initiation to induction failure, relapse, or death from any cause. Treatment response was evaluated according to the 2017 European LeukemiaNet (ELN) criteria (12). Composite CR rate included CR+CRi. The study was approved by the University of Maryland Baltimore Institutional Review Board (IRB).

Data Source

We reviewed the medical records of patients diagnosed with AML at the University of Maryland Greenebaum Comprehensive Cancer Center (UMGCCC) between 2013 and 2020. UMGCCC uses the Epic electronic medical record (EMR) system. We used Epic and its features such as Care Everywhere and CRISP to extract relevant chart data from our site as well as all other available clinical sites within University of Maryland Medical System. The Care Everywhere feature allows access to a health network connecting all hospitals that utilize Epic. CRISP is a state-designed Health Information Exchange for a Maryland online database to extract relevant data from other clinical sites (13). We included all patients whose blood or bone marrow aspirate were examined for IDH mutation with Sanger sequencing which started at UMGCCC in 2013; no exclusion was performed. Data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the University of Maryland (14, 15).

Variables and Comparison Groups

Data extracted included age, gender, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, baseline comorbidities, AML categories (*de novo* AML, myelodysplasia-related AML, myeloproliferative-related AML, therapy-related AML), cytogenetics, myeloid mutations including *IDH1*/*IDH2*/*FLT3*/*Tumor Protein 53 (TP53)*, treatments received, and outcomes. Data were checked multiple times by independent data collectors. We compared patients with and without the *IDH1* c.315C>T (p.Gly105=) SNP.

Molecular Testing

Analysis of IDH1 and IDH2 Gene Alterations

IDH1 and *IDH2* gene alterations were investigated using Sanger DNA sequencing. *IDH1* Codon 132, *IDH2* codons 140 and 172, and the surrounding sequences within exon 4 were analyzed on whole blood or bone marrow aspirate by Sanger DNA sequencing on an Applied Biosystems 3730XL genetic analyzer, using Sequencher™ DNA Sequence Analysis Software (version 5). The c.315C>T SNP in *IDH1* codon 105 is in the same exon as the R132 mutation. These sequences were compared to NCBI reference sequences for the *IDH1* (NM_005896.3 and NP_005887.2) and *IDH2* (NM_002168.3 and NP_002159.2) genes. The lower limit of detection for this assay is approximately 20% allele proportion.

Propensity Score Estimation

This study obtained the Average Treatment Effect on the Treated (ATT) (16). We included the following variables in the propensity score model: age at diagnosis, gender, ethnicity, comorbidities, ECOG performance status, type of AML, cytogenetics at diagnosis, *FLT3*, *IDH1*, *IDH2* and *TP53* mutational status and first-line treatment. Different methods for matching were attempted, including 1:1 nearest neighbor, 1:2 nearest neighbor, full matching, inverse probability weighting, and weighting by the odds. Full matching was chosen as the matching method because it achieved the lowest standardized biases differences, smallest coefficients of variations and smallest weights. Weights obtained from full matching were used to adjust outcomes. No patients were dropped in the matching process. The choice of estimand (ATT) was based on achieving standardized bias scores less than 0.25 (17). We used balance tables and Love plots to assess for covariate balance before and after matching. As a sensitivity check, we repeated the analysis using inverse probability weighting and obtained average treatment effect as an estimand. Generalized boosted model was used to calculate weights. The results of inverse probability weighting are provided as supplementary

data. Cluster-robust standard errors were used to account for subclass membership in the matching process. The R statistical package "MatchIt" and "WeightIt" were used for propensity score weighting (18).

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics of patients with and without *IDH1* c.315C>T. Categorical variables were presented as absolute numbers and percentages. Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQR). Baseline characteristics were compared using Pearson chi-square or Fisher's exact test when categorical or t-test when continuous. OS and EFS were compared using log-rank and Gehan Breslow-Wilcoxon rank tests. Multivariable and univariable Cox proportional hazards models were used to assess relative mortality. Regression diagnostics were used to evaluate model assumptions. All statistical tests were two-sided, and P-values <0.05 were considered statistically significant. R-statistical software (version 4.1.1) was used for statistical analyses.

RESULTS

Cohort Characteristics

We identified a total of 444 AML patients treated at UMGCCC during the study period that we had Sanger sequencing data on patients (2013–2020). All patients tested for IDH1 mutations using the Sanger technique were included (2015-2020). Patients not tested for *IDH1* mutations were excluded; ultimately, 248 patients were included. There was no other exclusion criteria. The median age was 65 years [IQR 54-75] and 42% were female. Median follow-up was 27.33 months [IQR 17.6-46.9]. Median OS for the whole population was 17.1 months (CI 13.8-21.8). The *IDH1* c.315C>T SNP was found in 23 patients (9%). **Table 1** shows propensity score-adjusted baseline characteristics in patients with and without the *IDH1* c.315C>T SNP. After matching, there were no statistically significant differences in baseline characteristics between the two groups. Covariate balance before and after propensity score weighting is shown in **Supplemental Figure 1**. Unadjusted baseline characteristics are shown in **Supplementary Table 1**. In the unadjusted cohort, patients with the *IDH1* c.315C>T SNP compared to patients without received the following treatments: intensive chemotherapy (30% vs. 34%), hypomethylating agent with or without others treatments (30% vs. 21%), hypomethylating agents with venetoclax (22% vs. 18%), clinical trial (9% vs. 19%), other treatments (0 vs. 4%) and none (9% vs. 4%).

Outcomes

Excluding patients who did not have a bone marrow biopsy, the adjusted composite CR rate for patients with and without the *IDH1* c.315C>T SNP was 77.10% compared to 65.30%; this finding was not statistically significant (P=0.53). The death at the end of observation in the IDH mutated group was 14 patients (39.10%) vs. 81 in the wildtype group (36%); P=0.944. The adjusted median OS for patients with compared to without the *IDH1* c.315C>T SNP was 17.1 months (CI 8.37-Not calculable (NC)) compared to 15.1 months (CI 8.1-77.3, P=0.57). The unadjusted median OS for patients with and without the *IDH1* c.315C>T SNP was 17.1 months (CI 9.8-NC) and 17 months (CI 13-22.2) (P=0.9). Adjusted OS difference at years 1-3 for patients with and without the *IDH1* c.315C>T SNP showed no statistically significant difference (**Supplementary Table 2**). On weighted-univariable Cox proportional hazards regression of the total cohort, there was no statistically significant difference in relative mortality (HR 1.08, CI 0.62-1.93, P=0.79). **Figure 1** demonstrates propensity score-adjusted OS for patients with and without the *IDH1* c.315C>T SNP.

The adjusted median EFS for patients with and without the *IDH1* c.315C>T SNP was 5.8 months (CI 4.47-74) compared to 7.97 (CI: 4.43-12.1, P=0.73). Adjusted EFS at years 1-3 for patients with and without the SNP also showed no statistical significance (**Supplementary Table 3**). The relative mortality and progression were not different in patients with and without the SNP (HR 1.18, CI 0.71-1.98, P=0.5) using Cox proportional hazards regression. **Figure 2** demonstrates propensity score-adjusted EFS for patients with vs. without the IDH1 c.315C>TSNP. As a sensitivity check, we repeated analysis using inverse probability weighting. There was no statistically significant difference in adjusted median OS or median EFS between the two groups. The results are provided in supplementary file (**Supplementary Tables 4–6** and **Supplementary Figures 2–4**).

DISCUSSION

Prognostic models for AML largely rely on cytogenetic aberrations and somatic mutations such as *FLT3*-ITD and *NPM1* and *CEBPA* mutations in patients with a normal karyotype (4). However, many intermediate-risk patients have poorly understood AML genetic profiles, which may hinder accurate prognostication and clinical decision-making. We, therefore, aimed to study the *IDH1* c.315C>T SNP, a poorly understood VUS seen in ~5-10% of AML cases (8, 9).

Previous data on the prognostic significance of this variant have been mixed; while it was shown to have inferior outcomes for cytogenetically normal AML in two studies (9, 10), another study showed inferior outcomes that were attributable to association with *FLT3*-ITD (11). Of the two studies that showed the adverse prognostic significance of the *IDH1* c.315C>T SNP, one (10) (N=51, 8 with variant) reported that the SNP confers an inferior prognosis in *NPM1*/*CEBPA* wild-type Egyptian patients with AML. The other study (9) showed that the SNP had a negative effect on outcomes in univariate, but not multivariate, analysis, with the greatest impact in *NPM1*/*FLT3* high-risk patients (either *NPM1* wild-type or *FLT3*-ITD). These studies proposed that the synonymous SNP may induce genetic alteration at the mRNA level, such as alterations mRNA stability, folding, or splicing; however, all these studies were vulnerable to inadequate design (10). In order to evaluate such potential mechanisms, future RNA-seq studies to analyze

TABLE 1 | Adjusted baseline characteristics of patients with IDH1 c.315C>T mutated vs. IDH1 wild-type AML.

	IDH1 c.315C>T Mutated	Percentage/SD/IQR	IDH1 wild-type AML	Percentage/SD/IQR	P-value
Number	23	–	51[β]		
Female	8	0.35	19	0.37	0.85
Ethnicity			0	0	0.85
Caucasian	13	0.57	30	0.59	
Other	10	0.43	21	0.41	
Unknown	0	0	0	0	
Comorbidities					
Cardiovascular disease	6	0.26	11	0.21	0.65
Diabetes mellitus	7	0.3	18	0.36	0.53
Hypertension	11	0.48	21	0.41	0.66
CKD stage III-V/ESRD	1	0.04	2	0.04	0.95
Asthma/COPD	4	0.17	8	0.15	0.77
Active Cancer	2	0.09	3	0.06	0.54
AML type					0.96
AML, *de novo*	15	0.65	33	0.65	
AML with MDS/CMML changes	4	0.17	9	0.17	
AML with prior MPN	2	0.09	6	0.11	
Therapy-Related AML	2	0.09	4	0.07	
Cytogenetic Category					0.98
Favorable Risk	1	0.04	2	0.04	
Intermediate Risk	29	0.82	43	0.83	
Unfavorable Risk	2	0.09	4	0.07	
Not performed or Inadequate	1	0.04	3	0.06	
IDH1 mutated	2	0.09	7	0.14	0.65
IDH2 mutated	3	0.13	6	0.12	0.93
FLT3-ITD status					0.99
FLT3-ITD mutated 1-49%	1	0.04	2	0.04	
FLT3-ITD mutated 50-100%	1	0.04	2	0.039	
FLT3 WT	19	0.83	42	0.83	
Not tested	2	0.09	5	0.09	
FLT3-TKD status					0.95
FLT3-TKD mutated	4	0.17	8	0.15	
FLT3 WT	17	0.74	39	0.76	
Not tested	2	0.09	5	0.09	
P53 status					0.98
P53 mutated	3	0.13	7	0.14	
P53 WT	8	0.35	17	0.33	
Not tested	12	0.52	27	0.53	
ECOG status III/IV	1	0.04	4	0.08	0.6
First treatment received					0.95
Anthracycline-based regimen	8	0.35	16	0.32	
Other*	13	0.57	31	0.6	
None	2	0.09	4	0.08	
Age (Average ± SD)	65.6	15.9	66.5	15.2	0.81
Age (Median, IQR)	68.5	59.6-77.7	69.1	58.1-77.9	0.8

*[β]Estimated sample size, the unweighted control number is 225 patients. *Other therapies include but are not limited to Venetoclax, decitabine, and cytarabine regimens. N.B. In this propensity-score model, no patients were excluded from the analysis. FLT3, fms-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain; WT, wild type.*

transcriptome profile and to characterize changes in ribosome-associated mRNA (i.e. translatome) are warranted.

We hypothesized that due to the synonymous nature of *IDH1* c.315C>T mutation resulting in uninterrupted presence of glycine in position 105 of the protein, the biochemical function of IDH1 enzyme remains intact; hence has no impact on the clinical outcome of patient. In this report, we confirm our hypothesis. Compared to prior studies, our study had greater power, with a large sample size (N=248), more patients with the variant (23 patients, 9%), and adjustment for more extensive disease profile data, allowing for many variables to be controlled. In addition, our study used propensity score weighting to adjust for baseline confounding, which showed no statistical prognostic difference between cohorts while controlling for baseline characteristics, including *FLT3* mutations. This is consistent with the previous multivariate analysis (9). Our study adds to the current data, revealing that with greater power and tight statistical control of an extensive number of confounding variables, there was no negative prognostic value for the *IDH1* c.315C>T SNP, with statistically insignificant differences in clinical outcome.

The major limitation of this study is that it was a retrospective single-site model. To control for observable confounding variables, we adjusted outcomes using propensity score analysis. After matching, the standardized mean difference was less than 0.2 in all variables. As a sensitivity analysis, we conducted weighted-multivariable Cox proportional hazards

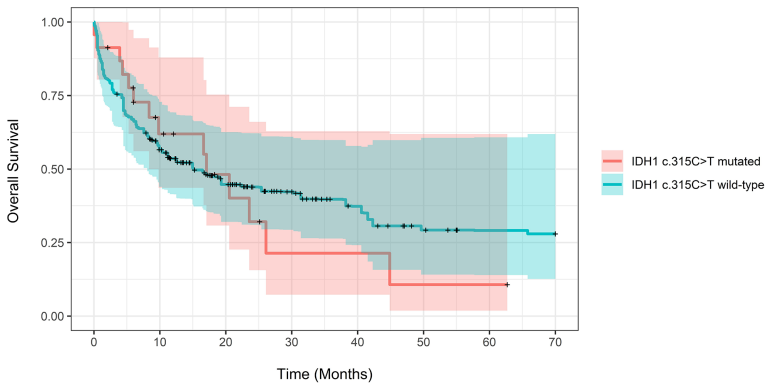

FIGURE 1 | Propensity score-adjusted Overall Survival for patients with IDH1 c.315C>T mutated vs. IDH1 wild-type AML. Log-Rank adjusted P-Value was non-significant (P = 0.57).

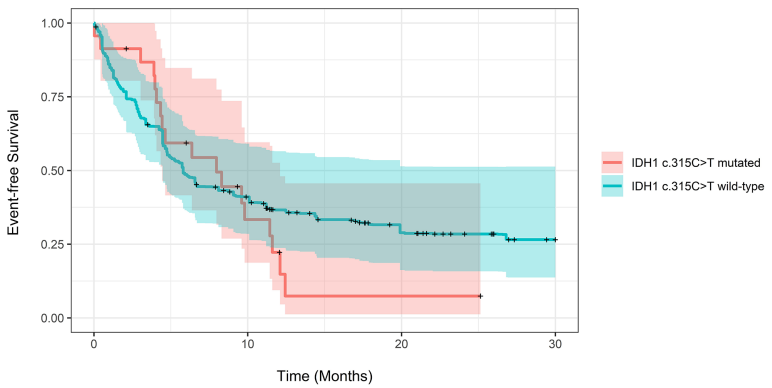

FIGURE 2 | Propensity score-adjusted Event-free Survival for patients with IDH1 c.315C>T mutated vs. IDH1 wild-type AML. Log-Rank adjusted P-Value was non-significant (P = 0.73).

regression to adjust for possible remaining confounding, and there was no qualitative difference in outcomes.

CONCLUSION

Our retrospective cohort study showed that, unlike in previous studies and concordant with our mechanism-based hypothesis, the presence of *IDH1* c.315C>T SNP was not associated with inferior OS, PFS or CR+CRi rates compared with its absence. Due to the rarity of this SNP, further collaborative study with multiple institutions is warranted to understand the impact of this SNP fully.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from MMA, Moaath.mustafaali@umm.edu, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Maryland Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Study conception and design: EC, MMA, and AE. Data Collection: EC, MMA, HA, KK, and DS. Analysis and Interpretation: EC, MMA, HA, KK, DS, JL, SL, SN, VD, MB, and AE. Draft manuscript preparation: EC, MMA, and AE. Statistical analysis: MMA. Critical Review of Manuscript: HA, KK, DS, JL, SL, SN, VD, MB, and AE. Administrative and technical support: MMA.

Supervision: MMA and AE. All authors reviewed the results and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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The Prognostic Utility of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography-Based Analyses of Metabolic Response Rates in Newly Diagnosed Diffuse Large B Cell Lymphoma Patients

Cong Li[1,2], *Haifeng Yu*[1,2], *Xi Chen*[1,2], *Shuiyun Han*[1,2], *Shuailing Peng*[1,2], *Tao Lei*[1,2] *and Haiyan Yang*[1,2*]

[1] Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China, [2] Institute of Cancer and Basic Medicine (IBMC), Chinese Academy of Sciences, Hangzhou, China

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Edited by:
Claudia Vener,
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Monica Balzarotti,
Humanitas Research Hospital, Italy
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Nanjing Medical University, China

***Correspondence:**
Haiyan Yang
yanghy@zjcc.org.cn

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Background: Roughly one third of diffuse large B cell lymphoma (DLBCL) patients experience relapsed or refractory disease, and their prognosis is unsatisfactory. It is thus important to identify patients who respond poorly to first-line treatment. Some studies have evaluated the prognostic value of interim PET-CT (iPET-CT) or end-of-treatment PET-CT (ePET-CT) in lymphoma patients, but there have been few studies exploring the prognostic value of metabolic response rates in the evaluation of DLBCL patients.

Methods: Consecutive newly diagnosed DLBCL patients were screened from March 2013 to June 2020. Patients received at least four cycles of chemotherapy, and underwent baseline, iPET-CT and ePET-CT scanning. Kaplan-Meier survival curves with log-rank tests were employed to assess survival outcomes including overall survival (OS) and progression-free survival (PFS). Independent predictors of survival were identified through univariable and multivariable Cox regression analyses.

Results: 307 patients were evaluated. At the time of iPET-CT scanning, 250, 45, and 12 patients exhibited complete response (CR), partial response (PR), and stable disease (SD)/ progressive disease (PD), respectively. The percentage of negative iPET-CT was 81.4% (250/307). Among 295 patients with ePET-CT, 262 (88.8%) achieved negativity and 33 (11.2%) exhibited positivity including 26 PR and 7 PD. The 2-year PFS and 2-year OS for patients with iPET-CT positivity were 50.7% and 76.5%, respectively, and were significantly shorter than those for patients with iPET-CT negativity (2-year PFS 82.7%, $p<0.001$; 2-year OS 94.2%, $p<0.001$). Patients with ePET-CT positivity had significant poorer 2-year PFS (48.1%) and 2-year OS (78.5%) compared with those ePET-CT negativity (2-year PFS 83.8%, $p<0.001$; 2-year OS 94.9%, $p<0.001$). The positivity rates on iPET-CT and ePET-CT evaluation were significantly higher in patients in the high/high-intermediate risk group

compared with patients in the low/low-intermediate group. In a multivariable analysis, high/high-intermediate international prognostic index (IPI) and ePET-CT positivity were independently associated with poor PFS and OS.

Conclusions: Our results suggest that the speed of metabolic response to treatment is of limited prognostic value in newly diagnosed DLBCL patients. Patients exhibiting PR at iPET-CT evaluation should carefully consider whether to change chemotherapy regimen.

Keywords: diffuse large B cell lymphoma (DLBCL), interim 18 F-FDG PET, prognosis, RCHOP, treatment response

INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) is the prevalent non-Hodgkin lymphoma subtype (1). Roughly 60% of patients with DLBCL can undergo successful curative first-line RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy (2). Unfortunately, one third of patients still experience relapsed or refractory disease (3). Just 30-35% of these relapsed/refractory patients will undergo successful rescue by high-dose chemotherapy following autologous stem-cell transplantation (ASCT) (4). Therefore, further work is needed to efficiently identify patients that respond poorly to first-line therapy so that their chances of cure can be increased by early intensification.

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) is commonly employed in lymphoma patients for pretreatment staging, therapeutic efficacy evaluation, and transformation assessment (5). Positive end-of-treatment PET-CT (ePET-CT) scans are closely associated with residual/recurrent disease and with worse overall survival (OS) and progression-free survival (PFS) (6). However, the predictive role of the mid-treatment PET-CT remains controversial (7–9). As such, interim PET-CT-(iPET-CT)-guided therapy strategies in DLBCL patients have not been widely accepted to date.

In advanced mantle cell lymphoma (MCL), Jeon et al. suggested that the speed of metabolic response to treatment may be a powerful predictor of individual outcomes (10). It has been hypothesized that DLBCL patients who are rapid metabolic responders, as measured by reductions in the intensity of ^{18}F-FDG uptake, are reflective of early tumor regression with a high likelihood of curative outcomes, whereas slow metabolic responders are more likely to relapse. To test this hypothesis, we conducted the present retrospective analysis to explore the prognostic value of metabolic response rate measured by iPET-CT and ePET-CT, indexed by the Deauville five-point scale, in a cohort of DLBCL patients undergoing treatment with a RCHOP-like regimen.

MATERIALS AND METHODS

Patients and Study Design

Consecutive newly diagnosed DLBCL patients were screened from March 2013 to June 2020 at Zhejiang Cancer Hospital. The DLBCL diagnosis for these patients was confirmed *via* pathological review as performed by an independent experienced pathologist. Disease stage was judged according to the criteria of Lugano 2014 (11). First-line treatment consisted of at least four cycles of rituximab-containing anthracycline-based chemotherapy. Patients that completed fewer than four cycles were excluded. All patients underwent baseline whole-body PET-CT scans within four weeks before starting therapy, iPET-CT scans after four cycles of chemotherapy, and ePET-CT scans conducted within eight weeks after the completion of chemotherapy. Responses to chemotherapy were evaluated based upon the revised criteria published by Cheson et al. (12). The Deauville score (DS) was employed for measuring ^{18}F-FDG-uptake in PET-CT (13). A DS 1 to 3 was defined as PET negativity. DS 4 or DS 5 were used to define PET positivity. After completion of first-line chemotherapy, all patients underwent regular follow-up CT scans every 3 months over the first two years, every 6 months for the next three years, and once a year from the sixth year onward. A retrospective analysis of data extracted from patient electronic medical records including demographic information, pathological features, treatment regimens, therapeutic responses to initial or salvage chemotherapy, and survival was performed. The Zhejiang Cancer Hospital ethics committee approved this study, which was consistent with the Declaration of Helsinki.

Data Analysis

PFS was calculated from the start of first-line chemotherapy to the first recording of disease progression or disease relapse or death. OS was defined as the period from the start of first-line chemotherapy to the date of death from any cause or the last follow-up. Categorical variables are given as proportions and were analyzed with chi-squared tests and Fisher's exact test. Continuous variables are given as medians and ranges. PFS and OS were calculated using the Kaplan–Meier survival method and log-rank tests. Univariable and multivariable Cox regression analyses were performed to determine the independent factors affecting PFS or OS. $P < 0.05$ was the threshold of significance. To further explore exact survival differences, survival time distributions in four groups were compared pairwise. A Bonferroni corrected p-value was applied to the multifactorial logistic regression p–values to account for the multiple testing of six different comparisons (corrected $\alpha = 0.05/6 = 0.00833$). Statistical analyses were performed with Statistical Package for Social Sciences (SPSS), version 24. Survival curves were drawn with GraphPad Prism 8.

RESULTS

Clinical Characteristics

Initially, 505 total patients diagnosed with DLBCL were identified, of whom 198 were excluded due to ambiguous diagnoses (n=4), fewer than 4 chemotherapy cycles (n=12), or a lack of available iPET-CT or ePET-CT data (n=182). Therefore, 307 patients were analyzed in this study (**Figure 1**). Patient baseline clinical characteristics are shown in **Table 1**.

^{18}F-FDG PET-CT Treatment and Efficacy Evaluation

All 307 patients underwent initial pretreatment PET-CT and iPET-CT scanning (**Figure 1**). At iPET-CT evaluation, 250 patients achieved complete response (CR) and the proportion of patients with negative metabolic uptake was 81.4% (250/307). Moreover, 45 patients achieved partial response (PR), all of whom continued to complete prior chemotherapy regimens for at least 2 cycles, and 15 of them (33.3%) achieved CR at ePET-CT. Twenty-six patients maintained PR, while 4 patients ultimately exhibited progressive disease (PD). Additionally, 12 patients exhibited SD/PD at iPET-CT, of whom just 3 underwent biopsy and 2 were confirmed to have progressive disease. Of these 12 patients, 10 underwent second-line treatment, while one underwent palliative radiotherapy. The remaining patient did not receive any treatment, and died 5 months later.

At time of ePET-CT evaluation (n=295), 262 patients (88.8%) achieved CR and were considered as negative ePET-CT, whereas 33 patients (11.2%) exhibited ePET-CT positivity, including 26 patients with PR and 7 patients with PD. Among the 26 patients with PR at time of ePET-CT, 10 received second-line chemotherapy and 2 of them underwent subsequent autologous stem-cell transplantation (ASCT) with no evidence of disease. Eight patients received palliative radiotherapy for residual lesions without chemotherapy. Another 8 patients did not receive any treatment, and 7 of them were still alive. All 7 patients with PD at ePET-CT received salvage chemotherapy, but only 3 patients remained alive at last follow-up.

PET-CT-Based Survival Outcomes

After a median follow-up of 45.1 months (range: 5.1 - 100 months), 81 patients (26.4%) experienced disease progression or relapse, and 36 patients (11.7%) were censored due to death. The 2-year PFS rate and 2-year OS rate for the whole cohort (n=307) were 76.6% (95% confidence interval (CI), 71.8 to 81.4%) and 91.0% (95% CI, 87.7 to 94.2%), respectively.

The iPET-CT and ePET-CT results for these patients were both significantly associated with survival outcomes (**Figure 2**). The 2-year PFS and 2-year OS for patients with iPET-CT positivity were 50.7% (95%CI, 37.6 to 63.8%) and 76.5% (95% CI, 65.3 to 87.7%), respectively, and were significantly shorter than those for patients with iPET-CT negativity (2-year PFS: 82.7% (95% CI, 78 to 87.4%), $p<0.001$; 2-year OS: 94.2% (95% CI, 91.3 to 97.1%), $p<0.001$). The survival outcomes for patients with SD/PD at iPET-CT were extremely poor, with median PFS and OS were only 3.2 months and 11.0 months, respectively.

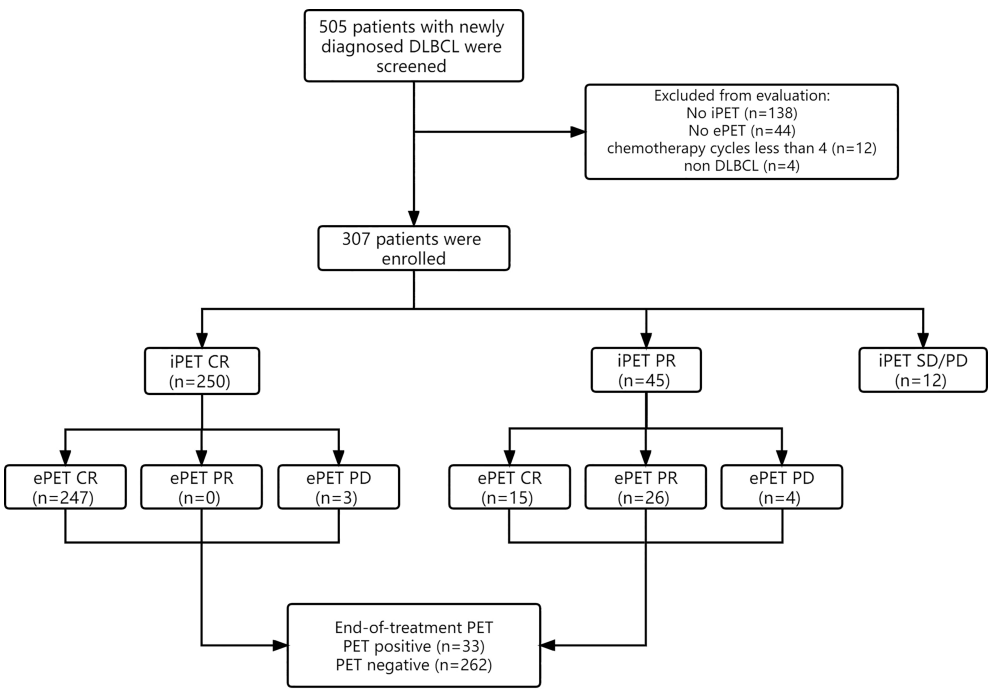

FIGURE 1 | Flow diagram of 505 patients with newly diagnosed DLBCL. 198 patients were excluded from the study, resulting in 307 patients being analyzed. Response evaluation of iPET-CT and ePET-CT were showed.

TABLE 1 | Baseline characteristics of DLBCL patients with frontline chemotherapy (n=307).

Characteristics	Number (%)
Age (in years)	Median 55 (range 15-84)
Gender	146 (47.6)
Males	161 (52.4)
Females	
Pathological subtype	89 (29)
GCB	218 (71)
non-GCB	
Ann-Arbor stage	149 (48.5)
I-II	158 (51.5)
III-IV	
Bulky disease (>5cm)	78 (25.4)
Yes	229 (74.6)
No	
ECOG performance status	270 (87.9)
0-1	37 (12.1)
2-3	
Presence of B symptoms	57 (18.6)
Yes	250 (81.4)
No	19 (6.2)
Bone marrow involvement	288 (93.8)
Yes	
No	
Elevated LDH	145 (47.2)
Yes	162 (52.8)
No	
IPI	145 (47.2)
0-1	123 (40.1)
2-3	39 (12.7)
4-5	
First-line chemotherapy regimen	240 (78.2)
RCHOP	63 (20.5)
REPOCH	4 (1.3)
R2CHOP	

GCB, germinal center B cell; ECOG, Eastern Cooperative Oncology Group; LDH, lactic dehydrogenase; IPI, international prognostic index; RCHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; REPOCH, rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine and prednisone; R2CHOP, lenalidomide, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

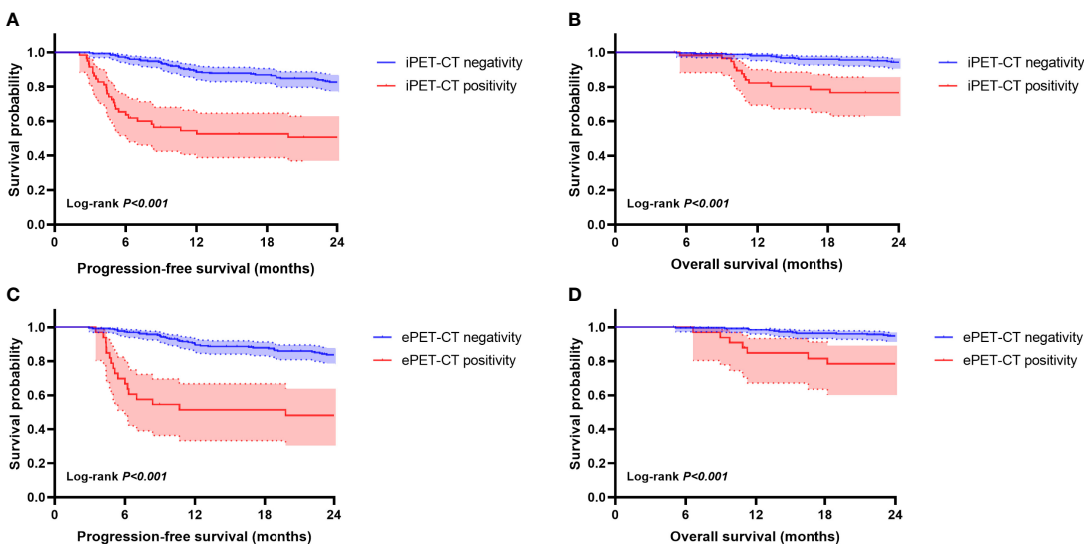

FIGURE 2 | Kaplan-Meier survival curves according to interim PET-CT (iPET-CT) and end-of-treatment (ePET-CT). Progression-free survival (PFS) **(A)** and overall survival (OS) **(B)** according to iPET-CT evaluation. PFS **(C)** and OS **(D)** according to ePET-CT.

Similarly, patients with ePET-CT positivity had a significantly poorer 2-year PFS (48.1%, 95% CI, 30.9 to 65.3%) and 2-year OS (78.5%, 95% CI, 64.4 to 92.6%) rates compared with those of patients with ePET-CT negativity (2-year PFS: 83.8% (95% CI, 79.3 to 88.3%), $p<0.001$; 2-year OS: 94.9% (95% CI, 92.2 to 97.6%), $p<0.001$).

These results suggest that there are significant relationships between PET avidity at different follow-up time points and DLBCL patient survival. In light of these results, we conducted a further examination of the prognostic value of the speed of metabolic response. As patients with SD/PD at iPET-CT began undergoing second-line chemotherapy and lacked available ePET-CT scans, so they were excluded in this section. The remaining 295 patients were divided into the following 4 groups: EMR (early metabolic responders, iPET-CR+ePET-CR, n=247), DMR (delayed metabolic responders, iPET-PR+ePET-CR, n=15), IMR (incomplete metabolic responders, iPET-PR+ePET-PR, n=26), and MP (metabolic progressors, iPET-CR/PR+ePET-PD, n=7). The 2-year PFS rates were significantly different in these four groups (83.7%, 86.2%, 61.1%, and 0%, respectively; $p<0.001$). The 2-year OS rates were also significantly different in these four groups (94.6%, 100%, 84.3%, and 57.1%, respectively; $p<0.001$). The survival distribution of the four groups was compared in a pairwise manner. For 2-year PFS rate, there was a significant difference between MP and EMR ($p<0.001$), DMR ($p<0.001$), and IMR ($p<0.001$). There was also a difference between EMR and IMR ($p=0.002$). Between the other groups, no significant difference was found ($p>0.0083$). For 2-year OS, there was a difference between MP and EMR ($p<0.001$), and DMR ($p=0.006$). No significant difference was found between the other groups ($p>0.0083$). After Bonferroni correction, results showed a significant prognostic difference between MP and EMR/DMR. In **Figure 3**, a Kaplan-Meier plot for PFS and OS of the different groups of patients is shown.

The iPET-CT and ePET-CT positivity rates in different international prognostic index (IPI) risk groups were significantly different. Overall, 13.9% (29/209) patients with low/low-intermediate risk exhibited iPET-CT positivity, while 29.6% (29/98) patients with high/high-intermediate risk exhibited iPET-CT positivity ($p=0.001$). Moreover, 8.8% (18/205) patients with low/low-intermediate risk exhibited ePET-CT positivity, while 16.7% (15/90) patients with high/high-intermediate risk exhibited ePET-CT positivity ($p=0.048$). Additionally, bulky nodes (> 5 cm) and elevated serum C reactive protein (CRP) were more common in patients with positive iPET-CT (28.2% vs 15.7%, $p=0.015$; 26.1% vs 14.6%, $p=0.013$).

Analysis of Prognostic Factors Associated With Patient Survival Outcomes

Factors including iPET-CT (positivity vs negativity), ePET-CT (positivity vs negativity) and IPI (high/high-intermediate vs low/low-intermediate) were analyzed in univariable and multivariable analysis for potential significance in terms of PFS and OS. In univariable analysis, positive iPET-CT, positive ePET-CT and high/high-intermediate IPI were all associated with inferior PFS and latter two factors were also associated with inferior OS. In multivariable analysis, positive ePET-CT and high/high-intermediate IPI were independent prognostic factors for poor PFS and OS (**Table 2**).

DISCUSSION

In this cohort of 307 newly diagnosed DLBCL patients undergoing first-line rituximab-containing anthracycline-based chemotherapy treatment, the 2-year PFS and OS were 76.6% and 91.0%, respectively, in line with previous reports (14, 15).

Our study had several important findings. First, 81.4% (250/307) of patients achieved negative iPET-CT, of whom 98.8% (247/250) maintained CR after the completion of chemotherapy. These early metabolic responders had excellent survival outcomes, with a 2-year PFS of 83.7% and a 2-year OS of 94.6%. Second, only approximately 3.9% (12/307) of patients exhibited rapid disease progression and were considered as SD/PD at iPET-CT. The survival outcomes for these patients were poor, with median PFS and OS of just 3.2 months and 11.0 months, respectively. Third, although patients achieved negative iPET-CT findings, about 1.2% (3/250) of them still exhibited new metabolic lesions at ePET-CT. The survival outcomes of these 3 patients were poor. Intriguingly, among patients with PR at iPET-CT, 33.3% (15/45) of patients achieved CR at the end of chemotherapy. These delayed metabolic responders exhibited durable remission outcomes similar to those of early metabolic responders. Multivariable analyses further confirmed that

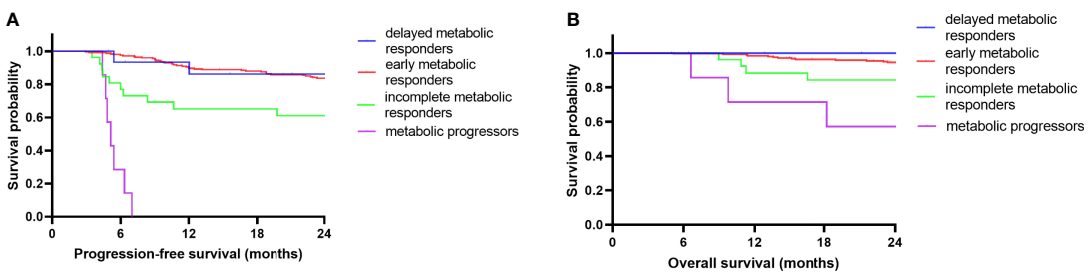

FIGURE 3 | Kaplan-Meier survival curves according to serial changes in PET-CT response. PFS **(A)** and OS **(B)** according to early metabolic responders (n=247), delayed metabolic responders (n=15), incomplete metabolic responders (n=26) and metabolic progressors (n=7) during frontline RCHOP.

TABLE 2 | Univariable and multivariable analysis of PFS and OS.

Survival	Univariable Cox Proportional hazard regression			Multivariable Cox proportional hazard regression		
	HR	95%CI	*p*	HR	95%CI	*p*
PFS						
iPET-CT positivity	2.4	1.4-4.0	0.002	0.4	0.1-1.3	0.129
ePET-CT positivity	4.1	2.4-7.0	<0.001	8.0	2.4-26.3	0.001
high/high-intermediate IPI	2.6	1.6-4.2	<0.001	2.3	1.4-3.8	0.001
OS						
iPET-CT positivity	2.2	0.9-5.0	0.057	0.5	0.1-1.8	0.272
ePET-CT positivity	3.9	1.8-8.6	0.001	5.6	1.5-20.2	0.009
high/high-intermediate IPI	4.8	2.3-10.4	<0.001	4.3	2.0-9.3	<0.001

PFS, progression-free survival; OS, overall survival; iPET-CT, interim positron emission tomography-computed tomography; ePET-CT, end-of-treatment positron emission tomography-computed tomography; IPI, international prognostic index.

ePET-CT positivity, but not iPET-CT positivity, was independently associated with patient prognosis. In summary, our study failed to confirm the hypothesis that there is a survival difference between early metabolic responders and delayed metabolic responders when evaluating DLBCL patients. These findings also indicate that the intensification of treatment regimens based upon iPET-CT positivity would likely expose many patients to the risk of unnecessary treatment.

A delayed metabolic response group has been noted in a few previous studies (10, 16, 17). A large, multinational, prospective study analyzed survival of patients with different metabolic response rates and found that 192 of 312 (62%) patients had negative iPET-CT and ePET-CT findings consistent with a rapid response, with a 2-year EFS of 97% and a 2-year OS of 97%. Moreover, 58 of 107 (54%) patients with positive iPET-CT findings achieved CR at ePET-CT, with an EFS of 86% and OS of 92%. The remaining 49 (16%) cases with positive iPET-CT and ePET-CT findings had a 2-year EFS of 35% and continuing relapses beyond 2 years. The delayed metabolic responders had approximately double the risk of 2-year relapse compared with early metabolic responders (18). Therefore, serial PET scans are important tools for the evaluation of lymphoma patients.

One possible explanation for delayed metabolic response is false-positive PET-CT results. Persistent ^{18}F-FDG uptake can be indicative not only of residual lymphoma lesions but also of inflammatory reactions within necrotic tumor tissue (19). Such false positivity is more common in areas exposed to rituximab treatment (20). According to previous reports, the positive predictive value of iPET-CT ranged from 18% to 74% (16, 17, 21–23). This indicates that a single iPET-CT scan offers limited value as a means of identifying patients with poor outcomes. In addition, in patients exhibiting persistent FDG uptake in only one locus or the appearance of FDG uptake in a previously non-avid site, unrelated secondary neoplasms should be excluded (20). Particularly in cases of highly metabolically active PET-CT lesions within 1.5 cm in diameter, contrast-enhanced CT scans are important to exclude lymphoma lesions. Unfortunately, in this study, only a small number of patients with positive iPET-CT/ePET-CT findings underwent biopsy to confirm the presence of lymphoma and rule out potential secondary neoplasms.

Different criteria for the interpretation of PET results have certain limitations. The Deauville criteria, which is a visual assessment method, has been recommended by international guidelines and adopted for current clinical practice throughout the globe. In the present study, Deauville scores of 1-3 were considered as CR and PET negativity. But some patients with high Deauville scores could still achieve long survival time. As such, other semi-quantitative response assessment methods, including International Harmonization Project (24), Gallamini criteria (25), $\triangle SUV_{max}$ (26) and $SUV_{max\text{-}liver\text{-}based}$ interpretation (27) can be used for response evaluation in patients with DLBCL.

There are certain limitations to this analysis that warrant consideration when interpreting these results. For one, this was a retrospective, single-center study without any prospective surveillance, and so these results may have been influenced by biases and other confounding variables. Secondly, this study excluded patients that only underwent CT scanning in order to focus on patients that had undergone iPET-CT and ePET-CT, thereby introducing selection bias. For survival analysis, we excluded patients with SD/PD at iPET-CT. The selection bias might influence the final survival outcome. Lastly, in most cases, disease progression was diagnosed in these patients based on imaging findings rather than biopsy results.

CONCLUSIONS

Our results suggest that the speed of metabolic response to treatment offers limited prognostic value in newly diagnosed DLBCL patients. Patients exhibiting PR at iPET-CT evaluation should carefully consider whether to change chemotherapy regimen.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Zhejiang Cancer Hospital ethics committee.

The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HYY, CL, and HFY participated in study design, evaluated the results, wrote the first and revised manuscript. CL performed the statistical analyses. SYH supervised patient care and collected data. CL, TL, HFY, XC, SP, and SH contributed to patient care and collected clinical information. All authors critically revised the manuscript and have approved the final version of the manuscript.

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All colleagues contributing to the manuscript have been listed as authors.

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Clear Improvement in Real-World Chronic Myeloid Leukemia Survival: A Comparison With Randomized Controlled Trials

Claudia Vener[1,2], Silvia Rossi[3], Pamela Minicozzi[1,4], Rafael Marcos-Gragera[5,6,7], Hélène A. Poirel[8], Marc Maynadié[9], Xavier Troussard[10], Gabriella Pravettoni[2], Roberta De Angelis[3†], Milena Sant[1†] and the EUROCARE-6 Working Group*

[1] Analytical Epidemiology and Health Impact Unit, Department of Research, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milan, Italy, [2] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy, [3] Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy, [4] Cancer Survival Group, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, [5] Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology, Girona Biomedical Research Institute (IdiBGi), Universitat de Girona, Girona, Spain, [6] Biomedical Network Research Centers of Epidemiology and Public Health (CIBERESP), Madrid, Spain, [7] Group of Descriptive and Analytical Epidemiology of Cancer, Josep Carreras Leukemia Research Institute, Girona, Spain, [8] Belgian Cancer Registry, Brussels, Belgium, [9] Côte d'Or Hematological Malignancies Registry, Dijon, France, [10] Basse Normandie Cancer Registry, Centre Hospitalier Universitaire (CHU) de Caen, Normandie, Caen, France

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***Correspondence:**
Claudia Vener
claudia.vener@unimi.it

†*These authors share last authorship*

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Tyrosine kinase inhibitors (TKIs) have been improving the prognosis of patients with chronic myeloid leukemia (CML), but there are still large differences in survival among European countries. This raises questions on the added value of results from population-based studies, which use real-world data, compared to results of randomized controlled trials (RCTs) involving patients with CML. There are also questions about the extent of the findings on RCTs effectiveness for patients in the general population. We compare survival data extracted from our previous systematic review and meta-analysis of CML RCTs with the latest updated population-based survival data of EUROCARE-6, the widest collaborative study on cancer survival in Europe. The EUROCARE-6 CML survival estimated in patients (15–64 years) diagnosed in 2000–2006 vs. 2007–2013 revealed that the prognostic improvement highlighted by RCTs was confirmed in real-world settings, too. The study shows, evaluating for the first time all European regions, that the optimal outcome figures obtained in controlled settings for CML are also achievable (and indeed achieved) in real-world settings with prompt introduction of TKIs in daily clinical practice. However, some differences still persist, particularly in Eastern European countries, where overall survival values are lower than elsewhere, probably due to a delayed introduction of TKIs. Our results suggest an insufficient adoption of adequate protocols in daily clinical practice in those countries where CML survival values remain lower in real life than the values obtained in RCTs. New high-resolution population-based studies may help to identify failures in the clinical pathways followed there.

Keywords: cancer registries, chronic myeloid leukemia (CML), randomized controlled trials (RCTs), real-world data, survival, Europe, tyrosine kinase inhibitor (TKI), population-based studies

HIGHLIGHTS

1. The EUROCARE-6 CML survival estimates revealed that the prognostic improvement highlighted by RCTs was confirmed in the European real-world setting.
2. There are still large differences in CML survival throughout Europe: the prompt introduction of TKIs in daily clinical practice is undelayable.

1 INTRODUCTION

The European incidence of chronic myeloid leukemia (CML) was about 1.1/100,000 inhabitants (1), increasing to about 4.0/100,000 in patients aged 75–99 at the time of diagnosis. The disease is characterized by the presence of the *BCR-ABL1* fusion gene located in the Philadelphia (Ph) chromosome and is classified as being in a chronic (CP), accelerated (AP), or blastic phase (BP), with the last two phases accounting for about 4% and 3% of cases, respectively (2, 3) and being associated with a worse prognosis (4).

For many years, CML was associated with a poor life expectancy (5), but the 2001 introduction of imatinib mesylate, the first tyrosine kinase inhibitor (TKI) and, more recently, of second- and third-generation TKIs (dasatinib, nilotinib, bosutinib, and ponatinib) has profoundly changed the CML curative-intent treatment, previously based on hematopoietic stem cell transplantation. TKIs have greatly improved CML survival rates and now make it possible to consider CML a chronic disease (6–11). Imatinib was approved as first-line treatment for all CML phases and is now available as a generic drug, as its patent has expired. Dasatinib and nilotinib were approved in 2006–2007 as second-line treatments for patients resistant to, or intolerant of, previous treatments (including imatinib): dasatinib in all CML phases and nilotinib only in the CP or AP. Since 2010–2011, both have been authorized for the first-line treatment of newly diagnosed Ph-positive adult cases of CP CML. Bosutinib was licensed in the United States in 2012 (and in Europe in 2013) for the treatment of adults with CP, AP, or BP CML who are resistant to, or intolerant of, previous treatments with one or more TKIs. In December 2017, the recommendation was extended in the United States to include newly diagnosed adult patients with CP CML. Ponatinib was approved in the United States in 2012 (and in Europe in 2013) for the treatment of adults with CP, AP, or BP CML who are resistant to, or intolerant to, other TKIs and also for the treatment of those with CP, AP, or BP CML who have the T315I mutation, which is known to be involved in resistance to all previous TKIs.

The 5-year survival estimates for patients with CML increased from 1997 to 2008 throughout Europe (particularly after 2000), although with large differences among European countries (10, 12): they increased slightly in Southern Europe, more in the United Kingdom, and considerably more in Northern, Central, and Eastern Europe, although in the latter region, survival remained lower than elsewhere (10). These improvements were plausibly linked to the widespread introduction of targeted and other new treatments (10). There was only a small increase in survival estimates among the elderly, possibly because of the under-use of imatinib (90% of patients aged 20–59 received imatinib, 75% of those aged 60–79, and 46% of those aged ≥80) and the newer TKIs (13). Furthermore, the cancer registry (CR) of Girona showed that the 5-year survival rate in patients with CML treated with TKIs in 1994–2008 was about 80%, compared with 44% among those who were not (14).

Population-based studies including all cases occurring in the region covered by a CR reflect the effectiveness of healthcare services in controlling the disease and are more likely to highlight socioeconomic disparities potentially associated with cancer survival. People who live in more affluent areas have better access to optimal care than those living in deprived areas, and this leads to discrepancies in overall survival (OS) figures (15). Moreover, access to optimal treatment is related to per capita income and healthcare investments (16).

Clinical practice, particularly in oncological settings, often relies on randomized controlled trials (RCTs) because they provide more detailed information than population-based studies. However, the amount of data may be overwhelming (17), and it can be difficult to determine the health systems' sustainability, in terms of finance and uptake of new practices. As a consequence, oncological organizations have developed frameworks to help clinicians and policymakers quantify the real value of new therapies (17–21). Generalizing trial results to everyday clinical practice is not straightforward because of low overall trial accrual (<5% of all newly diagnosed patients with cancer) and under-representation by age, gender, disease stage, co-morbidities, and socioeconomic status. However, despite these limitations, approved treatments are frequently offered to patients who would have been ineligible for the related trials, but they rarely show the benefits detected in RCTs; furthermore, a survival advantage detected by RCTs is not always subsequently confirmed in real-life setting.

This raises questions as to how the results of population-based studies using real-world data can add to the results of RCTs involving patients with CML and to the findings on the extent of RCTs' effectiveness for the patient population as a whole. In an attempt to answer these questions, we compared the survival of patients with CP CML participating in RCTs with the data from EUROCARE, the widest collaborative population-based study on cancer survival in Europe (22).

2 MATERIALS AND METHODS

2.1 Study Design

We extracted the survival data from the RCTs included in our previous systematic review and meta-analysis comparing first-line imatinib and second- and third-generation TKIs in adults with newly diagnosed CP CML [International Prospective Register of Systematic Review (PROSPERO) Registration No. CRD42016032903] (**Table 1**) (58, 59).

Population-based survival data were extracted from the EUROCARE-6 dataset (22). ICD-O-3 (International Classification of Disease for Oncology, 3rd edition) (60) morphology codes 9863

(CML with no cytogenetic information or CML not otherwise specified, NOS) and 9875 (CML, BCR-ABL1-positive; Ph+ CML) according to HAEMACARE (61) groupings were selected. Code 9876 (Atypical CML, BCR-ABL1-negative; Ph− aCML) was not included.

Quality and completeness of CRs data were evaluated by applying standardized check procedures in conjunction with the ENCR-JRC technical report, to ensure data comparability (62). At the end of the quality checks of the 101 population-based CRs in the EUROCARE-6 database (that provided continuous incidence data for hematological malignancies from January 1, 2000, to December 31, 2013, with follow-up data up until December 31, 2014), only 84 with adequate information for the purposes of the study (sufficient time coverage, follow-up completeness, and morphology accuracy) were selected (**Supplementary Table 1**).

The survival analyses were therefore based on 18,083 eligible CML cases, aged between 15 and 64 (the age selection corresponding to the age of patients with CML usually enrolled in RCTs), provided by 84 regional or national CRs in 28 European countries (**Table 2**). In particular, 8,793 CML cases were diagnosed in 2000–2006 and 9,290 CML cases in 2007–2013. We have defined the threshold of 2006–2007 because it corresponds to the introduction of second-generation TKIs (dasatinib and nilotinib) in clinical practice (first approval in 2006–2007).

The EUROCARE-6 patient complete selection is reported in the **Supplementary Material**.

2.2 Statistical Methods

2.2.1 RCT Meta-Analysis Data

OS data by follow-up time, number of deaths and hazard ratios (HRs), and cancer-specific mortality were collected through the RCTs included in the published meta-analysis (58, 59).

The OS data were pooled using the inverse variance method. Study heterogeneity was evaluated by calculating the I-squared statistic (I^2) with little, moderate, and substantial heterogeneity being indicated by I^2 values of <50%, 50%–75%, and >75%, respectively. Ninety-five percent confidence intervals (CIs) and two-sided p-values were calculated for each result.

2.2.2 Population-Based Data

Five-year crude OS of CML cases (9863, 9875 ICD-O-3 codes), aged between 15 and 64, diagnosed in 2000–2006 and 2007–2013, by European region and country, was estimated from the EUROCARE-6 study dataset. The 64-year threshold was determined, considering CML RCTs inclusion criteria and to make the age of patients more comparable between RCTs (median age: 50 years; range: 18–91) (**Table 1**) (58, 59) and population-based EUROCARE-6 results (median age: 50 years) (**Table 3**). The period of diagnosis threshold (pre- and post-2006) was established considering the timing of second-generation TKIs introduction (dasatinib and nilotinib) in clinical practice.

As most CRs do not collect data concerning disease phase, we used conditional survival (63) to select patients who are potentially in the CP, thus excluding the short-term mortality associated with BP or AP CML. Therefore, conditional crude OS (i.e., the probability of being alive after 5 years, conditional on surviving 3 years after diagnosis, in brief 5-/3-year OS ratio) was computed on the assumption that patients with CML surviving more than 3 years are not likely to include patients in AP and BP.

Relative survival (RS) (64), defined as OS divided by the expected survival of a comparable group (i.e., of the same age, sex and area) from the general population not affected by CML, was estimated using the complete approach (65). Expected survival was estimated using the Ederer II method (66). Conditional crude RS was computed in terms of 5-/3-year RS ratio.

Standard errors (SEs) of OS and RS were derived by applying Greenwood's formula (67). SE for conditional survival were calculated with the delta method (63). To obtain two-sided 95% CIs, the data were logarithmically transformed. The statistical significance of survival differences between patients diagnosed before and after 2006 (2000–2006 vs. 2007–2013) was tested with the Z-test (68).

2.2.3 Comparison Between RCTs and Population-Based Survival

We compared both OS, including all causes of death for patients with CML, and RS, a proxy of cause-specific survival, i.e., discarding competitive causes of mortality other than CML. Because, for RCTs, RS is not available (as they record the specific cause of death), we estimated the 5-year cause-specific survival (i.e., "freedom from death due to advanced CML") using data extracted from the corresponding RCTs included in the meta-analysis (58, 59).

The analyses were made using Review Manager v. 5.3 and SEER*Stat software 8.3.9.

3 RESULTS

3.1 RCTs Results

Many of the RCTs did not report OS at each and every one of the time points, but the patients were closely followed-up (**Table 1**). Only two RCTs reported OS up to 60 months (data not pooled), and only one reported OS up to 72 months. Five-year OS in the ENESTnd (38, 45) study was similar in the imatinib and nilotinib groups [92% vs. 94% for nilotinib of 300 mg (HR = 0.80; 95% CI, 0.43–1.50), and 96% for nilotinib of 400 mg (HR = 0.44; 95% CI, 0.21–0.93)]. Similar results were obtained in the DASISION (23, 32) study comparing imatinib with dasatinib: 5-year OS 90% vs. 91% (HR = 1.01; 95% CI, 0.58–1.73). The first follow-up time point at which it was possible to analyse pooled OS was 36 months (data from three RCTs), but, as it was not clinically relevant, we pooled the HRs roughly extracted from the printed OS curves of Radich et al. (33) (36-month of follow-up) and the ENESTnd (38, 45) and DASISION (23, 32) HRs (60-month follow-up) on the basis of the proportional hazards assumption; the result was not statistically significant (OS: HR = 0.78; 95% CI, 0.54–1.11) (58, 69).

The BFORE study update showed that 5-year OS was similar between bosutinib and imatinib (95% vs. 95%; HR = 0.95; 95% CI, 0.45–1.99) (56).

3.2 EUROCARE-6 Results

The numbers of patients with CML eligible for the survival analysis are reported by CR (**Table 2**). The main characteristics of patients included in survival analysis and the 5-year crude OS values of all CML cases (9863 - CML NOS, 9875 - Ph+ CML ICD-O-3 codes) are shown by European region and country (**Table 3**). The 9875 - Ph+ CML ICD-O-3 code is scarcely adopted (22%) (**Table 2**).

Comparing OS results between the two periods of diagnosis (2000–2006 vs. 2007–2013), a clear increase of OS values was observed for all European regions and for most countries (**Table 3**). A marked statistically significant increase was observed in the pool of all European countries (71.9% for patients diagnosed in 2000–2006 vs. 84.7% diagnosed in 2007–2013; absolute difference: 12.7%) and in all European areas, with higher improvements (>10%) in Eastern Europe (17.6%) and United Kingdom and Ireland (14.7%). Considering each country, the highest significant increases (>20%) were observed for Wales (21.0%), Slovenia (32.4%), Bulgaria (22.3%), Lithuania (29.5%), and Slovakia (22.8%). Notably, in most Western European countries, OS of patients diagnosed in 2007–2013 was similar to CP CML OS reported in RCTs (**Table 1**).

The study evaluated crude 5-/3-year conditional OS of all CML cases (i.e., the probability of being alive after 5 years, conditional on surviving 3 years after diagnosis), likely representing patients with CML in CP, diagnosed in 2000–2006 and 2007–2013, by European region and country (**Table 4**). A significant increase was observed in Europe as a whole (92.9% in 2000–2006 vs. 96.1% in 2007–2013; absolute difference: 3.2%) and in all areas except in Northern and Central Europe, showing that the most substantial 5-year OS increase (12.7%, **Table 3**) was concentrated in the first 3-year prognosis. Notably, countries with more marked delta OS increases (Slovenia, Lithuania, Bulgaria, and Slovakia; **Table 3**) showed the highest growth even in the CP (**Table 4**). Time trends of crude 5-/3-year conditional RS of all CML cases are presented in **Supplementary Table 4**. Conditional RS values are slightly higher than conditional OS values (by 1.1% on average), reflecting the limited impact of excluding causes of death other than CML in patients aged under 65 at diagnosis. Time trends of conditional RS are quite similar to those estimated for conditional OS. Small significant overall increases were estimated in the European pool (94.0% in 2000–2006 vs. 97.2% in 2007–2013; absolute difference: 3.2%) and in all areas but Northern and Central Europe.

In **Supplementary Tables 2, 3** were reported 5-year crude OS and 5-year crude RS, respectively, of CML cases diagnosed in 2000–2006 and 2007–2013 by European region, country, and morphology code. The differences between OS and RS were small, probably due to the patients' age selection (15–64 years, with negligible competitive mortality). In particular, in **Supplementary Table 2**, were compared OS values between 9863 CML NOS and 9875 Ph+ CML codes in 2000–2006 and 2007–2013, by areas: in all areas, CML NOS cases showed a lower OS values in comparison with Ph+ CML, even if differences reduced over time (except for Eastern Europe).

3.3 Comparisons Between RCTs and EUROCARE-6 Results

The estimated values of 5-year cause-specific survival in the ENESTnd study were 97.7% (96.0–99.5%) for nilotinib of 300 mg, 98.5% (97.1–100.0%) for nilotinib 400 mg, 93.8% (90.8–96.7%) for imatinib of 400 mg (38, 45). The DASISION study (23, 32) only reported the number of patients who had died of CML-related causes after 5 years of follow-up: 17/260 in the imatinib arm and 9/259 in the dasatinib arm. The estimated values of 5-year cause-specific survival in CP CML RCTs (58, 59) were quite similar to 5-/3-year conditional crude RS of all CML cases estimated in the best ranking countries of the EUROCARE-6 dataset. They are also close to the 5-/3-year conditional crude RS estimates for the European pool (97.2% in 2007–2013) (**Supplementary Table 4**).

4 DISCUSSION

The comparison of EUROCARE-6 CML survival estimated in patients diagnosed in 2000–2006 vs. 2007–2013 confirmed that the prognostic improvement highlighted by RCTs was verifiable in real-world settings. In particular, the EUROCARE-6 OS values in many countries (**Table 3**) were very similar to CP CML OS reported in RCTs (**Table 1**) (58, 59). Moreover, the same brilliant achievement was observed comparing the estimated values of 5-year cause-specific survival in CP CML RCTs (58, 59) with 5-/3-year conditional crude RS estimated in almost all European countries in 2007–2013 (**Supplementary Table 4**). This means that the optimal outcome figures obtained in controlled settings are achievable (and, indeed, are achieved) in real-world settings, too. The high concordance between CRs and RCTs survival results could be explained by the fact that TKIs are responsible of the quite complete disappearance of AP and BP worse prognosis CML phases. Almost all patients are diagnosed in CP (or have been quickly brought back to CP), so survival results reported in the whole population are close to those of RCTs. Moreover, the high concordance between CRs and RCTs survival results could be related to the fact that we compared quite homogeneous groups of patients with CML aged lower than 65 years with probably few comorbidities.

Previous population studies reported similar or inferior survival results but estimated only on national or small pooled samples.

Swedish CML Registry (779 CMLs, from 2002 to 2010; median age, follow-up: 60 years, 61 months) showed 5-year RS close to 1.0 for those younger than 60 years, 0.9 for those aged 60 to 80 years, and 0.6 for those older than 80 years (70). Swedish Cancer Registry (2,662 CMLs, from 1973 to 2013; median age: 69 years) reported clear improvements in life expectancy over the study period (71). Swedish Cancer Registry and Swedish Cause of Death Registry (CMLs, from 1970 to 2012) showed 5-year OS increasing from 0.18 to 0.82, during the study period; between 2006 and 2012, 5-year RS was close to normal for 40-year-old but considerably lower for 80-year-old patients (72). UK's Haematological Malignancy Research Network (242 CMLs,

from 2004 to 2011; median age: 59 years) showed 5-year OS of 78.9% (72.3% to 84.0%) and 5-year RS of 88.6% (81.0% to 93.3%) (73). Other national studies are aligned with our survival results (74–80).

European Treatment and Outcome Study (EUTOS) (2,904 CMLs, from 2008 to 2013; median age, follow-up: 55 years, 29 months) showed a 30 months OS of 92% (81). US Surveillance, Epidemiology, and End Results (SEER) (13,869 CMLs, from 1975 to 2009) reported lower survival values: 5-year RS ratios increased from 0.26 in 1975–1989 to 0.36 in 1990–2000 and 0.56 in 2001–2009 (82). Moreover, SEER (5,138 CMLs, from 2000 to 2005) showed 5-year OS improvement for all patients during the study period (83, 84). Compared with patients diagnosed in 2000, 5-year OS improved among 15–44 years (from 71.6% to 86.4%), 45–64 years (from 67.5% to 76.3%), 65–74 years (from 38.1% to 51.2%), and 75–84 years patients (from 19.2% to 36.4%) (83).

Population-based studies using real-world survival data reveal differences from the values observed in RCTs that are often related to treatment disparities and largely due to different socioeconomic conditions. They also provide information concerning treatment effectiveness in everyday clinical practice without any patient or outcome selection: they are therefore more representative of what happens in real-life, despite lacking in clinical details offered by RCTs, particularly in relation to disease stage at the time of diagnosis and first-line treatments. The findings of RCTs are often used to guide clinical practice (particularly in oncology), but patient selection can reduce their applicability to the general population (17, 18, 20, 21). Conversely, results of population-based CR studies that fully cover the target population are less affected by patient selection biases, and they provide useful data complementing RCTs outcomes.

However, these two information sources need to be integrated and require the use of new study designs and methods of analysis. High-resolution population-based studies, which include representative patients, present more detailed clinical information than that which is routinely collected by population-based CRs: this approach may help to reduce the gap between RCTs and real-world studies (hrstudies.it; https://www.ipaac.eu/en/work-packages/wp7/).

In an attempt to quantify the difference between RCTs and population-based studies using tangible data, we compared OS and cause-specific survival observed in the RCTs included in our previous systematic review (58), and OS and RS values estimated using EUROCARE-6 (22) cases diagnosed up to age 64 over a comparable period of time. It was the first time that this was done for CML, considering all European regions and pooling survival results. Our study shows that CML survival values tend to become very similar between RCTs and population-based settings, regardless of the survival analysis methods used. However, some differences still persist, in particular in Eastern European countries, where OS values were lower than elsewhere, especially in the first period of time being considered: this is probably due to a delayed introduction of TKIs in daily clinical practice. To underline that the date of the introduction of TKIs reimbursement varied greatly between Europe: this could be useful to interpret the different survival outcomes observed by countries (**Supplementary Table 5**). Also to notice that the allogeneic bone marrow transplantations medium rate was 0.62 per million for Eastern European countries in comparison with 0.81 per million for other European countries [**Supplementary Table 6**, by calendar year from 2000 to 2022 and by country; data provided by the European Society for Blood and Marrow Transplantation (EBMT), Chronic Malignancies Working Party (CMWP)].

Residual discrepancies can be attributed to different case selection criteria: RCTs select patients on the basis of well-defined inclusion and exclusion criteria, and the results cannot be readily extended to the general population, whereas population-based studies involve unselected patients but often lack detail and, in the case of CML, the morphology code might be not very precise. Moreover, RCTs almost always record cancer-specific mortality, with off-study survival being reported by the investigator after study discontinuation, whereas population studies systematically update life status of all registered patients and use RS to make adjustments for general mortality by age, gender, and geographical area.

RCTs also generally include patients without comorbidities who are younger than those encountered in real-life populations: for example, it has been found that the elderly, women, and members of racial and ethnic minorities are less likely to be enrolled in American cooperative group cancer trials than patients who are younger, male, and Caucasian (85, 86).

Our previous meta-analysis did not reveal any difference in the OS of patients treated with the first- or the new-generation TKIs (58, 59). In the only two RCTs for which 5-year OS data are available [DASISION (23, 32) and ENESTnd (38, 45)], the 60-month OS value was similar in the patients treated with imatinib and those treated with dasatinib or nilotinib, and similar to EUROCARE-6 OS data for patients diagnosed in 2007–2013. To underline that second-generation TKIs introduction time in clinical practice (2006–2007) limits a strict comparison with survival data of previous years, but imatinib can be considered an historical arm because it has been introduced in 2001. Moreover, CML survival values under imatinib or second-generation TKIs are fairly superimposable (60 months RCTs OS ≥ 90%, **Table 1**).

We compared the first-line treatment of RCT patients with newly diagnosed CP CML with all treatment lines administered to patients with CML from the general population (including a small percentage of patients with AP and BP CML who have a different prognosis). Unfortunately, CRs do not routinely collect information on CML phase and treatment line; thus, it was not possible to select CP CML cases receiving first-line treatment. To overcome this drawback, we analyzed 5-/3-year conditional OS and RS to remove the contribution of BP and AP CML and improve estimates comparability. Considering conditional OS and RS for patients diagnosed in 2007–2013, population-based CRs survival values were very similar to those observed in the RCTs.

Code 9876 (Ph− atypical CML or aCML) was not included but, as most CRs do not distinguish Ph+ CML and Ph− aCML, and as

TABLE 1 | Summary of the findings of the RCTs included in the meta-analysis.

RCT	No. of patients	Median age (range), years	Males (No., %)	FU (months)	Authors, year	Journal	OS (%) (I/C)						
							12 months	18 months	24 months	36 months	48 months	60 months	72 months
DASISION*	519	I: 49 (18–78)	I: 163 (63)	12	Kantarjan H.M. et al., 2010 (23)	N Engl J Med‡	99.0/97.0	–	–	–	–	–	–
(D)		D: 46 (18–84)	D: 144										
(NCT00481247)			(56)	18	Shah N. et al., 2010 (24)	Blood§	-	97.9/96.0	–	–	–	–	–
				24	Kantarjan H.M. et al., 2011 (25)	J Clin Oncol§	-	98.0/96.0	–	–	–	–	–
				24	Hochhaus A. et al., 2011 (26)	Blood§	-	–	–	–	–	–	–
				24	Hochhaus A. et al., 2012 (27)	J Clin Oncol§	-	–	–	–	–	–	–
				24	Kantarjian H.M. et al., 2012 (28)	Blood‡	-	–	95.2/95.3	–	–	–	–
				36	Jabbour E. et al., 2014 (29)	Blood‡	-	–	–	93.2/93.7	–	–	–
				48	Cortes J.E. et al., 2013 (30)	Blood§	-	–	–	–	92.0/93.0	–	–
				60	Cortes J.E. et al., 2014 (31)	Blood§	-	–	–	–	–	90.0/91.0	–
				60	Cortes J.E. et al., 2016 (32)	J Clin Oncol‡	-	–	–	–	–	90.0/91.0	–
NCT00070499†	253	I: 50 (19–89)	I: 72 (59)	12°	Radich J.P. et al., 2012 (33)	Blood‡	-	–	–	97.0/97.0	–	–	–
(D)		D: 47 (18–90)	D: 74 (60)										
NordCML006*	46	I: 60 (38–77)	I: 15 (63)	18	Mustjoki S. et al., 2013 (34)	Leukemia‡	-	–	–	–	–	–	–
(D)		D: 54 (29–71)	D: 7 (32)										
(NCT00852566)				24	Hjorth-Hansen H. et al., 2013 (35)	Blood§	-	–	–	–	–	–	–
				36	Hjorth-Hansen H. et al., 2015 (36)	Eur J Haematol‡	-	–	–	–	–	–	–
ENESTnd*	846	I: 46 (18–80)	I: 158 (56)	12	Larson R.A. et al., 2010 (37)	J Clin Oncol§	-	–	–	–	–	–	–
(N)		N300: 47 (18–85)	N300:										
(NCT00471497)		N400: 47 (18–81)	158 (56)	12	Saglio G. et al, 2010 (38)	N Engl J Med‡	-	–	–	–	–	–	–
			N400:										
			175 (62)	18	Hughes T.P. et al., 2010 (39)	Blood§	-	96.9/ 98.5 (N300) 99.3 (N400)	–	–	–	–	–
				24	Kantarjian H.M. et al., 2011 (40)	Lancet Oncol‡	-	–	96.3/ 97.4 (N300) 97.8 (N400)	–	–	–	–
				36	Kantarjian H.M. et al., 2012 (41)	Blood§	-	–	–	94.0/ 95.1 (N300) 97.0 (N400)	–	–	–
				36	Larson R.A. et al., 2012 (42)	Leukemia‡	-	–	–	94.0/ 95.1 (N300) 97.0 (N400)	–	–	–
				36	Hochhaus A. et al., 2013 (43)	Blood‡	-	–	–	–	–	–	–
				48	Hughes T.P. et al., 2014 (44)	Blood‡	-	–	–	–	93.3/ 94.3 (N300) 96.7 (N400)	–	–
				60	Hochhaus A., 2016 (45)	Leukemia‡	-	–	–	–	–	91.7/ 93.7	–

(Continued)

TABLE 1 | Continued

RCT	No. of patients	Median age (range), years	Males (No., %)	FU (months)	Authors, year	Journal	OS (%) (I/C)						
							12 months	18 months	24 months	36 months	48 months	60 months	72 months
												(N300) 96.2 (N400)	
				72	Hochhaus A. et al., 2015 (46)	Blood[§]	-	–	–	–	–	–	–
				72	Hughes T.P. et al., 2015 (47)	Haematologica[§]	-	–	–	–	–	–	91.4/91.6 (N300) 95.8 (N400)
BELA[†] **(B) (NCT00574873)**	502	I: 47 (18–89) B: 48 (19–91)	I: 135 (54) B: 149 (60)	12	Cortes J.E., 2012 (48)	J Clin Oncol[‡]	97.0/99.0	–	–	–	–	–	–
				18	Gambacorti-Passerini C., 2011 (49)	J Clin Oncol[§]	-	–	–	–	–	–	–
				24	Brummendorf T.H, 2015 (50)	Br J Haematol[‡]	-	–	95.0/97.0	–	–	–	–
				30	Brummendorf T.H., 2012 (51)	Haematologica[§]	-	–	95.0/97.0	–	–	–	–
				30	Gambacorti-Passerini C., 2014 (52)	Am J Hematol[‡]	-	–	–	–	–	–	–
				48	Cortes J.E., 2016 (53)	Am J Hematol[‡]	-	–	–	–	–	–	–
BFORE* **(B) (NCT02130557)**	536	I: 53 (19–84) B: 52 (18–84)	I: 135 (56) B: 142 (58)	12	Cortes J.E., 2018 (54)	J Clin Oncol[‡]	97.9/99.6	–	–	–	–	–	–
				18	Gambacorti-Passerini C., 2017 (55)	Blood[§]	-	96.6/99.6	–	–	–	–	–
				60	[Brummendorf T.H, 2020[^] (56)]	Blood[§]						94.6/94.5	
EPIC[†] **(P) (NCT01650805)**	307	I: 52 (18–86) P: 55 (18–89)	I: 92 (61) P: 97 (63)	12	Lipton J.H, 2016 (57)	Lancet Oncol[‡]	-	–	–	–	–	–	–

RCT, randomized controlled trial; OS, overall survival; FU, follow-up; (–), not evaluated; I/C, imatinib/comparator (B, bosutinib; D, dasatinib; N300, nilotinib of 300 mg; N400, nilotinib of 400 mg; P, ponatinib).
**RCT.*
[†]Quasi-RCT.
[‡]Full paper.
[§]Abstract.
[°]36-month OS.
[^]Updated in 2022.

78.0% of cases are classified as CML NOS (**Table 2**), some aCML cases were inevitably included. This has little impact on our analysis as 90%–95% of CML diagnoses have the characteristic t(9;22)(q34; q11.2) reciprocal translocation, leading to the Ph chromosome and to the *BCR-ABL1* fusion gene that is the target for specific TKIs (4). However, this partly explains why OS values for ICD-O-3 code 9863, including CML NOS and (probably) patients with poorer prognosis (such as aCML cases not targeted by TKIs), were, at all evaluable times and in all evaluable regions, lower compared to the values for Ph+ CML for which TKIs are indicated.

Code 9875 (Ph+ CML) was hardly used in Northern Europe or the United Kingdom and Ireland, and the implausibly small number of cases in the other regions/countries considered is attributable to differences in registration criteria or inaccurate pathological description. It is also likely that the underuse of code 9875 for Ph+ CML is due to a bad translation of the ICD-O-3 classification: code 9863 refers to "chronic myeloid leukemia, NOS" and code 9875 refers to "chronic myelogenous leukemia, BCR/ABL positive" (Ph+ CML) and, although hematologists normally correctly diagnose cases of code 9875 as Ph+ CML, the use of the word "myelogenous" is ambiguous for non-hematologists. This may also explain the considerable difference in the use of code 9875 between specialized hematological registries and general CRs. CRs should correctly code CML morphology by specifying ICD-O-3 9875 (Ph+ CML) or 9876 (Ph– aCML), the phase of the disease at the time of diagnosis, first-line therapy, and the occurrence of transformation into AP or BP to make a more precise analysis possible: one that is potentially comparable with other types of studies. Some strategies should be adopted to avoid CML code misuse and to reduce the number of CML NOS cases, such as to plan specific training courses to increase the precision of coding or to link CML population-based data with other available data sources, for example, national health insurance databases, to discover patients really treated with TKIs (87). Unfortunately, 9875 (Ph+ CML) code is so underused in CRs in the studied period 2000–2013 not to permit to design a population-based study excluding 9863 code (CML NOS).

A clear improvement in real-world CML survival was observed in European regions and countries comparing EUROCARE-6 with RCTs OS data. However, some discrepancies with RCTs still

TABLE 2 | Myeloid malignancies diagnosed in European patients (15–64 years) in 2000–2013 and quality indicators by Cancer Registry (CR). EUROCARE-6 study dataset.

Area/Country		Cancer registry (CR)	Overall period of diagnosis[1]	Myeloid malignancies[2] 2000–2013					
							CML cases included in survival analysis[3]		
				Cases 2000–2013	% Microscopically Verified (MV)	% Not otherwise specified (NOS)[4]	CML total cases	CML NOS (9863) cases (%)	CML Ph+ (9875) cases (%)
Northern Europe	DENMARK	**Denmark**	1978–2014	3,404	98.9	1.3	470	122 (26)	348 (74)
	FINLAND	**Finland**	1978–2013	2,309	90.9	6.9	304	300 (99)	4 (1)
	ICELAND	**Iceland**	1978–2014	78	98.7	1.3	23	22 (96)	1 (4)
	NORWAY	**Norway**	1978–2016	2,557	98.9	1.8	312	283 (91)	29 (9)
UK and Ireland	IRELAND	**Ireland**	1994–2012	1,986	98.6	5.7	240	234 (98)	6 (3)
	UK-ENGLAND	**UK-England**	1995–2013	15,100	91.1	5.1	3,548	3,449 (97)	99 (3)
	UK-SCOTLAND	**UK-Scotland**	1978–2013	3,564	95.2	0.8	344	335 (97)	9 (3)
	UK-WALES	**UK-Wales**	1991–2012	959	76.1	3.1	229	229 (100)	0 (0)
Central Europe	AUSTRIA	**Austria**	1983–2012	2,629	96.8	4.1	623	541 (87)	82 (13)
	BELGIUM	**Belgium**	2004–2013	5,727	99.9	1.1	772	426 (55)	346 (45)
	FRANCE	Bas Rhin	1990–2014	698	99.1	1.1	100	16 (16)	84 (84)
		Basse Normandie, HM	2002–2010	994	93.1	1.5	113	5 (4)	108 (96)
		Calvados	1990–2014	42	100.0	7.1	2	2 (100)	0 (0)
		Cote dOr, HM	1990–2014	393	100.0	0.3	53	0 (0)	53 (100)
		Doubs	1990–2014	436	100.0	0.7	58	2 (3)	56 (97)
		Gironde, HM	2002–2014	884	100.0	0.2	132	3 (2)	129 (98)
		Haut-Rhin	1990–2014	511	100.0	1.6	83	24 (29)	59 (71)
		Herault	1995–2014	729	100.0	0.5	111	30 (27)	81 (73)
		Isere	1990–2014	791	100.0	0.6	108	12 (11)	96 (89)
		Loire-Atlantique/ Vendée	1991–2014	1,195	100.0	0.8	195	36 (18)	159 (82)
		Manche	1994–2014	45	100.0	4.4	8	8 (100)	0 (0)
		Somme	1990–2014	435	99.8	0.7	66	10 (15)	56 (85)
		Tarn	1990–2014	264	100.0	0.4	41	7 (17)	34 (83)
	GERMANY	Bremen	2000–2013	377	98.9	0.5	51	19 (37)	32 (63)
		Common Cancer Registry of 4 Federal States[5]	2002–2013	5,493	99.1	3.1	705	442 (63)	263 (37)
		Hamburg	1998–2012	587	99.1	2.6	147	131 (89)	16 (11)
		Rhineland-Palatinate	2004–2012	1,198	93.2	2.1	198	188 (95)	10 (5)
		Saarland	1993–2012	521	99.6	1.7	77	77 (100)	0 (0)
		Schleswig-Holstein	2003–2012	1,062	94.5	1.2	158	117 (74)	41 (26)
	SWITZERLAND	Graubunden and Glarus	1989–2013	115	100.0	2.6	19	17 (89)	2 (11)
		Eastern Switzerland	1981–2013	236	100.0	2.1	51	45 (88)	6 (12)
		Ticino	2000–2012	219	100.0	1.8	33	15 (45)	18 (55)
	THE NETHERLANDS	**The Netherlands**	1989–2013	9,759	99.9	0.6	1,199	152 (13)	1047 (87)
Southern Europe	CROATIA	**Croatia**	2000–2012	1,178	100.0	18.1	265	265 (100)	0 (0)
	CYPRUS	**Cyprus**	2004–2014	232	100.0	3.0	38	36 (95)	2 (5)
	ITALY	Alto Adige	1995–2010	193	100.0	3.1	17	0 (0)	17 (100)
		Biella	1995–2010	191	97.9	0.5	12	10 (83)	2 (17)
		Brescia	1999–2010	290	94.1	9.3	65	65 (100)	0 (0)
		Catania-Messina-Enna	2003–2013	1,259	99.5	4.7	152	126 (83)	26 (17)
		Catanzaro	2003–2009	171	90.6	3.5	25	25 (100)	0 (0)
		Como	2003–2011	238	97.1	2.1	31	31 (100)	0 (0)
		Ferrara	1991–2011	247	100.0	2.4	26	26 (100)	0 (0)
		Friuli Venezia Giulia	1995–2010	343	100.0	3.8	75	75 (100)	0 (0)
		Genova	1986–2010	650	73.1	2.8	57	55 (96)	2 (4)
		Latina	1996–2012	308	79.5	1.9	43	37 (86)	6 (14)
		Lodi	2003–2010	129	99.2	5.4	29	28 (97)	1 (3)
		Mantova	1999–2010	123	100.0	5.7	26	26 (100)	0 (0)
		Modena	1988–2013	518	99.0	1.2	86	37 (43)	49 (57)
		Napoli	1996–2013	652	95.7	7.7	75	49 (65)	26 (35)
		Nuoro	2003–2012	114	100.0	0.0	14	14 (100)	0 (0)
		Palermo	2003–2013	712	95.2	7.0	95	94 (99)	1 (1)
		Parma	1978–2014	314	100.0	0.6	44	26 (59)	18 (41)

(Continued)

TABLE 2 | Continued

Area/Country		Cancer registry (CR)	Overall period of diagnosis[1]	Myeloid malignancies[2] 2000–2013					
							CML cases included in survival analysis[3]		
				Cases 2000–2013	% Microscopically Verified (MV)	% Not otherwise specified (NOS)[4]	CML total cases	CML NOS (9863) cases (%)	CML Ph+ (9875) cases (%)
		Ragusa	1981–2012	375	99.7	4.3	45	44 (98)	1 (2)
		Reggio Emilia	1996–2014	407	98.8	1.0	68	30 (44)	38 (56)
		Romagna	1986–2014	934	99.0	3.5	96	87 (91)	9 (9)
		Salerno	1996–2010	571	96.1	4.9	77	76 (99)	1 (1)
		Sassari	1992–2011	209	98.6	1.4	42	42 (100)	0 (0)
		Siracusa	1999–2012	222	90.5	13.5	27	25 (93)	2 (7)
		Sondrio	1998–2013	156	84.0	4.5	20	20 (100)	0 (0)
		Trapani	2002–2010	164	100.0	2.4	33	29 (88)	4 (12)
		Trento	1995–2010	165	97.6	9.1	39	39 (100)	0 (0)
		Umbria	1994–2013	692	98.7	4.9	96	96 (100)	0 (0)
		Varese	1978–2012	348	92.2	12.9	85	83 (98)	2 (2)
		Veneto	1987–2010	1,244	96.1	2.7	147	145 (99)	2 (1)
	MALTA	**Malta**	1993–2013	192	99.0	7.8	19	19 (100)	0 (0)
	PORTUGAL	Northern Portugal	2000–2010	939	99.9	3.8	145	124 (86)	21 (14)
		Southern Portugal	2000–2012	2,055	99.9	7.8	305	262 (86)	43 (14)
	SLOVENIA	**Slovenia**	1983–2012	1,000	100.0	1.6	102	93 (91)	9 (9)
	SPAIN	Balearic Islands	1988–2012	456	99.8	1.3	65	41 (63)	24 (37)
		Basque Country	1986–2012	1,163	99.1	6.0	174	131 (75)	43 (25)
		Canarie	1996–2011	645	99.7	1.6	97	87 (90)	10 (10)
		Castellon	2004–2012	199	100.0	4.0	30	29 (97)	1 (3)
		Girona	1994–2014	475	99.8	0.4	64	14 (22)	50 (78)
		Granada	1985–2012	363	100.0	2.8	51	27 (53)	24 (47)
		Murcia	1990–2010	492	98.8	4.3	90	90 (100)	0 (0)
		Navarra	1978–2010	189	98.4	2.1	22	21 (95)	1 (5)
		Tarragona	1982–2011	336	100.0	3.0	53	35 (66)	18 (34)
Eastern Europe	BULGARIA	**Bulgaria**	1993–2013	2,899	100.0	8.2	690	690 (100)	0 (0)
	CZECH REPUBLIC	**Czech Republic**	1994–2013	2,975	72.2	25.8	586	468 (80)	118 (20)
	ESTONIA	**Estonia**	1978–2012	528	100.0	1.9	88	84 (95)	4 (5)
	LATVIA	**Latvia**	2000–2013	695	99.9	11.4	146	146 (100)	0 (0)
	LITHUANIA	**Lithuania**	1993–2012	2,012	99.3	3.6	325	250 (77)	75 (23)
	POLAND	**Poland**	2001–2013	8,093	95.6	9.8	2,197	2,197 (100)	0 (0)
	SLOVAKIA	**Slovakia**	1978–2010	2,067	100.0	2.0	311	257 (83)	54 (17)
Total 84 CRs				**106,419**	**96.1**	**4.5**	**18,083**	**14,105 (78)**	**3,978 (22)**

CML, chronic myeloid leukemia; CR, cancer registry; HM, hematological malignancies; Ph, Philadelphia chromosome.

[1]CRs period of diagnosis refers to overall data sent by each cancer registry.

[2]International Classification of Disease for Oncology, 3rd edition (ICD-O-3) codes for myeloid malignancies: 9740-9742, 9800-9801, 9805-9809, 9840, 9860-9861, 9863, 9865-9867, 9869-9876, 9891, 9895-9898, 9910-9911, 9920, 9930-9931, 9945-9946, 9950, 9960-9964, 9966, 9975, 9980, 9982-9987, 9989, 9991-9992.

[3]ICD-O-3 codes of CML cases eligible for the survival analysis: 9863 (CML with no cytogenetic information, CML NOS) and 9875 (Ph+, BCR/ABL1-positive CML).

[4]Myeloid NOS cases ICD-O-3 codes: 9800, 9801, 9805, and 9860.

[5]Four Federal States: Brandenburg, Mecklenburg-Western Pomerania, and the Free States of Saxony and Thuringia.

CRs with national coverage are in bold.

remain. Our results suggest an insufficient adoption of adequate protocols in daily clinical practice in countries where CML survival values still remain lower in real-life than those obtained in RCTs. In future works, it will be of interest to focus on populations usually excluded from RCTs, such as older patients, or with comorbidities and other cancers.

EUROCARE-6 WORKING GROUP

Austria: M. Hackl (*National CR*); **Belgium**: E. Van Eycken (*National CR*); **Bulgaria**: Z. Valerianova (*National CR*); **Croatia**: M. Sekerija (*National CR*); **Cyprus**: P. Pavlou (*National CR*); **Czech Republic**: L. Dušek (*National CR*); **Denmark**: H. Storm (*National CR*); **Estonia**: M. Mägi; K. Innos* (*National CR*); **Finland**: N. Malila; J. Pitkäniemi (*National CR*); **France**: M. Velten (*Bas Rhin CR*); X. Troussard (*Basse Normandie*, *Haematological Malignancies CR*); A.M. Bouvier; V. Jooste* (*Burgundy*, *Digestive CR*); A.V. Guizard (*Calvados*, *General CR*); G. Launoy (*Calvados*, *Digestive CR*); S. Dabakuyo Yonli (*Cote dOr*, *Gynaecologic* (*Breast*) CR); M. Maynadié (*Cote dOr*, *Haematological Malignancies CR*); A.S. Woronoff (*Doubs CR*); J.B. Nousbaum (*Finistere*, *Digestive CR*); G. Coureau (*Gironde*, *General CR*); A. Monnereau* (*Gironde*, *Haematological Malignancies CR*); I. Baldi (*Gironde*, *Central*

TABLE 3 | Five-year crude overall survival of CML cases (15–64 years) (9863, 9875 ICD-O-3 codes)[1] diagnosed in 2000–2006 and 2007–2013 by European region and country. EUROCARE-6 study dataset.

Country/Area	Total cases 2000–2013	Median age (years)	Male	M %	2000–2006					2007–2013					Absolute difference	p-value
					N at start	N_5	OS	95%CI		N at start	N_5	OS	95%CI			
Northern Europe (4 CRS)	**1,109**	**48**	**621**	**56.0**	**534**	**438**	**80.5**	**77.2**	**83.9**	**575**	**314**	**89.2**	**86.4**	**92.2**	**8.8****	**<0.001**
Denmark	470	48	267	56.8	225	186	80.8	75.8	86.1	245	135	88.7	84.0	93.6	**7.9***	**0.028**
Finland	304	49	175	57.6	165	135	80.0	74.1	86.3	139	73	86.0	79.8	92.6	6.0	0.187
Iceland	23	45	18	78.3	11	9	–	–	–	12	6	–	–	–	–	–
Norway	312	48	161	51.6	133	108	80.5	74.0	87.5	179	100	91.8	87.7	96.0	**11.3****	**0.005**
UK and Ireland (4 CRs)	**4,361**	**49**	**2,555**	**58.6**	**2,001**	**1,488**	**72.2**	**70.3**	**74.2**	**2,360**	**1,187**	**86.9**	**85.3**	**88.4**	**14.7****	**<0.001**
Ireland	240	52	141	58.8	117	97	79.5	72.5	87.2	123	58	90.7	85.3	96.5	**11.2***	**0.017**
England	3548	48	2080	58.6	1596	1167	70.9	68.7	73.2	1952	982	86.5	84.8	88.2	**15.5****	**<0.001**
Scotland	344	50	210	61.0	166	139	83.1	77.6	89.0	178	87	87.8	82.1	93.7	4.6	0.263
Wales	229	50	124	54.1	122	85	67.2	59.4	76.1	107	60	88.2	81.7	95.2	**21.0****	**<0.001**
Central Europe (25 CRs)	**5,103**	**50**	**2,958**	**58.0**	**2,186**	**1,829**	**82.6**	**81.0**	**84.2**	**2,917**	**1,407**	**88.5**	**87.1**	**89.9**	**5.9****	**<0.001**
Austria	623	51	379	60.8	347	262	74.6	70.2	79.4	276	146	84.2	79.6	89.1	**9.5****	**0.005**
Belgium	772	50	437	56.6	201	176	87.0	82.5	91.8	571	282	92.0	89.5	94.6	5.0	0.066
France (13 CRs Pool)	1070	50	628	58.7	444	394	88.5	85.6	91.5	626	321	92.1	89.5	94.7	3.6	0.076
Germany (6 CRs Pool)	1336	50	786	58.8	597	502	82.6	79.6	85.7	739	312	85.7	82.7	88.8	3.2	0.150
Switzerland (3CRs Pool)	103	50	60	58.3	51	47	90.2	82.4	98.7	52	26	85.8	74.4	99.0	–4.4	0.561
The Netherlands	1199	49	668	55.7	546	448	80.4	77.1	83.8	653	320	87.2	84.2	90.2	**6.7****	**0.003**
Southern Europe (44 CRs)	**3,167**	**49**	**1,855**	**58.6**	**1,738**	**1,396**	**78.1**	**76.2**	**80.1**	**1,429**	**816**	**86.9**	**85.0**	**88.8**	**8.8****	**<0.001**
Cyprus	38	49	28	73.7	10	9	–	–	–	28	19	–	–	–	–	–
Croatia	265	52	166	62.6	154	100	59.7	52.5	68.0	111	25	68.6	57.7	81.5	8.8	0.220
Italy (29 CRs Pool)	1647	50	950	57.7	906	752	81.3	78.8	83.9	741	441	88.3	85.8	90.8	**7.0****	**<0.001**
Malta	19	40	12	63.2	12	9	–	–	–	7	2	–	–	–	–	–
Portugal (2 CRs Pool)	450	49	253	56.2	254	191	74.0	68.8	79.6	196	121	82.9	77.5	88.6	**8.9***	**0.025**
Slovenia	102	49	65	63.7	54	35	59.3	47.5	73.9	48	30	91.7	84.2	99.8	**32.4****	**<0.001**
Spain (CRs Pool)	646	47	381	59.0	348	300	83.6	79.8	87.6	298	178	90.3	86.7	94.0	**6.7***	**0.014**
Eastern Europe (7 CRs)	**4,343**	**51**	**2,376**	**54.7**	**2,334**	**1,351**	**55.3**	**53.3**	**57.3**	**2,009**	**754**	**72.8**	**70.6**	**75.1**	**17.6****	**<0.001**
Bulgaria	690	53	374	54.2	390	174	41.3	36.7	46.5	300	106	63.6	58.0	69.7	**22.3****	**<0.001**
Czech Republic	586	50	329	56.1	336	228	66.1	61.2	71.3	250	81	75.0	68.5	82.2	**9.0***	**0.039**
Estonia	88	50	54	61.4	53	30	54.7	42.8	69.9	35	19	69.0	54.5	87.3	14.2	0.186
Latvia	146	50	82	56.2	67	40	56.7	46.0	69.9	79	28	63.8	52.8	77.1	7.1	0.414
Lithuania	325	49	173	53.2	179	92	49.1	42.3	57.0	146	73	78.7	71.9	86.1	**29.5****	**<0.001**
Poland	2197	50	1195	54.4	1105	669	57.8	55.0	60.8	1092	384	74.3	71.2	77.6	**16.5****	**<0.001**
Slovakia	311	50	169	54.3	204	118	55.4	49.0	62.7	107	63	78.2	70.3	86.9	**22.8****	**<0.001**
European Pool (84 CRs)	**18,083**	**50**	**10,365**	**57.3**	**8,793**	**6,502**	**71.9**	**71.0**	**72.9**	**9,290**	**4478**	**84.7**	**83.9**	**85.5**	**12.7****	**<0.001**

CI, confidence interval; CML, chronic myeloid leukemia; CR, cancer registry; ICD-O-3, International Classification of Disease for Oncology, 3rd edition; M, male; N at start, number of CML cases alive at the beginning of the period; N_5, number of CML cases alive at 5 years from diagnosis; OS, overall survival.

[1]ICD-O-3 codes of CML cases eligible for the survival analysis: 9863 (CML with no cytogenetic information, CML NOS) and 9875 (Ph+, BCR/ABL1-positive CML).

Survival estimates are not provided for strata including fewer than 10 cases.

***p-value <0.01 and *p-value <0.05.*

In bold European regions and statistically significant p values.

Nervous System CR); K. Hammas (*Haut-Rhin CR*); B. Tretarre (*Herault CR*); M. Colonna (*Isere CR*); S. Plouvier (*Lille Area CR*); T. D'Almeida (*Limousin CR*); F. Molinié; A. Cowppli-Bony (*Loire-Atlantique/Vendée CR*); S. Bara (*Manche CR*); C. Schvartz (*Marne-Ardennes*, *Thyroid CR*); G. Defossez (*Poitou-Charentes CR*); B. Lapôtre-Ledoux (*Somme CR*); P. Grosclaude (*Tarn CR*); **Germany**: S. Luttmann (*Bremen CR*); R. Stabenow [*Common CR of 4 Federal States* (*Brandenburg*, *Mecklenburg-West Pomerania*, *Saxony-Anhalt*, *Thüringen*)]; A. Nennecke (*Hamburg CR*); J. Kieschke (*Lower Saxony CR*); S. Zeissig (*Rhineland-Palatinate CR*); B. Holleczek (*Saarland CR*); A. Katalinic* (*Schleswig-Holstein CR*); **Iceland**: H. Birgisson (*National CR*); **Ireland**: D. Murray; P.M. Walsh (*National CR*); **Italy**: G. Mazzoleni; F. Vittadello (*Alto Adige CR*); F. Cuccaro (*Barletta-Andria-Trani CR*); R. Galasso (*Basilicata CR*); G. Sampietro (*Bergamo CR*); S. Rosso (*Biella CR*); M. Magoni (*Brescia CR*); M. Ferrante (*Catania-*

TABLE 4 | Conditional crude 5-/3-year overall survival[1] of CML cases (15–64 years) (9863, 9875 ICD-O-3 codes)[2] diagnosed in 2000–2006 and 2007–2013 by European region and country. EUROCARE-6 study dataset.

Country/Area	2000–2006					2007–2013					Absolute difference	p-value
	N_3	N_5	5-/3-year	95%CI		N_3	N_5	5-/3-year	95%CI			
Northern Europe (4 CRS)	**470**	**438**	**95.7**	**93.9**	**97.6**	**475**	**314**	**96.4**	**94.3**	**98.5**	0.7	0.642
Denmark	199	186	94.2	91.0	97.6	199	135	93.8	89.7	98.1	–0.4	0.873
Finland	143	135	96.4	93.3	99.5	114	73	96.0	91.7	100.6	–0.3	0.907
Iceland	9	9	–	–	–	10	6	–	–	–	–	–
Norway	119	108	97.3	94.3	100.4	152	100	100.0	100.0	100.0	2.7	0.079
UK and Ireland (4 CRs)	**1,641**	**1,488**	**92.9**	**91.6**	**94.2**	**1,872**	**1,187**	**97.2**	**96.2**	**98.1**	**4.3****	**<0.001**
Ireland	105	97	93.0	88.1	98.1	99	58	98.6	95.8	101.4	5.6	0.057
England	1293	1167	92.6	91.1	94.0	1537	982	97.3	96.3	98.4	**4.8****	**<0.001**
Scotland	146	139	94.5	90.9	98.3	144	87	95.1	90.6	99.9	0.6	0.832
Wales	97	85	94.3	89.5	99.3	92	60	96.6	92.0	101.4	2.3	0.497
Central Europe (25 CRs)	**1,937**	**1,829**	**96.3**	**95.4**	**97.1**	**2,372**	**1,407**	**96.0**	**95.0**	**97.0**	–0.2	0.719
Austria	280	262	96.3	94.0	98.6	252	146	93.9	90.2	97.7	–2.4	0.274
Belgium	185	176	96.7	94.1	99.3	471	282	98.2	96.5	99.8	1.5	0.344
France (13 CRs Pool)	415	394	97.3	95.7	98.9	523	321	96.6	94.6	98.6	–0.7	0.588
Germany (6 CRs Pool)	529	502	96.3	94.7	97.9	545	312	95.2	92.9	97.5	–1.1	0.453
Switzerland (3 CRs Pool)	50	47	95.8	90.3	101.7	42	26	91.9	81.5	103.6	–3.9	0.535
The Netherlands	478	448	95.2	93.3	97.2	539	320	95.7	93.6	97.9	0.5	0.725
Southern Europe (44 CRs)	**1,509**	**1,396**	**94.3**	**93.2**	**95.5**	**1,209**	**816**	**97.2**	**96.1**	**98.4**	**2.9****	**0.001**
Cyprus	10	9	–	–	–	27	19	–	–	–	–	–
Croatia	116	100	87.6	81.5	94.2	59	25	91.9	81.5	103.7	4.3	0.510
Italy (29 CRs Pool)	799	752	95.3	93.8	96.8	624	441	97.6	96.2	99.1	**2.3***	**0.028**
Malta	10	9	–	–	–	3	2	–	–	–	–	–
Portugal (2 CRs Pool)	219	191	93.5	90.2	97.0	173	121	96.0	92.7	99.5	2.5	0.301
Slovenia	41	35	86.5	76.1	98.2	44	30	100.0	100.0	100.0	**13.5***	**0.016**
Spain (CRs Pool)	314	300	95.7	93.5	98.0	279	178	97.4	95.1	99.7	1.7	0.313
Eastern Europe (7 CRs)	**1,636**	**1,351**	**86.6**	**84.9**	**88.4**	**1,295**	**754**	**93.4**	**91.6**	**95.1**	**6.7****	**<0.001**
Bulgaria	241	174	78.2	72.7	84.0	195	106	95.1	91.3	99.0	**17.0****	**<0.001**
Czech Republic	256	228	92.5	89.2	95.9	144	81	93.5	88.0	99.2	1.0	0.771
Estonia	39	30	80.6	68.6	94.6	29	19	86.4	73.1	102.0	5.8	0.556
Latvia	49	40	82.6	72.4	94.3	52	28	92.7	83.3	103.2	10.1	0.180
Lithuania	121	92	82.2	75.3	89.8	122	73	95.0	90.4	99.9	**12.8****	**0.004**
Poland	791	669	88.0	85.7	90.4	665	384	92.6	90.1	95.2	**4.6****	**0.010**
Slovakia	139	118	88.3	82.9	94.0	88	63	95.0	89.6	100.7	6.7	0.093
European Pool (84 CRs)	**7,193**	**6,502**	**92.9**	**92.3**	**93.5**	**7,223**	**4,478**	**96.1**	**95.5**	**96.7**	**3.2****	**<0.001**

CI, confidence interval; CML, chronic myeloid leukemia; CR, cancer registry; ICD-O-3, International Classification of Disease for Oncology, 3rd edition.

N_3 and N_5, number of CML cases alive at 3 and 5 years from diagnosis, respectively.

[1]The crude 5-/3-year conditional overall survival is the probability of being alive after 5 years, conditional on surviving 3 years after diagnosis.

[2]ICD-O-3 codes of CML cases eligible for the survival analysis: 9863 (CML with no cytogenetic information, CML NOS) and 9875 (Ph+, BCR/ABL1-positive CML).

Survival estimates are not provided for strata including fewer than 10 cases.

***p-value <0.01 and *p-value <0.05.*

In bold European regions and statistically significant p values.

Messina-Enna CR); A. Sutera Sardo (*Catanzaro CR*); M.L. Gambino (*Como CR*); P. Ballotari; E. Giacomazzi (*Cremona and Mantova CR*); S. Ferretti (*Ferrara CR*); A. Caldarella; G. Manneschi (*Firenze-Prato CR*); G. Gatta*; M. Sant*; P. Baili*; F. Berrino*; L. Botta; A. Trama; R. Lillini; A. Bernasconi; S. Bonfarnuzzo; C. Vener; F. Didonè; P. Lasalvia; G. Del Monego; M.C. Magri; L. Buratti (*Fondazione IRCCS Istituto Nazionale dei Tumori*, *Milan*); D. Serraino; L. Dal Maso (*Friuli Venezia Giulia CR*); R. Capocaccia* (*Epidemiologia e Prevenzione Board*); R. De Angelis*; E. Demuru; C. Di Benedetto; S. Rossi*; M. Santaquilani; S. Venanzi (*Istituto Superiore di Sanità*, *Rome*); R.A. Filiberti (*Genova CR*); S. Iacovacci (*Latina CR*); V. Gennaro (*Liguria*, *mesotheliomas CR*); A.G. Russo (*Lodi CR*); G. Spagnoli (*Modena CR*); L. Cavalieri d'Oro (*Monza and Brianza CR*); M. Fusco; M.F. Vitale (*Napoli CR*); M. Usala (*Nuoro CR*); F. Vitale (*Palermo CR*); M. Michiara (*Parma CR*); G. Chiranda (*Piacenza CR*); G. Cascone; E. Spata (*Ragusa CR*); L. Mangone (*Reggio Emilia CR*); F. Falcini (*Romagna CR*); R. Cavallo (*Salerno CR*); D. Piras (*Sassari CR*); A. Madeddu; F. Bella (*Siracusa CR*); A.C. Fanetti (*Sondrio CR*); S. Minerba (*Taranto CR*); G. Candela; T. Scuderi (*Trapani CR*); R.V. Rizzello (*Trento CR*); F. Stracci (*Umbria CR*); G. Tagliabue (*Varese CR*); M. Rugge (*Veneto CR*); A. Brustolin (*Viterbo CR*); **Latvia**: S. Pildava (*National CR*); **Lithuania**: G. Smailyte (*National CR*); **Malta**: M. Azzopardi (*National CR*); **Norway**: T.B. Johannesen* (*National CR*); **Poland**: J. Didkowska; U. Wojciechowska (*National CR*); M. Bielska-Lasota* (*National Institute of Public Health-National Institute of Hygiene-National Research Institute*, *Warsaw*); **Portugal**: A. Pais (*Central Portugal CR*); J.L. Pontes (*Northern Portugal CR*); A. Miranda (*Southern Portugal CR*); **Slovakia**: C. Safaei Diba (*National CR*); **Slovenia**: V. Zadnik; T. Zagar (*National CR*); **Spain**: C. Sánchez-Contador Escudero; P. Franch Sureda (*Balearic Islands*, *Mallorca CR*); A. Lopez de Munain; M. De-La-Cruz (*Basque Country CR*);

M.D. Rojas, A. Aleman (*Canary Islands CR*); A. Vizcaino (*Castellon CR*); R. Marcos-Gragera (*Girona CR*); M.J. Sanchez (*Granada CR*); M.D. Chirlaque (*Murcia CR*); M. Guevara Eslava*; E. Ardanaz (*Navarra CR*); J. Galceran; M. Carulla (*Tarragona CR*); **Switzerland**: Y. Bergeron (*Fribourg CR*); C. Bouchardy (*Geneva CR*); S. Mohsen Mousavi (*Graubünden and Glarus CR*); S. Mohsen Mousavi (*Eastern Switzerland CR*); A. Bordoni (*Ticino CR*); **The Netherlands**: O. Visser* (*National CR*); **UK-England**: J. Rashbass (*National CR*); **UK-Northern Ireland**: A. Gavin* (*National CR*); **UK-Scotland**: D. Morrison (*National CR*); **UK-Wales**: D. W. Huws* (*National CR*).*EUROCARE Steering Committee

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available. See EUROCARE-6 Collaborative Group Rules (http://www.eurocare.it). Requests to access the datasets should be directed to http://www.eurocare.it.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CV designed and carried out the study and analyzed the data; SR and PM did quality controls and analyzed the data; RA and MS designed the study and data quality checks; RM-G, HP, MM, XT, and GP provided advice and revised the results. EUROCARE-6 Working Group collected, prepared, and transmitted raw data for the study database; corrected data after quality controls; and checked the results of the analyses. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.892684/full#supplementary-material

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