Impact and utility of follicular lymphoma GELF criteria in routine care: an Australasian Lymphoma Alliance study

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Abstract

Follicular lymphoma (FL) treatment initiation is largely determined by tumor burden and symptoms. In the pre-rituximab era, the Group d'Etude des Lymphomes Folliculaires (GELF) developed widely adopted criteria to identify high tumor burden FL patients to harmonize clinical trial populations. The utilization of GELF criteria (GELFc) in routine therapeutic decision-making is poorly described. This multicenter retrospective study evaluated patterns of GELFc at presentation and GELFc utilization in therapeutic decision-making in newly diagnosed, advanced-stage rituximab-era FL. Associations between GELFc, treatment given, and patient survival were analyzed in 300 eligible cases identified between 2002-2019. One hundred and sixty-three (54%) had ≥1 GELFc at diagnosis. The presence or cumulative number of GELFc did not predict progression-free survival in patients undergoing watch-and-wait (W&W) or those receiving systemic treatment. Of interest, in patients with ≥1 GELFc, 16 of 163 (10%) underwent initial W&W (comprising 22% of the W&W cohort). In those receiving systemic therapy +/- radiotherapy, 74 of 215 (34%) met no GELFc. Our data suggest clinicians are using adjunctive measures to make decisions regarding treatment initiation in a significant proportion of patients. By restricting FL clinical trial eligibility only to those meeting GELFc, reported outcomes may not be applicable to a significant proportion of patients treated in routine care settings.

Introduction

Follicular lymphoma (FL) is the most common indolent B-cell non Hodgkin lymphoma, with a median survival approaching two decades.[1,2] Advanced-stage disease is present at diagnosis in up to 90% of cases and treatment initiation in these is predominantly determined by the patient's tumor burden and symptomatology; high-burden or symptomatic disease is generally managed with immunochemotherapy-based regimens. Over the past decades substantive improvements have been made to the outcomes of those with FL, with some responders to frontline treatment having similar survival to sex- and age-matched populations. Despite this however, many

patients subsequently experience relapse, with treatment causing acute and long-term toxicities.[1,3-5] In contrast, patients with low tumor burden, asymptomatic FL undergo initial surveillance or a so-called 'watch-and-wait' (W&W) approach, based on an absent survival advantage with early treatment initiation in both retrospective and randomized studies.[6-10] The 10% of patients presenting with limited-stage disease often undergo curative-intent radiotherapy.[11-15] In order to optimize long-term outcomes for all FL patients, the basis for a decision to treat, and its timing, are key.

In the pre-rituximab era, the French Groupe d'Etude des Lymphomes Folliculaires (GELF) established criteria for a standardized definition of the level of tumor burden requiring systemic treatment.[16] Patients required one or more of the following characteristics to be considered 'high' tumor burden according to GELF: any tumor mass >7 cm diameter; ≥3 nodal sites (each >3 cm diameter); B symptoms; splenomegaly; compression syndrome; serous effusion; leukemic phase or any peripheral blood cytopenias. These were then adopted globally by clinical trials of systemic therapy to define eligibility, including recent phase III studies informing modern therapy.[17,18] Additionally, multiple international guidelines such as European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) refer to GELF criteria (GELFc) to determine prompt initiation of active therapy in routine care.[19,20] Similar criteria defined by other groups including the British National Lymphoma Investigation (BNLI) group[21] and the Gruppo Italiano Midollo Osseo (GITMO)[22] have also been utilized, however GELFc remain the single most widely implemented tumor-burden assessment tool in modern-era FL trials. In more recent years, elevated lactate dehydrogenase (LDH) and β-2-microglobulin (B2MG) have been added to the traditional GELFc; the "modified GELF" (mGELF), however its use in clinical trials eligibility and guidelines is not uniform.

In the rituximab era, the utility of GELFc in therapeutic decisions by clinicians outside of a clinical trial context is poorly understood. Additionally, the impact on survival outcomes of the number of GELFc at presentation, is unknown. As enrolment for most modern FL trials restrict populations to those with at least 1 GELF criterion, benefits of newer therapies remain uncertain in patients with FL but absent GELFc, deemed to require treatment for other reasons. Despite this uncertainty, regulatory approvals for new treatments do not currently limit drug access to patients diagnosed with FL with GELFc present. In our large, multicenter study, we describe the frequency and patterns of GELFc in Australian patients with newly diagnosed, advanced stage, grade 1-3A FL treated in a routine care setting, both using W&W and upfront therapy strategies; additionally, we report the prognostic impact of presenting with one or more GELFc at diagnosis.

Methods

This was a multicenter, retrospective, observational study. Patients aged 18 years or older with newly diagnosed, advanced stage, grade 1-3A FL were identified from two institutional prospective databases between 2002-2019 and ten sites contributed data from the Australian and New Zealand Lymphoma and Related Diseases Registry (LaRDR) from 2016-2022.[23] Duplicate cases were identified and deleted. Advanced stage was defined as stage III-IV disease and stage II disease that was not amenable to definitive radiotherapy. Those with a history of grade 3B FL and/or diffuse large B cell lymphoma (DLBCL) were excluded. Data collected from hospital electronic patient records included baseline patient characteristics, details of disease presentation (FL histological grade, Ann Arbor stage, individual GELFc parameters), treatment details and outcomes. Whilst no strict individual drug access criteria for treatment are employed in Australia, or uniformly at participating sites, all sites followed evidence-based guidelines in management of patients and discussed all cases at a dedicated lymphoma multidisciplinary meeting to decide management.

The primary objective of the study was to describe the presence of GELFc in patients with newly diagnosed FL according to upfront treatment delivered (W&W or initial local or systemic treatment). Secondary outcomes included frequency of GELFc and the impact of the number of GELFc present at diagnosis on progression-free survival (PFS) and overall survival (OS). PFS was defined as time from diagnosis to progression or death. OS was calculated from time of diagnosis to death. Survival analyzes were performed according to the Kaplan-Meier method.[24] Differences in patient, disease and management related characteristics among groups (no GELFc *vs*. ≥1 GELFc) were analyzed using the Fisher exact test for discrete variables and the Kruskal-Wallis H test for continuous variables. The impact of GELFc on PFS was analyzed using the Cox proportional hazard model. Variables with $P<0.1$ on univariable analysis were included in the multivariable analysis, with $P<0.05$ considered statistically significant. All statistical analysis was performed using Stata statistical software. Data collection and transmission was compliant with local regulations and is included in the LaRDR protocol approved by Monash Health Human Research Ethics Committee (HREC/16/MonH/74).

Results

Baseline characteristics

Three hundred and eighty-five patients were identified from 12 Australian centres. Of these, 300 patients fulfilled eligibility criteria for inclusion in the study. Reasons for exclusion included incomplete GELFc data in eight, no staging

recorded in three, stage I disease in 65 and stage II disease receiving definitive radiotherapy in nine. Of those receiving systemic therapy, 239 of 240 had immunochemotherapy and one of 240 had rituximab monotherapy, which was reflective of regulatory approvals for therapy in Australia at the time of study (i.e., rituximab was required to be given with chemotherapy for indolent lymphoma). Baseline patient characteristics and initial treatment strategies are summarised in Table 1.

At diagnosis, 163 (54%) cases met at least one GELFc, with 1, 2 or ≥3, GELFc present in 91 (56%), 43 (26%), and 29 (18%) of cases respectively. Due to the small numbers with ≥3 GELFc, those with ≥2 GELFc were analyzed together. Those with GELFc had a significantly higher proportion of patients with elevated baseline LDH and B2MG, extranodal site involvement and bulk >7 cm (Table 1).

GELF according to treatment group

Table 2 summarizes the number of GELFc stratified by treatment approach. Of those with ≥1 GELFc present, 10% (16/163) underwent W&W as an initial strategy. In contrast, 54% (74/137) of patients who met no GELFc underwent initial systemic therapy +/- radiotherapy. Of note, despite systemic therapy being recommended by international guidelines for patients with high-burden disease according to GELFc, 22% (16/73) of the W&W cohort, and 50% (6/12) of the low-dose radiotherapy-alone group respectively, met one or more GELF criteria. Conversely, in the cohort that received systemic therapy +/- radiotherapy, 34% (74/215) met no GELF criteria. While there was a numerical difference in the median age of patients with GELFc managed with W&W (67 years) and those treated with systemic therapy +/- radiotherapy (62 years), this did not reach statistical significance (*P*=0.34).

In patients with no documented GELFc who received systemic therapy +/- radiotherapy, reasons for treatment were available in 15 of 74 (20%) and included: pain associated with enlarged lymph nodes, cosmesis, nausea, fatigue and clinical suspicion for higher grade transformation which was based on factors including the size of the nodal mass, rapid growth trajectory, and high maximum standardized uptake values on positron emission tomography imaging.

Table 3 overviews the frequency of each GELF criterion corresponding to management strategy. The most common GELFc present was tumor mass >7 cm which was present in 26% of all cases; of these, 5% were managed with W&W.

Table 1. Patient, disease and management characteristics.

	Whole cohort	GELF criteria			
Characteristic	**N=300**	**No GELF N=137**	**1 GELF N=91**	**≥2 GELF N=72**	***P***
Age in years					
median (range)	62 (24-92)	63 (27-92)	64 (24-87)	62 (37-89)	0.86
>60 years, N (%)	171 (57)	76 (44)	55 (32)	40 (23)	0.78
Sex, N (%)					
Male	158 (53)	71 (45)	45 (28)	42 (27)	0.50
Stage at diagnosis, N (%)					
II	42 (14)	26 (62)	11 (26)	5 (12)	0.05
III/IV	258 (86)	111 (43)	80 (31)	67 (26)	
Performance status, N (%)					
ECOG 0-1	263 (94)	120 (46)	80 (30)	63 (24)	0.78
ECOG 2-3	18 (6)	9 (50)	4 (22)	5 (28)	
LDH >ULN, N (%)	82 (29)	24(29)	33 (40)	25 (30)	0.06
B2MG >ULN, N (%)	56 (32)	16 (29)	16 (29)	24 (42)	<0.001
>5.0x10^9/L circulating lymphoma cells, N (%)	8 (3)	0 (0)	2 (25)	6 (75)	<0.001
Extranodal site, N (%)	130 (43)	44 (34)	44 (34)	42 (32)	0.001
Bulk >7 cm, N (%)	79 (26)	0 (0)	30 (38)	49 (62)	<0.001
FLIPI score, N (%)					
Low (0-1)	93 (33)	52 (56)	26 (28)	15 (16)	0.001
Intermediate (2)	84 (30)	40 (48)	22 (26)	22 (26)	
High (3-5)	102 (37)	29 (27)	39 (38)	34 (33)	
Treatment strategy, N (%)					
Watch-and-wait	73 (24)	57 (78)	13 (18)	3 (4)	<0.001
Systemic therapy +/- RT	215 (72)	74 (34)	74 (34)	67 (32)	
RT alone	12 (4)	6 (50)	4 (33	2 (17)	

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; B2MG: beta-2 microglobulin; cm: centimeters; FLIPI: Follicular Lymphoma International Prognostic Index; GELF: Groupe d'Etude des Lymphomes Folliculaires; RT: radiotherapy.

Table 2. GELF criteria by treatment group.

Management	N of GELF criteria							Total
	0	1	2	3	4	5	6	
Watch-and-wait, N	57	13	2	0	0	1	0	73
Systemic therapy +/- RT, N	74	74	39	20	6	1	1	215
RT alone, N	6	4	2	0	0	0	0	12
Total, N	137	91	43	20	6	2	1	300

GELF: Groupe d'Etude des Lymphomes Folliculaires; RT: radiotherapy.

Table 3. Distribution of GELF criteria present by management group.

Management strategy	Specific GELF critereon							
	Mass >7 cm N=79	≥3 sites each >3 cm diameter N=47	B symptoms N=46	Splenomegaly compression		Effusion N=20	Leukemic phase N=8	Cytopenias N=5
				N=27	N=45			
Watch-and-wait, N (%)	4 (5)	5 (11)	7 (15)	2 (7)	1 (2)	1 (5)	1 (12)	1 (20)
Systemic therapy +/- RT, N (%)	73 (92)	42 (89)	35 (76)	24 (89)	43 (96)	19 (95)	7 (88)	4 (80)
RT alone, N (%)	2 (3)	0 (0)	4 (9)	1 (4)	1 (2)	0 (0)	0 (0)	0 (0)

GELF: Groupe d'Etude des Lymphomes Folliculaires; cm: centimeters; RT: radiotherapy.

The most common GELFc present in the W&W cohort was the presence of B symptoms (10%).

Survival analysis

Median follow-up was 5 years (range, 0.8-18.4) with a 5-year PFS and OS of 77% (95% confidence interval [CI]: 71-82) and 90% (95% CI: 86-93) respectively. In both the W&W and the systemic therapy +/- radiotherapy cohorts, the number of GELF criteria present at diagnosis did not predict PFS outcomes (W&W hazard ratio [HR]=1.26, 95% CI: 0.60-2.64, *P*=0.53; systemic therapy +/- radiotherapy HR=1.27, 95% CI: 0.91-1.76, *P*=0.16) (Figure 1A, B). When analyzed by treatment type, there was no statistically significant difference in PFS between patients with no GELFc and those with ≥1 GELFc in both the W&W and systemic therapy +/- radiotherapy groups (W&W group PFS: HR=1.12, 95% CI: 0.40-3.16, *P*=0.83; systemic therapy +/- radiotherapy group PFS: HR=1.63, 95% CI: 0.89-2.98, *P*=0.10). There were insufficient numbers in the radiotherapy alone group for detailed subgroup analysis.

Modified GELF criteria (GELFc with lactate dehydrogenase and β-2-microglobulin) sub-group analysis

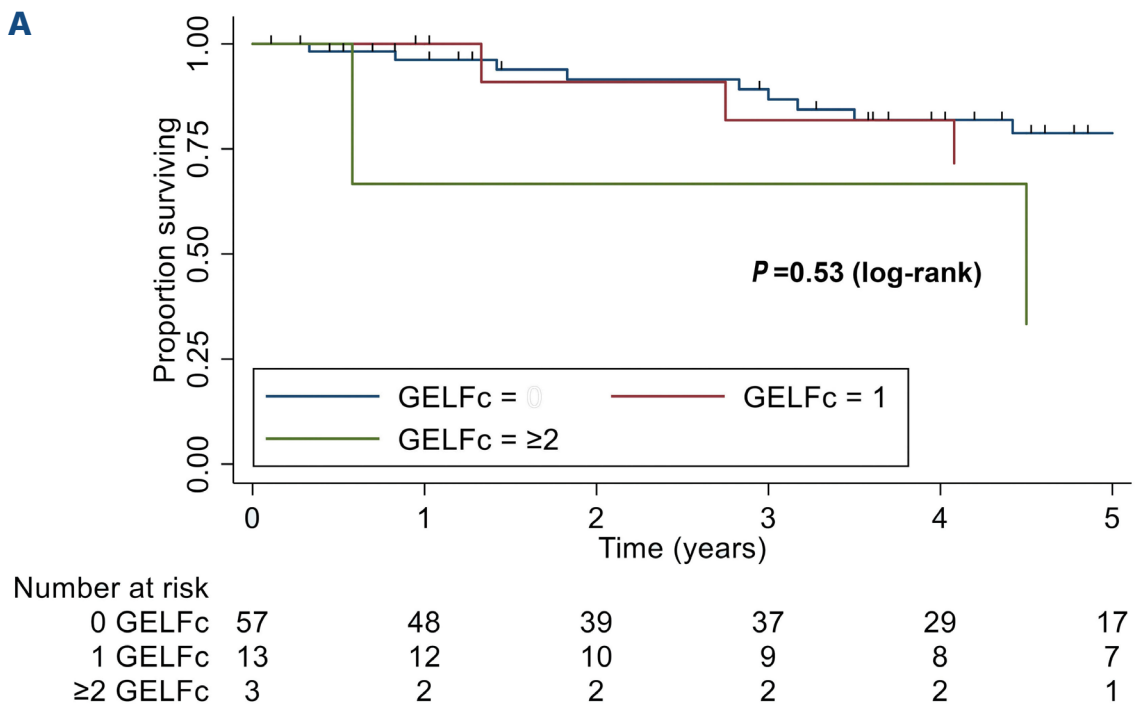
One hundred and seventy-three of 300 (58%) patients had complete data for analysis of the mGELF. 122 of 173 (71%) cases met at least one mGELFc, with 1, 2 or >3, mGELFc present in 53 of 122 (43%), 25 of 122 (21%), and 44 of 122 (36%) of cases respectively. A summary the number of mGELFc by treatment approach is available in the *Online Supplementary Appendix (Online Supplementary Table S1*).

Of those with ≥1 mGELFc present, 19% (22/122) underwent W&W as an initial strategy. The most common mGELFc in the untreated group were elevated B2MG, LDH and B symptoms with LDH and/or B2MG being the only criteria in ten of 23 cases. In contrast, 55% (28/51) of patients who met no mGELFc underwent initial systemic therapy +/- radiotherapy. The most common mGELFc in the treated group were elevated B2MG, LDH and bulk >7 cm with LDH and/or B2MG being the only criteria in 13 of 121 cases (details in the *Online Supplementary Appendix*; *Online Supplementary Table S2*).

In both the W&W and treated groups, the presence of and the number of mGELFc at diagnosis did not predict PFS outcomes. For the W&W cohort the PFS HR were as follows; no mGELFc *versus* ≥1 mGELFc: HR=0.88, 95% CI: 0.26-2.92, *P*=0.83; 0 mGELFc *versus* 1 mGELFc *versus* ≥2 mGELFc: HR=1.16, 95% CI: 0.49-2.72, *P*=0.74. For those receiving systemic therapy +/- radiotherapy the PFS HR is as follows; no mGELFc *versus* ≥1 mGELFc: HR=1.36, 95% CI: 0.60-3.06, *P*=0.46; 0 mGELFc *versus* 1 mGELFc *versus* ≥2 mGELFc: HR=1.18, 95% CI: 0.74-1.86, *P*=0.49.

Discussion

GELFc is the most commonly used determination of disease burden in modern FL trials and treatment guidelines. In this national, multicenter, retrospective study, we analyzed the presence of GELFc according to upfront treatment strategy in newly diagnosed, advanced-stage, grade 1-3A FL patients in the rituximab era. Despite inter-



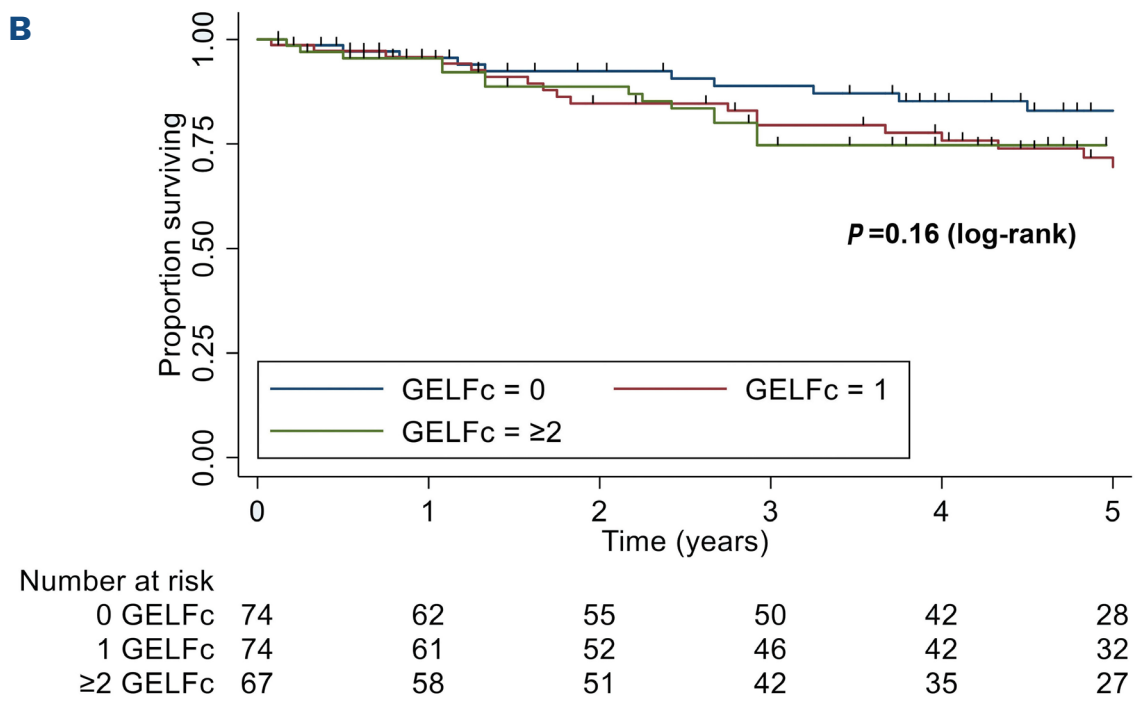


Figure 1. Progression-free survival according to upfront management and GELF. (A) Progression-free survival in watch-and-wait (W&W) patients according to number of Groupe d'Etude des Lymphomes Folliculaires criteria (GELFc) present. (B) Progression-free survival in treated patients according to number of GELFc present.

national guidelines recommending patients meet at least one GELFc prior to proceeding with treatment, 22% of our W&W cohort (16/73) met ≥1 GELFc, and 34% (74/215) treated with systemic therapy +/- radiotherapy met no GELFc at the time of treatment initiation. Our cohort exhibited comparable baseline demographics, PFS and OS to those of published FL trial populations which used GELFc to determine eligibility.[17,18] The high frequency of GELFc present in our W&W cohort is consistent with recently published data.[25] The most common GELFc in our W&W group was the presence of B symptoms (7/73) followed by >3 nodal sites each >3 cm diameter (5/73) and then tumor mass size >7 cm (4/73).

Our study demonstrates that clinicians are not only deferring therapy in almost one quarter of patients meeting GELFc but also using adjunctive or alternative factors to GELFc when recommending upfront treatment. One third of FL patients who received treatment had no demonstrable GELFc in our analysis. Triggers for pursuing treatment were available in 20% of our patients, and included patient factors such as nausea, cosmesis, nodal pain and fatigue. Clinician-driven factors included concern for high grade transformation based on metabolic imaging or disease growth trajectory. These results support the notion that clinicians are using additional information as they consider the risks and benefits of commencing active therapy in

their patients. Notably, there was no difference in median age between patients who were initially observed *versus* treated. The population undergoing therapy in the absence of GELFc is not represented in recent practice-changing randomized studies that led to the regulatory approval for upfront obinutuzumab-chemotherapy and rituximab-lenalidomide combinations.[17,18] Thus, the applicability of these results to patients without GELFc remains to be elucidated. Criteria such as GELF, BNLI and GITMO assist in ensuring that FL patients enrolled into clinical trials warrant treatment and provide a degree of trial cohort homogeneity to minimise bias but vary considerably in their contribution to prognosis. Yet, reasons for treatment, the specific GELFc present within trial populations, or their prognostic implications, are poorly reported alongside trial outcomes.

The prognostic value of GELFc in the rituximab era is not well established. In our analysis of both treated and untreated patients with FL, both the presence ≥1 GELFc compared to no GELFc or an increasing number of GELFc at diagnosis did not influence PFS. Our data supports the finding from Khurana *et al*., that the presence of GELFc do not confer inferior outcomes in patients assigned to W&W.[25] Approximately 50% of the dedicated W&W cohort analyzed by Khurana and colleagues demonstrated at least one 'treatment initiation' criterion at diagnosis (a combination of GELFc, GITMO or BNLI criteria) and these patients were not more likely to commence therapy in the first 5 years, undergo transformation to diffuse large B-cell lymphoma or experience higher rates of lymphoma-related death.[25] The higher proportion of those with 'treatment initiation criteria' compared with our study is likely due to our analysis being limited to GELFc alone.

Factors other than the presence, or total number of GELFc are clearly influencing prognosis in the modern era, particularly in W&W patients and must be better elucidated to form part of the decision-making for trials and routine care in patients with FL. Importantly, our W&W cohort results, taken together with those from Khurana *et al*., suggest a proportion of patients with common GELFc, particularly isolated asymptomatic tumor bulk, or mGELF criteria such as elevated LDH or B2MG, are at potential risk of over-treatment, unnecessary acute and long term toxicity and adverse quality of life outcomes, if enrolled into upfront systemic therapy trials.[16,26,22,27]

The limitations of our study include the retrospective nature as well as institutional variation in follow-up and restaging intervals. Our study findings can only be generalizable to those treated with combination chemoimmunotherapy, as only one patient received rituximab monotherapy, and none received lenalidomide and rituximab. Moreover, clinically assessed GELFc such as compression syndromes and serous effusions may not have been uniformly defined or captured in hospital records. The additional mGELF criteria, LDH and B2MG, were available in only 58% of cases, likely reflecting its absence from guidelines; thus, the mGELF sub-analysis may be impacted by low case numbers and bias from varied clinician use of LDH and B2MG. Reasons for treatment in those with absent GELFc were also not captured routinely, and data are limited. The moderate median follow-up time limits the ability to examine the true effect of clinical therapeutic decision-making on long-term outcomes, but our study does reflect the decisions of contemporary routine care.[28] While the treatment heterogeneity in our cohort reflects practice for the study period; low case numbers in each subgroup causes challenges in drawing any firm conclusions regarding the prognostic impact of cumulative GELFc.

Further prospective analyzes to confirm our findings could assist in modifications to trial eligibility and clinical care criteria for therapy. Additionally, advances in molecular and other biological prognostic data are likely to contribute to stratifying patients for W&W *versus* upfront therapy.[29] Our data have already led to broadening of eligibility criteria and data capture of our own FL trials to incorporate and report reasons for treatment within patient eligibility and trial registration requirements beyond GELFc.[30,31]

In conclusion, our findings suggest that for a significant proportion of newly diagnosed patients with FL treated with immunochemotherapy, the initial decision regarding W&W *versus* systemic treatment relies on adjunctive and alternative factors to GELFc and thus questions the ongoing sole use of GELFc to determine treatment justification as part of clinical trial eligibility. Broader eligibility criteria are important to ensure applicability of trial results to patients treated in routine care and details of treatment triggers need to be documented in both clinical and trial settings. Future research needs to focus on biological factors which influence trial enrolment, stratification and clinical decision making in order to refine management of this complex disease.

Disclosures

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Contributions

AB and EAH designed the study, performed data collection, management, and analysis, and wrote the manuscript. SA performed data management and analysis and co-wrote the manuscript. EY, CYC, DT, BN, FT, JH, CK, ML, TC, AMJ, MD, and JT contributed data and co-wrote the manuscript. SO, ZKM, EMW, GSG, and GC co-wrote the manuscript.

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Data-sharing statement

Access to data that support the findings of this study are available from the LaRDR with permission from the Steering Committee and in accordance with the LaRDR Data Access Policy. More information is available at lardr.org or via email, sphpm-lymphoma@monash.edu. Additional original institutional data will be shared on requests made by emailing the corresponding author.

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