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Multicentre retrospective study of intravascular large B-cell lymphoma treated at academic institutions within the United States

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Summary

Intravascular large B-cell lymphoma (IVLBCL) is a rare entity, with a generally aggressive course that may vary based on geographic presentation. While a United States (US) registry study showed relatively good outcomes with IVLBCL, clinicopathological and treatment data were unavailable. We performed a detailed retrospective review of cases identified at 8 US medical centres, to improve understanding of IVLBCL and inform management. We compiled data retrieved via an Institutional Review Board-approved review of IVLBCL cases identified from 1999 to 2015 at nine academic institutions across the US. We characterized the cohort's clinical status at time of diagnosis, presenting diagnostic and clinical features of the disease, treatment modalities used and overall prognostic data. Our cohort consisted of 54 patients with varying degrees of clinical features. Adjusting for age, better performance status at presentation was associated with increased survival time for the patients diagnosed *in vivo* (hazard ratio: 2·12, 95% confidence interval 1·28, 3·53). Based on the data we have collected, it would appear that the time interval to diagnosis is a significant contributor to outcomes of patients with IVLBCL.

Keywords: lymphomas, diagnostic haematology, B cells.

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Key Points

- IVLBCL is a rare subset of DLBCL that presents a unique diagnostic dilemma that delays diagnosis and impacts outcome.
- Improvements in diagnostic testing are needed to improve time from symptom onset to diagnosis in an effort to improve clinical outcomes.

Intravascular large B-cell lymphoma (IVLBCL) is a rare disease with a body of literature built primarily upon single case studies and a collection of small case series. Initially described by Pfleger and Tappeiner (1959), IVLBCL is now recognized as a distinct subtype of mature B-cell lymphoma. The disease is characterized by lymphomatous involvement of small vessels, typically without significant or any extravascular disease, with a high incidence of central nervous system (CNS) involvement.

The ability of IVLBCL to affect any organ system is well documented, and the resulting occlusion of the microvasculature in the afflicted organ makes the signs and symptoms of the disease particularly heterogeneous and notoriously difficult to diagnose. Previous retrospective studies have recognized the presence of distinct phenotypes within the disease. The Classical, or Western, variant presents with evidence of neurological involvement and cutaneous findings (Ferreri *et al*, 2004) The Asian variant is associated with bone marrow infiltration and haemophagocytic syndrome without overlapping classical features (Murase *et al*, 1997, 2000). A 'cutaneous variant', representing isolated limited skin involvement, was described by Ferreri *et al* (2004) and tends to occur in young female patients with retained performance status.

Historically, IVLBCL has been known to have a rapidly progressive and fatal course. To date, no diagnostic markers or imaging studies have been validated to detect the presence of IVLBCL, and diagnosis requires biopsy of an affected organ. As such, patients frequently present for treatment late in the disease course with disseminated involvement. A previous study from Japan appeared to indicate that treatment could be improved with the addition of rituximab to frontline therapy (Shimada *et al*, 2008), but this has yet to be verified in any large studies. In Western variants, survival was markedly better in those able to receive standard anthracycline-based therapy plus rituximab (3-year overall survival [OS]: 89% vs. 38%; Ferreri *et al*, 2008). The cutaneous variant is associated with better outcomes potentially due to its underlying biology *versus* visible evidence of disease leading to more accessible sites for biopsy (Ferreri *et al*, 2004; Röglin & Böer, 2007). A significant number of IVBCL cases (34–60%) are first diagnosed at time of autopsy depending upon the affected organ systems.

Given the overall rarity of the disease, with an incidence recently estimated at 0·095 per 1 million per year (Howlader et al, 2018), no prospective studies have evaluated treatment strategies. Emerging work has demonstrated that with timely treatment, particularly with the addition of CD20-directed therapy, outcomes may be more similar to those seen in diffuse large B-cell lymphoma (DLBCL) than historically anticipated. Indeed, a recent United States registry study demonstrated that patients with IVLBCL had survival outcomes comparable to DLBCL-not otherwise specified (NOS) in the rituximab era although specific clinical, pathological, and treatment data were unavailable given the nature of the analysis (Rajyaguru *et al*, 2016). In order to gain further insight into the prognosis of IVLBCL and its management, we report on a multicentre, retrospective review of 54 IVLBCL patients diagnosed across nine academic medical centres in the US and compare these data with five previously published studies of IVLBCL.

Methods

We performed a retrospective analysis of data retrieved via IRB-approved review of IVLBCL cases identified at nine academic institutions across the United States. Only adult patients with histologically confirmed IVLBCL between 1999 and 2015 were included.

Collected information included: demographic information, clinical symptoms, date and site of diagnosis, biochemical data, staging information, bone marrow involvement including presence of haemophagocytosis, molecular markers, treatment regimens used (including first, second and third line therapies and transplantation status), and clinical outcomes. The Ann Arbor staging system was used in disease staging. Response to therapy, described as complete remission (CR), sustained disease (SD) or progressive disease (PD), was determined by the contributing institutions.

We collected OS data from five previously published studies of IVLBCL (DiGiuseppe *et al*, 1994; Ferreri *et al*, 2004; Murase *et al*, 2007; Hong *et al*, 2013; Brunet *et al*, 2017). When the patient-level data was not provided in these reports, we used the GraphClick software (http://www.arizona-software.ch/graphclick/) to extract the fitted survival probabilities from the published Kaplan-Meier plots. The studies used various methods to incorporate post-mortem diagnoses, including reporting OS as time from presentation of symptoms to death.

Statistical analysis

Descriptive statistics are presented for continuous and categorical variables. OS was calculated as time from diagnosis to death or loss to follow-up. Patients in our study population were retrospectively grouped into two categories: post-mortem diagnosis (i.e. OS of "0 months") or *in vivo* diagnosis. Survival curves and median survival time were estimated using the Kaplan-Meier method, both for all patients and the subset of patients who were recorded to have received treatment. We fit univariable Cox proportional hazard models for patients diagnosed *in vivo* to determine the associations of

sex, white blood cell count, International Prognostic Index (IPI), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and lactate dehydrogenase (LDH) per 100-unit increase with survival, adjusting for age. All analyses were conducted in R version 3.4.3 (R Core Team 2018).

Results

Patient demographics

Our cohort consisted of 54 patients, including 23 men and 30 women (Male:Female ratio of 0·77 and one individual whose sex was not recorded), with varying degrees of clinical data available (Table 1). Race and ethnicity of individual cases were unknown. Median age at time of diagnosis was 63 years (range 40–88 years). For patients with performance status (PS) data available, the median ECOG PS at presentation was 2, with 62% of patients having PS greater than 1. For deceased patients/those diagnosed post mortem, we utilized the PS from the time of initial presentation/hospitalization. Of the 17 patients with scores of 0–1, 7 (41%) were noted to have primarily cutaneous findings. Staging per the Ann Arbor staging system (Rosenberg, 1977; Moormeier *et al*, 1990) was available for 45 patients, with all but 6 (87%) presenting with stage IV disease.

The most common symptom type was non-specific systemic B-symptoms, such as fevers, night sweats or weight loss for 29 of the 44 patients assessed (66%). Neurological symptoms were present in 41% (18/43) of patients and included altered mental status or confusion (23%), weakness (18%), headache (14%), stroke symptoms (12%), paresthesia (9%), vision changes (9%) and seizure (5%). Skin involvement, including rash, cutaneous nodules and haemangiomas, was seen in 9 patients (21%). Respiratory symptoms including shortness of breath, cough and respiratory failure were noted in 21% of patients ($n = 9$). Gastrointestinal symptoms consisted of abdominal pain ($n = 3$) and ascites ($n = 1$). Two patients had evidence of endocrinopathy on presentation, including panhypopituitarism ($n = 1$) and goitre ($n = 1$). Imaging data was not available for correlation of presenting symptoms or organ involvement with specific radiographic findings.

Primary diagnosis was made at time of autopsy in 6 patients and *in vivo* for 35 patients. Time of diagnosis was not available for the remaining patients. The most common site of disease identification *in vivo* was in the CNS, either by brain biopsy ($n = 10$) or identification of atypical cells in the cerebrospinal fluid ($n = 2$). The bone marrow was the primary diagnostic site in 10 patients. Of the 11 patients that were diagnosed by skin biopsy, only 9 patients had documented cutaneous findings at that time. Other sites of primary pathological diagnosis included lung ($n = 5$), liver ($n = 3$), gastrointestinal tract ($n = 3$), muscle ($n = 3$), spleen ($n = 2$), genito-urinary tract ($n = 2$), temporal artery ($n = 2$) and thyroid ($n = 1$).

A total of 43 patients had record of a bone marrow biopsy performed with 26 (60%) patients having IVLBCL in the bone marrow. Haemophagocytosis was seen in 12% of patients ($n = 5$); 15% of the total patients had unreported data ($n = 8$). Organomegaly was present in 20 patients and in 58% of patients with bone marrow involvement. Conversely, for those with organomegaly who underwent bone marrow biopsy, 93% had concurrent bone marrow involvement (14/15). The occurrence of bone marrow involvement in patients without organomegaly was 38%.

Immunophenotypic markers that were available for review varied between cases (Table 2). CD5 positivity was seen in 50% of the reported cases ($n = 28$). CD10, MUM1 and BCL6 were used to determine cell of origin (COO) in 28 patients who had all the required data via the Hans algorithm (Hans *et al*, 2004). Using this algorithm, the COO was determined to be non-germinal centre (GC) B-cell in 82% of these cases. High-risk markers, BCL2 and MYC were evaluated, but collection was sporadic, with MYC being reported in only 8 of the cases with 63% of those being positive. We had a total of 15 reports of BCL-2 expression, with 80% of those being positive. Results of fluorescence *in situ* hybridisation (FISH) testing was not available to evaluate for the occurrence of double hit lymphoma in our population but, given the majority of patients with data classified as non-GC by COO, we would expect very few patients to possess this molecular abnormality. On the other hand, we would expect

Table I. Descriptive statistics. Median (IQR) for continuous data and frequency (% of nonmissing data) for count data is included. $n = 54$

Variable Total stratified	Median (IQR) or *n* (%)	*N* missing (%)
Age (years), $n = 53$	63·0 (55·0, 69·0)	1 (1·9)
Post-mortem diagnosis ($n = 6$)	74·0 (69·8, 79·0)	
In vivo diagnosis ($n = 34$)	61·0 (53·0, 67·6)	
Sex (female), $n = 53$	30 (56·6)	1 (1·9)
Post-mortem diagnosis ($n = 6$)	3 (50·0)	
In vivo diagnosis ($n = 34$)	18 (52·9)	
White blood cell count, $n = 43$	6·0 (3·8, 8·9)	11 (20·4)
Post-mortem diagnosis ($n = 6$)	6·8 (5·0, 8·9)	
In vivo diagnosis ($n = 30$)	5·8 (3·7, 7·7)	
Lactate dehydrogenase, $n = 42$	576·0 (338·5, 1459·8)	12 (22·2)
Post-mortem diagnosis ($n = 6$)	1248·5 (712·8, 1707·8)	
In vivo diagnosis ($n = 27$)	596·0 (303·5, 1405·5)	
International Prognostic Index, $n = 40$	4·0 (3·0, 5·0)	14 (25·9)
Post-mortem diagnosis ($n = 6$)	5·0 (4·2, 5·0)	
In vivo diagnosis ($n = 26$)	3·5 (3·0, 4·0)	
ECOG PS, $n = 45$	2·0 (1·0, 3·0)	9 (16·7)
Post-mortem diagnosis ($n = 6$)	3·5 (3·0, 4·0)	
In vivo diagnosis ($n = 31$)	2·0 (1·0, 3·0)	

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

Table II. Available immunophenotypic marker information. Counts are stratified by diagnoses made *in-vivo* or post-mortem

Variable	Positive, *n* (%)	Negative, *n* (%)	Missing, *n*
CD5 Total, *n* = 28	14 (50·0)	14 (50·0)	26
Post-mortem diagnosis	0	2	4
In vivo diagnosis	11	8	16
CD10 Total, *n* = 35	6 (17·1)	29 (82·9)	19
Post-mortem diagnosis	0	3	3
In vivo diagnosis	6	18	11
MUM1 Total, *n* = 21	20 (95·2)	1 (4·8)	33
Post-mortem diagnosis	1	1	4
In vivo diagnosis	12	0	23
BCL6 Total, *n* = 25	14 (56·0)	11 (44·0)	29
Post-mortem diagnosis	0	3	3
In vivo diagnosis	9	6	20
MYC Total, *n* = 8	5 (62·5)	3 (37·5)	46
Post-mortem diagnosis	0	1	5
In vivo diagnosis	2	1	32
BCL2 Total, *n* = 15	12 (80·0)	3 (20·0)	39
Post-mortem diagnosis	1	0	5
In vivo diagnosis	8	1	26

a higher percentage of patients to potentially classify as "double expressers", but with our limited collection of this information in the entire cohort only four patients were noted to have expression of both markers.

Laboratory findings

Patients frequently presented with an elevated LDH at time of first diagnosis (median 576 iu/l), interquartile range 338·0–1459·8). This contributed to a median IPI score at time of diagnosis of 4 (60% of patients presented with high-risk disease by IPI). Cytopenias were frequently seen, with anaemia being the most common at (69%; 29/42) followed by thrombocytopenia (48%; 20/42). Hypoalbuminaemia was frequent among patients with an average albumin level of 28·7 g/l. Abnormalities in serum creatinine or total bilirubin levels were rare.

Treatment regimen

The initial treatment course was known for 36 patients (Table 3). One patient was noted to have received treatment prior to diagnosis. Of the 36 patients who received initial therapy, one was treated with surgery alone, and the remaining patients received some form of chemotherapy treatment, 23 (64%) obtained CR (one patient achieved this response after 2nd line therapy), 2 (6%) of patients had a partial response (PR), 7 (19%) had PD and 4 (11%) had unknown response. A total of 18 patients received either no treatment (*n* = 3), were diagnosed post-mortem and had no record of treatment prior (*n* = 5), or had no clinical data available in records (*n* = 10). A total of 31 patients received anthracycline-based chemotherapy and 31 received CD20-directed therapy with rituximab. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) was the most common initial therapy (*n* = 16) with an additional 4 patients also receiving high dose methotrexate. Other common initial regimens were CHOP (*n* = 4) with 2 patients reaching CR and 2 achieving PR, and R-CODOX-M (rituximab, cyclophosphamide, cytarabine, doxorubicin, vincristine, methotrexate)/R-IVAC (rituximab, ifosfamide, cytarabine,

Table III. Treatments

	Therapy line				Stem cell transplantation	
Regimen	Initial	2nd	3rd	4th	1st remission	2nd remission
CHOP ± R	25				autologous: 7	autologous: 6 allogeneic: 1
R-CODOX-M R-IVAC	4					
R-EPOCH	1	1				
Rituximab/Steroids	2					
R-DeAngelis	1					
R-Hyper-CVAD	1	1				
Steroids/XRT	1					
Surgery	1					
R-MVP		1				
R-ESHAP		1				
ICE ± R		5				
Rituximab		1				
MIME-R		1				

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CODOX-M, cyclophosphamide, cytarabine, doxorubicin, vincristine, methotrexate; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; ICE, ifosfamide, carboplatin, etoposide; IVAC, ifosfamide, cytarabine, etoposide; MIME, mitoguazone, ifosfamide, methotrexate, etoposide; MVP, mitomycin, vinblastine, cisplatin; R, rituximab; XRT, radiotherapy.

Table IV. Overall survival time based on patient inclusion

Cohort	*n*	Events (death)	Median survival time (years)	95% confidence interval
All patients	41	26	1·84	0·33, 8·83
Patients diagnosed *in vivo*	35	20	5·25	0·58, not reached
Patients who received therapy	27	13	5·25	1·84, not reached

etoposide) ($n = 4$) with 3 patients in CR and one death due to sepsis after a single round of therapy. R-EPOCH (rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone) and rituximab + -hyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) were each used in one patient, both achieving CR followed by autologous stem cell transplantation (ASCT). The remaining regimens used were: R-DeAngelis ($n = 1$ with PD), R-prednisone ($n = 1$ with unknown response), R-dexamethasone ($n = 1$ with PD), R-methotrexate (MTX) ($N = 1$ with CR), and 'high-dose steroids' ($n = 1$ with PD).

CNS prophylaxis was provided in 16 (44%) of the patients who received initial therapy (first line) with MTX being used in all cases. Intrathecal MTX was given in 10 of the 16 cases (63%) while in the remaining 37% of the cases ($n = 6$) prophylaxis was provided with intravenous high dose MTX with varying dosages (3·5 8 g). Due to the components of the regimens chosen for induction therapy, some patients did receive cytarabine. Of note, 1 patient received intrathecal cytarabine and three patients received intravenous cytarabine as part of their treatment regimen.

A total of 11 patients received second-line therapy (Table 3). R-ICE (rituximab, ifosfamide, carboplatin, etoposide) was the most common second line regimen (2 CR; 2 SD). Other regimens included hyperCVAD ($n = 1$; CR), R-MVP (rituximab, mitomycin, vinblastine, cisplatin; $n = 1$; unknown response), R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; $n = 1$; PR), ICE ($n = 1$; CR), R-EPOCH ($n = 1$; CR), R-MIME (rituximab, mitoguazone, ifosfamide, methotrexate, etoposide; $n = 1$; PR), and rituximab alone ($n = 1$; PD). A total of 13 patients underwent ASCT, 7 following induction therapy and 6 after a second course of therapy. A single patient underwent allogenic stem cell transplantation following relapse after ASCT.

Survival

Of the 54 total patients in the study, only 41 patients had a recorded survival time. As outlined in Table 4, 6 (15%) were diagnosed post-mortem and 35 (85%) were diagnosed *in vivo*. Sixty five percent (35 patients) of all patients were treated with chemotherapeutic agents. Median OS across all patients was 1·08 years (95% CI 0·11, 8·83). Upon further restricting to the 27 patients who were diagnosed *in vivo* and whose treatment status was available, median OS was 5·25 years (95% CI 1·84, not reached; Figure S1). Comparing these findings to the data that we extracted from previous reports: median OS reported by Brunet *et al* (2017) was approximately 0·14 years (all diagnoses) and 0·88 years (*in vivo* diagnoses); in Hong *et al* (2013) it was 3·24 years (*in vivo* diagnoses); in Ferreri *et al* (2004) it was 0·52 years (all diagnoses); and in DiGiuseppe *et al* (1994), it was 1·33 years (*in vivo* diagnoses, all patients treated with chemotherapy). Figure 1 compares our survival data with that reported by Brunet *et al* (2017) and Ferreri *et al* (2004). The shape of the survival curves across all reports was qualitatively similar (Fig 2), characterized by an initial steep decrease in survival in the first 1–2 years, and a long-term surviving fraction between 20% and 40%. Murase *et al* (2007) only reported survival stratified by CD5 and CD10 status but, consistent with the rest of the data, still found that survival at 7 months was approximately 60%, regardless of CD5/CD10 status, and reported that the 3-year survival rate was 27% for those with *in vivo* diagnosis.

Prognostic factors

Adjusting for age, better performance status at presentation was associated with increased survival time for the patients diagnosed *in vivo* (HR: 2·12, 95% CI 1·28, 3·53; Table 5). Due to high amounts of missing data, we could not determine if biomarkers were significantly associated with survival.

Discussion

While significant advances have been made in the understanding of IVLBCL as a distinct entity within non-Hodgkin lymphomas, the rarity of the disease, its heterogeneity, nonspecific presentation and the limited means available to diagnosis the disease have severely limited improvement in clinical outcomes. Thus, this retrospective review, which represents the largest collection of cases compiled in the United States to date, provides valuable insight into clinical features, outcomes and prognostic factors. A comparison of our findings to those in other recent reports suggests qualitatively similar trends in survival.

This study reaffirms the complex and variable presentation of IVLBCL. No unifying diagnostic signs or symptoms were noted at any of the participating centres, which closely matches previous case reports from other North American populations (Detsky *et al*, 2006; Brunet *et al*, 2017). Of note, neurological and cutaneous involvement was common and, unlike other reported cohorts, our study had much higher rates of bone marrow involvement (60% vs. 28%). Previous

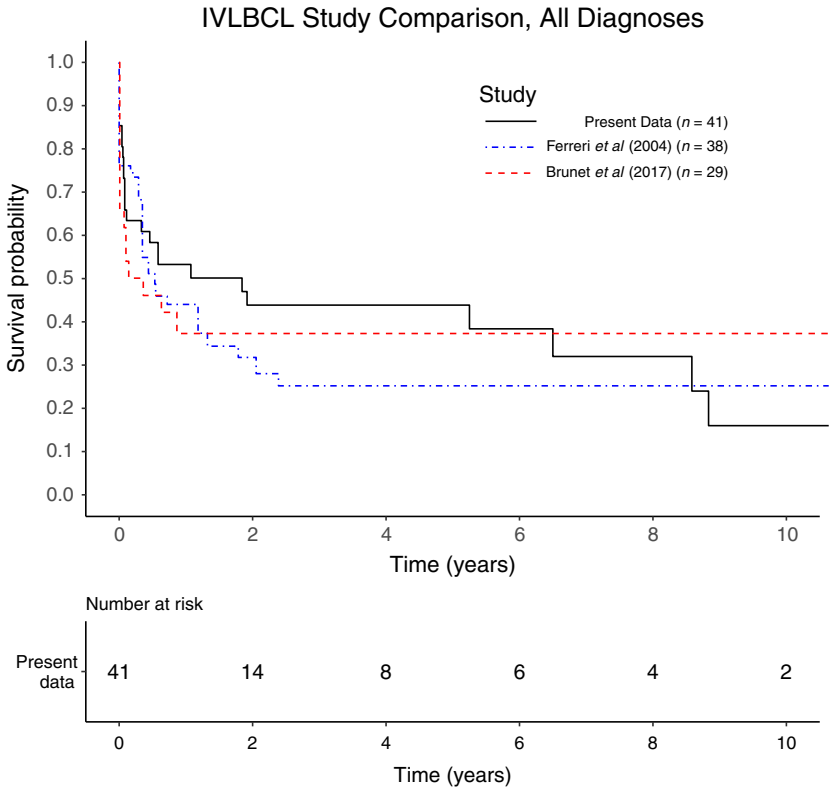

Fig 1. Kaplan-Meier survival curves from the current study and previous literature of all diagnoses including those made post mortem. The studies reported by DiGiuseppe *et al* (1994) and Hong *et al* (2013) are excluded here because they excluded post-mortem diagnoses. [Colour figure can be viewed at wileyonlinelibrary.com]

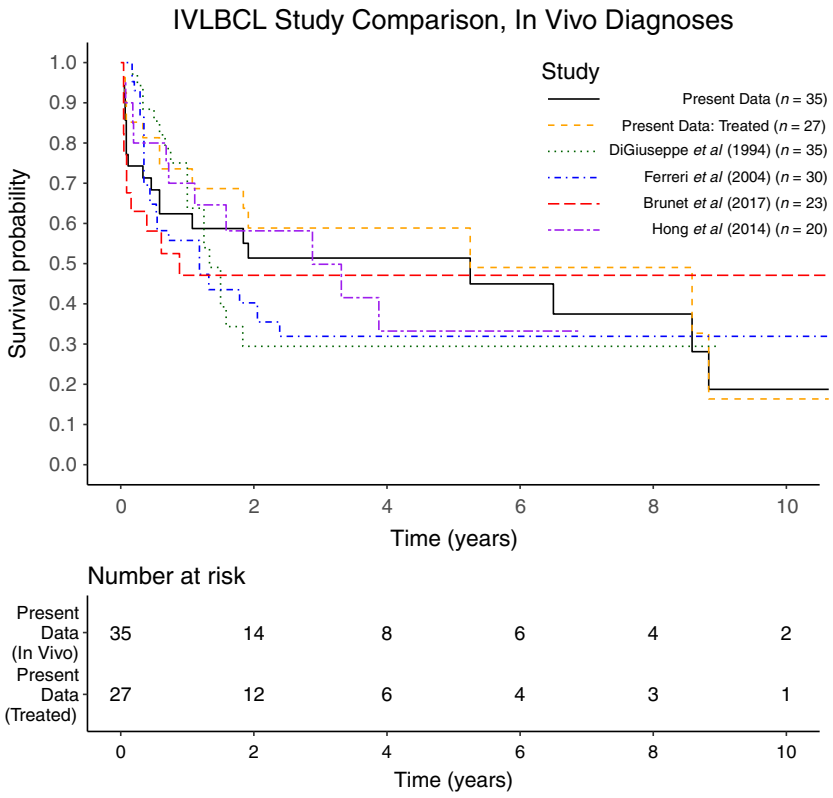

Fig 2. Survival curves from the current study and previous literature of *in vivo* diagnoses. The survival curves from Murase *et al* (2007) could not be recreated due to published survival curves being stratified. Across the subgroups, the survival probability at 7 months reached 60%. [Colour figure can be viewed at wileyonlinelibrary.com]

Table V. Cox regression models for predicting survival after diagnosis fit to the up -to 35 patients diagnoses *in vivo*. All models were adjusted for age at baseline

Variable	*n*	*n* events	Hazard ratio	95% CI	*P*-value
Age	34	19	1·04	0·99, 1·09	0·100
Sex (male)	34	19	2·31	0·91, 5·84	0·093
Lactate dehydrogenase	27	17	1·04	1·00, 1·08	0·079
White blood cell count	29	18	1·03	0·99, 1·06	0·113
International Prognostic Index	25	16	1·49	0·94, 2·37	0·092
ECOG PS	30	16	2·12	1·28, 3·53	0·004

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

retrospective work describing the Asian variant had documented rates of haemophagocytosis reaching 79% (Murase *et al*, 2000). Our study showed that while bone marrow involvement was common in this population, the rate of haemophagocytosis was rare, at 11%. Given that no race or ethnicity information was collected, further correlation to a particular geographic or hereditary background cannot be made and remains a point of further study.

A wide variability of other immunophenotypic markers has been reported. CD5 positivity has ranged from 23 to 76% in prior literature, compared to 50% in the current study. Taking into account the limitation of the data, our results of this case series appears to correspond with previous literature, which has reported a predominantly non- GC COO with a distribution of 80% non-GC and 20% GC (Murase *et al*, 2007; Shimada *et al*, 2008) compared to 83% and 17% in this study. While the presence of BCL2 and MYC by increased protein expression detectable by immunohistochemistry or through genetic rearrangement detected by FISH is known to significantly impact outcome, we are unable to confidently make any connection to the patients in our data set, again due to limitation of this retrospective study.

As recently as 1989, over half of IVLBCL cases were diagnosed post mortem. Our study, in which the vast majority of cases (five cases with post-mortem diagnosis) have *in vivo* data after diagnosis, represents a large shift in earlier recognition of the disease despite a lack of improvement in non-invasive diagnostic tools. As expected, this is probably critical to patient outcomes as ECOG PS at time of diagnosis was independently associated with survival. While the median survival for all patients diagnosed *in vivo* was 5·25 years, this encompasses patients receiving a wide range of treatment modalities and also included those who were unable to receive therapy. In fact, this more closely aligns with the survival historically expected for DLBCL NOS.

In conclusion, while recognizing the limitations of a retrospective study and the variability in available patient data illustrated in Figure S2. This study demonstrates that there is a wide degree of variability in IVLBCL in the United States and its inability to fit into either of the discreet phenotypes previously described. While future studies with larger populations are needed to determine the best approach to therapy, additional research needs to be directed at improving the diagnostic modalities that are available to clinicians who treat DLBCL. Newer diagnostic modalities, such as circulating tumour DNA (ctDNA) have shown potential to detect DLBCL prior to identification using traditional radiographic techniques, such as computed tomography/positron emission tomography and has preliminarily been looked at in this difficult patient population (Kurtz *et al*, 2018; Roschewski, 2015; Roschewski *et al*, 2015; Suehara *et al*, 2017). We believe that techniques might further decrease the time interval from symptom onset to disease diagnosis in these patients. Based on the data we have collected, it would appear that this time interval is an important contributor to patient outcomes, given that longer periods of unrecognized and untreated aggressive lymphoma generally lead to a decline in PS and impact the tolerance and ability of the patient to receive appropriate therapy. It is possible, based on the limitations of this retrospective study with respect to missing data sets, that we could potentially be underestimating the impact that the ability to receive treatment has on this patient population. As it would appear that patients who are able to receive therapy may not have as dismal an outcome as it generally believed with this diagnosis.

Authors contribution

All authors contributed to the data collection at the individual sites. T.P. designed the research. M.S., M.G. and T.P collected the data and collated in a single database. M.G., E.R., P.B., and T.P were responsible for analysis of the data. M.G., E.R., T.P. wrote the paper.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Supporting Information

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

Fig S1. Survival curves from treated patients only in current study.

Fig S2. This missingness plot demonstrates which variable values were available for each patient. The frequency of recorded values is reported for each variable.

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