https://doi.org/10.46765/2675-374X.2025v7n1e351 REVIEW ARTICLE

Effectiveness of dose-intensified regimens in early progressed follicular lymphoma before autologous stem cell transplantation: A systematic review and meta-analysis

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Section editor: Fernando Barroso Duarte

Received: Apr. 27, 2026 • **Accepted:** Nov. 1, 2026

ABSTRACT

Introduction: Despite the substantial advances in the management of follicular lymphoma, approximately 20% of these patients have worse outcomes, experiencing early progression of the disease after induction therapy. Autologous stem cell transplantation may improve survival in this context. Little is known about the optimal salvage regimen. **Purpose:** To evaluate the effectiveness of dose-intensified *versus* standard-dose salvage regimen in adult patients diagnosed with early progressed follicular lymphoma before autologous stem cell transplantation. **Methods:** This systematic review and meta-analysis adhere to the Joanna Briggs Institute methodology for systematic reviews of effectiveness and Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched Medline, Embase, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), Cochrane Library databases and gray literature for eligible studies. **Results:** In total, 494 studies were considered for title and abstract screening. After full review, two studies were eligible for data extraction. Both studies were single arm retrospective cohorts with patients receiving dose-intensified regimens as salvage regimen. Due to missing values, we could not perform a pooled analysis of time-dependent outcomes. We performed a proportional meta-analysis for overall response rate. An *odds ratio* of 0.93 (95% confidence interval 0.81–0.97) was demonstrated using the random-effects model. Data synthesis showed a low degree of heterogeneity. **Conclusion:** Using the GRADE approach, our data suggested that dose-intensified salvage regimens are a feasible option with low certainty of evidence, due to serious risk of bias and serious indirectness.

Keywords: Lymphoma, Follicular; Bone Marrow Transplantation; Drug Therapy.

INTRODUCTION

Follicular lymphoma (FL) is an indolent B-cell neoplasm characterized as a non-Hodgkin lymphoma and ranked as the second most prevalent non-Hodgkin lymphoma in the United States of America and Europe. It has a heterogeneous nature, impacting around 15,000 patients annually in the United States of America[1]. Significant improvement has been made in FL management over the past years, especially after the introduction of rituximab to induction chemotherapy[2–5]. Regardless, around 20% of patients are refractory to or experience

progression of disease (POD) within two years of induction therapy[3,4,6]. Moreover, it has been demonstrated that this subgroup of patients experience worse outcomes when compared to those who relapse later than 24 months after induction therapy[7].

As observed in the PRIMA trial[6], time to progression has emerged as a preeminent prognostic factor, influencing outcomes, even when patients undergo rituximab (R) maintenance. Casulo et al.[7] proposed the term POD24 to identify those patients who experienced POD within 24 months of the induction therapy despite the regimen. In the scientific literature, the term "early therapy failure" has been used interchangeably for the same purpose. These authors have demonstrated a median five-year overall survival (OS) of 50% to the early relapsed or refractory patients, compared to a 90% OS in the non-POD24 group[7].

Furthermore, transformation to a histologically aggressive lymphoma has been observed in approximately 75% of these patients upon relapse, inducing a deterioration in clinical outcomes[8]. New approaches have been investigated as second line treatments, aiming better outcomes. Still, there remains a gap in the availability of these therapies. Considering its effectiveness in treating relapsed indolent and aggressive lymphomas, the use of salvage chemotherapy followed by high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) have been proposed to be an alternative therapeutic option in this context.

A retrospective analysis of two randomized trials, published by the German Low Grade Lymphoma Study Group (the German group), suggested that POD24 patients who presented chemotherapy sensitiveness to salvage regimens and were submitted to HDC and ASCT had improved five-year second line progression free survival (PFS), as well as OS[9]. Using data from patients registered by the Center for International Blood and Marrow Transplant Research (CIBMTR) and by the National LymphoCare Study, Casulo et al.[10] identified two distinct groups: the ASCT group derived from the CIBMTR registry and the non-ASCT cohort obtained from the NCLS[10]. In this study, patients diagnosed with refractory or POD24 FL were included. Patients who presented histologic transformation at the time of relapse were excluded from the analysis. An improved five-year OS rate was observed for patients classified as primary refractory or early relapsed, who underwent HDC and ASCT within one year of treatment failure (73 *versus* 60%, $p = 0.05$).

Although the role of HDC followed by ASCT as a consolidative approach has been consistently proved beneficial in this context, little is known about the optimal salvage regimen as a cytoreductive therapy for these patients. Up to this time, the choice relies on institutional experience, with no published consensus regarding which would result in the best outcomes. Therefore, we searched the literature for data analyzing salvage regimens before HDC and ASCT as a consolidative approach in patients diagnosed with refractory or POD24 FL to establish whether the use of dose-intensified regimens improves outcomes when compared to standard dose regimens. This study protocol was published online and is registered in the PROSPERO platform under the registration number: CRD 42022373345[11].

METHODS

Search strategy and selection criteria

This study is reported based on Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines[12]. Initially, a limited search of Medline, Scopus, Latin American and Caribbean Health Sciences Literature (LILACS), and Cochrane Library was conducted to identify articles on the topic. The full search strategy was developed and adapted to each database. After, we searched Medline, Embase, Scopus, Web of Science, LILACS and Cochrane Library, as well as gray literature source, ClinicalTrials.gov registry, Google Scholar, ScienceDirect, Networked Digital Library of theses and Dissertations, DART-Europe E-theses Portal and Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES) theses banks to locate both published and unpublished studies. The main databases search strategies used were:

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- Web of Science: (("Follicular Lymphoma") OR ("Lymphoma, Follicular")) (Topic) AND (("Early relapse") OR ("Refractory") OR ("POD24")) (Topic) AND (("Autologous Transplantation") OR ("Bone Marrow Transplantation")) (Topic);
- Scopus: TITLE-ABS-KEY-AUTH ("Follicular Lymphoma") OR ("Lymphoma, Follicular" [mesh]) AND TITLE-ABS-KEY-AUTH ("Early relapse") OR ("Refractory") OR ("POD24") AND TITLE-ABS-KEY-AUTH ("Autologous Transplantation") OR ("Bone Marrow Transplantation");
- Embase: TITLE-ABS-KEY-AUTH ("Follicular Lymphoma") OR ("Lymphoma, Follicular" [mesh]) AND TITLE-ABS-KEY-AUTH ("Early relapse") OR ("Refractory") OR ("POD24") AND TITLE-ABS-KEY-AUTH ("Autologous Transplantation") OR ("Bone Marrow Transplantation");
- Medline: (("Follicular Lymphoma" [tw]) OR ("Lymphoma, Follicular" [Mesh])) AND (("Early relapse" [tw]) OR ("Refractory" [tw]) OR ("POD24" [tw])) AND (("Autologous Transplantation" [tw]) OR ("Bone Marrow Transplantation" [tw]));
- LILACS: (Follicular Lymphoma) AND (POD24 or Early Therapy Failure) AND (Bone Marrow Transplant);
- Cochrane Library: ("Follicular Lymphoma") OR ("Lymphoma, Follicular") in Title Abstract Keyword AND ("Early relapse") OR ("Refractory") OR ("POD24") in Title Abstract Keyword AND ("Autologous Transplantation") OR ("Bone Marrow Transplantation") in Title Abstract Keyword (word variations have been searched);
- Google Scholar: (("Follicular Lymphoma") OR ("Lymphoma, Follicular" [Mesh])) AND (("Early relapse") OR ("Refractory") OR ("POD24")) AND (("Autologous Transplantation") OR ("Bone Marrow Transplantation")).

No limitations regarding study language or date of publication were imposed. The structured searches were conducted on October 25th, 2023. Titles and abstracts were screened for assessment against the inclusion criteria. Potentially relevant studies were then retrieved and fully assessed. The study selection process was carried out by two independent reviewers (FPM and GFA), and disagreements were solved through discussion with a third reviewer (AEHN). The reference list of all studies selected for critical appraisal were screened for additional studies. Randomized controlled trials, non-randomized controlled trials, analytical observational studies including prospective and retrospective cohorts, case-control studies, and analytical cross-sectional studies were deemed eligible for inclusion. The limitation about which type of studies to include was made to guarantee less heterogeneity amongst results.

Inclusion and exclusion criteria

This review considered papers that included patients ≥ 18 years old, diagnosed with FL refractory to or experiencing POD24 after induction chemotherapy and who were submitted to HDC and ASCT as consolidation therapy. Studies that evaluated participants with aggressive transformation of indolent lymphoma at relapse, HIV/AIDS infection, estimated glomerular filtration rate < 15 mL/min/1,73 m^2 body surface area or those undergoing renal replacement therapy in their analyses were excluded.

Interventions and outcomes

Patients who were submitted to dose-intensified (*e.g.*, platinum based or ifosfamide based) salvage regimens in presence or absence of anti-CD20 antibodies constituted the intervention arm. Meanwhile, patients submitted to standard-dose (*e.g.*, CHOP or CHOP-like) salvage regimens in presence or absence of anti-CD20 antibodies constituted the control arm. All patients must have been referred to HDC and ASCT as a consolidative approach after the salvage regimen. We considered PFS as the primary outcome to be analyzed. OS, partial response rate, complete response rate, and overall response rate were considered secondary outcomes. All outcomes were assessed in accordance with the International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)[13,14].

Assessment of methodological quality

Eligible studies were critically appraised by two independent reviewers (FPM and GFA) using standardized critical appraisal instruments from Joanna Briggs Institute (JBI) for experimental, quasi-experimental, and observational studies after imported into JBI SUMARI software[15]. Items were rated as "yes," "no," "unclear," or "not applicable" according to information provided by each study. The number of items varied according to the type of study analyzed. Following critical appraisal, studies that did not achieve at least a score of 50% in accordance with the quality assessment JBI instrument mentioned above were excluded. Risk of bias was assessed using the Cochrane Risk of Bias (ROBINS-I) tool for non-randomized studies[16]. Disagreements were resolved through discussion with a third reviewer (AEHN).

Data extraction

Two independent authors (FPM and GFA) extracted the data from the included studies. The following information was extracted: citation, publication year, study design, sample size, median population age, refractoriness (%), number of previous chemoimmunotherapy lines, five-year OS (%), five-year PFS (%), complete response rate (%), partial response rate (%), and overall response rate (%). We contacted authors twice in a 30-day period via e-mail for missing or additional data. Those that did not respond had their papers excluded from the analysis.

Data synthesis

Studies were pooled into JBI SUMARI for statistical analysis, critical appraisal, and risk of bias assessment[15]. Heterogeneity was assessed statistically using the standard χ^2 test and I-squared (I^2) test. The p-value < 0,05 in the χ^2 test presumed the presence of heterogeneity. The inconsistency calculation (I^2) measured the depth of heterogeneity among the studies as follows: 0–30% indicated no major heterogeneity; 30–40% indicated moderate heterogeneity; 50–90% indicated substantial heterogeneity; and 75–100% indicated major heterogeneity. The random-effects model was chosen due to high clinical and methodological variability between studies. We reported the findings in narrative form where statistical analysis was not possible.

RESULTS

Studies characteristics and risk of bias

The search of databases yielded 340 studies, while the search of gray literature yielded 154 papers. Of these, 128 duplicates were removed. After reviewing titles and abstracts, 24 articles were identified as potentially eligible for inclusion. After full review, nine studies were deemed eligible. Reasons for exclusion can be found in Chart 1.

Regarding additional or missing data, seven of these studies presented the need to e-mail their authors. Three responded claiming not to have the specific data needed, and four did not answer. Two out of the nine studies had the intended data and were considered for data extraction (Fig. 1).

The total number of patients included was 51. One of the studies did not present the median age of the sample. All patients had the diagnosis of POD-24 relapsed FL, histologically graded from 1 to 3A, and none had a refractory disease. Both studies included were single-arm retrospective cohorts, thereby not having a control arm and reflecting specific center experience on treating such patients. All patients analyzed were submitted to intensive-dose salvage regimens comprising gemcitabine, dexamethasone, and cisplatin; ifosfamide, carboplatin, and etoposide; dexamethasone, cytarabine, and cisplatin or oxaliplatin (DHAP/Ox) in presence or absence of anti-CD20 antibodies. Using JBI critical appraisal tool for retrospective cohorts, both studies obtained a score higher than the previously established value of 50% in accordance with the

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Chart 1. Reasons for exclusion after screening titles and abstracts.

Citation	Study design	Reason for exclusion
Jurinovic et al.[9]	Retrospective analysis	Salvage regimen not stratified according to being POD24 and receiving HDC and ASCT.
Casulo et al.[10]	Retrospective analysis	Data on survival and response not stratified according to salvage regimens.
Sebban et al.[17]	Retrospective analysis	Missing data on salvage regimen.
Manna et al.[18]	Retrospective analysis	Missing data on salvage regimen.
Klyuchnikov et al.[19]	Retrospective analysis	Missing data on salvage regimen. Survival and response analysis not stratified for time of relapse.
Lunning et al.[20]	Retrospective analysis	Missing data on salvage regimen.
Muntañola et al.[21]	Retrospective analysis	Patients diagnosed with POD24 FL not eligible for HDC and ASCT included in response analysis. Survival analysis did not stratify into early relapse or late relapse.
van Besien et al.[22]	Retrospective analysis	Patients who received HDC and ASCT in the induction regimen included.
Kirschey et al.[23]	Phase II clinical trial	Patients not classified according to time of relapse.
Evens et al.[24]	Retrospective analysis	Patients not classified according to time of relapse.
Keeney et al.[25]	Retrospective analysis	Patients not classified according to time of relapse. Missing data on salvage regimen.
Arcaini et al.[26]	Phase II clinical trial	Patients not classified according to time of relapse.
Jiménez-Ubieto et al.[27]	Retrospective analysis	Missing data on salvage regimen.
Peters et al.[28]	Retrospective analysis	Histologically aggressive transformed FL included.
Kato et al.[29]	Retrospective analysis	Patients not classified according to time of relapse.
Berinstein et al.[30]	Retrospective analysis	Patients not classified according to time of relapse.
Arcaini et al.[31]	Phase II clinical trial	Patients not classified according to time of relapse.
Rohatiner et al.[32]	Retrospective analysis	Patients not classified according to time of relapse.
Jiménez-Ubieto et al.[33]	Retrospective analysis	Salvage regimen data were not stratified according to being POD24 and receiving HDC and ASCT.
Smith et al.[34]	Retrospective analysis	Missing data on salvage regimen.
Jurinovic et al.[35]	Poster	Not an original article.
Metzner et al.[36]	Retrospective analysis	Salvage regimen data were not stratified according to being POD24 and receiving HDC and ASCT.

HDC: high dose chemotherapy; ASCT: autologous stem cell transplantation; POD24: progression of disease in 24 months; FL: follicular lymphoma.

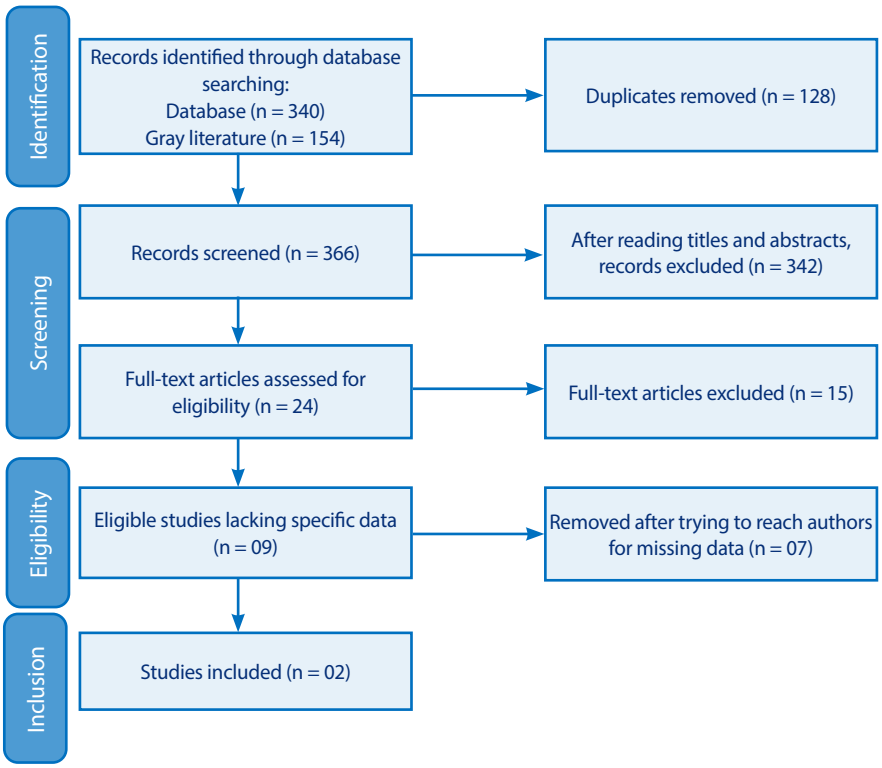


Figure 1. Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) flowchart of study selection.

mentioned tool. The main issues related to risk of bias of the included studies were very much alike and referred not having a random sequence generation (convenience sample) nor allocation concealment or blindness of participants and personnel. Methodological quality issues are reported in Fig. 2.

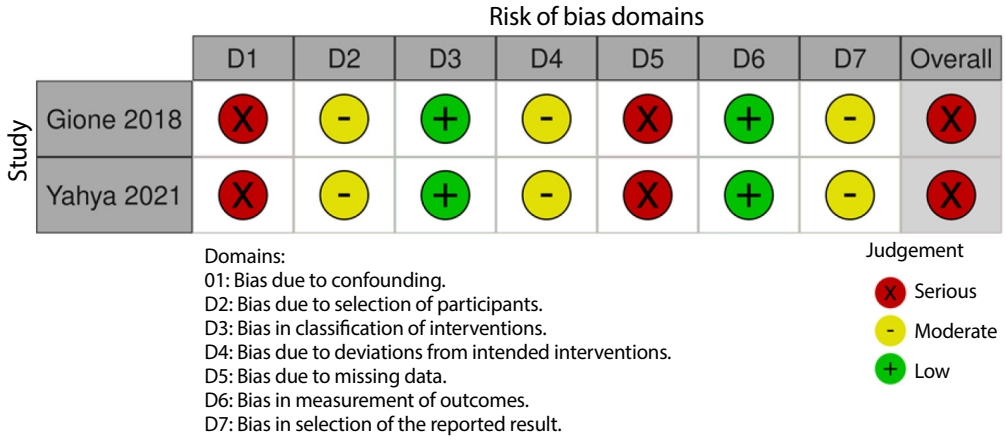


Figure 2. Cochrane Risk of Bias (ROBINS-1) assessment.

Statistical analysis and outcomes

The evaluation of time-dependent variables such as the primary outcome PFS and the secondary outcome OS was compromised by the absence of a control arm and missing values such as the absolute number of events (including its confidence intervals), the calculation of a hazard ratio and standard error. Extracted data can be found in Table 1. In both studies, the PFS and OS were presented in percentages at a five-year follow-up time point. Ghione et al.[37] did not presented a PFS data and estimated a five-year OS of 83.8% ± 6.7 (95% confidence interval [95%CI] 70.6–96.9%), while Yahya et al.[38] reported a 53,6% (95%CI 25–75) PFS and a 71,8% (95%CI 31–91) OS at a five-year follow-up.

Table 1. Data extraction instrument.

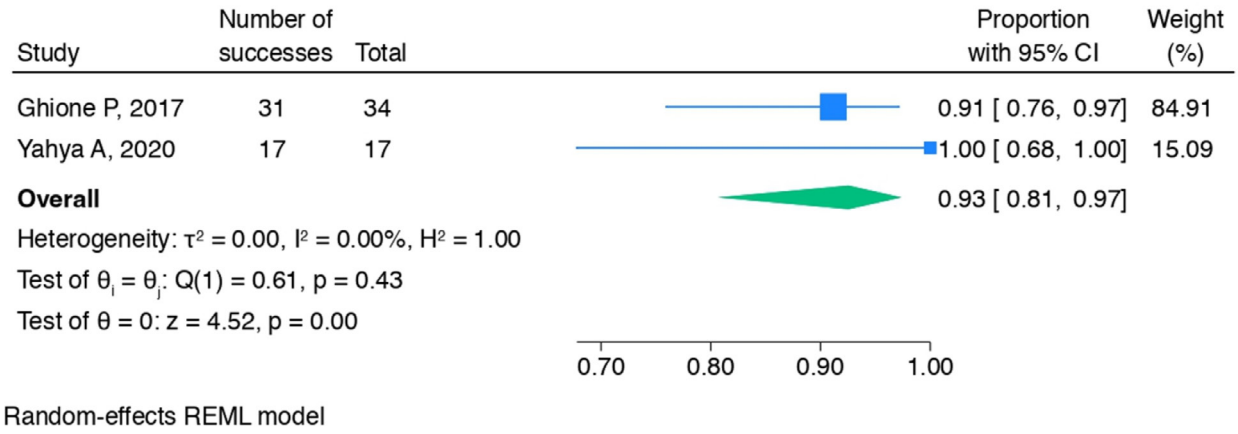
Citation	Study design	Sample size	Salvage regimens used	5-year OS, % (95%CI)	5-year PFS, %	ORR, %
Ghione et al.[37]	Retrospective analysis	34	R-DHAP/Ox	83.8 ± 6.7 (70.6–96.9)	*	91.3
Yahya et al.[38]	Retrospective analysis	17	ICE DHAP GDP	71.8 (31–91)	53,6	100

95%CI: 95% confidence interval; *missing data; OS: overall survival; PFS: progression free survival; ORR: overall response rate; R: rituximab; DHAP/Ox: dexamethasone, cytarabine, cisplatin or oxaliplatin; ICE: ifosfamide, cytarabine and etoposide; GDP: gemcitabine, dexamethasone and cisplatin.

It was decided to perform a proportional meta-analysis using overall response rate, which was the best documented outcome regarding time of analysis and thoroughness of data. Yahya et al.[38] reported an overall response rate of 100% after dose-intensified salvage regimens, which comprised the whole sample analyzed in this study (17 out of 17 patients). The evaluation of complete response and partial response rate was conducted two/three months after submission to HDC and ASCT, thus affecting analysis of variables involved in such degree of response. On the other hand, Ghione et al.[37] described an overall response rate of 91.3% and a complete response of 79.4% following R-DHAP/Ox regimen, not providing absolute number of events and confidence interval on such matter. Therefore, it was decided to estimate the absolute number of events by multiplying the total sample exposed by the percentage shown in the article. The resulting number was rounded down to the nearest integer. An odds ratio of 0.93 (95%CI 0.81–0.97) was demonstrated. Although

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the missing absolute values raises concern about the possibility of hidden biases, the low heterogeneity calculated by the χ^2 test and the I^2 test ($\chi^2 = p > 0,05$ and $I^2 = 0\%$) using the random-effects model shows robustness and precision of the result found, displayed in Fig. 3. The estimation of effect was based on Freeman-Tukey's proportion for each study analyzed.



95%CI: 95% confidence interval.

Figure 3. Forest plot of pooled data, using random-effects model, regarding overall response rate of patients submitted to dose-intensified salvage regimens. Odds ratio of 0.93 (95%CI 0.81–0.97) was demonstrated.

Assessing certainty in the findings

Using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, the certainty of the evidence was assessed[39]. After uploading data into the GRADEpro GDT, a summary of findings was created evaluating only one outcome, the overall response rate as presented in Fig. 4.

Certainty assessment							N. of patients		Effect			
N. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salvage dose intensified chemotherapy	salvage standard dose chemotherapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Overall Response Rate (follow-up: median 60 months)												
2	Observational studies	Serious[a]	Not serious	Serious[b]	Not serious	none	48/51 (94.1%)	0/0	not estimable		⨁⨁◯◯ Low	

CI: confidence interval.

a. Both studies were retrospective cohorts with chosen treatment at the discretion of the assistent physician. There was no mention to randomized allocation or blinding of participants. personnel and data analysts. Missing data (absolute values of occurrence) regarding the evaluated outcomes also raised concerns. Moreover, complete response and partial response rates were analyzed in different time frames. one of which analyzed not after exposure to the intended treatment, but after submission to high dose chemotherapy and a utol ogo us stem c ell transplantation.

b. Studies included do not compare directly the intended interventions. Both of them are single arm interventions, retrospectively analyzed, reporting centre experience or group experience.

Figure 4. GRADE summary of findings for overall response rate outcome. The evidence level was rated as low certainty due to serious indirectness and serious risk of bias.

We did not analyze the pre-intended outcomes of survival and complete and partial response rates due to the limitations mentioned above. The certainty of findings was graded as low, due to serious risk of bias and serious indirectness. We have rated our outcome as precise due to the high occurrence of the event "overall response rate" in relation to the total sample size and the narrow confidence interval shown in the proportional meta-analysis, despite the small sample size.

DISCUSSION

Early relapsed FL still poses a challenge for the treating physician. The identification of time of relapse as a prognostic factor, defining a subgroup of high-risk patients, allowed researchers to address this specific issue[6,7,40]. HDC followed by ASCT has been demonstrated as a viable and effective therapeutic approach for treating this group of patients[9,10], with no consensus on which salvage regimen would be optimal. Our study showed an important gap in the literature since the lack of well-designed randomized comparative studies evaluating different approaches makes it difficult to establish recommendations.

Salvage regimens used for treating early relapsed or refractory FL are generally based on center experience, and most data taken to support this decision is derived from diffuse large B cell lymphoma studies[37,41,42]. Although data from different studies such as the LymphoCare study and retrospective analysis from the German group (regarding the GLSG 1996 and GLSG 2000 trials) analyze HDC and ASCT as a consolidative treatment for POD24 patients, they did not stratify survival analysis and response rate analysis according to which salvage regimen patients were submitted to before progressing to ASCT[9,10]. In addition, timeframe of response and survival assessment varies between center experience retrospective analysis.

To our knowledge, this is the first systematic review and meta-analysis addressing the matter of salvage regimens before HDC and ASCT therapy. Our results suggested that dose-intensified salvage treatment is effective in FL POD24 patients treated with rituximab containing regimens in induction therapy. Moreover, the addition of rituximab to second line intensive dose regimens of pre-exposed POD24 patients did not seem to impact overall response rate.

This data is in line with the results presented by the German group, contrasting with data shown by the GELA study[17], in which, despite not analyzing specifically POD24 patients, the addition of rituximab ensured greater OS to participants who were also submitted to HDC and ASCT. It is important to notice that those patients included in the GELA study had all been rituximab naïve. Regarding OS, both studies included were consistent with data shown in the literature. Jurinovic et al.[9] demonstrated a five-year OS of 77% for POD24 patients submitted to HDC and ASCT[9], while Manna et al.[18] reported an 87.9% OS in the same context. The overall response rate reported by Yahya et al.[38], as well as Ghione et al.[37], were higher than that shown by the German group (100 *versus* 91.3 *versus* 79%, respectively)[9], although we should consider that the latter study included patients with standard-dose salvage regimens in the pooled analysis. The progression five-year free survival achieved by those patients analyzed in the Canadian cohort are also in line with those reported by the GLSG 1996 and the GLSG 2000 post-hoc analysis (53,6 *versus* 51%, respectively)[9,38].

Limitations

There may be a selection bias related to patient allocation in both studies included since it is a clinical practice to select fit patients to receive dose intensive immunochemotherapy, as well as HDC and ASCT. Therefore, although these patients present a high-risk profile, the baseline characteristics may favor more intensive treatment, impacting outcome. Retrospective analysis may raise concerns about report bias. There was no mention to randomized allocation or blinding of participants, personnel, and data analysts. Missing data (absolute values of occurrence) regarding the evaluated outcomes also raises concerns. Complete response and partial response rates were analyzed in different timeframes, one of which analyzed not after exposure to the intended treatment, but after submission to HDC and ASCT. Still, it is unclear how many patients in the included studies were intended for ASCT and how many received it or were unable to undergo ASCT due to progressive disease or salvage regimen toxicity. Moreover, we cannot extract from any of the included studies how many participants were submitted to the evaluated salvage regimen after the second or subsequent line of therapy, making comparisons difficult.

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CONCLUSION

Our systematic review contributes to the emerging topic of optimal therapeutical approaches to patients diagnosed with early relapsed follicular lymphoma, and it is the first study to our knowledge that addresses this issue in a systematic way. The lack of standardized evaluation of high-dose salvage regimens and standard-dose rescue treatments in this population precludes recommendations and highlights the need for further studies on the matter, since newer drugs are not an option to many patients.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data are presented in the article.

AUTHORS' CONTRIBUTION

Conception and design: Mesquita FP, Santos KB, Pereira J and Hallack Neto AE; **Acquisition of data:** Mesquita FP, Takahashi JA and Alvim GF; **Analysis and interpretation of data:** Mesquita FP, Santos KB, Alvim GF and Hallack Neto AE; **Statistics analysis:** Mesquita FP and Santos KB; **Manuscript preparation:** Mesquita FP, Santos KB and Hallack Neto AE; **Manuscript writing:** Mesquita FP and Alvim GF; **Critical revision:** Santos KB, Pereira J and Hallack Neto AE; **Final approval of the version to be published:** Mesquita FP.

FUNDING

Not applicable.

DECLARATION ON THE USE OF ARTIFICIAL INTELLIGENCE TOOLS

Artificial intelligence tools were not used.

ACKNOWLEDGEMENTS

We would like to thank Ms. Nila Larisse Silva de Albuquerque, who helped develop the statistical analysis.

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