University of Thessaly

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Master of Science Thesis

Assessment of the reporting quality of randomized controlled trials for Bruton's Tyrosine Kinase inhibitors (ibrutinib, acalabrutinib, zanubrutinib) and idelalisib in the treatment of Chronic Lymphocytic Leukemia published from 2014 to 2023 using the CONSORT statement

Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων κλινικών δοκιμών για τους αναστολείς της Τυροσινικής Κινάσης του Bruton (ιμπρουτινίμπη, ακαλαμπρουτινίμπη, ζανουμπρουτινίμπη) και της ιδελαλισίμπης στη θεραπεία της Χρόνιας Λεμφοκυτταρικής Λευχαιμίας που δημοσιεύτηκαν από το 2014 έως το 2023 χρησιμοποιώντας την δήλωση CONSORT.

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Αφιερώνεται στον παππού μου

Abstract

Introduction: Bruton's Tyrosine Kinase (BTK) inhibitors have made a great advance in the treatment of Chronic Lymphocytic Leukemia (CLL), a very common type of leukemia. Although there is a good number of Randomized Clinical Trials being conducted around the subject of BTK inhibitors for patients with CLL, the reporting quality of these trials has to be evaluated in order to provide comprehensive, transparent and evidence-based information to the health-care community.

Aim: To assess the reporting quality of Phase 3 Randomized Clinical Trials for patients with Chronic Lymphocytic Leukemia, receiving Bruton's Tyrosine Kinase inhibitors (ibrutinib, acalabrutinib, zanubrutinib) or idelalisib.

Methods: PubMed database was searched for RCTs involving patients with CLL and Bruton's Tyrosine Kinase inhibitors or idelalisib for interventions. Randomized Controlled Trial filter was used and a flow chart was created after excluding studies that didn't meet the inclusion criteria. A full text quality assessment of the remaining articles took place based on the CONSORT statement followed by a statistical analysis to interpret and visually present the results. A maximum of a 37-point score could be achieved based on the 25-item CONSORT checklist.

Results: PubMed search returned 89 articles and after the screening process 18 were eligible for quality assessment. 27.4% of the articles had a score of 30 and 54% of the CONSORT items were found in every study, whereas item 11b (5.6%) and 6b (11.1%) were only found in 1 and 2 studies respectively.

Conclusion: Although some items were underreported, the overall reporting quality of the 18 studies included in this analysis remains high. This leaves room for improvement in the reporting quality, but also for further analysis to take place using the data provided by these studies.

Keywords: Chronic Lymphocytic Leukemia; CLL; Ibrutinib; Acalabrutinib; Zanubrutinib; Idelalisib

Περίληψη

Εισαγωγή: Οι αναστολείς της Τυροσινικής Κινάσης του Bruton (BTK) έχουν σημειώσει σημαντική πρόοδο στη θεραπεία της χρόνιας λεμφοκυτταρικής λευχαιμίας (ΧΛΛ), μιας πολύ συνηθισμένης μορφής λευχαιμίας. Παρά την διεξαγωγή πολλών τυχαιοποιημένων κλινικών δοκιμών γύρω από το αντικείμενο των αναστολέων της BTK για ασθενείς με ΧΛΛ, πρέπει να αξιολογηθεί η ποιότητα αναφοράς αυτών των δοκιμών προκειμένου να παρασχεθούν πλήρεις, διαφανείς και βασισμένες σε αποδείξεις, πληροφορίες στην κοινότητα της υγείας.

Στόχος: Να αξιολογηθεί η ποιότητα αναφοράς των τυχαιοποιημένων κλινικών δοκιμών Φάσης 3 για ασθενείς με Χρόνια Λεμφοκυτταρική Λευχαιμία που λαμβάνουν αναστολείς της Τυροσινικής Κινάσης του Bruton (ιμπρουτινίμπη, ακαλαμπρουτινίμπη, ζανουμπρουτινίμπη) ή ιδελαλισίμπη.

Μέθοδοι: Πραγματοποιήθηκε αναζήτηση στη βάση δεδομένων PubMed για τυχαιοποιημένες κλινικές δοκιμές που περιλάμβαναν ασθενείς με ΧΛΛ και αναστολείς της Τυροσινικής Κινάσης του Bruton ή ιδελαλισίμπη ως παρεμβάσεις. Χρησιμοποιήθηκε φίλτρο για τυχαιοποιημένες ελεγχόμενες δοκιμές και δημιουργήθηκε ένα διάγραμμα ροής μετά τον αποκλεισμό των μελετών που δεν πληρούσαν τα κριτήρια ένταξης. Στη συνέχεια έγινε αξιολόγηση της ποιότητας του πλήρους κειμένου των υπολειπόμενων άρθρων, βασισμένη στη δήλωση CONSORT και ακολούθησε στατιστική ανάλυση για την ερμηνεία και την οπτική παρουσίαση των αποτελεσμάτων. Η μέγιστη δυνατή βαθμολογία ήταν 37 βαθμοί, βασισμένη στην λίστα των 25 στοιχείων της δήλωσης CONSORT.

Αποτελέσματα: Κατά την αναζήτηση στη βάση δεδομένων PubMed ανευρέθηκαν 89 άρθρα και μετά τη διαδικασία διαλογής επιλέχθηκαν 18 για αξιολόγηση ποιότητας. Το 27,4% των άρθρων είχε βαθμολογία 30 και το 54% των στοιχείων της CONSORT βρέθηκαν σε κάθε μελέτη, ενώ το στοιχείο 11b (5,6%) και το 6b (11,1%) βρέθηκαν μόνο σε 1 και 2 μελέτες αντίστοιχα.

Συμπέρασμα: Παρά την ανεπαρκή αναφορά ορισμένων στοιχείων, η συνολική ποιότητα αναφοράς των 18 μελετών που περιλαμβάνονται σε αυτήν την ανάλυση παραμένει υψηλή. Αυτό δίνει τη δυνατότητα βελτίωσης της ποιότητας αναφοράς, αλλά και την περαιτέρω ανάλυση χρησιμοποιώντας τα δεδομένα που παρέχονται από αυτές τις μελέτες.

Λέξεις κλειδιά: Χρόνια Λεμφοκυτταρική Λευχαιμία; ΧΛΛ; Ιμπρουτινίμπη; Ακαλαμπρουτινίμπη; Ζανουμπρουτινίμπη; Ιδελαλισίμπη

1. Introduction

Chronic Lymphocytic Leukemia (CLL),which is the type of leukemia most commonly found in the Western World, has some basic main characteristics. These are the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Patients diagnosed with CLL have a median age of 65 years, whereas just a 10 to 15 percent of them are under the age of 50. In most cases, men tend to be more affected compared to women. The outcome of the disease tends to vary. On one hand, there is a number of patients with CLL that has a normal life span, where on the other hand some other patients die within five years after being diagnosed. In recent years, there have been many important advances in the field of the biology, the natural history, and the treatment of CLL.(1)

Such an advance in the treatment of CLL, was targeting the B-cell receptor signaling pathway through the inhibition of BTK , which has proved to be an effective way to treat Chronic Lymphocytic Leukemia (CLL). Covalent BTK inhibitors (BTKis) have led to an unapparelled improvement in the course of CLL and specifically in subgroups of high-risk, that are characterized with TP53 aberration and unmutated immunoglobulin heavy-chain variable-region gene (IGHV). (2)

Nowadays, available Randomized Clinical Trials (RCTs) have grown exponentially in number. This imposes a great difficulty on clinicians in managing to keep up with the increased volume of available scientific data from original research (3). The review of literature in health care has one significant goal. That is to make a summary of the evidence that the clinicians will essentially utilize to provide care for their patients and make important clinical decisions. The quality of both the RCTs and the review process often seems to reflect on the overall conclusions of a review (4,5). A systematic review can be distinguished from a narrative review if there is a clear designation of the strategies that are used for data identification, selection and integration(6,7). Over the last few years, the assessment of the methodological quality of the clinical trials has a significant impact on the substance of many systematic reviews (8,9).

The concept of “quality” is a complex one and therefore a definition is not easy to be given. The quality of RCTs has recently been referred to as “the likelihood of the trial design to generate unbiased results” (10) .Only the dimension of internal validity is covered by this definition. The majority of articles that propose a list of criteria for the assessment of the methodological quality of RCTs, don’t give an explicit definition of the quality’s concept (11). However, most of the lists are taking into consideration at least three dimensions that may encompass the concept of quality in its broadest sense. That is the internal and external validity and the statistical analysis as well.(12–16). There are some authors who even recognize an ethical component in the concept of quality(17,18).

The CONSORT stands for “Consolidated Standards of Reporting Trails” and its idea was conceived in order to assist in securing standardization and reproducibility of Randomized Clinical Trials. The articles that publish the CONSORT 2010

STATEMENT accompanying their bibliographies were identified and thoroughly reviewed. This statement doesn't only act as a quality assessment tool, but also grants authors a base on which they can both structure and present an RCT in a comprehensive, transparent and absolute manner. It consists of a checklist of 25 items and sets criteria for the design of the trial, its analysis and also the interpretation of the final results. For the purpose of evading systematic reporting errors while at the same time confirming the high-quality reporting standards of RCTs, the concept of CONSORT STATEMENT was coined back in 1996. (20–22) The CONSORT has been revised throughout the years in order to provide more thorough explanations and elaborations of its principles. A CONSORT flowchart can also be accessed , which displays the progress of all participants through the trail, as seen in the APPENDIX. (22)

2. Methods

2.1 Search Strategy

We performed an advanced search in the PubMed database using the terms *''Chronic Lymphocytic Leukemia OR CLL AND ibrutinib OR acalabrutinib OR zanubrutinib OR idelalisib"* and Randomized Controlled Trial filter to access articles regarding RCTs with our desired characteristics.

2.2 Eligibility Citeria

Only Phase 3 RCTs with patients with Chronic Lymphocytic Leukemia receiving ibrutinib or acalabrutinib or zanubrutinib or idelalisib were eligible. Studies referring to other diseases or syndromes or to patients receiving different interventions were not considered eligible. Articles of irrelevant subject were excluded from title before screening commenced. At screening and full text assessment Phase 1 and 2 studies were excluded, as well as Protocols for Clinical Trials, Reports of updated findings after follow-up and extended analysis of existing Phase 3 Trials. A flow chart was designed to depict the process of article inclusion and exclusion with specific reasons.

2.3 Quality Evaluation

The full texts of the final eligible articles were assessed for their quality using the CONSORT statement. The statement consists of a total of 25 items regarding the Title, Methods, Results, Discussion and Other information of a clinical trial. For each item included, the study received 1 point whereas in the absence of an item the study received 0 points. The maximum points a study could be awarded is 37.

2.4 Statistical Analysis

The statistical analysis of the thesis was performed using Microsoft Excel 2021 and IBM SPSS 29 software, provided by the University of Thessaly. The first analysis was the calculation of the percentages of the total scores for each study. The total scores were compared in a bar chart displaying their percentages. The second analysis included the calculation of the percentages of each item included in each study. In order to calculate the percentages and frequencies of each item, a multiple response model was used in the SPSS Software. A list of all the items with their percentages was created along with a bar chart to visually present the results and allow for comparisons to be made. In order to compare the items further, the studies were grouped based on the median of the journals 2-year impact factors (IFs) and new item percentages and frequencies were calculated and displayed for each group. Fischer's exact test was used to compare each item between the two groups, and p-values were calculated for statistical comparison.

3. Results

The search in the PubMed database returned 89 results. 18 articles were immediately excluded due to lack of relevance from their title. The remaining 71 articles were screened and assessed for eligibility. 53 studies were excluded in total. 11 were Phase 1 and 2 studies, 4 were Protocols, 9 were Reports of updated findings after follow-up and 29 were extended analysis of existing Phase 3 clinical trials. The final 18 Phase 3 clinical studies were included in the quality assessment analysis using the CONSORT statement.

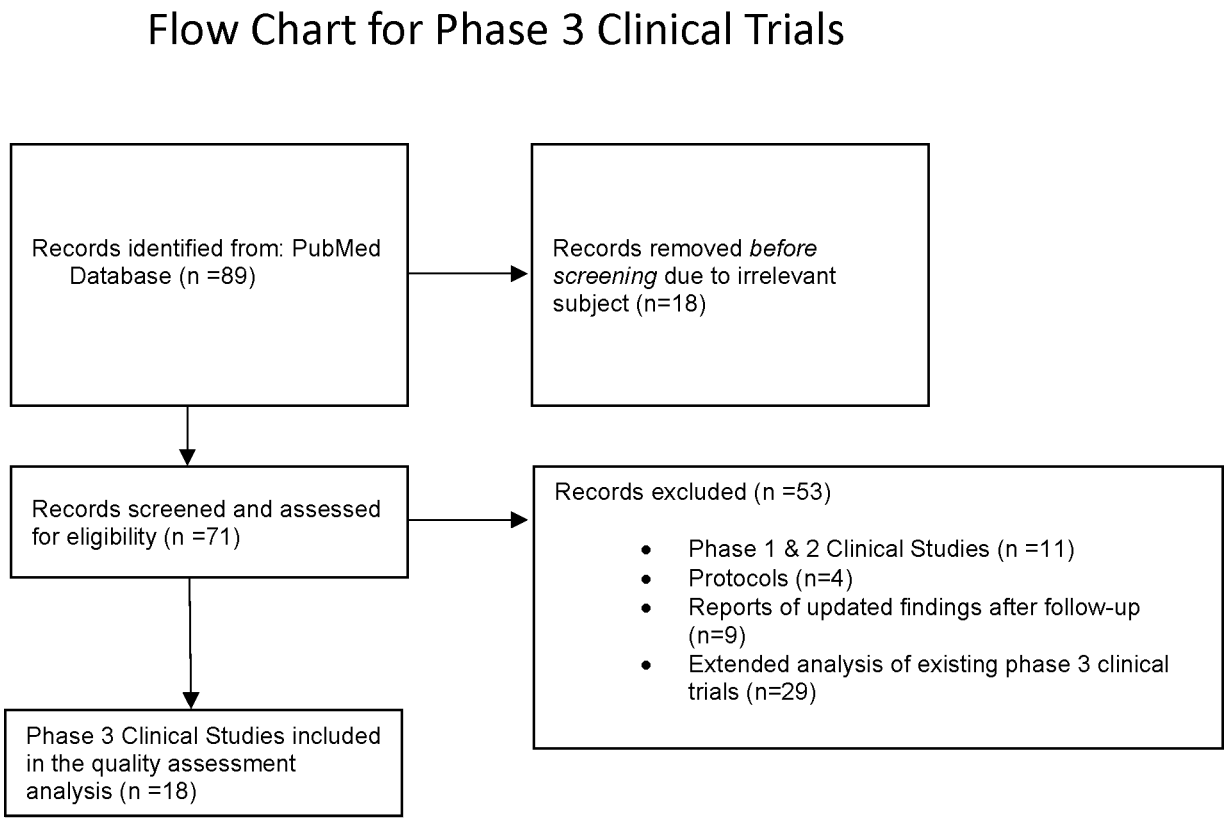


Figure 1. Flow chart of studies included in the analysis

The full text of each study was evaluated for each of the 25 items included in the statement. The full list of items can be accessed in the CONSORT statement in the APPENDIX. The maximum total score achieved was 34 (5.6%) whereas the minimum was 27(5.6%) as it is shown in the bar chart (Figure 2). The most frequent score was 30 as it was awarded to the highest percentage of studies (27.8%).

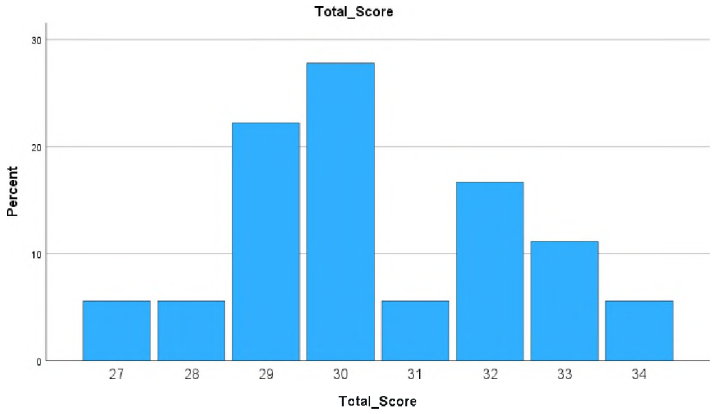


Figure 2. Total scores of overall studies

The statistical analysis performed for the frequency of each item of the statement showed that 20 items (54%) were found in every study. The table (Table 1.) and the bar chart (Figure 3.) showcase the percentage of each item found in the 18 studies included in the analysis. Item 11b (Blinding) had the lowest frequency as it was only found in one study (5.6%). Another item that was observed in a lower frequency compared to the rest was item 6b (Outcomes) found in just two studies (11.1%). Two items that were also found in less than 50% of the articles were item 11a (Blinding)(27.8%) and item 3b (Trial Design) (33.3%). The rest of the items in the CONSORT checklist had an equal or higher percentage of 50%. The median of the journals 2-year impact factors was calculated at 48. Ten studies were published in journals with a 2-year impact factor higher than the median whereas the rest of the studies were published in journals with a 2-year impact factor lower than the median. The results of the comparison between the two groups revealed that there is a statistically significant difference in the reporting of item 24 (Other information-Protocol) with a p-value=0.007. 10 (100%) of studies over the median 2-year IF reported item 24 when only 3 (37.5%) studies under the median 2-year IF reported the aforementioned item.

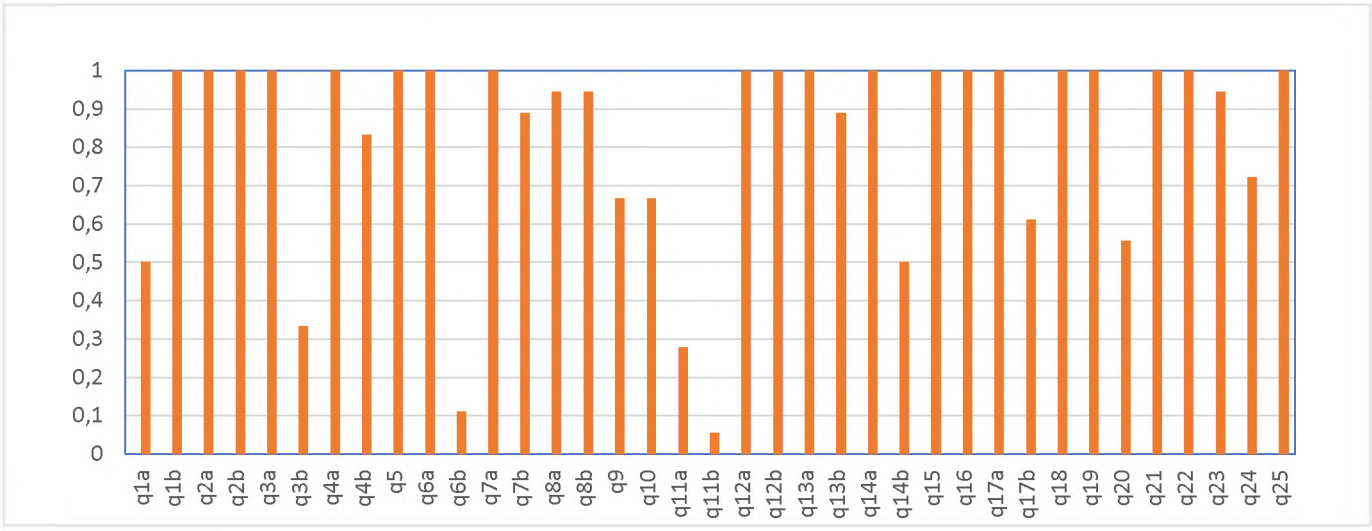


Figure 3. Percentages of CONSORT items found in overall studies

Figure 4. Percentages of CONSORT items found in studies over and under journals median 2-year impact factor

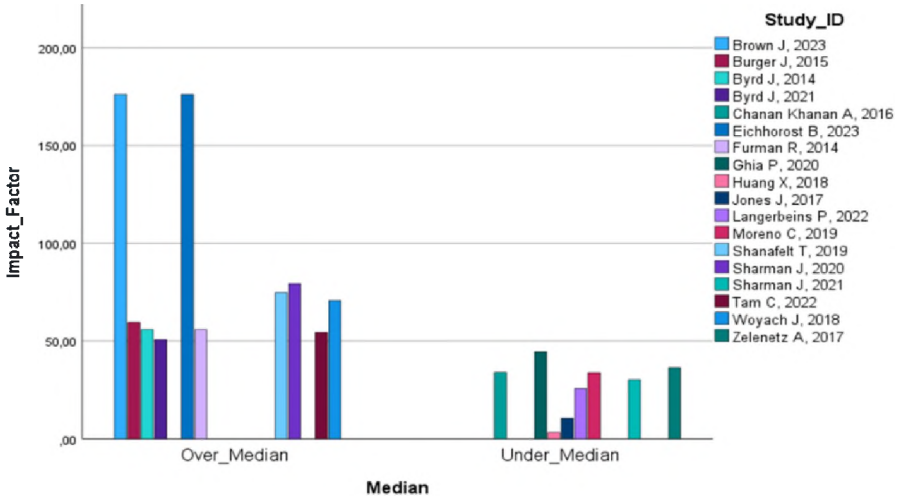
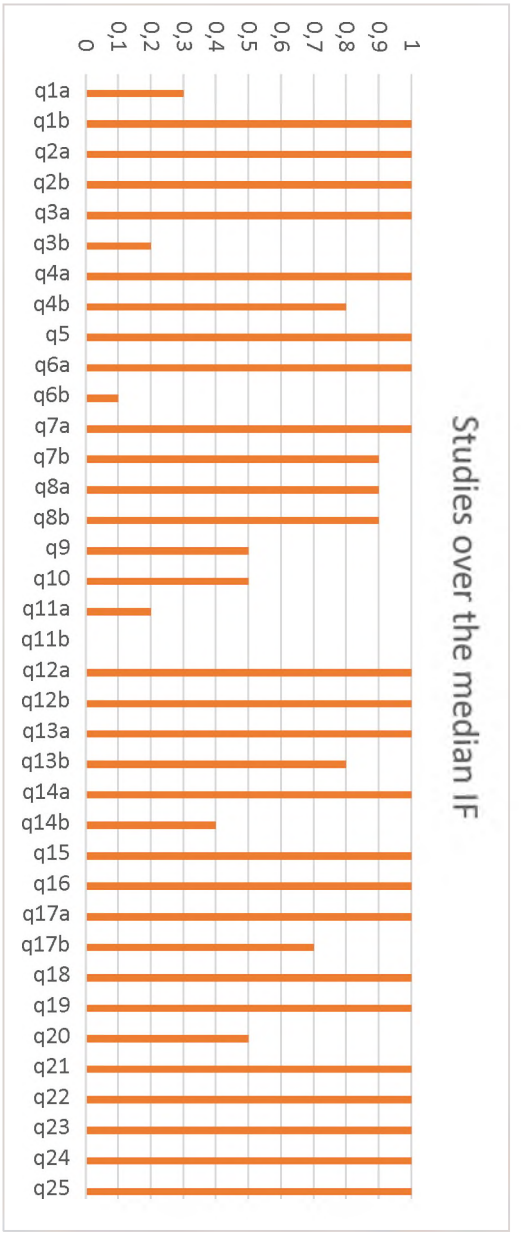
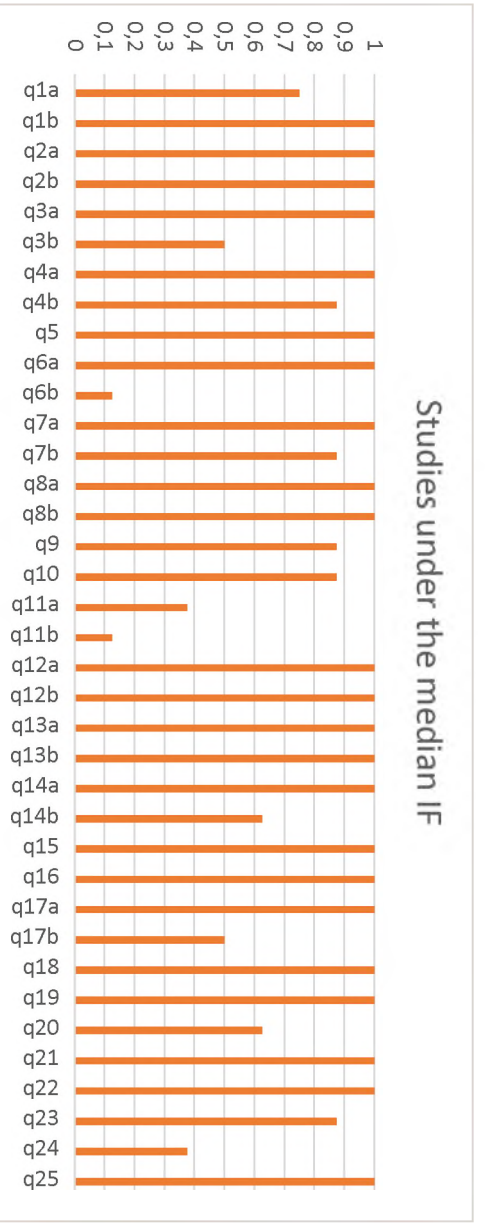


Figure 5. Studies over and under the median 2-year impact factor





Consort Items	Overall studies	Studies under median IF	Studies over median IF	P-value
q1a	9 (50%)	6 (75%)	3 (30%)	0,153
q1b	18 (100%)	8 (100%)	10 (100%)	-
q2a	18 (100%)	8 (100%)	10 (100%)	-
q2b	18 (100%)	8 (100%)	10 (100%)	-
q3a	18 (100%)	8 (100%)	10 (100%)	-
q3b	6 (33,3%)	4 (50%)	2 (20%)	0,321
q4a	18 (100%)	8 (100%)	10 (100%)	-
q4b	15 (83,3%)	7 (87,5%)	8 (80%)	1
q5	18 (100%)	8 (100%)	10 (100%)	-
q6a	18 (100%)	8 (100%)	10 (100%)	-
q6b	2 (11,1%)	1 (12,5%)	1 (10%)	1
q7a	18 (100%)	8 (100%)	10 (100%)	-
q7b	16 (88,9%)	7 (87,5%)	9 (90%)	1
q8a	17 (94,4%)	8 (100%)	9 (90%)	1
q8b	17 (94,4%)	8 (100%)	9 (90%)	1
q9	12 (66,7%)	7 (87,5%)	5 (50%)	0,152
q10	12 (66,7%)	7 (87,5%)	5 (50%)	0,152
q11a	5 (27,8%)	3 (37,5%)	2 (20%)	0,608
q11b	1 (5,6%)	1 (12,5%)	0 (0%)	0,444
q12a	18 (100%)	8 (100%)	10 (100%)	-
q12b	18 (100%)	8 (100%)	10 (100%)	-
q13a	18 (100%)	8 (100%)	10 (100%)	-
q13b	16 (88,9%)	8 (100%)	8 (80%)	0,477
q14a	18 (100%)	8 (100%)	10 (100%)	-
q14b	9 (50%)	5 (62,5%)	4 (40%)	0,637
q15	18 (100%)	8 (100%)	10 (100%)	-
q16	18 (100%)	8 (100%)	10 (100%)	-
q17a	18 (100%)	8 (100%)	10 (100%)	-
q17b	11 (61,1%)	4 (50%)	7 (70%)	0,63
q18	18 (100%)	8 (100%)	10 (100%)	-
q19	18 (100%)	8 (100%)	10 (100%)	-
q20	10 (55,6%)	5 (62,5%)	5 (50%)	0,664
q21	18 (100%)	8 (100%)	10 (100%)	-
q22	18 (100%)	8 (100%)	10 (100%)	-
q23	17 (94,4%)	7 (87,5%)	10 (100%)	0,444
q24	13 (72,2%)	3 (37,5%)	10 (100%)	0,007
q25	18 (100%)	8 (100%)	10 (100%)	-

Table 1. CONSORT items percentages and frequencies along with the calculated p-values

4. Conclusion

In this assessment of the reporting quality of RCTs including patients with CLL receiving Bruton's Tyrosine Kinase inhibitors or idelalisib, eighteen studies were finally included. The analysis revealed that the overall reporting quality was high based on the 25-item list of the CONSORT statement. In general, this analysis shows that the researchers of CLL put a great effort in providing the health care community with clear, transparent, thorough and evidence-based information.

Although the overall reporting quality of the studies was high, some observations have to be made regarding the items found in the articles analyzed. More specifically, item 11b and 6b were found in 1 and 2 articles respectively. Item 11b asks if the similarity of the interventions of the trial is mentioned and item 6b refers to any changes that occurred in the outcomes of the trial. The next two items that were found in less than 50% of the articles were items 3b (Trial Design) and 11a (Blinding). These four items refer to two basic aspects of a Randomized Clinical Trial, and that is the description of any changes occurred in the methods or outcomes of the trial and also the blinding methods. Since most of the articles describe open-label studies, we expected items referring to blinding methods to have a lower frequency than the rest. The p-values calculated from the analysis of the items frequencies between the two groups of studies indicate that there is a statistically significant difference in the reporting of the trial's protocol in studies of journals with a 2-year impact factor lower than 48.

To conclude, the reporting quality of RCTs involving patients with CLL and receiving Bruton's Tyrosine Kinase inhibitors or idelalisib as treatment is high but some items seem to be underreported. This leaves room for improvement in the reporting quality aspect of Randomized Clinical Trials but is also a reflection of the attention paid by the authors to the different aspects of the Trial that need to be reported in the final paper.

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Appendix

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	
Background and objectives	#2b	Specific objectives or hypothesis	
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	#4a	Eligibility criteria for participants	
Participants	#4b	Settings and locations where the data were collected	
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	#7a	How sample size was determined.	
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	

		describing any steps taken to conceal the sequence until interventions were assigned
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.
Blinding	#11b	If relevant, description of the similarity of interventions
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results		
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason
Recruitment	#14a	Dates defining the periods of recruitment and follow-up
Recruitment	#14b	Why the trial ended or was stopped
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)
Discussion		

Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Registration	#23	Registration number and name of trial registry
Other information		
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Registration	#23	Registration number and name of trial registry
Protocol	#24	Where the full trial protocol can be accessed, if available
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders

Table 2. CONSORT STATEMENT Checklist

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

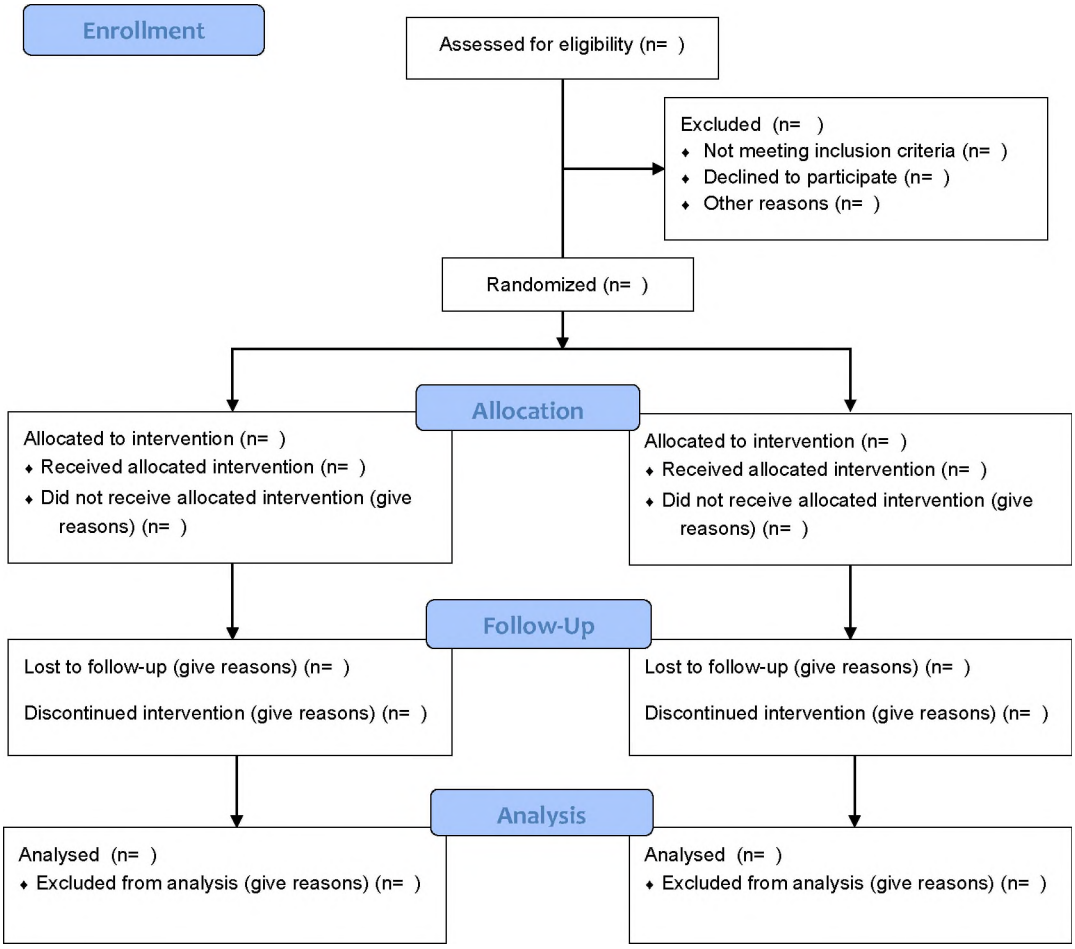

Figure 6. CONSORT Flow chart