Supplementary Information

A Meta-analysis and Trial sequential analysis

Contents

Supplementary Information S1 - PRISMA Checklist

| Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	5
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	6
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	6
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	7

Section/topic	Item No	Checklist item	Reported on page No
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6-7
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	3, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	8
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	8-9
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	9
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	S6
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	S5
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	13-14, S3-4, S8

Section/topic	Item No	Checklist item	Reported on page No
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	14-15
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	16-17
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	18

**Supplementary Information S2 - Search strategies and detailed records**

Relevant text of Population & Type	Relevant text of Intervention & Outcome
1. B cell Leukemia	1. Lenalidomide
2. Lymphocytic leukemia	2. Revlimid
3. Chronic lymphocytic leukemia	3. Linamide
4. Small lymphocytic leukemia	E = #1 or #2 or #3
A= #1 or #2 or #3 or #4	*. All search keyword with [Mesh Terms] or [All Fields]
5. Maintenance	
6. Maintenance therapy	
7. Consolidation	**PUBMED**:
8. Consolidation therapy	http://www.ncbi.nlm.nih.gov/pubmed
B = #5 or #6 or #7 or #8	
9. Trial	
10. Clinical trial/ trials	**EMBASE**:
11. Randomized	https://www.embase.com
12. Randomization	
13. Controlled trial/trials	
14. Randomized controlled trial/trials	**COCHRANE CENTRAL**:
15. Controlled clinical trial	*https://www.cochrane.com*
16. RCT	
17. Persepctive study	
18. Clinical study	
19. Clinical article	
C = #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19	
20. Progression free survival	
21. Overall Survival	
22. Response	
23. Adverse Events	
24. Mortality	
D = #20 or #21 or #22 or #23 or #24	

Supplementary Information S3 - Assessment of risk of bias

Supplementary Information S4 - Secondary outcomes of meta-analysis.

Study	Lenalidomide Event	Total	Observation Event	Total	Grade 3−4 neutropenia	OR	95%−CI	Weight
Chanan−Khan, 2017	94	157	35	154		5.07	[3.10; 8.31]	27.6%
Fink, 2017	19	60	2	29		6.26	[1.35; 29.06]	17.5%
Byrd, 2018 (FR)	77	109	76	117		1.30	[0.74; 2.27]	27.1%
Byrd, 2018 (FCR)	22	31	22	26		0.44	[0.12; 1.66]	19.6%
Jindal, 2021	4	25	0	15		6.49	[0.33; 129.52]	8.2%
Random effects model		382		341		2.30	[0.84; 6.28]	100.0%
Heterogeneity: I^2 = 81%, p < 0.01								
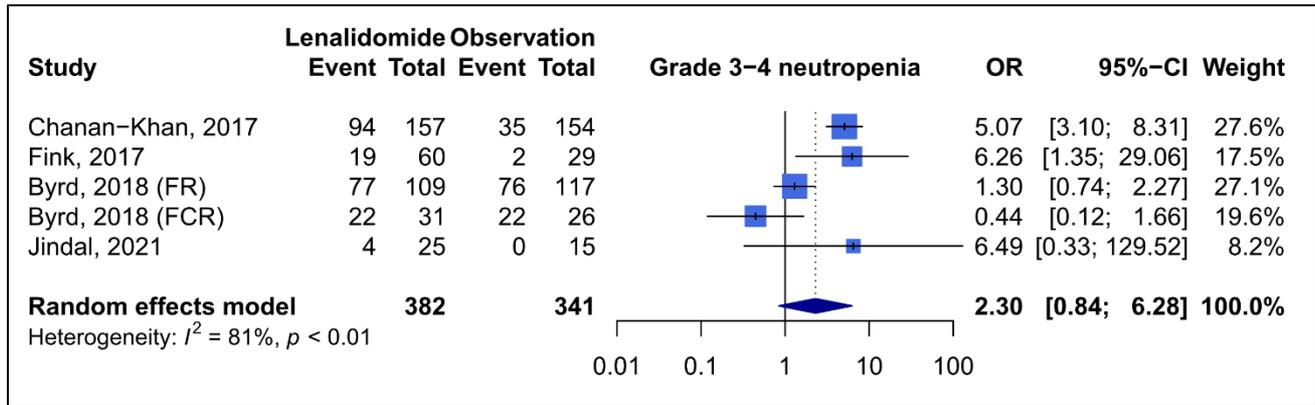
Secondary outcomes of meta-analysis - **Grade 3-4 neutropenia**

Study	Lenalidomide Event	Total	Observation Event	Total	Treatment discontinuation	OR	95%−CI	Weight
Chanan−Khan, 2017	103	157	121	154		0.52	[0.31; 0.86]	25.7%
Fink, 2017	24	60	21	29		0.25	[0.10; 0.67]	21.6%
Byrd, 2018 (FR)	53	109	34	117		2.31	[1.34; 4.00]	25.4%
Byrd, 2018 (FCR)	18	31	19	26		0.51	[0.17; 1.57]	20.0%
Jindal, 2021	3	25	0	15		4.82	[0.23; 100.11]	7.3%
Random effects model		382		341		0.76	[0.29; 1.99]	100.0%
Heterogeneity: I^2 = 84%, p < 0.01								
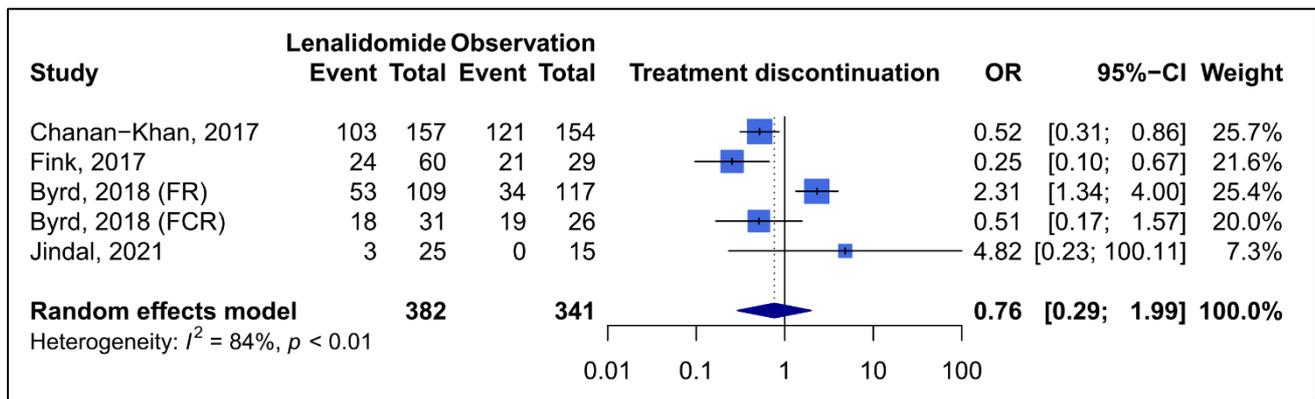
Secondary outcomes of meta-analysis **– Treatment discontinuation**

Study	Lenalidomide Event	Total	Observation Event	Total	Serious adverse events	OR	95%−CI	Weight
Chanan−Khan, 2017	127	157	69	154		5.21	[3.13; 8.68]	77.3%
Fink, 2017	35	60	9	29		3.11	[1.22; 7.96]	22.7%
Fixed effect model		217		183		4.64	[2.96; 7.26]	100.0%
Heterogeneity: I^2 = 0%, p = 0.34								
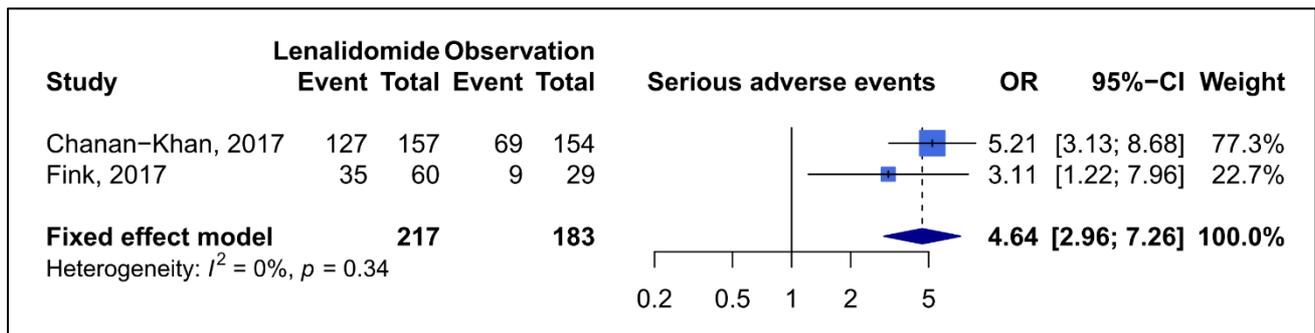
Secondary outcomes of meta-analysis **– Serious adverse events**

Study	Lenalidomide Event	Total	Observation Event	Total	Fatal adverse events	OR	95%−CI	Weight
Chanan−Khan, 2017	3	157	2	154		1.48	[0.24; 8.99]	38.7%
Fink, 2017	1	60	1	29		0.47	[0.03; 7.87]	16.0%
Byrd, 2018 (FR)	2	109	1	117		2.17	[0.19; 24.26]	21.6%
Byrd, 2018 (FCR)	0	31	1	26		0.27	[0.01; 6.91]	12.0%
Jindal, 2021	0	25	1	15		0.19	[0.01; 4.96]	11.8%
Fixed effect model		**382**		**341**		**0.86**	**[0.28; 2.63]**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $p = 0.66$
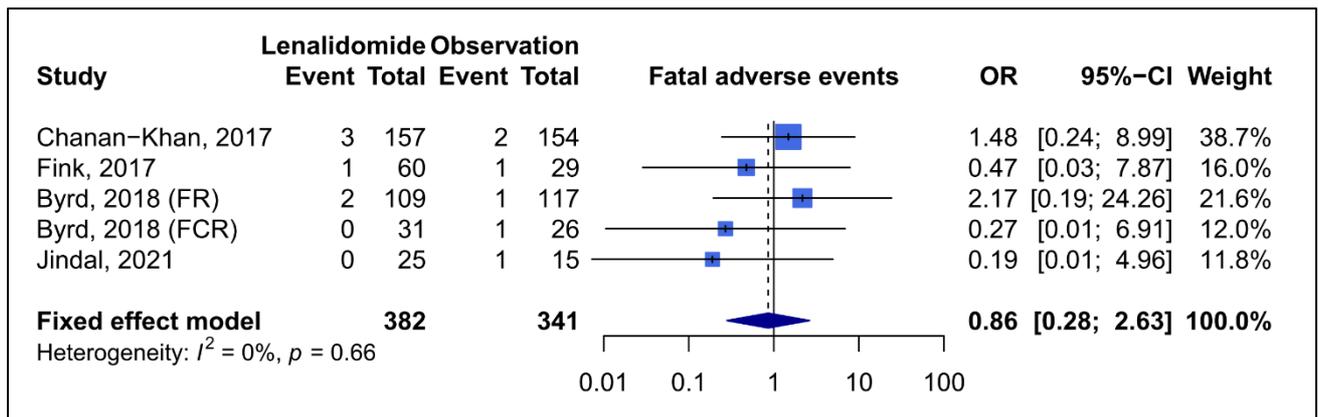
Secondary outcomes of meta-analysis - Fatal adverse events

**Supplementary Information S5 - Subgroup analysis of outcomes**

Study	Lenalidomide	Observation	PFS(high MRD)	HR	95%−CI	Weight
Fink, 2017	60	29		0.17	[0.05; 0.50]	75.3%
Jindal, 2021	25	15		0.22	[0.03; 1.51]	24.7%
Fixed effect model	**85**	**44**		**0.18**	**[0.07; 0.46]**	**100.0%**
Heterogeneity: $I^2 = 0\%$, $p = 0.80$			0.1 0.5 1 2 10			
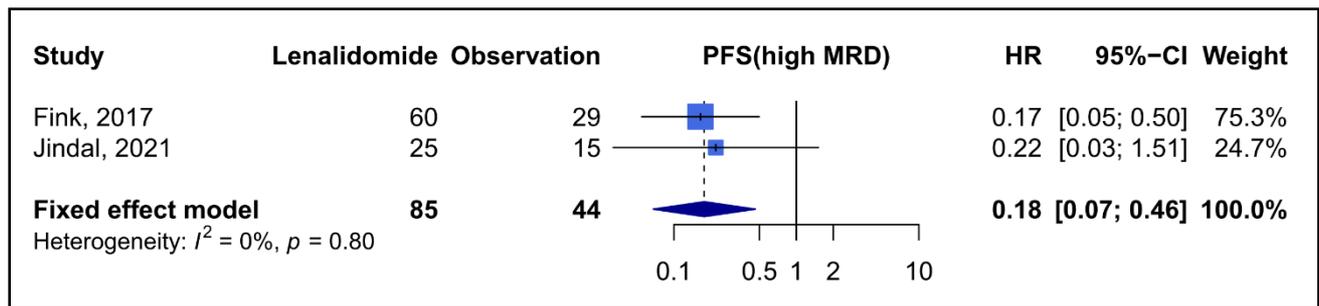
Subgroup analysis of Progression-Free Survival (PFS) in patients with high minimal residual disease (MRD)

The included patients were categorized with high minimal residual disease level. Outcome analyses were performed using hazard ratio with related 95% confidence intervals (95% CI).

HR, Hazard ratio; **CI**, Confidence intervals

**Supplementary Information S6 - Funnel plots and Egger's test**
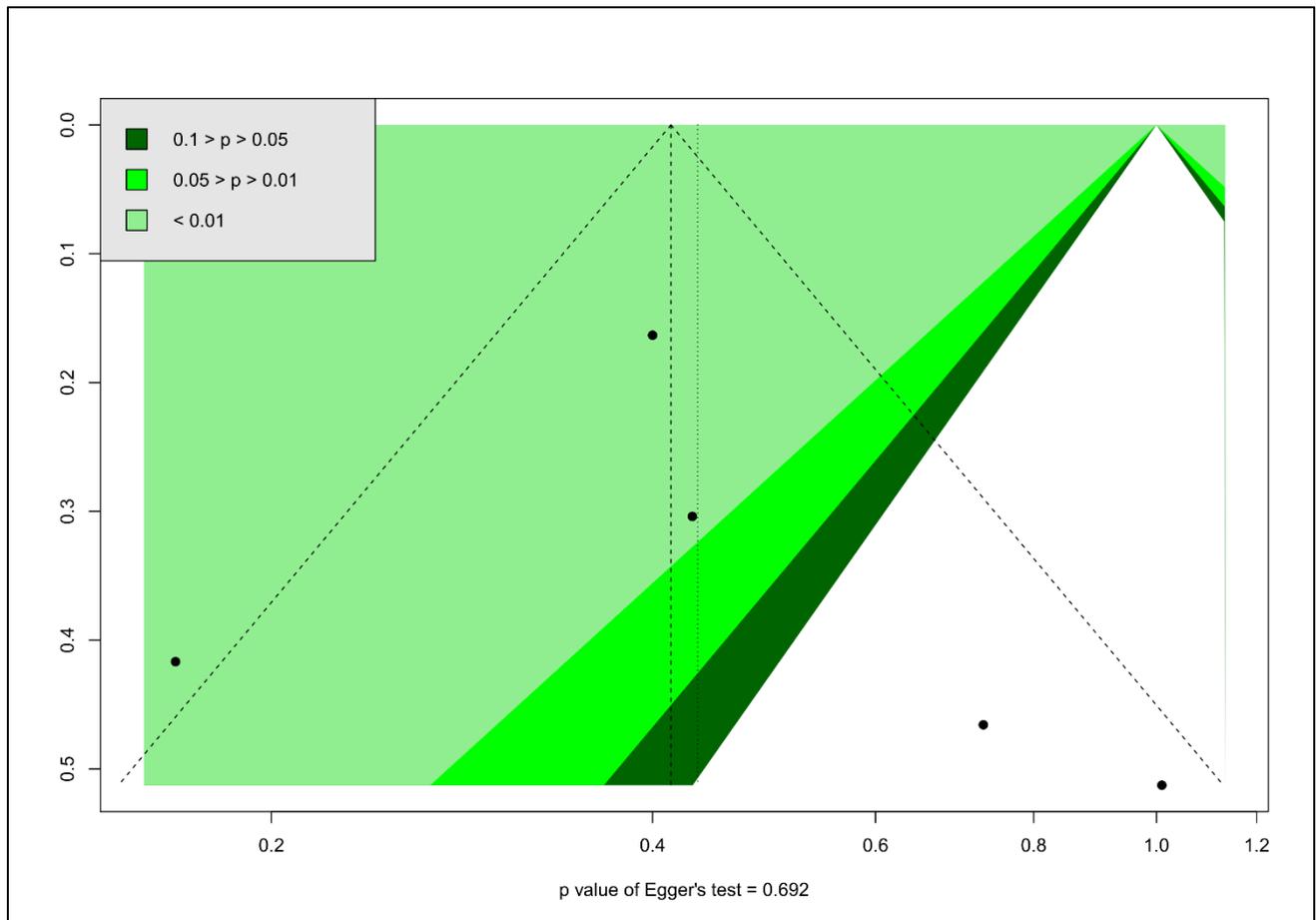
Funnel plots and Egger's test in outcome for Progression-Free Survival (PFS)

P-value: The significant level was set as 0.05;
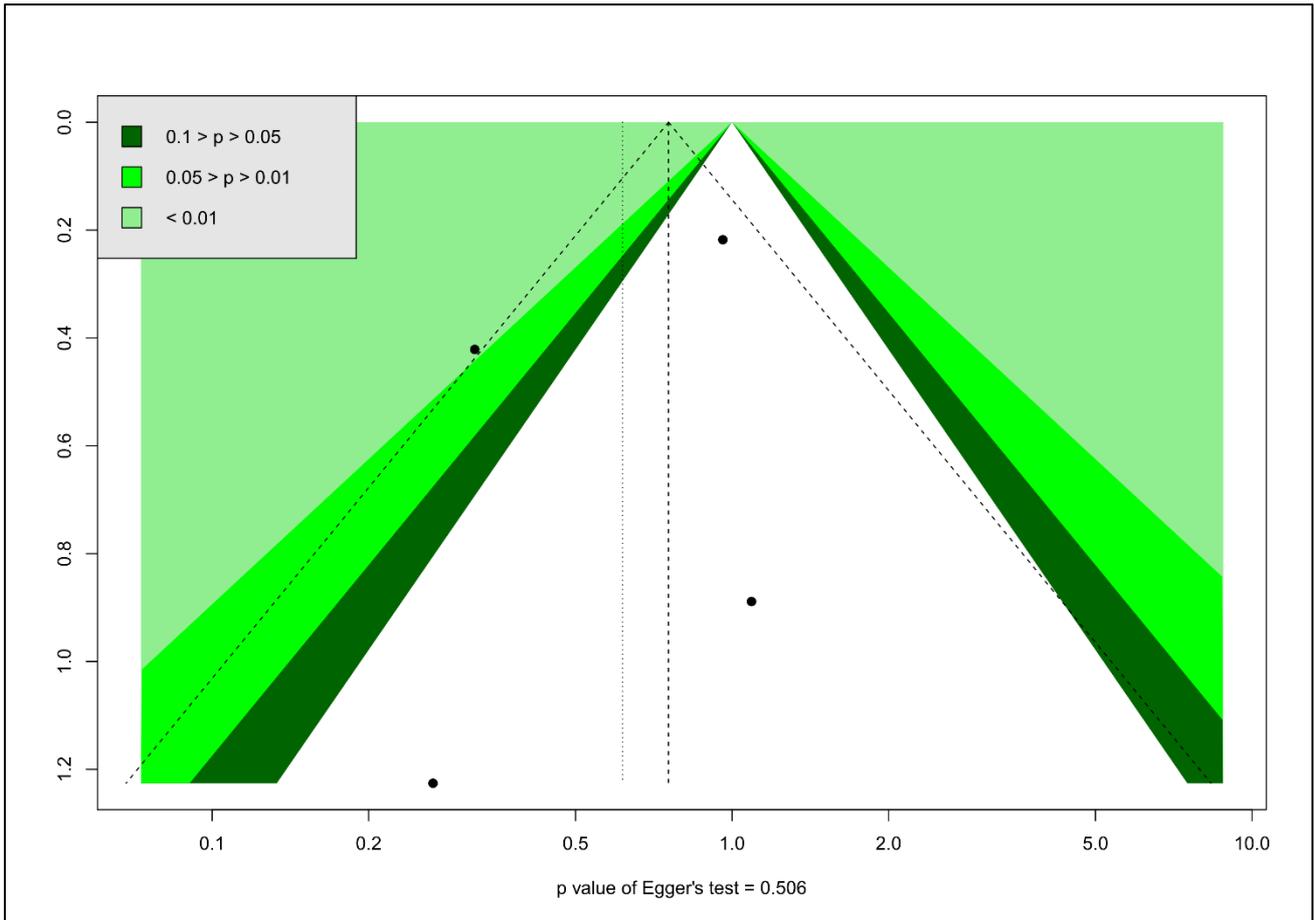
Funnel plots and Egger's test in outcome for Overall Survival (OS)

P-value: The significant level was set as 0.05;
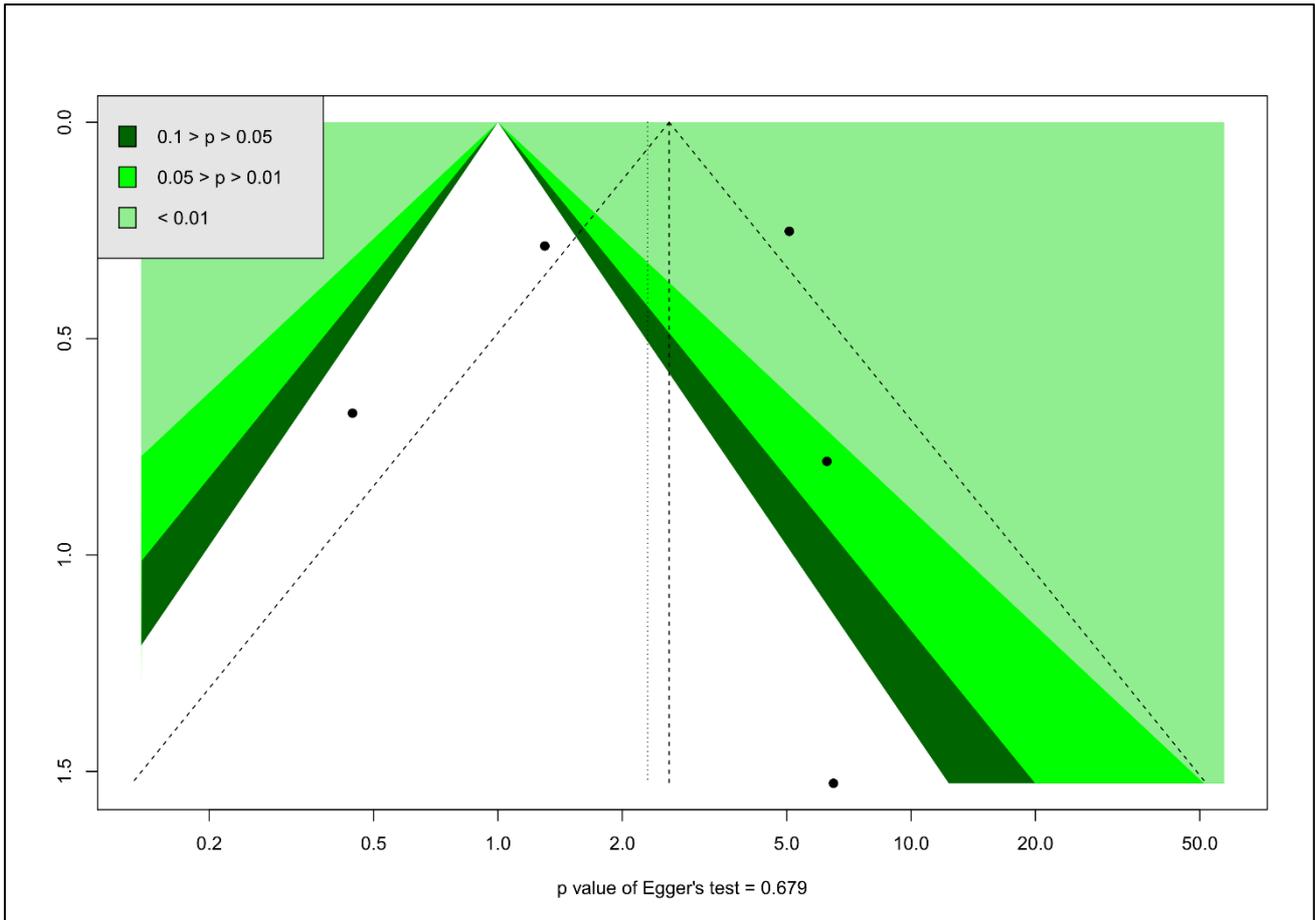
Funnel plots and Egger's test in outcome for Grade 3-4 neutropenia

P-value: The significant level was set as 0.05;
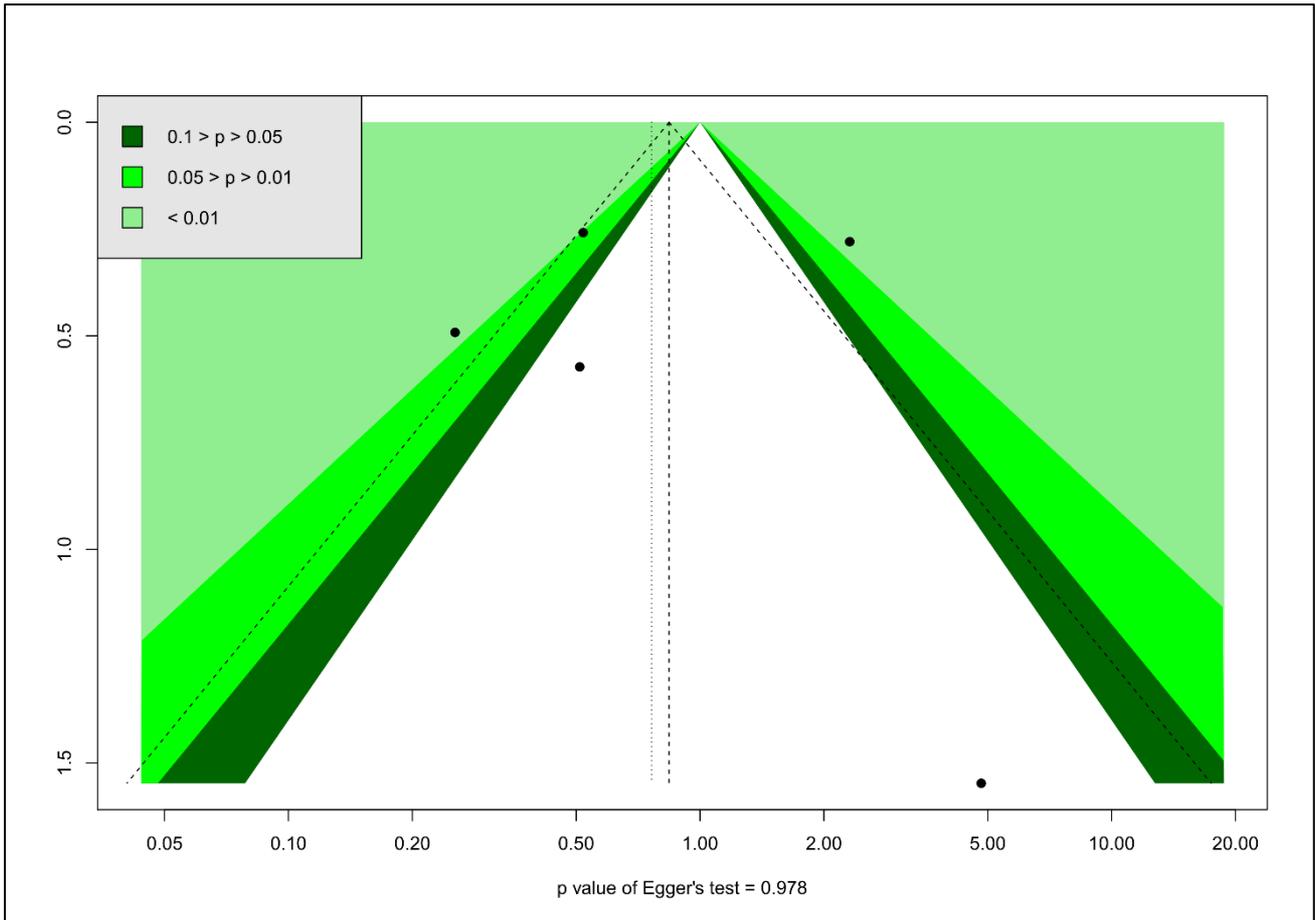
Funnel plots and Egger's test in outcome for Treatment discontinuation (TD)

P-value: The significant level was set as 0.05;
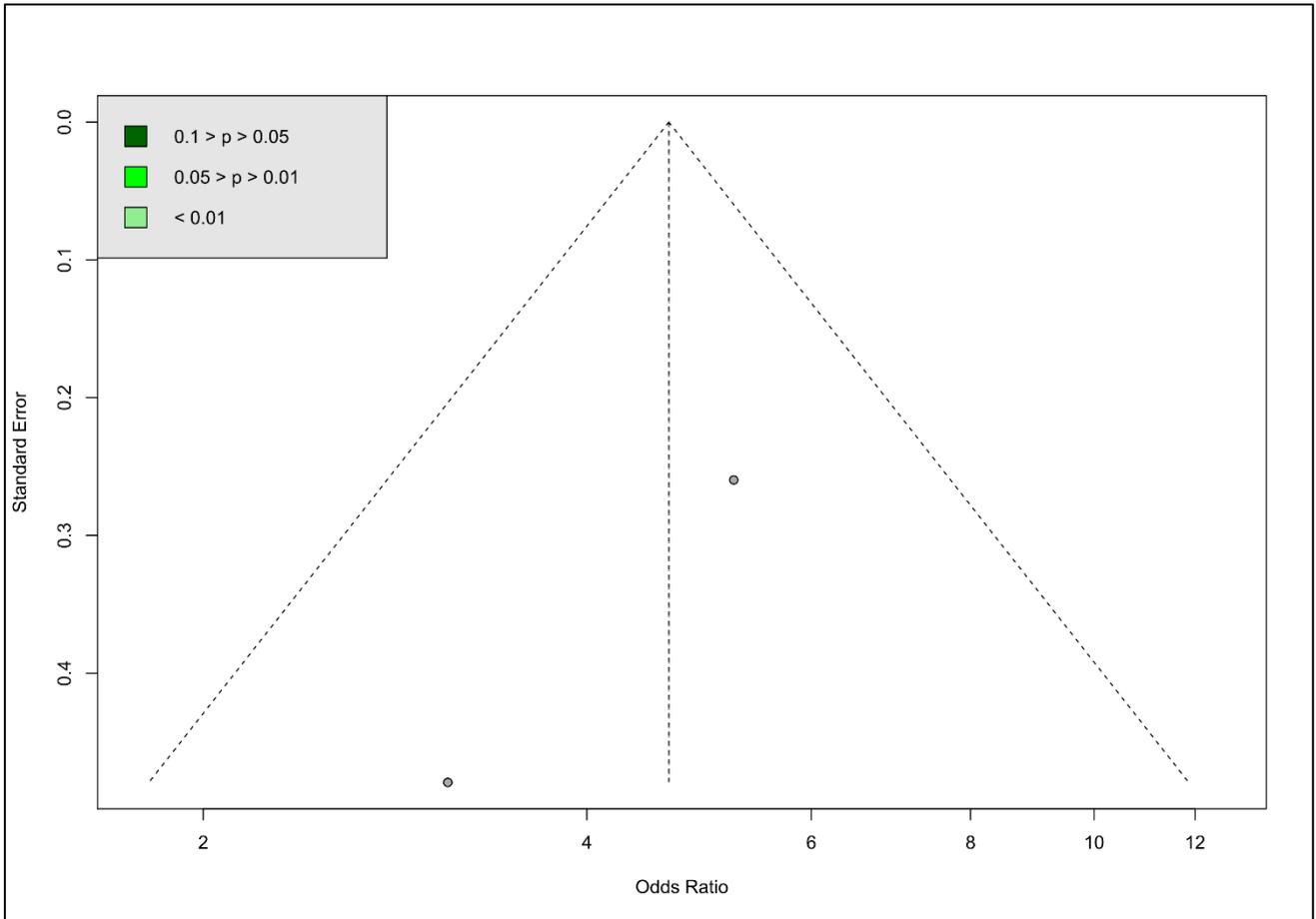
Funnel plots and Egger's test in outcome for Serious adverse events (SAE)

P-value: The significant level was set as 0.05;
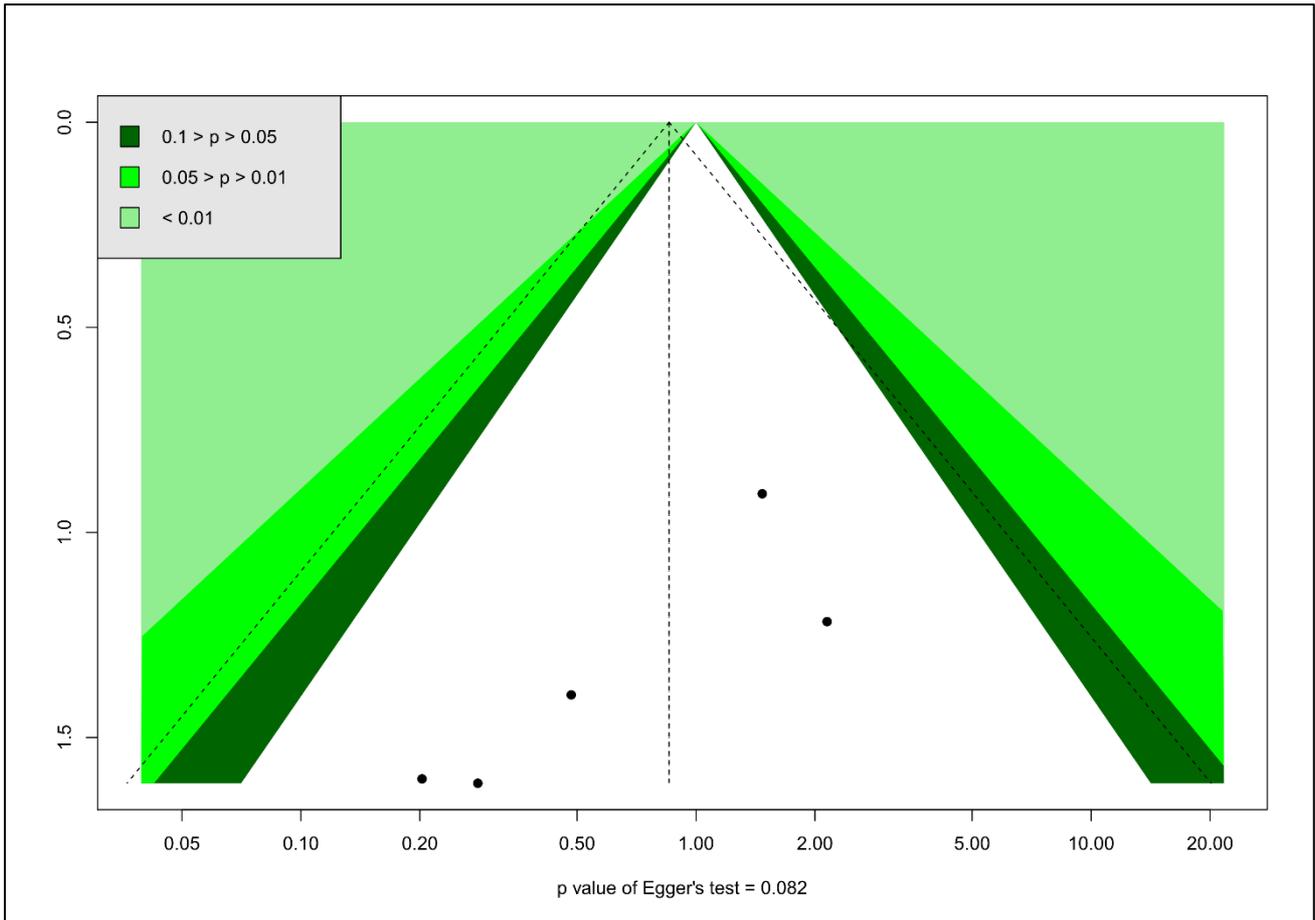
Funnel plots and Egger's test in outcome for Fatal adverse events (FAE)

P-value: The significant level was set as 0.05;

Note:

The funnel plots and Egger's test should be interpreted in caution, because the studies included in those outcomes were few in numbers.