Mediterranean Journal of Hematology and Infectious Diseases

Review Article (Advance Online Publication not corrected by the authors)

Efficacy and Safety of Thalidomidein Patients with Transfusion-Dependent B-Thalassemia: A Systematic Review, Meta-Analysis and GRADE Evaluation

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Supplementary Files:

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Electronic supplementary material

Supplementary table 1. Grouping criteria for subgroup analysis

Covariate	Sample size	Age	Dosage group 1	Dosage group 2	Follow-up	Baseline Hb level	Baseline HbF level	Baseline SF level
1	< 50 patients	< 18 years	≤50mg	≤3mg/kg	< 12 months	< 7g/dL	< 10%	< 2500ng/mL
2	≥50 patients	≥18 years	50-100mg	3-5mg/kg	≥12 months	≥7g/dL	10%-20%	≥2500ng/mL
3			> 100mg	> 5mg/kg			> 20%	

Supplementary table 2. The Hb, HbF and SF level of TDT patients before and after treatment

Study ID	In	Sample size	Follow-up (months)	Before treatment			After treatment		
				Hb level (g/dl)	HbF level(%)	SF level(ng/ml)	Hb level (g/dl)	HbF level(%)	SF level(ng/ml)
Ramanan 2017[17]	T	104	14±3*2	NR	NR	4534±2025.42*2	NR	NR	2061.5±1816.67*2
Jiskani 2018[18]	T	70	6	8.93±1.04	NR	3125±143.51	10.54±1.18	NR	1241±135.94
Begum 2020[19]	T	51	NR	7.04±0.53	NR	3258.11±2291.91	8.39±1.44	NR	2589.65±2072.74
Islam 2020[20]	T	50	16±8.75*2	6.05±0.69*1	NR	NR	9±1.16*1	NR	2255±951.26*1
Nag 2020[21]	T	21	3	6.5±1.08#2	NR	1919#2	7.2±1.74#2	NR	1404#2
Yang K 2020[22]	T	23	3	R	34.7±21.3	NR	R	52.2±22.7	NR

Study ID	In	Sample size	Follow-up (months)	Before treatment			After treatment		
				Hb level (g/dl)	HbF level(%)	SF level(ng/ml)	Hb level (g/dl)	HbF level(%)	SF level(ng/ml)
	T	14	12	5.6±1.8	NR	NR	9.1±1.6	NR	NR
Chandra 2021[23]	T	37	6	9.45±0.67	2.95±2.6	1758.9±835.1	8.89±0.6	49.2±33.3	1549.6±1016.9
Chen JM 2021[24]	T	49	3	7.24 ±1.62	13.9±5.32*1	3102.2±900.13*1	9.16 ± 1.74	56.3±9.71*1	3058.73±727.63*1
	C	50	3	7.57 ±1.49	17.93±7.64*1	5377.03±878.72*1	NR	24.68±9.29*1	5010.5±926.57*1
Chen JM 2021b[24]	T	90	24	7.08 ± 1.28	NR	3880.75±837.67*1	11.00 ± 2.37	NR	2047.5±352.89*1
Li JY 2022[26]	T	41	12	7.463±1.329	NR	NR	11.041±1.868	NR	NR
	H	41	12	11.027±1.523	NR	NR	11.284±1.748	NR	NR
Ali 2023[27]	T	532	30	6#1	NR	2195#1	8#1	NR	528#1
Bhattacharjee 2023[28]	T	14	6	8.7±0.99	NR	3309.4±3342.39	9.2±1.56	NR	2587.4±2204.39
	C	12	6	9.5±0.95	NR	2055.6±2182.30	9.2±1.24	NR	2496.8±2379.63
Huang L 2023[31]	T	20	12	5.744±0.723	28.32±4.75	3 851.87±157.63	9.862±0.867	63.98±6.13	3601.69±120.67
	C	20	12	5.617±0.705	27.93±4.64	3 855.16±154.81	8.858±0.812	34.14±5.08	3719.69±147.78
Jian X 2023[30] & Yang K 2024[32]	T	22	3	8.30±0.86	17.1±15.9	4167.97±3167.21*1	10.41 ± 1.77	50.1±33.8	1963.1±3142.26*3
Zhu WJ 2024[34]	T	42	24	7.73± 1.19	NR	NR	10.26± 1.02	NR	NR
	T	25	48	NR	16.09±12.79	5164.3±4966.7	R	74.40±20.10	1651.45±1247.6
Guo LM 2024[35]	T	20	12	5.617±0.711	27.56±4.01	3851.47±157.63	9.852±0.847	63.99±6.02	3600.14±117.20
	C	20	12	5.622±0.705	27.55±4.23	3855.17±154.82	8.852±0.820	34.52±5.02	3719.58±147.63
Hossain 2025[37]	T	54	12	7.06 ± 0.99	NR	NR	9.33±1.16	NR	NR
Podder 2025[39]	T	52	12±0.75*2	NR	NR	2733.84#1	NR	NR	1883#1
Rahman 2025[40]	T	72	30	6.12±0.65	NR	3367.5±1972.9*1	8.36±2.04	NR	1017.7±830.3*1
	C	92	30	5.96±0.96	NR	3009.7±1984.2*1	6	NR	4111.8±1724.7*1
Singha 2025[41]	T	25	6	7.8±0.7	NR	1194.2±452.5	8.8± 1.3	NR	839.4±443.1
Nie YJ 2025[42]	T	40	6	6.968±1.719	NR	3971.66±378.48	8.736±1.916	NR	3831.29±287.91
	C	40	6	6.955±1.733	NR	3963.84±375.52	7.468±1.824	NR	3943.54±293.85

*1 Estimate using the method of Wan; *2 Estimate using the method of Hou; *3 **Calculate by merging subgroups after estimating using the method of** Wan; **#1 No data conversion was performed; #2 No data conversion was performed, and the original data is the median**; R=reported; NR=not reported; In=Intervention; T=Thalidomide arm; C=Control arm; H=healthy arm; Hb=hemoglobin; HbF =fetal hemoglobin; SF= serum ferritin.

Supplementary table 3. Changes in Hb, HbF and SF level from baseline to endpoint in RCTs

Study ID	Design	Coutry	Sample size	Thalidomide dose (per day)	Age in year	Follow-up (months)	Changes from baseline to endpoint		
							Hb level(g/dL)	HbF level(%)	SF level(ng/mL)
Chen JM 2021a[24]	RCT	China	49	100-150 mg	18.4 ± 5.5	3	1.70±0.78*1	34.60±7.43*1	-192.10±320.05*1
			50	Placebo arm	18.4 ± 5.8	3	-0.49±0.28*1	3.55±2.45*1	-621.85±537.73*1
Bhattacharjee 2023[28]	RCT	India	14	50 mg	26.14±4.276	6	0.56±1.34	NR	-1059.30±1571.58
			12	Control arm	28.83±4.387	6	−0.31± 0.94	NR	441.20± 1439.31
Huang L 2023[31]	RCT	China	20	100 mg	26.55±2.48	12	4.12±0.80*2	35.66±5.57*2	-250.18±142.78*2
			20	Control arm	26.35±2.43	12	3.24±0.76*2	6.21±4.87*2	-135.47±151.42*2
Guo LM 2024[35]	RCT	China	20	100 mg	26.34±2.85	12	4.24±0.79*2	36.43±5.31*2	-251.33±141.81*2
			20	Control arm	26.52±1.21	12	3.23±0.77*2	6.97±4.68*2	-135.59±151.35*2
Nie YJ 2025[42]	RCT	China	40	25~175 mg	14.68±2.23	6	1.77±1.83*2	NR	-140.37±342.30*2
			40	Control arm	14.35±2.16	6	0.51±1.78*2	NR	-20.30±342.08*2

*1 Estimate using the method of Wan; *2 SD of change imputed assuming a pre-post correlation of *r*= 0.5 .NR=not reported; Hb=hemoglobin; HbF =fetal hemoglobin; SF= serum ferritin.

Supplementary table 4. Responses of TDT patients in our study and included studies

Study ID	Sample size	In	Follow-up (months)	In our study			In included study	
				MiR	MaR	Overall response	Response definitions	Response data
Ramanan 2017[17]	104	T	14±3*2	NR	97	97	Only a simple description: Ninety-seven patients were off blood transfusion for a duration ranging from 1 month to 42 month (mean: 10.22 months)	transfusion independent: 97
Begum 2020[19]	51	T	NR	NR	18	18	Only a simple description: There is no blood transfusion required for 35.3% (n=18) of the patients after the treatment	transfusion independent: 18
Islam 2020[20]	50	T	16±8.75*2	NR	30	30	Only a simple description: 30 patients, 60% became transfusion independent for more than 12 months with HB > 2-3gm/dl from baselines	transfusion independent:30
Nag 2020[21]	21	T	3	1	15	16	**Complete response** was defined as transfusion independence (100% reduction in transfusion requirement). **Partial response** was defined as a 50–99% reduction in transfusion requirement. Anything less than partial response was categorized as '**no response**'	Complete response: 15 Partial response: 1 No response: 5
Yang K 2020[22]	23	T	3	12	10	22	**MaR**, removal from the blood transfusion, **MiR**, ≥50% reduction in transfusion requirement, and **NR**, <50% reduction in transfusion requirement.	MaR: 10 MiR: 12 NR: 1
Chandra 2021[23]	37	T	6	4	15	19	Subjects with more than 50% reduction in transfusion requirement as compared to pre-study transfusion requirement were classified as having **major response**; those with 25-50% reduction in transfusion requirement were classified as **moderate response**, and those with less than 25% decrease in transfusion requirement were classified as **minimal/no response**	major response: 19 (with transfusion independent: 15) moderate response: 12 minimal/no response:6
Chen JM 2021a[24]	49	T	3	NR	34	34	**excellent response**, an elevation in total Hb level of ≥20 g/L and the patients were free of blood transfusion for at least 6 weeks; **good response** an elevation in total Hb level of 10 to 20 g/L was achieved, or Hb not substantially increased (<10 g/L) but the patients had Hb >70 g/L and were free of blood transfusion for at least 6 weeks; **no**	Excellent response: 20 Good response : 14 No response: 15
	50	C	3	NR	5	5		Excellent response: 0 Good response : 5 No response: 45
Chen JM 2021b[24]	90	T	3	NR	76	76		Excellent response: 51

Study ID	Sample size	In	Follow-up (months)	In our study			In included study	
				MiR	MaR	Overall response	Response definitions	Response data
							response, an elevation in total Hb level of <10 g/L and the patients were still transfusion-dependent	Good response : 25 No response: 14
Li XY 2021[25]	77	T	6	11	51	62	For patients with TDT β-thalassemia, maintenance of hemoglobin above 90 g·L-1 without blood transfusion after treatment was defined as a **major response**; and maintenance of hemoglobin above 90 g·L-1 with 50% or over 50% reduction of transfusion volume was defined as a **minor response**; otherwise, the treatment was considered **ineffective**.	major response: 51 minor response: 11 ineffective: 15
Ali 2023[27]	532	T	6	NR	408	408	**Excellent Response (ExR)**: maintenance of Hb level ≥ 9 g/dL without blood transfusion in last ≥ 56 days, **good response (GR):** maintenance of Hb level in the range of 7–8.9 g/ dL without blood transfusion in last ≥ 56 days, and **partial response (PR)**: maintenance of Hb level in the range of 6–6.9 g/dL without blood transfusion in last ≥ 56 days. Whereas, **no response (NR)**: maintenance of Hb level < 6 g/dL. Blood transfusion was administered, if at any stage Hb level dropped below 6 g/dL	ExR: 137 GR: 165 PR: 106 NR: 124
Idrees 2023[29]	384	T	19.2±8.8*2	NR	184	184	remaining transfusion independent in the last two months and maintaining an Hb levels of ≥9.0g/dl were labeled as **Excellent Responders (ExR)**, patients maintaining an Hb levels of 7.0 to 8.9g/dl were labeled as **Good Responders (GR)**, patients maintaining an Hb levels of 6.0 to 6.9g/dl as **Partial Responders (PR)** and those showing no significant improvement in Hb levels as **Non-Responders (NR)**.	ExR: 184 GR: 96 PR: 60 NR: 44
Jian X 2023[30] & Yang K 2024[32]	22	T	3	3	14	17	independence from transfusion and maintenance of the hemoglobin (Hb) concentration greater than 9.0 g/dL after treatment was defined as a **major response**; and maintenance of the Hb concentration more than 9.0 g/dL with a 50% or higher reduction in transfusion was defined as a **minor response**; otherwise. In the absence of a major or minor response, treatment was considered **ineffective**.	major response: 14 minor response: 3 ineffective: 7
Yang WJ 2024[33]	34	T	6	0	21	21	**main response (MaR)**, characterized by Hb elevation≥2.0 g/L or no need for blood transfusion; **minor response (MiR)**, characterized by Hb elevation of 1.0–2.0 g/L or a	MaR: 21 MiR: 0 SLR: 9

Study ID	Sample size	In	Follow-up (months)	In our study			In included study	
				MiR	MaR	Overall response	Response definitions	Response data
							decrease in total transfusion volume of ≥50%; **slow response (SLR)**, characterized by Hb elevation <1.0 g/L or a decrease in total transfusion volume between 25 and 50%; and **no response (NR)** or basically ineffective, characterized by Hb elevation<1.0 g/L or a decrease in total transfusion volume<25%.	NR: 4
Zhu WJ 2024[34]	25	T	48	1	21	22	**excellent response**, free of blood transfusion for at least 6 weeks, reaching a fnal total Hb level of 90 g/L, or an elevation in total Hb level of ≥ 20 g/L; **good response,** a reduction in the transfusion burden of at least 50% from baseline (the 3-month period before the first of thalidomide); **minor response**, reduction of at least 33% and <50% from baseline; and **no response**, reduction in transfusion burden of <33%	Excellent response: 21 Good response : 1 Minor response:3 No response: 0
Yang K 2025[36]	25	T	3	5	15	20	**major response**, transfusion independence, and maintenance of hemoglobin level > 9.0 g/dL; **minor response**, ≥ 50% reduction in transfusion requirement and maintenance of hemoglobin level > 9.0 g/dL; and **no response**, < 50% reduction in transfusion requirement to maintain a pretransfusion hemoglobin level of 9.0 g/dL.	major response: 15 minor response: 5 no response: 5
Li XY 2025[38]	170	T	12	39	102	141	When haemoglobin ≥90 g/L, maintaining transfusion independence was considered a **major response**, and when haemoglobin ≥90 g/L, reducing transfusion volume by ≥50% was considered a **minor response**. Otherwise, it was defined as **ineffective**	major response: 102 minor response: 39 ineffective: 29
Podder 2025[39]	49	T	12±0.75*2	10	34	44	**Complete response (CR)** were defined by cessation of transfusion requirement with a hemoglobin of 8 g/dl. **Partial response (PR)** were defined as >50% reduction of transfusion requirement over 1 year. **No response** is defined as <50% reduction in transfusion requirement	CR: 34 PR: 10 NR: 5
Rahman 2025[40]	72	T	30	/	53	53	Patients were grouped on the basis of thalidomide response. **Excellent Responders (ER)** had Hb levels ≥9.0 g/dL without transfusion in the past two months. **Good Responders (GR)** had Hb levels of 7.0–8.9 g/dL without transfusion in the last two months. **Partial Responders (PR)** had Hb levels of 6.0–6.9 g/dL for two months	ER: 25 GR: 18 PR: 10 NR: 19
	92	C	30	/	/	/		Not reported

Study ID	Sample size	In	Follow-up (months)	In our study			In included study	
				MiR	MaR	Overall response	Response definitions	Response data
							without transfusion. **Non responders (NR)** had no signifcant Hb improvement from baseline	
Singha 2025[41]	25	T	6	12	10	22	**Complete response:** Achievement of transfusion independence. **Partial response**: ≥ 50% reduction in transfusion volume. **No response**: <50% reduction or no change in transfusion needs	Complete response: 10 Partial response:12 No response:3

/ not reported; In=Intervention; T=Thalidomide arm; C=Control arm; Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement); Minor response (MiR) was defined as ≥50% reduction of transfusion requirement; Overall response=numbers of MaR+ MiR.

Supplementary Table 5. Meta-regression analysis of outcomes in pre-post studies

Outcome	Covariate	Coefficient	SD	z	P>|z|	[95% conf. interval]		tau2
MRR	sample size	0.001	0.000	0.40	0.691	-0.001	0.001	0.041
	age	0.005	0.011	0.45	0.65	-0.017	0.027	0.039
	dosage group 1	0.050	0.049	1.01	0.312	-0.047	0.146	0.007
	follow up	0.004	0.004	0.90	0.366	-0.005	0.013	0.032
	baseline SF level	0.000	0.000	2.16	0.031	0.000	0.000	0.026
ORR	sample size	0.000	0.000	-0.70	0.485	-0.001	0.000	0.029
	age	0.012	0.009	1.26	0.207	-0.006	0.030	0.026
	dosage group 1	0.066	0.046	1.43	0.151	-0.024	0.156	0.007
	follow up	0.000	0.004	0.00	0.998	-0.008	0.007	0.024
	baseline SF level	0.000	0.000	0.94	0.346	0.000	0.000	0.018
Hb level	sample size	0.021	0.019	1.11	0.268	-0.016	0.057	1.711
	age	-0.100	0.115	-0.87	0.384	-0.325	0.125	1.707
	follow up	0.120	0.048	2.50	0.012	0.026	0.214	1.211
	baseline Hb level	-0.680	0.283	-2.40	0.016	-1.235	-0.125	0.988
ADEs	age	0.001	0.001	0.76	0.449	-0.002	0.003	0.000
	follow up	-0.003	0.001	-4.49	0.000	-0.004	-0.002	0.0005
	sample size	-0.0001	0.000	-2.09	0.037	0.000	0.000	0.001
ADEsLDD	age	0.000	0.000	1.02	0.309	0.000	0.000	1.60E-07
	follow up	0.000	0.000	-1.76	0.079	0.000	0.000	1.90E-07
	sample size	0.000	0.000	-1.22	0.224	0.000	0.000	1.90E-07

Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement). Minor response (MiR) was defined as ≥50% reduction of transfusion requirement. Major response rate (MRR) = numbers of MaR+ MiR/number of cases observed. Overall response rate (ORR) =numbers of MaR+ MiR/number of cases observed. Hb= Hemoglobin (g/dL), ADEs = adverse drug events; ADEsLDD = ADEs leading to drug discontinuation.

Supplementary Table 6. Leave-one-out analysis of outcomes of TDT patients

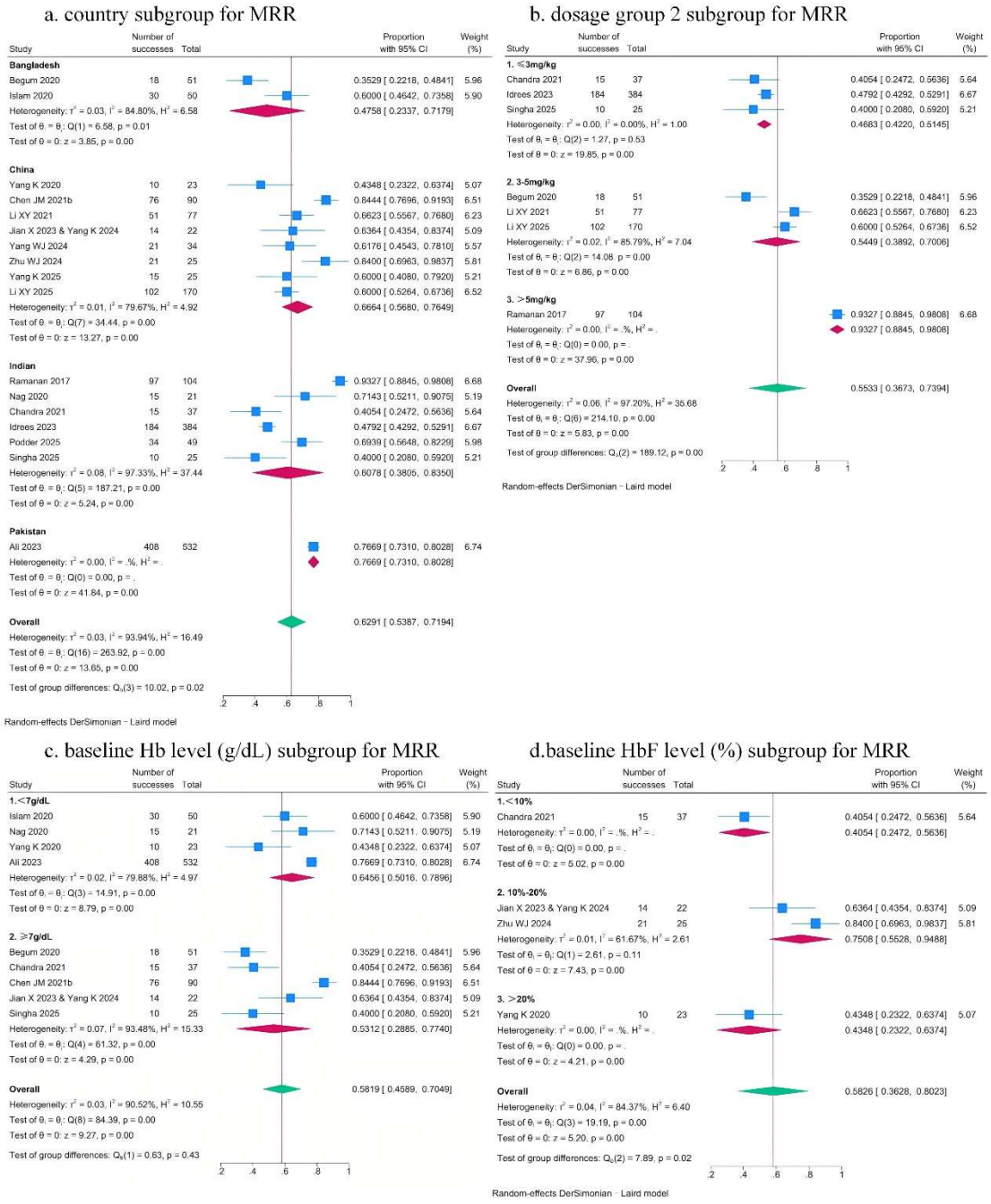
MRR of pre-post studies						**ORR of pre-post studies**					
study ID	Proportion	[95% conf.	interval]	p	|ΔES|	study ID	Proportion	[95% conf.	interval]	p	|ΔES|
Ramanan 2017[17]	60.86%	52.61%	69.10%	0	2.05%	Ramanan 2017[17]	73.82%	65.41%	82.22%	0	1.25%
Begum 2020[19]	64.71%	55.73%	73.69%	0	1.80%	Begum 2020[19]	77.52%	69.52%	85.53%	0	2.45%
Islam 2020[20]	63.07%	53.66%	72.49%	0	0.16%	Islam 2020[20]	75.97%	67.46%	84.49%	0	0.90%
Nag 2020[21]	62.43%	53.07%	71.78%	0	0.48%	Nag 2020[21]	75.01%	66.47%	83.54%	0	0.06%
Yang K 2020[22]	63.95%	54.72%	73.18%	0	1.04%	Yang K 2020[22]	73.71%	65.24%	82.18%	0	1.36%
Chandra 2021[23]	64.26%	55.09%	73.43%	0	1.35%	Chandra 2021[23]	76.41%	68.00%	84.82%	0	1.34%
Chen JM 2021b[24]	61.39%	51.86%	70.91%	0	1.52%	Chen JM 2021b[24]	74.42%	65.64%	83.20%	0	0.65%
Li XY 2021[25]	62.65%	53.11%	72.20%	0	0.26%	Li XY 2021[25]	74.69%	65.95%	83.44%	0	0.38%
Ali 2023[27]	61.78%	51.16%	72.40%	0	1.13%	Ali 2023[27]	74.86%	65.12%	84.60%	0	0.21%
Idrees 2023[29]	64.19%	55.80%	72.58%	0	1.28%	Idrees 2023[29]	77.47%	71.09%	83.84%	0	2.40%
Jian X 2023[30] & Yang K 2024[32]	62.86%	53.52%	72.20%	0	0.05%	Jian X 2023[30] & Yang K 2024[32]	74.95%	66.41%	83.49%	0	0.12%
Yang WJ 2024[33]	62.96%	53.58%	72.34%	0	0.05%	Yang WJ 2024[33]	75.81%	67.31%	84.32%	0	0.74%
Zhu WJ 2024[34]	61.59%	52.21%	70.97%	0	1.32%	Zhu WJ 2024[34]	74.28%	65.70%	82.85%	0	0.79%
Yang K 2025[36]	63.06%	53.72%	72.40%	0	0.15%	Yang K 2025[36]	74.79%	66.22%	83.35%	0	0.28%
Li XY 2025[38]	63.06%	53.42%	72.71%	0	0.15%	Li XY 2025[38]	74.49%	65.49%	83.50%	0	0.58%
Podder 2025[39]	62.47%	53.00%	71.94%	0	0.44%	Podder 2025[39]	74.09%	65.45%	82.72%	0	0.98%
Singha 2025[41]	64.18%	54.98%	73.37%	0	1.27%	Singha 2025[41]	74.28%	65.70%	82.85%	0	0.79%
theta	62.91%	53.87%	71.94%	0	0.00%	theta	75.07%	66.82%	83.33%	0	0.00%
Hb level changes of RCTs						**Hb level changes of pre-post studies**					
study ID	SMD	[95% conf.	interval]	p	|ΔES|	study ID	MD	[95% conf.	interval]	p	|ΔES|
Chen JM 2021a[24]	0.90	0.60	1.19	0	0.60	Jiskani 2018[18]	1.96	0.96	2.96	0	0.04
Bhattacharjee 2023[28]	1.69	0.37	3.01	0	0.19	Begum 2020[19]	1.99	1.00	2.97	0	0.06
Huang L 2023[31]	1.60	0.20	3.00	0	0.10	Islam 2020[20]	1.82	0.91	2.73	0	0.11
Guo LM 2024[35]	1.56	0.15	2.96	0	0.06	Nag 2020[21]	2.04	1.11	2.97	0	0.12
Nie YJ 2025[42]	1.71	0.34	3.08	0	0.21	Yang K 2020[22]	1.79	0.88	2.70	0	0.14

theta	1.50	0.40	2.60	0	0.00	Chandra 2021[23]	2.18	1.60	2.75	0	0.25
						Chen JM 2021b[24]	1.72	0.86	2.58	0	0.21
						Jian X 2023[30] & Yang K 2024[32]	1.91	0.98	2.84	0	0.02
						Zhu WJ 2024[34]	1.86	0.92	2.81	0	0.06
						Hossain 2025[37]	1.89	0.92	2.86	0	0.03
						Singha 2025[41]	2.02	1.07	2.97	0	0.10
						theta	1.93	1.05	2.80	0	0.00
HbF level changes of RCTs						**HbF level changes of pre-post studies**					
study ID	SMD	[95% conf. interval]		p	|ΔES|	study ID	MD	[95% conf. interval]		p	|ΔES|
Chen JM 2021a[24]	5.64	4.67	6.61	0	0.03	Yang K 2020[22]	46.99	33.52	60.47	0	7.78
Huang L 2023[31]	5.64	4.90	6.38	0	0.03	Chandra 2021[23]	36.59	10.27	62.91	0	2.63
Guo LM 2024[35]	5.57	4.84	6.30	0	0.04	Jian X 2023[30] & Yang K 2024[32]	41.03	18.50	63.55	0	1.81
theta	5.61	4.96	6.26	0	0.00	Zhu WJ 2024[34]	32.47	14.64	50.31	0	6.74
						theta	39.21	21.31	57.12	0	0.00
SF level changes of RCTs						**SF level changes of pre-post studies**					
study ID	SMD	[95% conf. interval]		p	|ΔES|	study ID	MD	[95% conf. interval]		p	|ΔES|
Chen JM 2021a[24]	-0.61	-0.90	-0.32	0	0.26	Ramanan 2017[17]	-1263.72	-1887.20	-640.24	0	168.68
Bhattacharjee 2023[28]	-0.21	-1.08	0.66	0.64	0.14	Jiskani 2018[18]	-1414.20	-2222.01	-606.38	0	18.20
Huang L 2023[31]	-0.25	-1.16	0.66	0.59	0.10	Begum 2020[19]	-1534.92	-2137.95	-931.88	0	102.53
Guo LM 2024[35]	-0.25	-1.16	0.66	0.60	0.10	Chandra 2021[23]	-1630.07	-2193.14	-1067.00	0	197.67
Nie YJ 2025[42]	-0.36	-1.42	0.70	0.51	0.01	Chen JM 2021b[24]	-1429.63	-2256.39	-602.86	0	2.77
theta	-0.35	-1.13	0.43	0.38	0.00	Jian X 2023[30] & Yang K 2024[32]	-1384.55	-1971.82	-797.29	0	47.84
						Zhu WJ 2024[34]	-1314.73	-1896.87	-732.59	0	117.66
						Singha 2025[41]	-1595.08	-2047.54	-1142.62	0	162.68
						theta	-1432.39	-1999.80	-864.99	0	0.00
ADEs incidence of RCTs											
study ID	Risk ratio	[95% conf. interval]		p	|ΔES|						

Chen JM 2021a[24]	1.297	0.565	2.977	0.539	0.64
Huang L 2023[31]	1.961	1.656	2.321	0	0.02
Guo LM 2024[35]	1.936	1.637	2.291	0	0.00
Nie YJ 2025[42]	1.946	1.642	2.305	0	0.01
theta	1.937	1.638	2.29	0	0.00

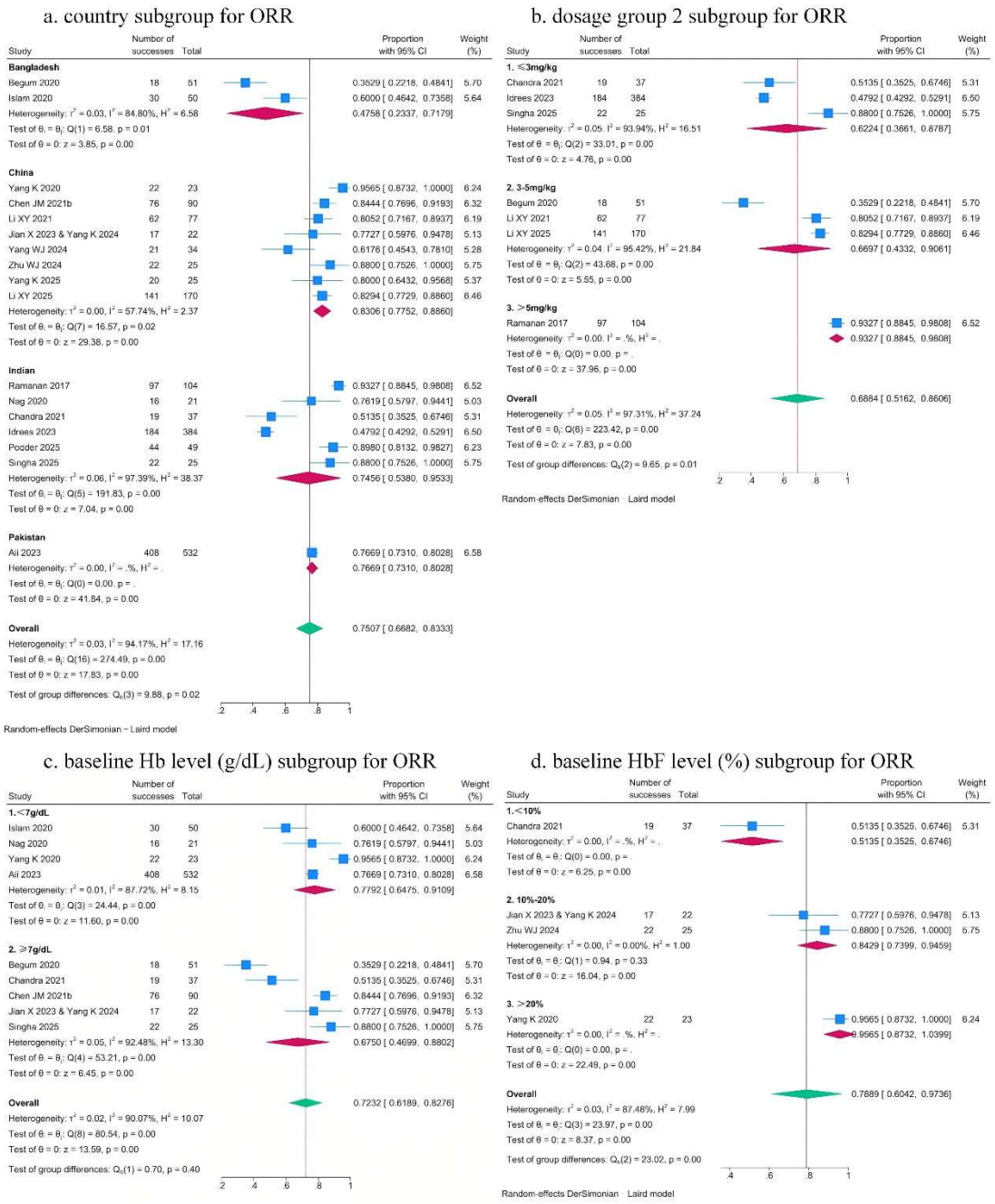
ADEs incidence of pre-post studies						**ADEsLDD of pre-post studies**					
study ID	MD	[95% conf. interval]		p	|ΔES|	study ID	MD	[95% conf. interval]		p	|ΔES|
Ramanan 2017[17]	5.5%	4.1%	6.9%	0	0.8%	Ramanan 2017[17]	0.0%	0.0%	0.1%	0.06	0.0%
Begum 2020[19]	4.9%	3.8%	6.1%	0	0.2%	Begum 2020[19]	0.0%	0.0%	0.1%	0.04	0.0%
Islam 2020[20]	5.3%	4.0%	6.5%	0	0.6%	Islam 2020[20]	0.0%	0.0%	0.1%	0.05	0.0%
Nag 2020[21]	4.5%	3.4%	5.6%	0	0.2%	Nag 2020[21]	0.0%	0.0%	0.1%	0.04	0.0%
Chandra 2021[23]	4.1%	3.0%	5.2%	0	0.6%	Chandra 2021[23]	0.0%	0.0%	0.1%	0.04	0.0%
Chen JM 2021b[24]	4.0%	2.9%	5.0%	0	0.7%	Chen JM 2021b[24]	0.0%	0.0%	0.1%	0.04	0.0%
Li XY 2021[25]	3.9%	2.8%	5.0%	0	0.8%	Li XY 2021[25]	0.0%	0.0%	0.1%	0.05	0.0%
Ali 2023[27]	5.7%	4.2%	7.2%	0	1.0%	Ali 2023[27]	0.1%	0.0%	0.2%	0.02	0.1%
Idrees 2023[29]	4.9%	3.7%	6.1%	0	0.2%	Idrees 2023[29]	0.1%	0.0%	0.2%	0.01	0.1%
Jian X 2023[30] & Yang K 2024[32]	4.8%	3.6%	5.9%	0	0.1%	Jian X 2023[30] & Yang K 2024[32]	0.0%	0.0%	0.1%	0.04	0.0%
zhu WJ 2024[33]	4.9%	3.7%	6.1%	0	0.2%	zhu WJ 2024[33]	0.1%	0.0%	0.1%	0.03	0.1%
Li XY 2025[38]	3.9%	2.9%	4.9%	0	0.8%	Li XY 2025[38]	0.0%	0.0%	0.0%	0.06	0.0%
Podder 2025[39]	4.9%	3.7%	6.0%	0	0.2%	Podder 2025[39]	0.0%	0.0%	0.1%	0.04	0.0%
theta	4.7%	3.6%	5.7%	0	0.0%	theta	0.0%	0.0%	0.1%	0.04	0.0%

Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement). Minor response (MiR) was defined as ≥50% reduction of transfusion requirement. Major response rate (MRR) = numbers of MaR+ MiR/number of cases observed. Overall response rate (ORR) =numbers of MaR+ MiR/number of cases observed. Hb= Hemoglobin, HbF= fetal hemoglobin, SF= serum ferritin, MD=mean difference, SMD= standardized mean difference, ADEs = adverse drug events; ADEsLDD = ADEs leading to drug discontinuation. |ΔES|=Absolute difference between the effect size after exclusion and the overall effect size.



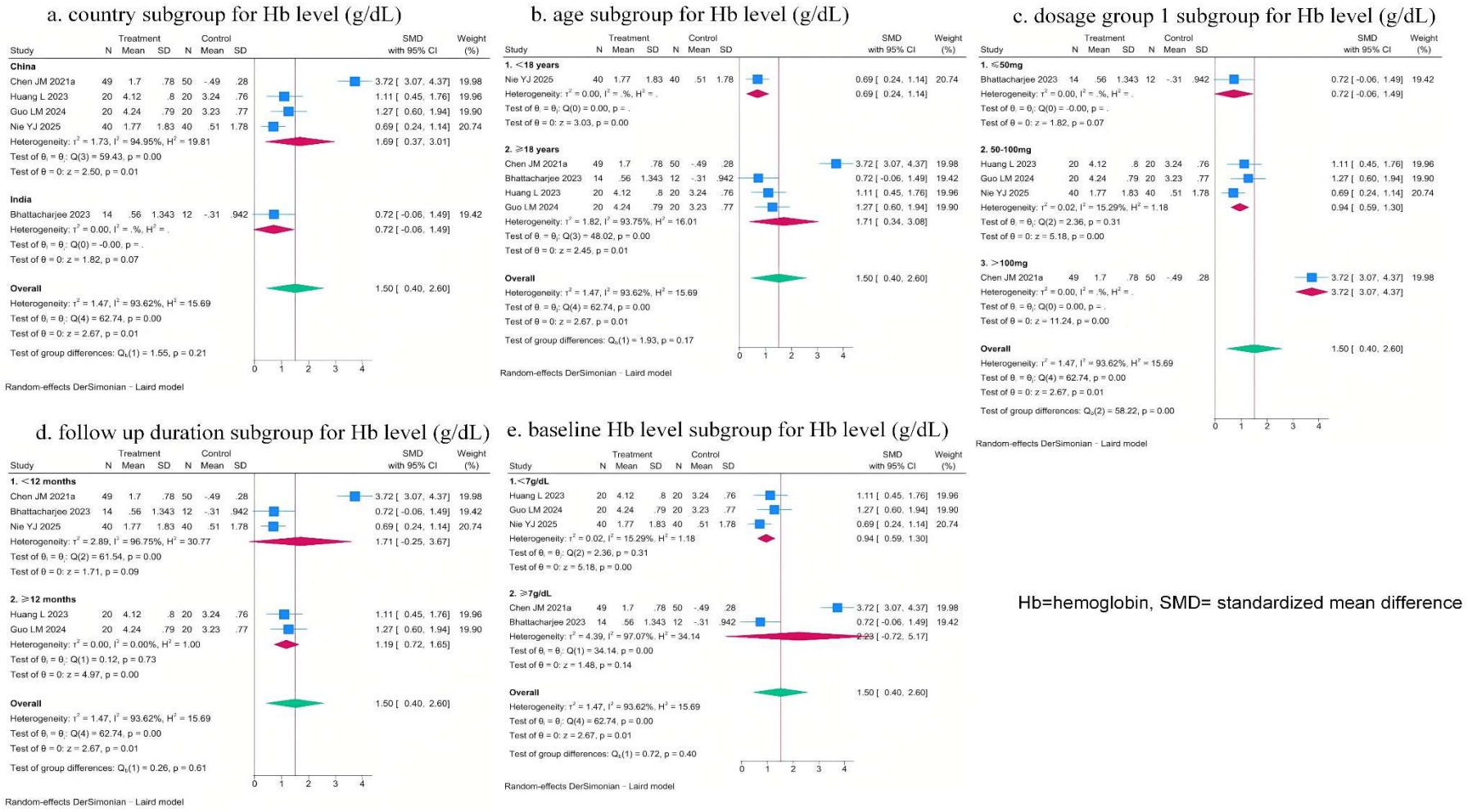
Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement). Major response rate (MRR) = numbers of MaR+ MiR/number of cases observed. Hb = Hemoglobin, HbF = fetal hemoglobin

Supplementary Figure 1. Subgroup analysis for MRR in pre-post studies

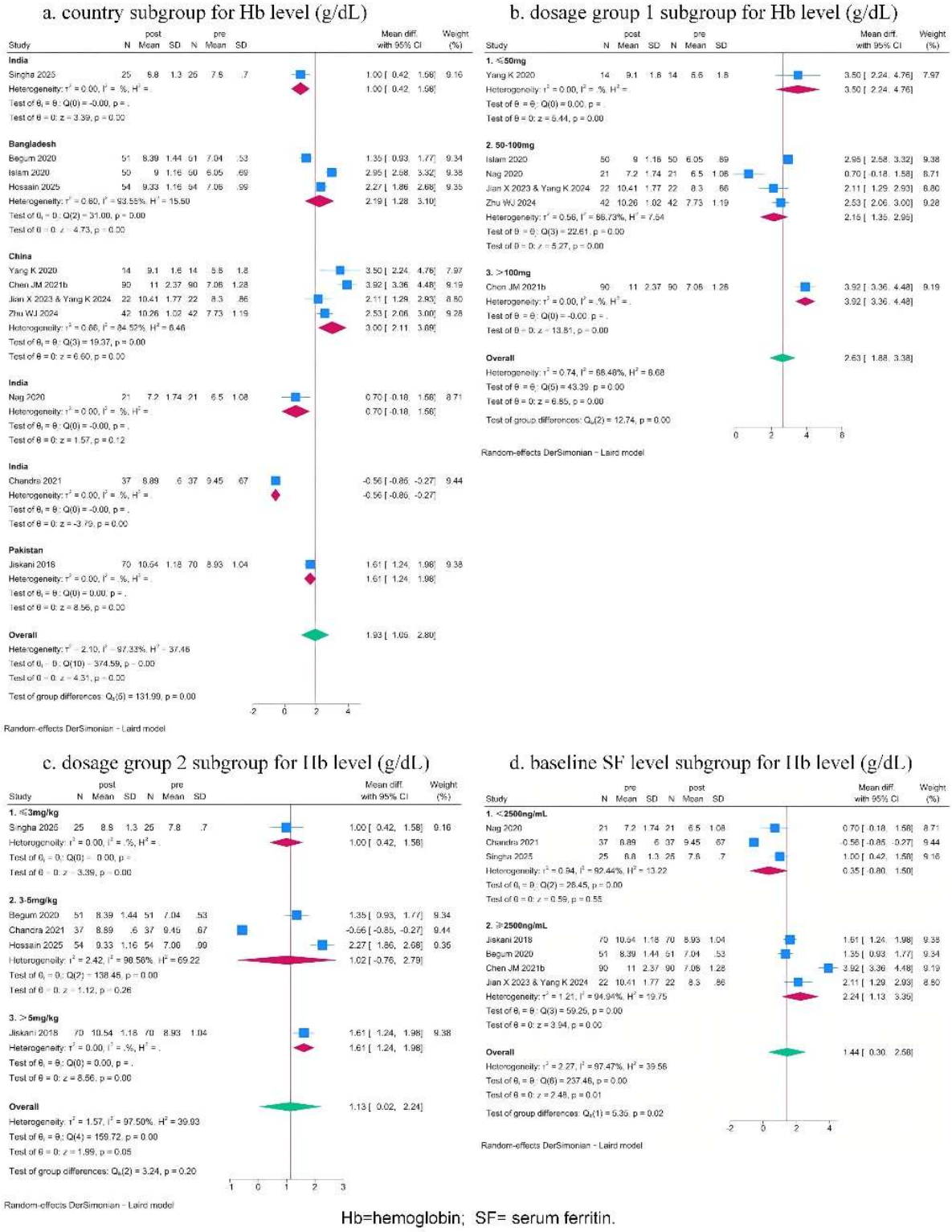


Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement). Minor response (MiR) was defined as ⩾50% reduction of transfusion requirement. Overall response rate (ORR) =numbers of MaR+ MiR/number of cases observed. Hb= Hemoglobin, HbF= fetal hemoglobin.

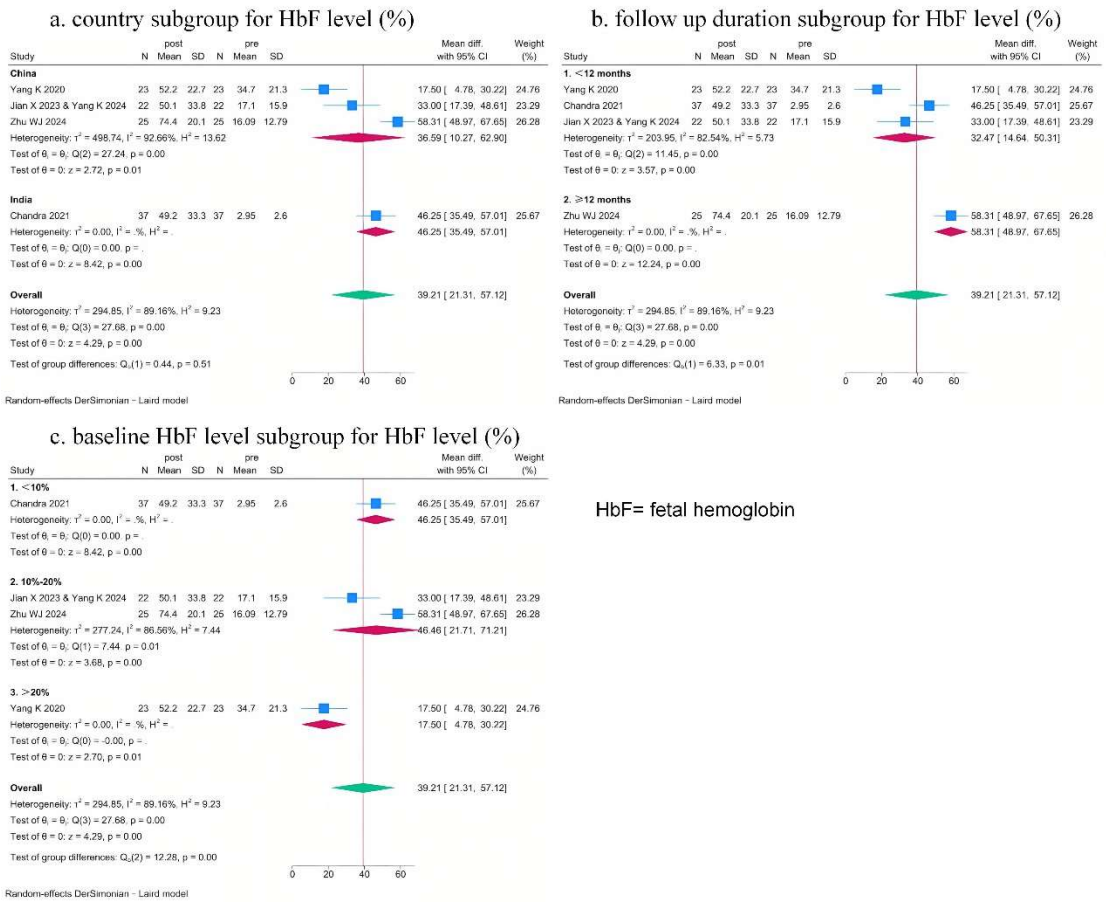
Supplementary Figure 2. Subgroup analysis for ORR in pre-post studies



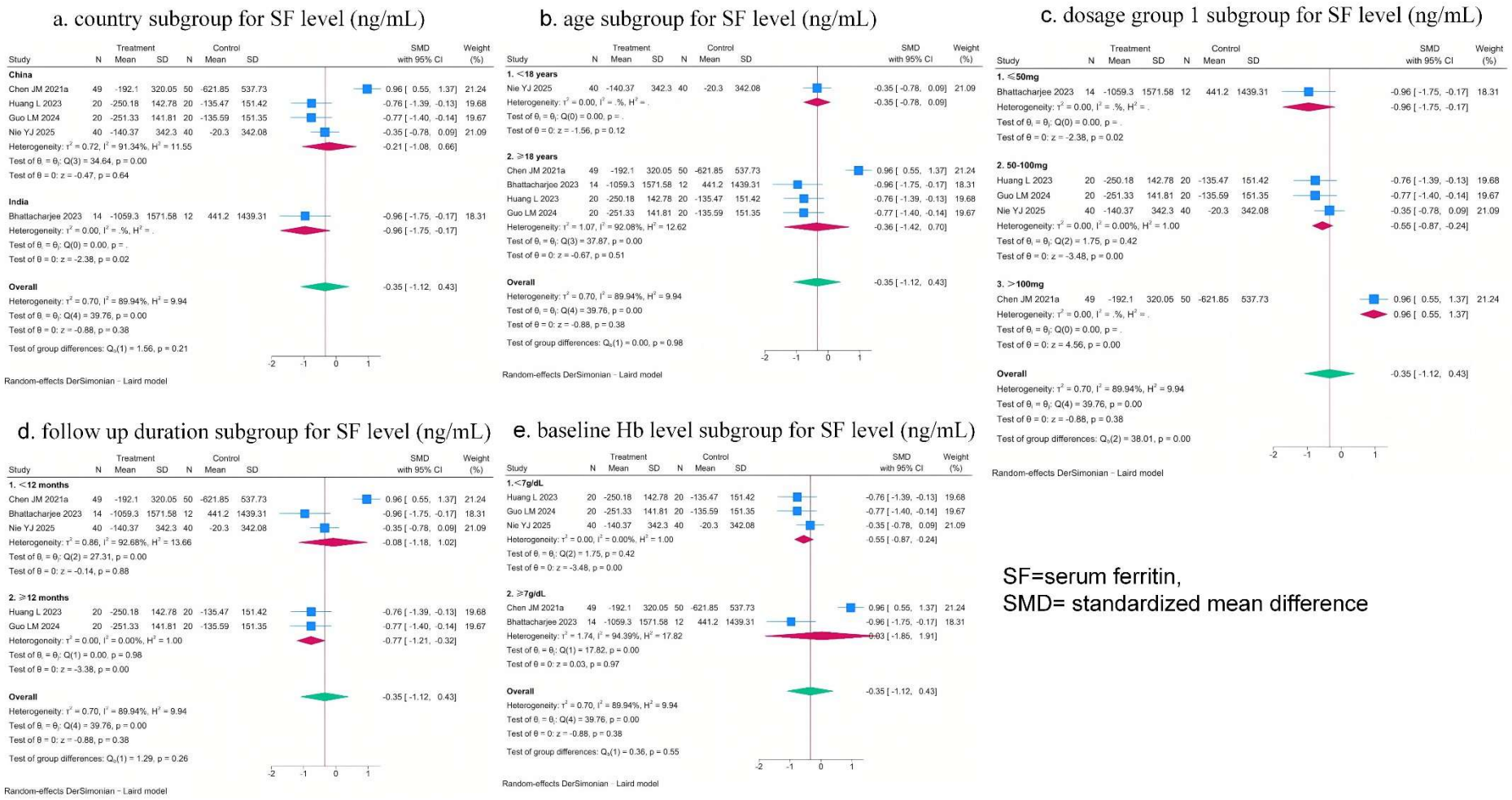
Supplementary Figure 3. Subgroup analysis of hemoglobin level in RCTs



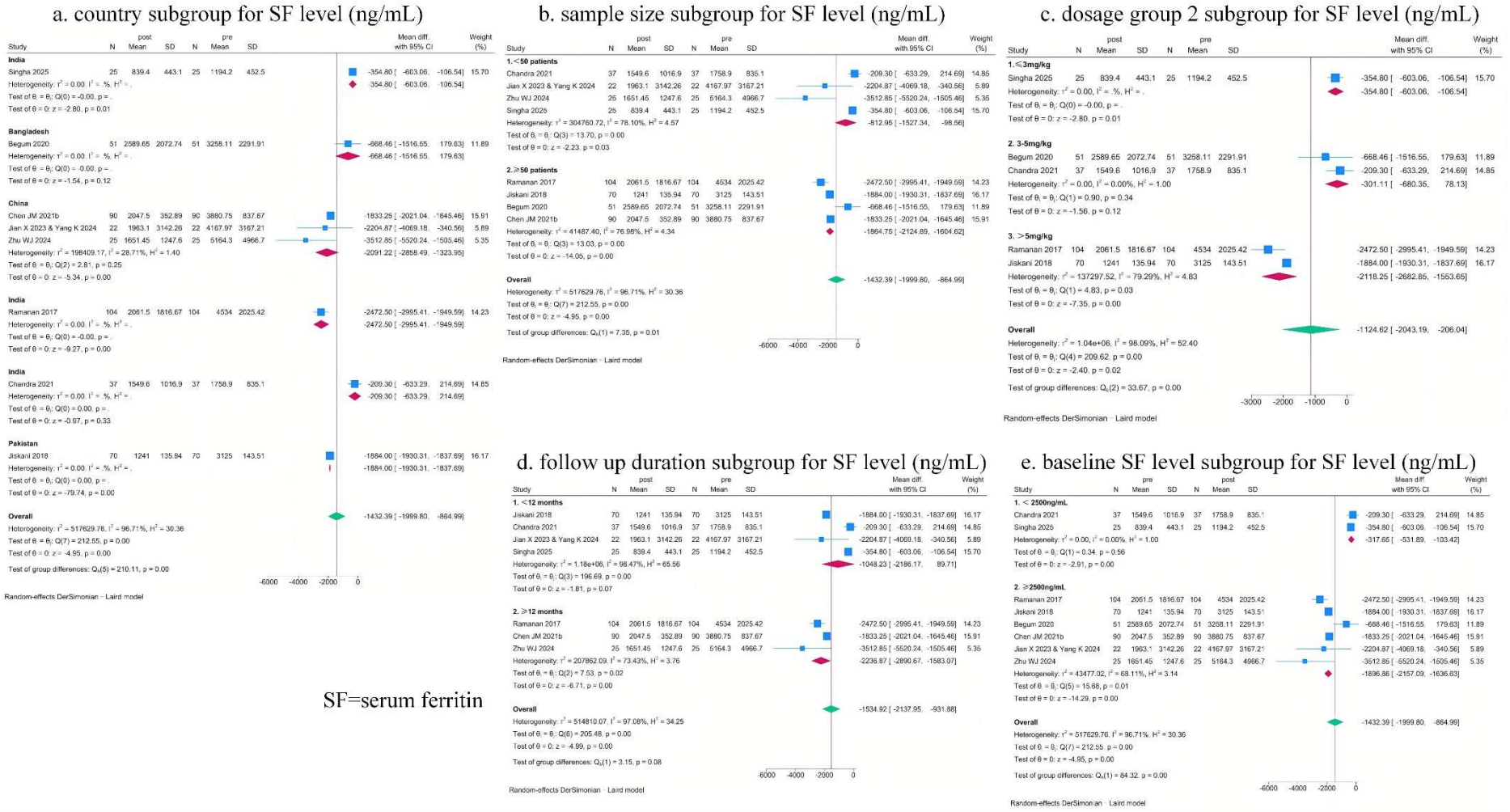
Supplementary Figure 4. Subgroup analysis of hemoglobin level in pre-post studies



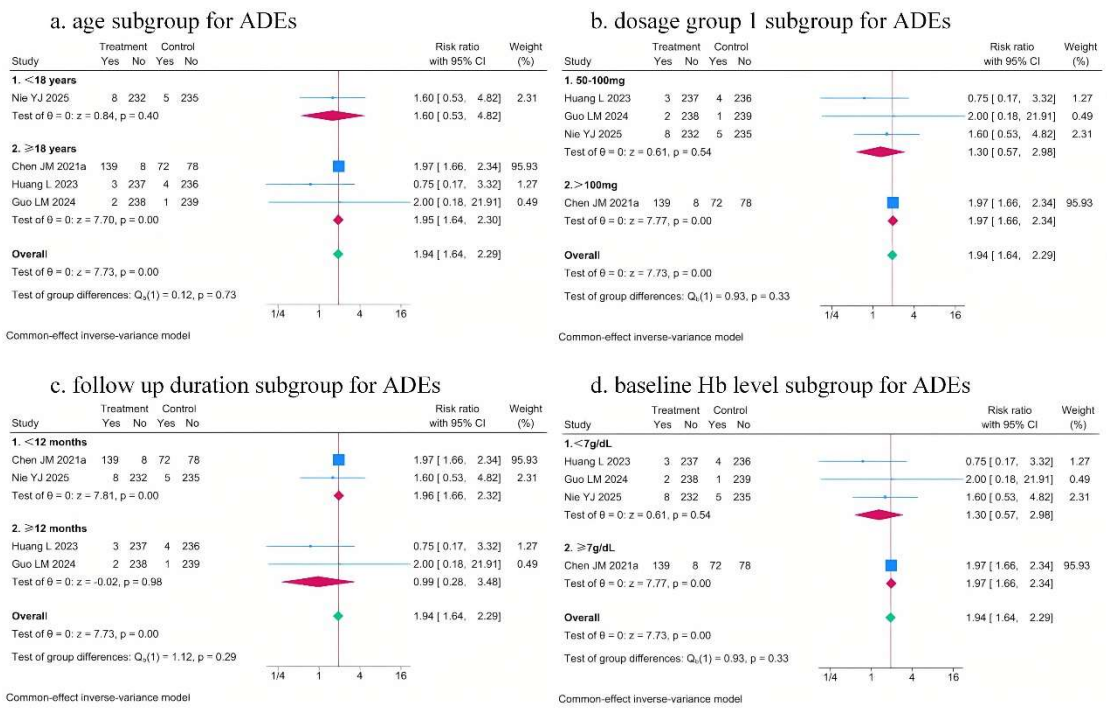
Supplementary Figure 5. Subgroup analysis of fetal hemoglobin level in pre-post studies



Supplementary Figure 6. Subgroup analysis of serum ferritin level in RCTs

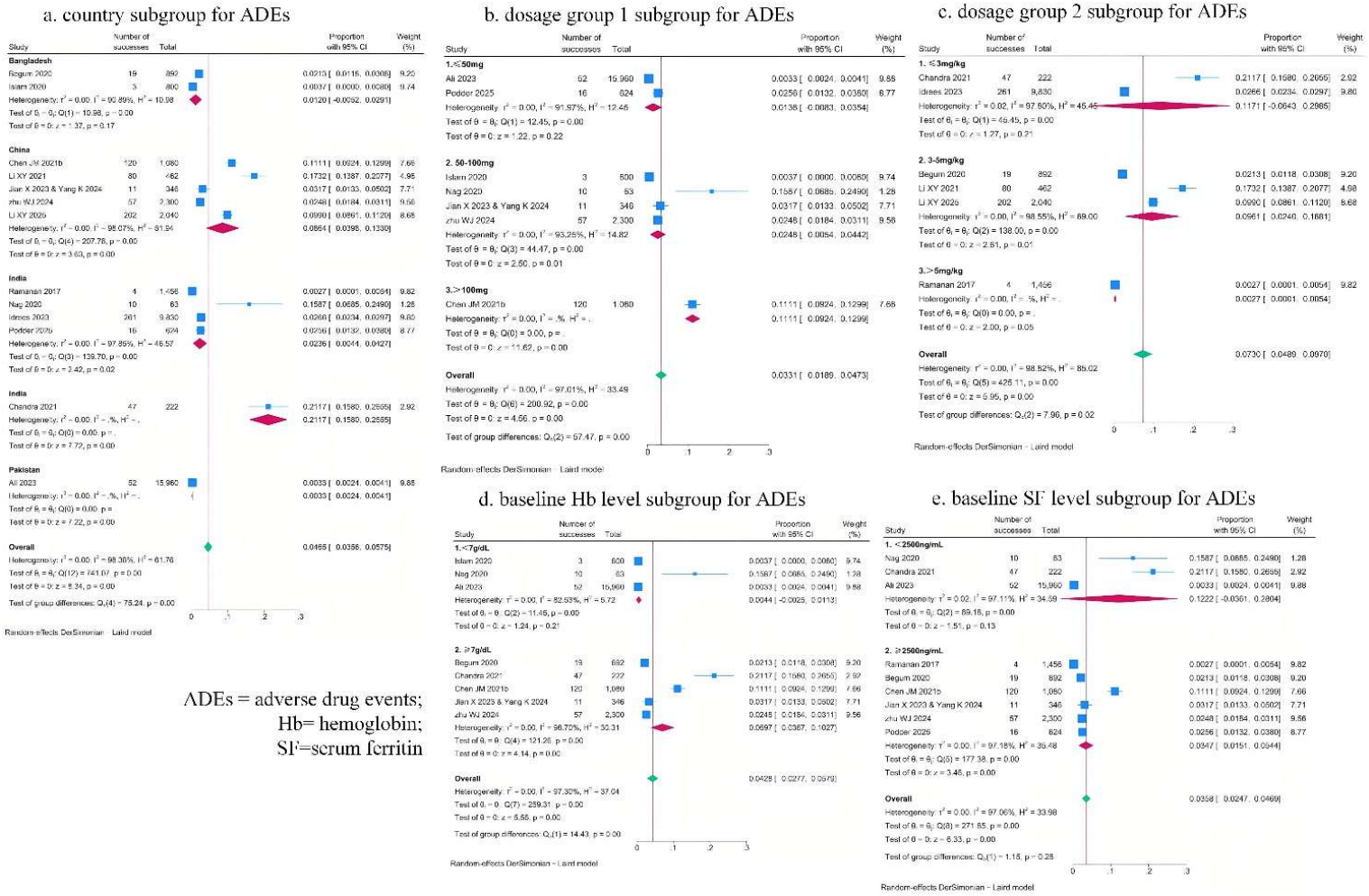


Supplementary Figure 7. Subgroup analysis of serum ferritin level in pre-post studies



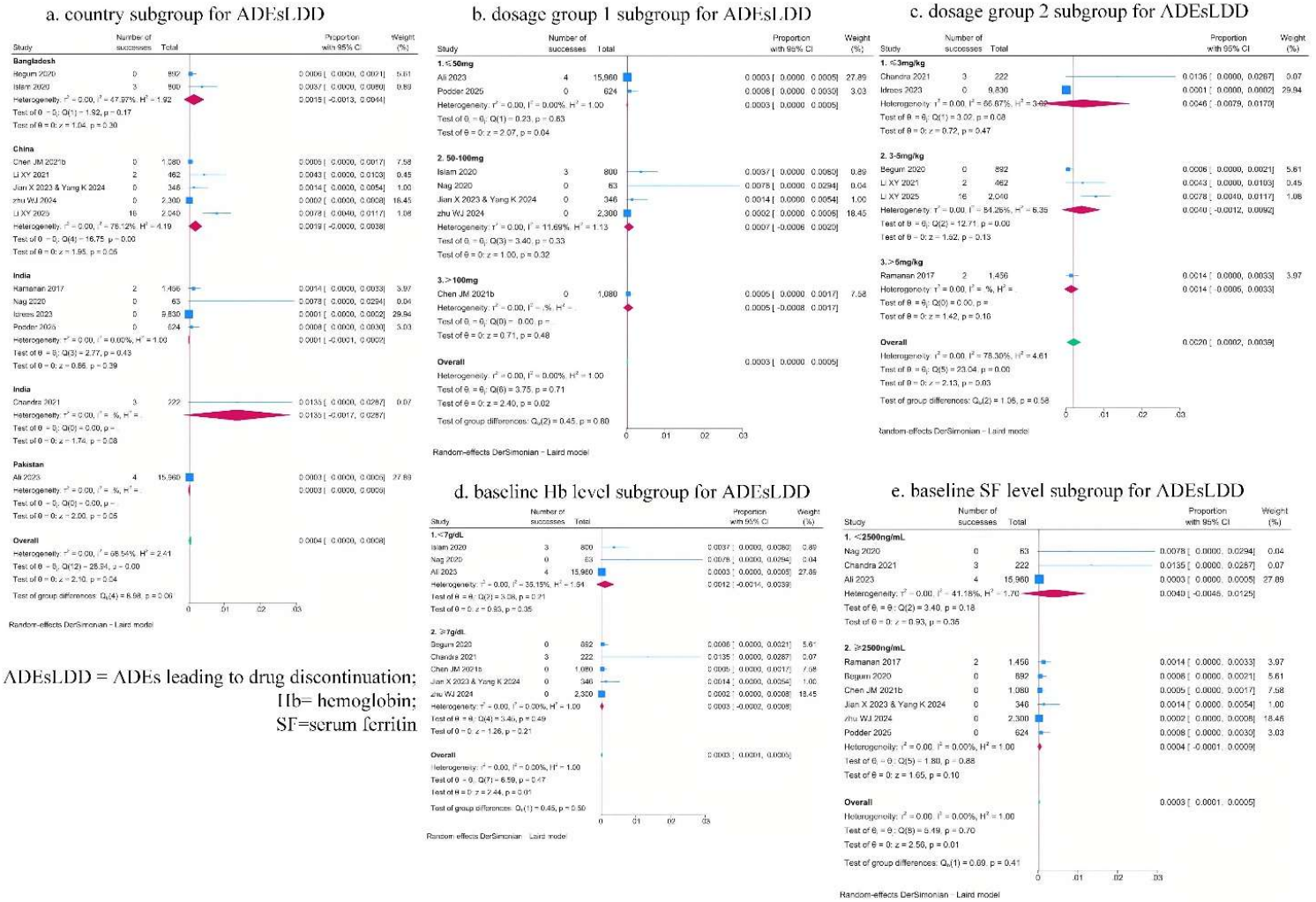
ADEs = adverse drug events; RCT= randomized controlled clinical trial; Hb = hemoglobin

Supplementary Figure 8. Subgroup analysis of ADEs incidence in RCTs



ADEs = adverse drug events;
Hb= hemoglobin;
SF=serum ferritin

Supplementary Figure 9. Subgroup analysis of ADEs incidence in pre-post studies



Supplementary Figure 10. Subgroup analysis of ADEsLDD incidence in pre-post studies

Supplementary table 7. Incidence of ADEs in patients with thalidomide treatment

ADEs	Number	Proportion	ADEs	Number	Proportion
Nervous System			**Digestive System**		
dizziness	144	13.47%	constipation	146	13.66%
drowsiness	83	7.76%	abdominal pain	88	8.23%
fatigue	57	5.33%	nausea	62	5.80%
headache	27	2.53%	vomiting	26	2.43%
anxiety	22	2.06%	transaminitis	9	0.84%
numbness of extremities	21	1.96%	hyperbilirubinemia	7	0.65%
paresthesia	8	0.75%	diarrhea	5	0.47%
restlessness	5	0.47%	anorexia	4	0.37%
anorexia	4	0.37%	**Immune System**		
irritability	4	0.37%	skin rash	61	5.71%
myalgia	2	0.19%	infections	20	1.87%
depression	2	0.19%	allergies	4	0.37%
flustered	2	0.19%	lymphadenectasis	1	0.09%
glossoplegia	2	0.19%	**Respiratory System**		
syncope	2	0.19%	pyrexia	18	1.68%
insomnia	1	0.09%	sore throat	10	0.94%
seizure	1	0.09%	respiratory tract infection	6	0.56%
presyncope	1	0.09%	nosebleed	6	0.56%
Circulatory System			oral and nasal dryness	4	0.37%
neutropenia	54	5.05%	cough	3	0.28%
thrombocytosis	42	3.93%	parotitis	1	0.09%
leukocytopenia	30	2.81%	**Urinary System**		
D-dimer was elevated	6	0.56%	edema	22	2.06%
venous thrombosis	5	0.47%	acute kidney injury	1	0.09%
chest pain	3	0.28%	**Locomotor System**		
oedema	3	0.28%	arthralgia	14	1.31%
cerebrovascular accident	2	0.19%	ostealgia	5	0.47%
palpitation	1	0.09%	**Endocrine System**		
			weight gain	6	0.56%
			gynecomastia	2	0.19%
			amenorrhea	2	0.19%
			high TSH	2	0.19%

ADEs = adverse drug events

Supplementary table 8. Incidence of the ADEsLDD in patients with thalidomide treatment

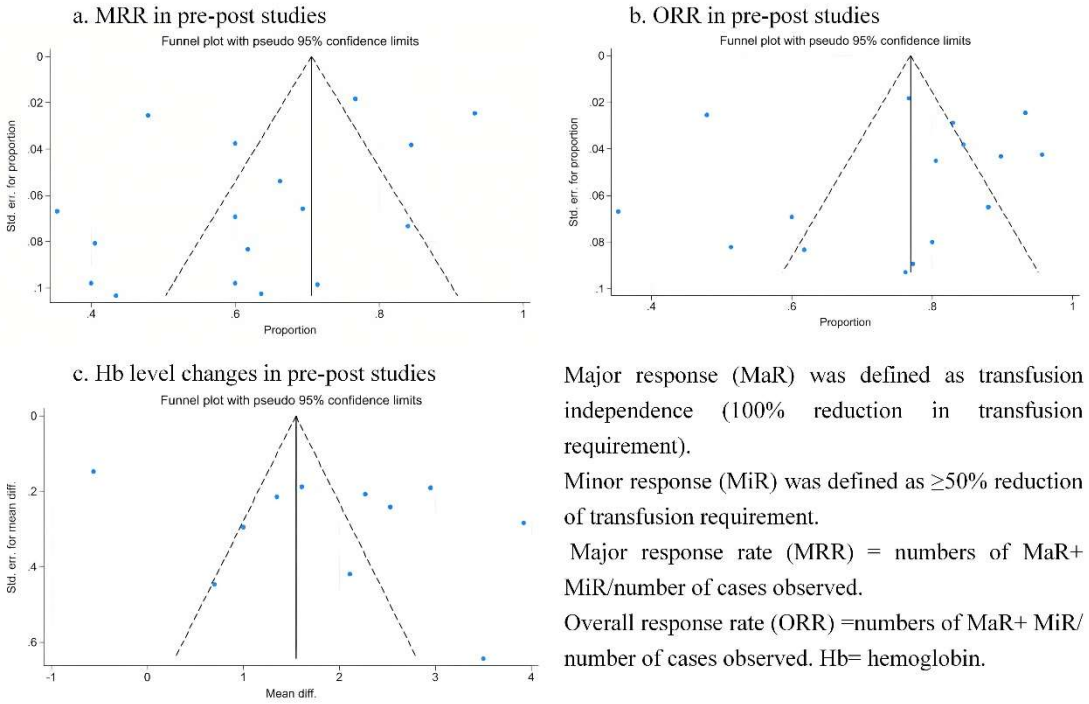
ADEsLDD	Number	Proportion	ADEsLDD	Number	Proportion
Nervous System			**Circulatory System**		
dizziness	1	2.94%	haemolysis	6	17.65%
seizure	1	2.94%	venous thrombosis	5	14.71%
drowsiness	1	2.94%	leukocytopenia and neutropenia	3	8.82%
syncope	1	2.94%	cerebrovascular accident	2	5.88%
headache	1	2.94%	**Immune System**		
lethargy due to trauma	1	2.94%	skin rash	4	11.76%
facial nerve paralysis	1	2.94%	varicella	1	2.94%
convulsion	1	2.94%	**Urinary System**		
nerve conduction disorders	1	2.94%	acute kidney injury	1	2.94%
			Digestive system		
			acute hepatic failure	2	5.88%
			abdominal pain	1	2.94%

ADEsLDD = adverse drug events leading to drug discontinuation

Supplementary table 9. Grade III/IV ADEs in patients with thalidomide treatment

Grade III/IV ADEs	Number	Proportion	Grade III/IV ADEs	Number	Proportion
Nervous System			**Circulatory System**		
syncope	2	11.11%	haemolysis	3	16.67%
lethargy due to trauma	1	5.56%	leukocytopenia and neutropenia	3	16.67%
facial nerve paralysis	1	5.56%	venous thrombosis	1	5.56%
convulsion	1	5.56%	**Immune System**		
nerve conduction disorders	1	5.56%	skin rash	1	5.56%
			varicella	1	5.56%
Digestive system			**Urinary System**		
abdominal pain	2	11.11%	acute kidney injury	1	5.56%

ADEs = adverse drug events



Supplementary figure 11. Funnel plots of the response outcomes of TDT patients

Supplementary table 10. Findings of our study and previous systematic reviews

		Our study	Lu YF 2022[43]	Ali 2022[44]	Atta 2024[45]
MRR	thalidomide vs control	RR: 6.94 (95%CI: 2.96 to 6.27)	OR: 20.40 (95% CI:6.75 to 61.64)	NR	NR
	pooled	62.91% (95% CI: 53.87 to 71.94%)	52% (95%CI: 30 to 73%)	54% (95%CI: 34 to 75%)	69.6% (=543/780)
ORR	thalidomide vs control	RR: 6.94 (95%CI: 2.96 to 6.27)	OR: 20.40 (95% CI:6.75 to 61.64)	NR	NR
	pooled	75.07% (95%CI:66.82 to 83.33%)	83% (95%CI:73 to 91%)	NR	NR
Hb level changes	thalidomide vs control	SMC: 1.50 (0.40 to 2.60)	NR	NR	NR
	pooled	MD: 1.93 g/dlL (95%CI: 1.05 to 2.80 g/dL)	SMD: 1.55 (1.92 to 1.17)	NR	NR
HbF level changes	thalidomide vs control	SMC: 5.61 (4.96 to 6.26)	NR	NR	NR
	pooled	MD: 39.21% (95%CI: 21.31 to 7.12%)	SMD: 0.68 (0.33 to 1.02)	NR	NR
SF level changes	thalidomide vs control	SMC: -0.35 (95%CI: -1.12 to 0.43)	NR	NR	NR
	pooled	MD: -1432.39 ng/mL (95%CI: -1999.80 to -864.99 ng/mL)	SMD: 0.02 (-0.38 to 0.43)	NR	NR
ADEs		● The pooled ADEs incidence was 4.65 per 100 person-months (95% CI: 3.56-5.75 per 100 person-months), and the pooled ADEsLDD incidence was 0.04 per 100 person-months (95% CI: 0.00– 0.08 per 100 person-months). ● Most ADEs are mild. ● Common ADEs included constipation, dizziness, abdominal pain, drowsiness, and nausea. Common ADEsLDD included haemolysis, venous thrombosis, skin rash and leukocytopenia and neutropenia.	● The results of meta-analysis revealed that about 30% (95% CI:15–47%). ● Most ADEs are mild. ● Common ADEs included constipation, somnolence, high alanine aminotransferase (ALT) level, and rash.	● Mild ADEs were reported in 44% of the patients, 8 (2%) patients stopped using thalidomide due to ADEs. ● Most ADEs are mild. Common ADEs included constipation, dizziness and/or lethargy, neutropenia, nausea/vomiting, and thrombocytosis.	● Adverse effects were reported in 41.2% (n=322) of patients. Fourteen patients discontinued treatment due to severe adverse effects. ● Most ADEs are mild. ● Common ADEs included constipation and dizziness .

Major response (MaR) was defined as transfusion independence (100% reduction in transfusion requirement). Minor response (MiR) was defined as ≥50% reduction of transfusion requirement. Major response rate (MRR) = numbers of MaR+ MiR/number of cases observed. Overall response rate (ORR) =numbers of MaR+ MiR/number of cases observed. Hb= hemoglobin, HbF= fetal hemoglobin, SF=serum ferritin, SMD= standardized mean difference. ADEs = adverse drug events; ADEsLDD = ADEs leading to drug discontinuation, RR= risk ratio, OR= odds ratio, SMC= *standardized mean change, NR= on reported.*