Induced pluripotent Stem Cell-derived cardiomyocytes therapy for ischemic heart disease in animal model: Systematic Review and Meta-analysis

Search query: ("iPScells" OR "induced pluripotent stem cells" OR "pluripotent stem cells" OR "reprogrammed stem cells") AND ("Ischemic Heart Disease" OR "coronary artery disease" OR "myocardial infarction" OR "heart ischemia" OR “agina” OR “arteriosclerosis coronary” OR “Myocardial Reperfusion”)

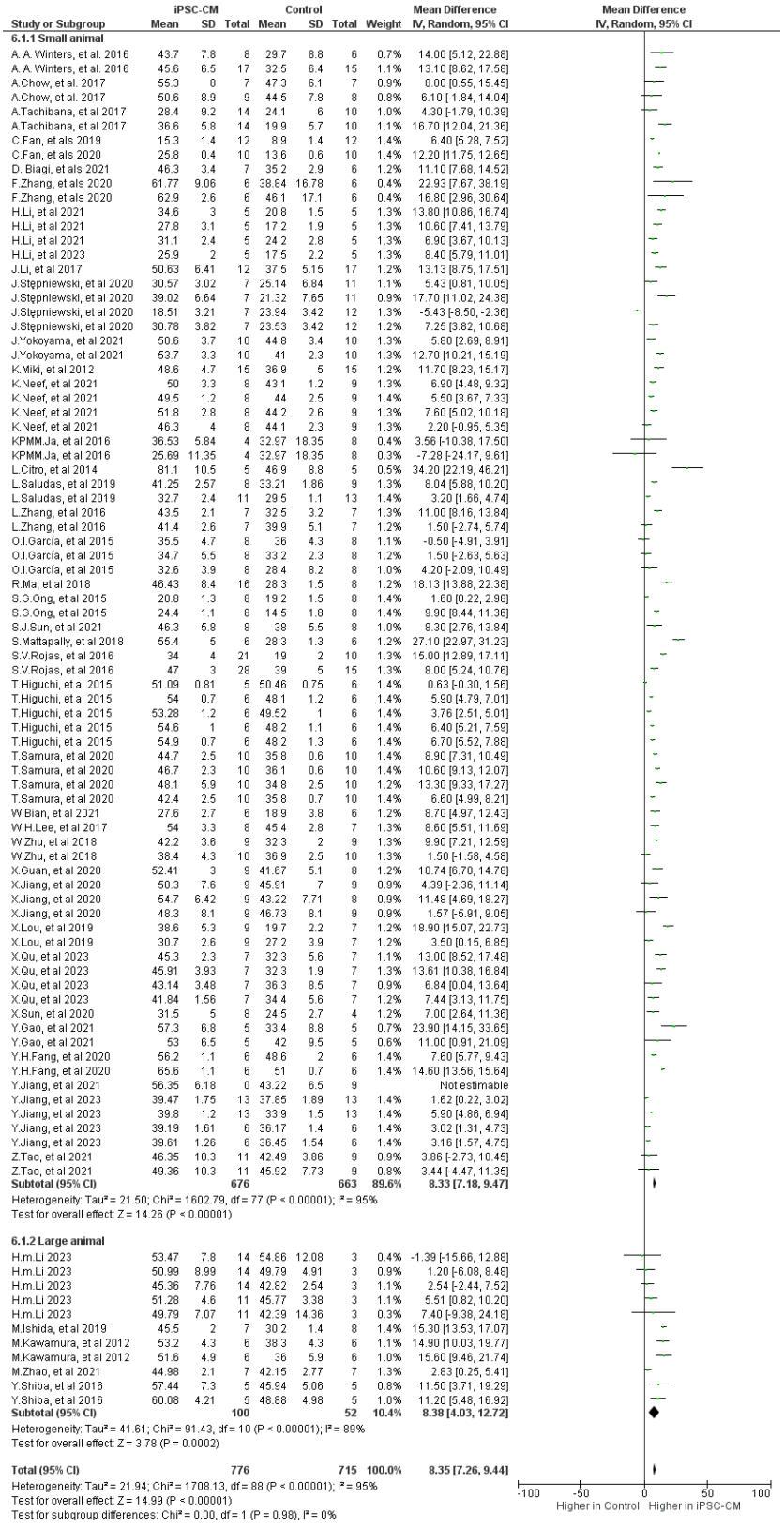

Figure S1. Cell-based effect on animal ejection fraction by animal size

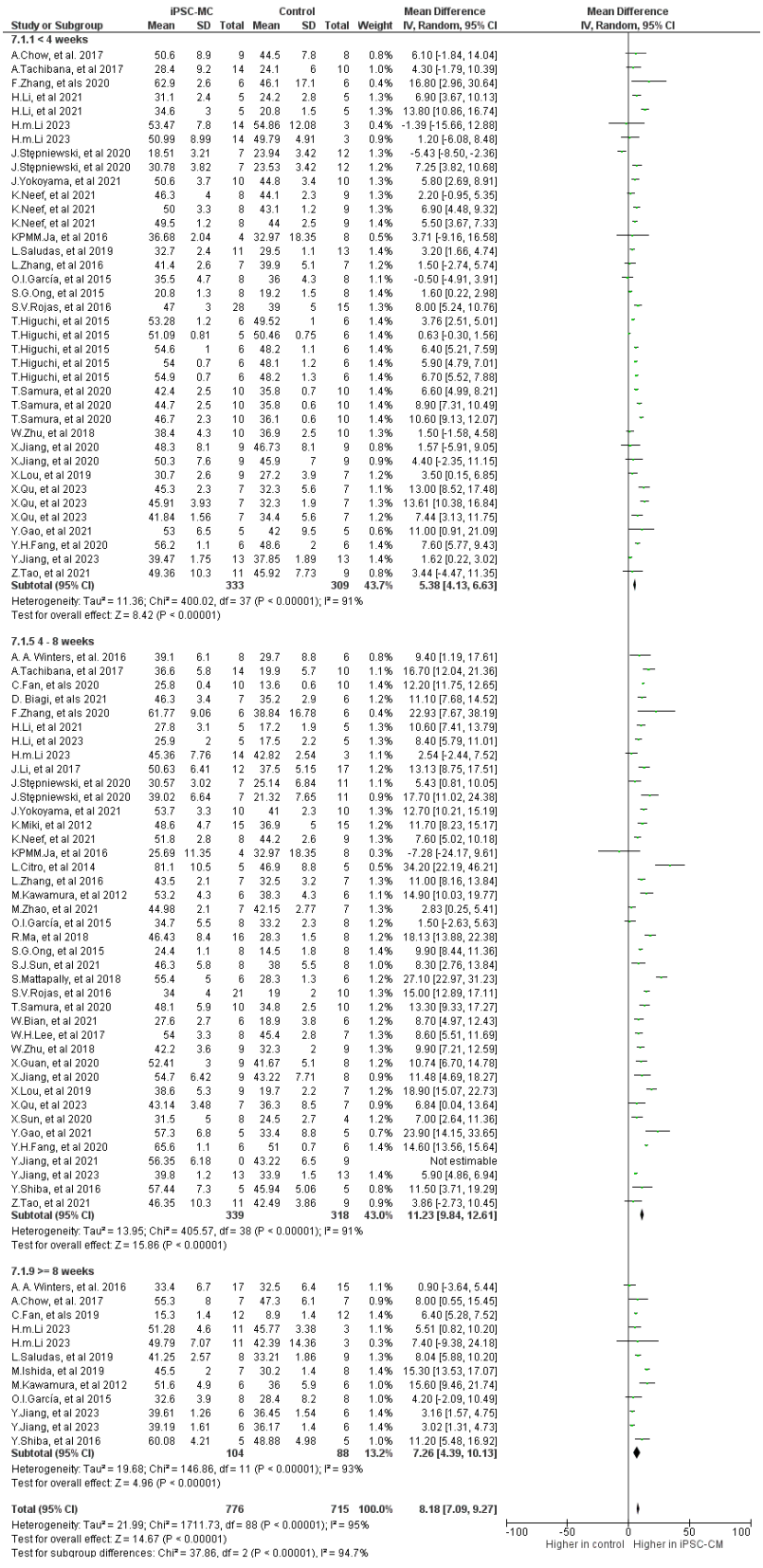

Figure S2. Cell-based effect on animal ejection fraction by follow-up time

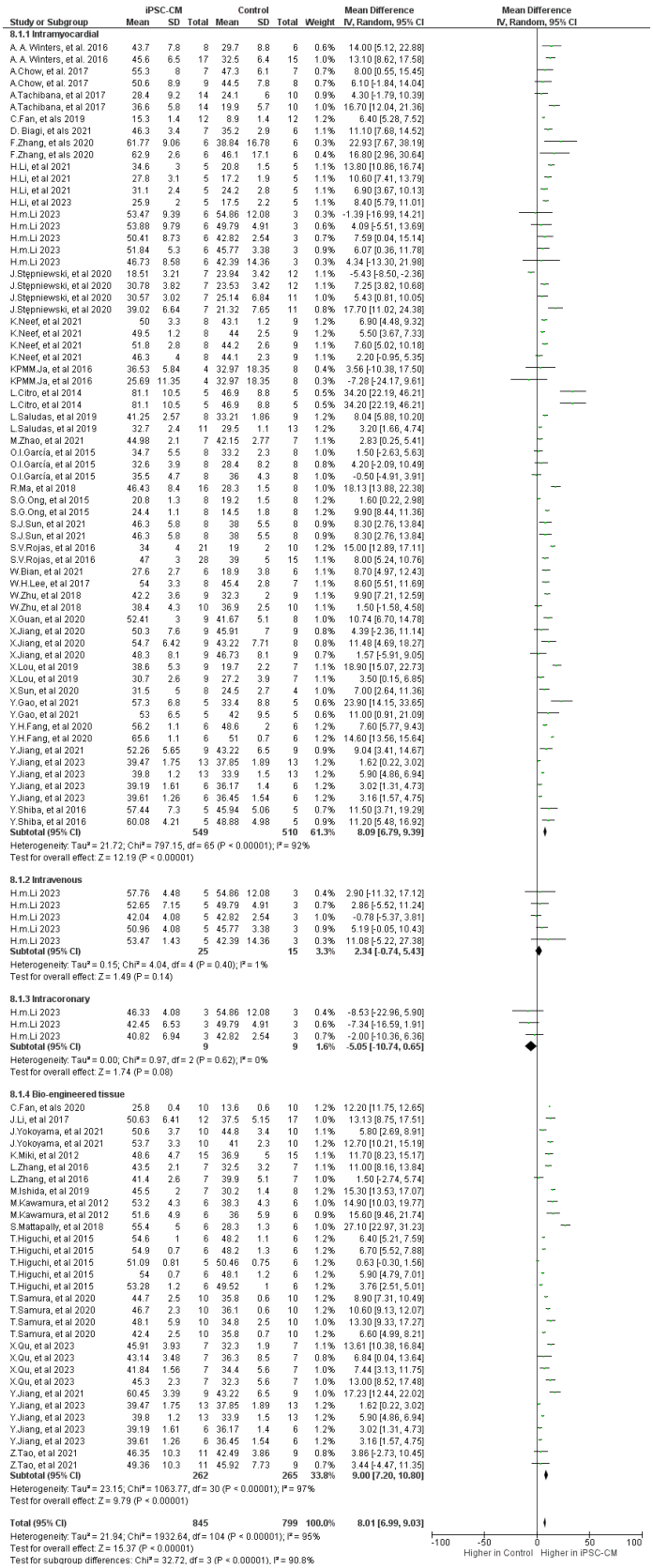

Figure S3. Cell-based effect on animal ejection fraction by delivery method

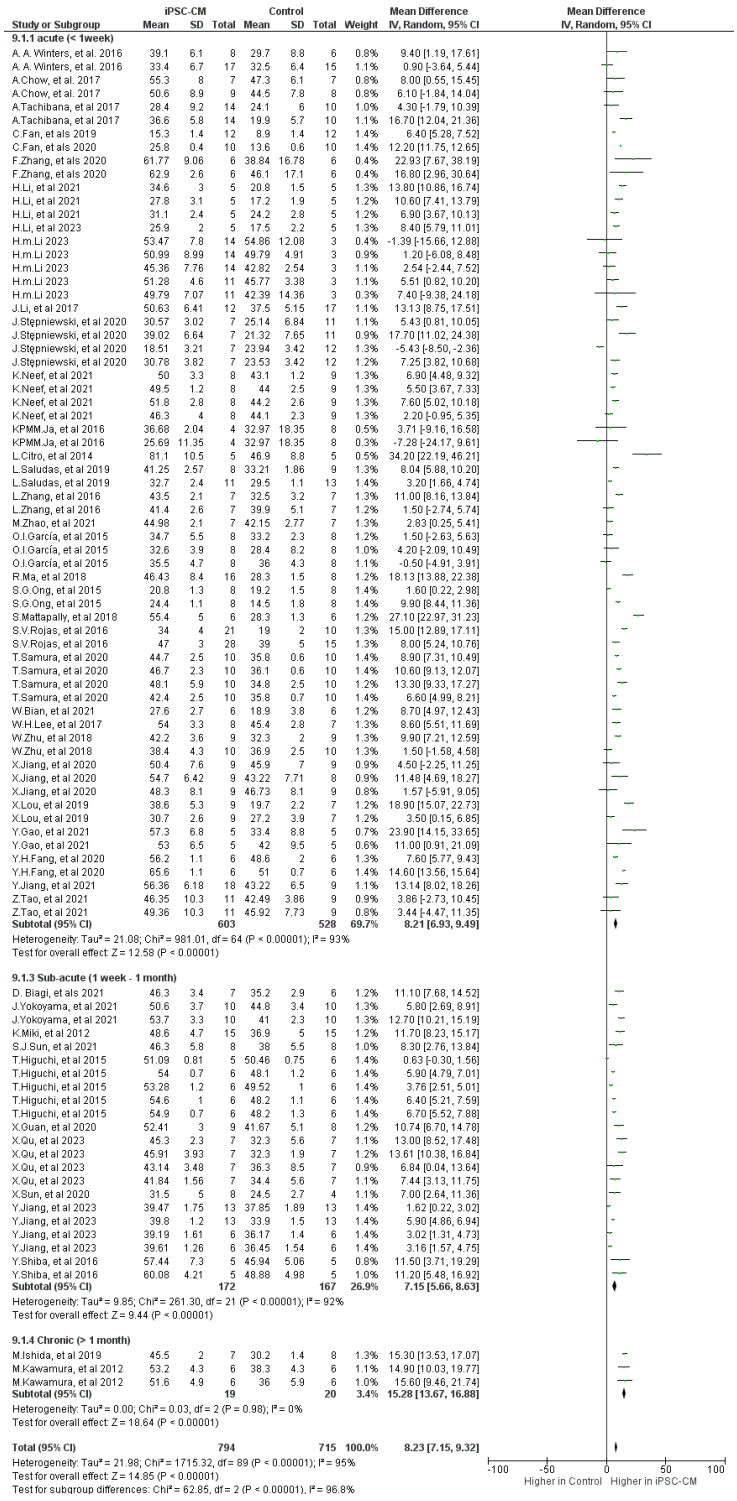

Figure S4. Cell-based effect on animal ejection fraction by time of injection

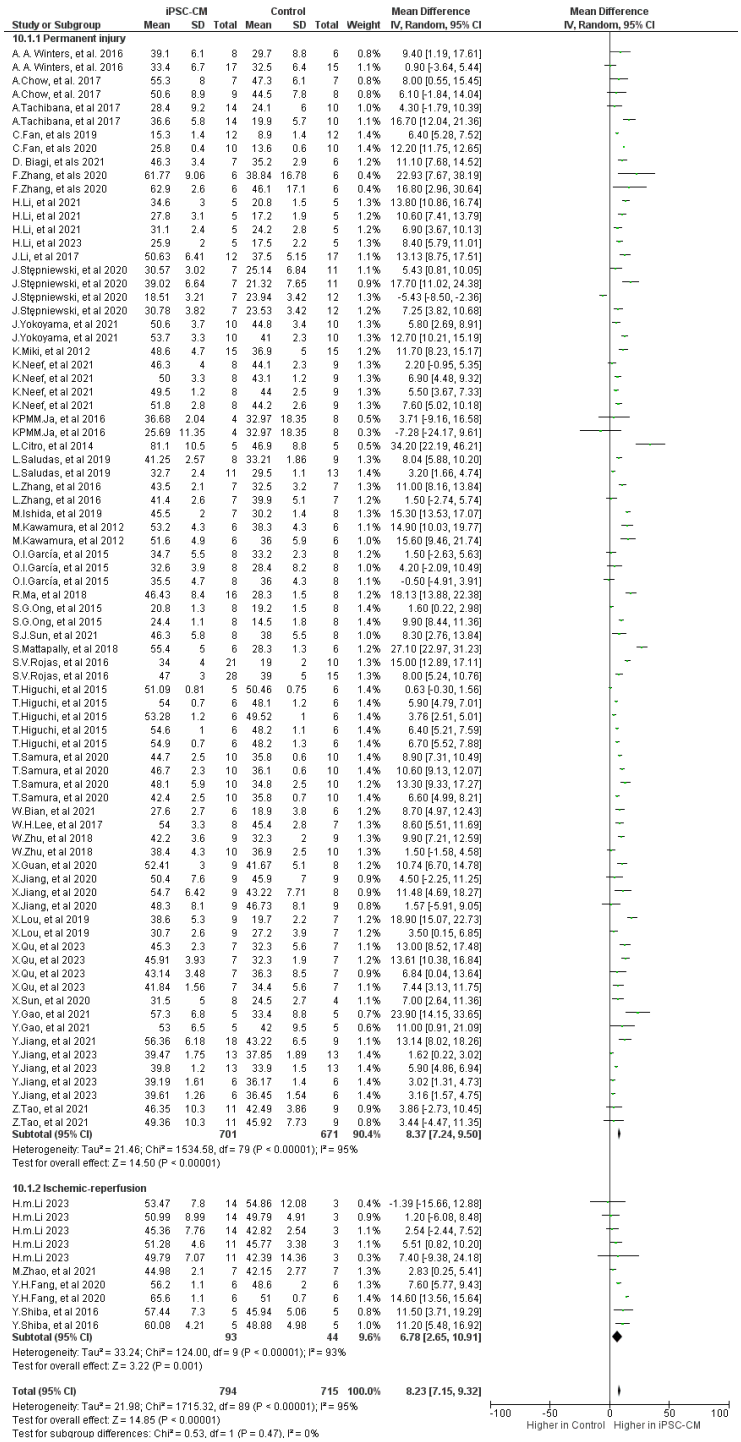

Figure S5. Cell-based effect on animal ejection fraction by disease model

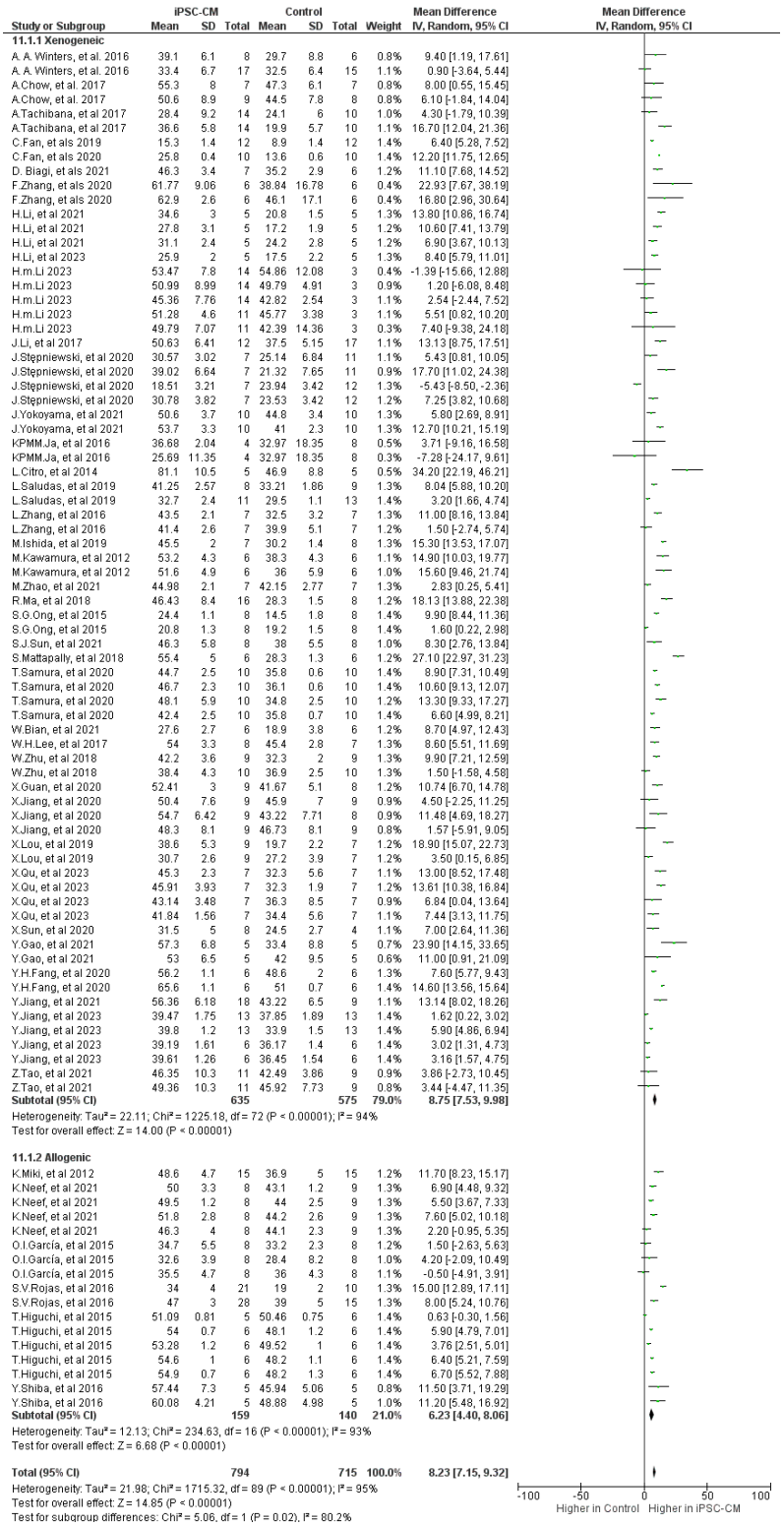

Figure S6. Cell-based effect on animal ejection fraction by origin of cell

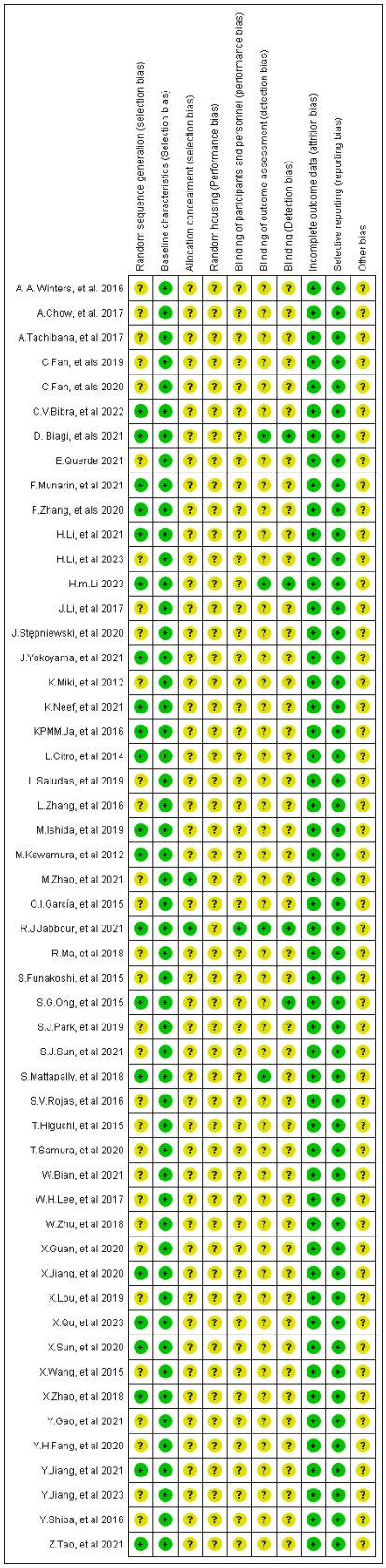

Figure S7. SYRCLE risk of bias. Yellow is unclear risk, green is low risk

Table S1. General information of included studies

Author (year)	Animal characteristics				Intervention characteristics				Outcome measures	
	Species	Age	Method of IHD induced	Immunosuppression	Type of treatment	Total dose	Time of treatment (after IHD-induced)	Control treatment	Time of assessment	Method of cardiac assessment
Small animal research										
Atsushi [1] (2017)	SCID mice	90-120 days	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	500000	immediately	PBS	2 weeks and 4 weeks	MRI
Amalia [2] (2016)	SCID mice	12 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	500000	immediately	Saline	4 weeks, 12 weeks	Echo
Chow [3] (2017)	nut rat	8 weeks	permanent LAD ligation	NR	intramyocardial cell injections	500000	10 minutes after	PBS	48 hours, 10 weeks	MRI
Diogo [4] (2021)	Wistar rats	8 weeks	permanent LAD ligation	Cyclosporine	intramyocardial cell injections	10000000	1 week after	free solution	30 days	Echo
Fan [5] (2019)	NOD/SCID Gamma mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	300000	immediately	PBS	6 months	Echo
Fan [6] (2020)	mice	NR	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	1000000	immediately	free patch	4 weeks	Echo
Fabiola [7] (2021)	Sprague Dawley rat	8-12 weeks	I/R	athymic	bio-engineered tissue treatment	10000000	4 days after	no treatment	1 week, 4 weeks	Echo
Fengzhi [8] (2021)	Sprague–Dawley rats	NR	permanent LAD ligation	NR	intramyocardial cell injections	8000000	10 minutes after	PBS	3 days, 4 weeks	Echo
Hekai [9] (2021)	C57BL/6 mice	6-8 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	200000	immediately	PBS	1 week, 2 weeks, 4 weeks	Echo

Hekai [10] (2023)	C57BL/6 mice	6-8 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	200000	immediately	PBS	4 weeks	Echo
Jacek [11] (2020)	Foxn1nu mice	6-8 weeks	permanent LAD ligation	athymic	intramyocardial cell injections	500000	immediately	Saline	1 week, 2 weeks, 4 weeks, 6 weeks	Echo
Junjun [12] (2017)	nude rats	8 weeks	permanent LAD ligation	no report	bio-engineered tissue treatment	7000000	immediately	free patch	4 weeks	Echo
Junya [13] (2021)	F344/NJcl-rnu/rnu rats	NR	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	3000000	2 weeks after	free patch	4 weeks, 12 weeks	Echo
Kenji [14] (2012)	F344/NJcl-rnu/rnu rats	NR	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	NR	2 weeks after	no treatment	1 week, 2 weeks, 4 weeks	Echo
Klaus [15] (2021)	C57BL/6 mice	8-10 weeks	cryo-infarction	Genetic immunodeficient animal	intramyocardial cell injections	500000	immediately	PBS	1 week, 2 weeks, 3 weeks, 4 weeks	MRI
KP My [16] (2015)	SCID mice	10-12 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	200000	immediately	PBS	2 weeks, 4 weeks	Echo
Laura [17] (2019)	BALB/C (Rag-2) mice	8-12 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	150000	15 minutes after	free solution	7 days, 60 days	Echo
Liying [18] (2015)	NOD/SCID/γc−/− (NSG) mice	12 weeks	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	600000	immediately	free solution	1 week, 4 weeks	Echo
Lucas [19] (2014)	nude rats	NR	permanent LAD ligation	athymic	intramyocardial injections	1000000	immediately	free solution	4 weeks	Echo
Olalla [20] (2015)	DBA/2J mice	8 weeks	permanent coronary ligation	Genetic immunodeficient animal	intramyocardial injections	200000	15 minutes after	PBS	3 days, 60 days	Echo
Ruilian [21] (2018)	SCID mice	10-12 weeks	permanent coronary ligation	Genetic immunodeficient animal	intramyocardial cell injections	200000	immediately	PBS	4 weeks	Echo
Saidulu [22] (2018)	NOD/SCID Gamma mice	NR	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	200000	immediately	no treatment	4 weeks	Echo

Sang-Ging [23] (2015)	NOD/SCID mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	2000000	immediately	Saline	7 days, 35 days	MRI
Sebastian [24] (2017)	SCID beige mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	1500000	immediately	PBS	3 days, 7 days, 14 days, 21 days, 28 days	MRI
Shunsuke [25] (2015)	NOG mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	1000000	immediately	PBS	1 week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks	Echo
Si-Jia [26] (2021)	ICR mice	12-16 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	1000000	immediately	PBS	4wks	Echo
Soon-Jung [27] (2019)	Fischer 344 rat	8-10 weeks	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	1000000	7 days after	no treatment	2 weeks, 4 weeks, 8 weeks	Echo
Takaaki [28] (2020)	nude rat	8 weeks	permanent LAD ligation	athymic	bio-engineered tissue treatment	5000000	immediately	free sheet	1 week, 2 weeks, 3 weeks, 4 weeks	Echo
Takahiro [29] (2015)	F344/NJcl-rnu/rnu rats	6 weeks	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	NR	2 weeks after	no treatment	7 days, 14 days	Echo
Weihua [30] (2021)	NOD/SCID Gamma mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	300000	immediately	PBS	4 weeks	Echo
Won [31] (2017)	nude rat	NR	permanent LAD ligation	athymic	intramyocardial cell injections	10000000	4 days after	PBS	30 days	MRI
Wuqiang [32] (2018)	NOD/SCID Gamma mice	NR	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	300000	immediately	PBS	1 week, 4 weeks	Echo
Xi [33] (2019)	NOD/ SCID gamma mic	8-10w	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	300000	immediately	no treatment	1 week, 4 weeks	Echo
Xiang [34] (2023)	NJcl-rnu/rnu nude rat	7w	permanent LAD ligation	Genetic immunodeficient animal	bio-engineered tissue treatment	5000000	2 weeks after	no treatment	1 week, 2 weeks, 3 weeks, 4 weeks	Echo

Xin Jiang [35] (2020)	ICR mice	12-16w	permanent LAD ligation	Genetic immunodeficient animal	intramyocardial cell injections	400000	10 minutes after	free solution	1 week, 2 weeks, 4 weeks	Echo
Xintong [36] (2015)	nude rats	NR	permanent LAD ligation	NR	intramyocardial cell injections	3000000	30 minutes after	PBS	2 weeks	Echo
Xuetao [37] (2020)	rnu/rnu rat	7-8 weeks	permanent LAD ligation	athymic	intramyocardial cell injections	10000000	2 weeks after	no treatment	4 weeks	Echo
Xumin [38] (2020)	Sprague Dawley rat	8 weeks	permanent LAD ligation	methylprednisolone	intramyocardial cell injections	10000000	10 days after	Albumin solution	4 weeks	Echo
Yi-Hsien [39] (2020)	Sprague Dawley rat	12 weeks	temporary LAD ligation	cyclosporine	intramyocardial cell injections	10000000	4 days after	free solution	4 weeks	Echo
Yu Jiang [40] (2021)	Sprague Dawley rat	NR	permanent LAD ligation	NR	1. intramyocardial cell injections 2. bio-engineered tissue treatment	1000000	immediately	Saline	4 weeks	Echo
Yuanxue [41] (2021)	Sprague–Dawley rat	NR	permanent LAD ligation	no report	intramyocardial cell injections	10000000	immediately	PBS	1 week, 5 weeks	Echo
Yun [42] (2023)	C57BL/6J mice	11-12 weeks	permanent LAD ligation	no report	bio-engineered tissue treatment	200000	7 days after	free solution	7 days, 28 days, 60 days, 90 days	Echo
Zhonghao [43] (2020)	Wistar rat	12 weeks	permanent LAD ligation	cyclosporine	bio-engineered tissue treatment	1000000	10 minutes after	free solution	6 weeks	Echo
Large animal research										
Constantin [44] (2022)	guinea pigs	NR	cryo-infarction	cyclosporine, methylprednisolone	bio-engineered tissue treatment	15000000	4 weeks after	free patch	4 weeks	Echo
Eva [45] (2021)	guinea pigs	8-9 weeks	cryo-infarction	cyclosporine, methylprednisolone	bio-engineered tissue treatment	9000000, 12000000, 15000000	7 days after	free patch	4ws	Echo

Hong-mei [46] (2023)	primate	4-6y years	I/R	methylprednisolone, mycophenolate mofetil, tacrolimus	1. intravenous, 2. intramyocardial 3. intracoronary cell injections,	100000000/ kg, 100000 (coronary)	24 hours after	no treatment	1 week, 2 weeks, 4 weeks, 6 weeks ,8 weeks, 12 weeks	Echo
Masashi [47] (2011)	minipig	NR	permanent LAD ligation	tacrolimus	bio-engineered tissue treatment	25000000	1 month after	no treatment	4 weeks, 8 weeks	Echo and CT scan
Masaru [48] (2019)	CLAWN miniature porcine	6-10 months	permanent LAD ligation	tacrolimus, mycophenolate mofetil, corticosteroids	bio-engineered tissue treatment	100000000	1 month after	no treatment	8	Echo and MRI
Meng [49] (2021)	Yorkshire pig	NR	I/R	no report	intramyocardial cell injections	60000000	60 minutes after	PBS	4 weeks	MRI
Richard [50] (2021)	New Zealand white rabbit	NR	permanent coronary ligation	ciclosporin, methylprednisolone	bio-engineered tissue treatment	17500000	immediately	free patch	1 week, 2 weeks, 4 weeks	Echo
Yuji [51] (2016)	Filipino cynomolgus monkeys	4-5 years	I/R	methylprednisolone, tacrolimus	intramyocardial cell injections	400000000	2 weeks after	free solution	4wks, 12wks	Echo

NR: not report

I/R: ischemia/reperfusion therapy

List of included research

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Table S2. Meta-regression of potential modifiers of FS

Variable	Coefficient	SE	t-value	P-value	95% Confidence Interval
Animal size -small	14.11	3.32	4.25	0.00	7.45 to 20.78
Treatment timing: chronic	13.36	5.45	2.45	0.02	2.44 to 24.28
Treatment timing: subacute	-2.10	1.74	-1.20	0.23	-5.59 to 1.40
Method delivery: Intracoronary	-8.39	3.34	-2.51	0.02	-15.10 to -1.69
Method delivery: Intramyocardial	-0.73	1.51	-0.48	0.63	-3.76 to 2.31
Method delivery: Intravenous	-1.03	2.97	-0.35	0.73	-6.98 to 4.91
Time of follow up: < 4w	-1.87	1.09	-1.72	0.09	-4.06 to 0.31
Time of follow up: > 8w	-0.63	1.89	-0.33	0.74	-4.43 to 3.17
Cell origin: Xenogeneic	-4.63	2.96	-1.57	0.12	-10.57 to 1.30
Disease model: Permanent injury	-7.36	2.92	-2.52	0.01	-13.22 to -1.5

Table S3. Meta-regression of potential modifiers of LV fibrosis

Variable	Coefficient	SE	t-value	P-value	95% Confidence Interval
Animal size: big	-1.64	2.31	-0.71	0.48	-6.31 to 3.01
Animal size: small	3.51	2.91	1.21	0.23	-2.28 to 9.31
Treatment timing: acute	-3.11	2.26	-1.37	0.17	-7.61 to 1.39
Treatment timing: chronic	8.16	4.65	1.75	0.08	-1.08 to 17.41
Treatment timing: sub-acute	-3.19	2.21	-1.44	0.15	-7.59 to 1.21
Method delivery: Bio-engineered tissue	3.91	2.14	1.82	0.07	-0.34 to 8.18
Method delivery: Intracoronary	-8.06	3.32	-2.42	0.**02**	-14.67 to -1.45
Method delivery: Intramyocardial	3.82	1.64	2.33	**0.02**	0.56 to 7.08
Method delivery: Intravenous	2.18	2.81	0.78	0.43	-3.37 to 7.75
Cell origin: Allogenous	-0.15	1.13	-0.13	0.89	-2.41 to 2.11
Cell origin: Xenogeneic	2.01	0.92	2.18	**0.03**	0.18 to 3.84
Disease model: IR	1.96	2.61	0.74	0.45	-3.24 to 7.16
Disease model: Permanent injury	-0.09	2.15	-0.04	0.96	-4.38 to 4.18
Follow up: < 4 weeks	1.01	1.29	0.77	0.43	-1.57 to 3.59
Follow up: 4-8 weeks	1.05	1.26	0.82	0.41	-1.47 to 3.57
Follow up: > 8 weeks	-0.96	2.45	-0.39	0.69	-5.84 to 3.91

Table S4. Meta-regression of potential modifiers of LVESV

Variable	Coefficient	SE	t-value	P-value	95% Confidence Interval
Treatment timing: sub-acute	-100.48	69.60	-1.44	0.169	-248.83 to 47.87
Method delivery: Intramyocardial	34.21	20.06	1.71	0.109	-8.56 to 76.97

Time of follow – up: < 4w	0.99	5.06	0.20	0.847	-9.79 to 11.77
Time of follow – up: 8w	-30.45	10.72	-2.84	0.012	-53.30 to -7.60
Cell origin: Xenogeneic	-5.17	8.22	-0.63	0.539	-22.70 to 12.35

Table S5. Meta-regression of potential modifiers of LVEDV

Variable	Coefficient	SE	t-value	P-Value	95% Confidence Interval
Animal size: small	-13.97	4.47	-3.12	0.005	-23.38 to -4.56
Treatment timing: acute	23.77	10.84	2.19	0.04	0.98 to 46.55
Treatment timing: sub-acute	-37.74	14.31	-2.63	0.01	-67.81 to -7.68
Method delivery: Bio-engineered tissue	-27.47	10.82	-2.53	0.02	-50.21 to -4.72
Method delivery: Intramyocardial	13.49	8.14	1.65	0.1	-3.61 to 30.59
Time of follow – up: 4w-8w	-3.59	6.94	-0.51	0.61	-18.18 to 10.99
Time of follow - up: < 4w	-9.15	7.67	-1.19	0.24	-25.28 to 6.97
Time of follow – up: > 8w	-1.2266	10.3233	-0.11	0.9	-22.91 to 20.46
Cell origin: Allogenous	-4.71	7.11	-0.67	0.51	-19.72 to 10.18
Cell origin: Xenogeneic	-9.20	5.73	-1.61	0.12	-21.25 to 2.85
Disease model: Permanent injury	-13.97	4.47	-3.12	0.006	-23.38 to -4.56