SUPPLEMENTAL MATERIAL

Effect of Immunomodulation on Cardiac Remodeling and Outcomes in Heart Failure: A Quantitative Synthesis of the Literature

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S1 Supplement Table 1: PRISMA checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1, Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3, paragraphs 1-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4, paragraph 1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4 paragraph 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5, paragraph 2, 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5, paragraph 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5, paragraph 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5, paragraph 5

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5, paragraph 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5, paragraph 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6, paragraph 1
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.	Page 6, paragraph 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6, paragraph 4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6, paragraph 4
Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7, paragraph 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7, paragraph 2
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.	Page 8, paragraph 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8, paragraph 1
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).	Page 8, paragraph 1

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8, paragraph 2; Page 9, paragraph 1, 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8, paragraph 1, 2; Page 9, paragraph 1, 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 9, Paragraph 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 10, Paragraph 1 Page 11, Paragraph 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12, paragraph 1, 2; Page 13, paragraph 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14, paragraph 1, 2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14, paragraph 3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 15, paragraph 1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

S2 Inclusion exclusion criteria for all trials

Author/Year	Inclusion criteria	Exclusion criteria	Primary Outcomes	Other Outcomes Studied
Parrillo[1]/1989	Dilated cardiomyopathy	Coronary, hypertensive, valvular, or congenital heart disease Excessive alcohol ingestion Unrelated serious injury	Improvement in LV function defined as ≥5% increase in LVEF, OR ≥10% decrease in LVEDD and ≥20% increase in exercise duration	Not recorded
Sliwa[2]/1998	Age 18-70 year Stable NYHA II /III CHF of unknown aetiology LVEF ≤40%	COPD Significant valvular heart disease Evidence ischemic heart disease SBP >170 mm Hg DBP >105 mm Hg Disorders other than cardiomyopathy that could increase TNF-α concentrations Pregnancy Severe liver disease Any clinical condition judged by the investigators to preclude inclusion in the study	NYHA functional class Left-ventricular dimensions Left-ventricular systolic and diastolic function	Not recorded
Deswal[3]/1999	LVEF <35% NYHA III TNF >3.0 pg/mL	Not recorded	Safety of etanercept in patients with NYHA class III heart failure improvement in LVEF, patient functional status, and TNF bioactivity	Pharmacokinetics of a single intravenous dose of etanercept

Gullestad[4]/2001	CHF >6 months NYHA II/III LVEF <40% No changes in medication in the past 3 months On optimal medical therapy And unsuitable for surgical intervention	Myocardial infarction/ Unstable angina in last 6 months Significant concomitant diseases such as infections, pulmonary disorders or connective tissue diseases.	Effect of IVIG on inflammatory and anti-inflammatory mediators in CHF patients	Change in clinical and hemodynamic variables, including LVEF
McNamara[5]/ 2001	LVEF ≤40% DCM or myocarditis ≤6 months of cardiac symptoms at time of randomization	Coronary artery disease Significant valvular disease Significant diabetes (therapy of insulin or an oral agent for more than 1 year) Significant hypertension (SBP>160 mmHg or DBP>95 mmHg) Uncorrected thyroid disease Evidence of giant cell myocarditis, sarcoidosis, or hemochromatosis	Change in LVEF from baseline to 6 and 12 months	Event-free survival (death, cardiac transplantation, or placement of an LVAD) Functional capacity assessed by metabolic stress testing at 12 months
Skudicky[6]/2001	Age 18-70 NYHA II/III CHF of unknown cause LVEF <40% sinus rhythm ability to obtain high-quality echocardiographic images	COPD Significant valvular heart disease History or evidence of ischemic heart disease SBP >160 mm Hg DBP >95 mm Hg Clinical conditions other than cardiomyopathy that could increase cytokine levels Pregnancy Severe liver disease (enzymes >2 times the upper limit of normal)	NYHA functional class Exercise tolerance LV systolic and diastolic function	Not recorded

		Any clinical condition that according to the investigators precluded inclusion in the study		
Bozkurt[7]/2001	NYHA III/IV LVEF <35%, On stable doses of ACE inhibitor, digoxin, and oral diuretics for 30 days before enrollment Able to walk ≥100 m in 6 minute walk test	Not recorded	Safety and tolerability of etanercept	Improvement in LV function and structure Functional and clinical status as measured by a clinical composite score
Wojnicz[8]/2001	Heart failure ≥6 months LVEF ≤40%	No increased expression of HLA molecules in biopsy Systolic heart failure for <6 months All known causes of heart failure ruled out, endocrine disease, significant renal disease, drug or alcohol abuse Steroid therapy within 6 months before the study	Cardiac death, heart transplantation, and readmission to the hospital	Change in EF, EDD, EDV, and ESV and NYHA class
Sliwa[9]/2002	Age ≥18 years NYHA IV LVEF ≤40% LVEDD >55 mm Sinus rhythm On dobutamine ≥ 72 hours High-quality echocardiographic images could be obtained	Coronary artery disease Pulmonary disease Organic valvular disease Conditions other than heart failure known to increase plasma cytokine concentrations Received anti-inflammatory agents	Effect on pump performance Plasma TNF, Fas/Apo-1 and IL-10 concentration	Effect on functional class, hemodynamics (BP, HR, LVEF), and cardiac dimensions (LVEDD and LVESD)
Chung[10]/2003	Age ≥18 years Stable NYHA III/IV	Hemodynamically significant obstructive valvular disease	Change in composite clinical score at 14	Change in inflammatory markers during the 28-

	LVEF ≤35%	Cor pulmonale Restrictive or hypertrophic cardiomyopathy Constrictive pericarditis Congenital heart disease Experienced an acute myocardial infarction or coronary revascularization procedure within 2 months Likely to undergo coronary revascularization or heart transplant during the study	weeks	week trial period Change in LVEF at 14 and 28 weeks risk of death or hospitalization for worsening heart failure at 28 weeks Change in Minnesota Living With Heart Failure score at 14 and 28 weeks
Bahrmann[11]/ 2004	Age 18-70 Stable NYHA II/III HF due to ischemic and hypertensive cardiomyopathy or idiopathic-dilated cardiomyopathy LVEF ≤40% Sinus rhythm	COPD Significant valvular disease Disorders other than cardiomyopathy that could increase TNF-α and IL-6 concentrations Pregnancy Severe liver disease Acute MI Hemorrhage Any clinical condition judged by the investigators to prevent inclusion in the study	Change in LVEF	Concentrations of TNF-α, IL-6, BNP, and VO_2 max Minnesota Living with Heart Failure Questionnaire NYHA class
Sliwa[12]/2004	Age 18-70 NYHA II/III LVEF <40% Sinus rhythm Ability to obtain high-quality echocardiographic images	Clinical conditions other than cardiomyopathy that could influence cytokine levels Pregnancy Severe exercise-induced malignant ventricular arrhythmia MI within the last 12 months Recent myocardial	Change in LVEF	Not recorded

		revascularization (<6 months) Any clinical condition that according to the investigators precluded inclusion into the study		
Torre-Amione[13]/ 2005	Age ≥18 NYHA III/IV LVEF <40% 6-minute walk distance >300m On standard medical treatment No change in active cardiac medications 2 weeks before enrollment	Not recorded	Change 6 minute walk distance Change in NYHA classification	Change in cardiac function All-cause mortality All-cause Hospitalization Change in the Minnesota Living With Heart Failure score
Gullestad[14]/2005	NYHA II/III LVEF <40% No changes in medication during the last 3 months Clinically and hemodynamically stable Optimally treated with medications No possibility of surgical improvement	Evidence of acute coronary syndromes during the last 6 months Significant concomitant disease Abnormal liver function test results Women of child-bearing potential Any form of neuropathy	Change in LVEF	Change in LVEDV, NYHA class HR, BP Minnesota Living With Heart Failure Questionnaire and McMaster Overall Treatment Evaluation questionnaire NT-proBNP Immunologic variables
Gong[15]/2006	Age 18-75 years NYHA II-IV High-quality echocardiographic images could be obtained LVEF <45% and LVEDD >55 mm	COPD. rheumatoid arthritis, infection, connective tissue disease, neoplasm, severe liver or renal dysfunction, Anemia, Acute MI within 6 weeks, Unstable angina pectoris	Change in concentration of inflammatory cytokines	LVEDD LVEF NYHA class 6MWT Quality OF Life Physical and mental health score

Frustaci[16]/2009	LVEF <45% Age 18-75 CHF >6 months Histologic and immunohistochemical evidence of active lymphocytic myocarditis Absence of cardiotropic viruses at PCR analysis Absence of congenital, valvular, and/or coronary artery disease	CHF <6 months Known causes of heart failure Steroid therapy within 6 months before enrollment Contraindication to treatment with steroids or azathioprine Pregnancy or lactation	Change in LVEF	Changes LV volumes and diameters Changes in heart failure symptoms NYHA class cardiac death or heart transplantation
Deftereos[17]/2014	Stable symptomatic heart failure LVEF ≤40%	Recently hospitalized patients (≤3 months) NYHA IV Recent (≤ 6 months) implantation of a cardiac resynchronization treatment device Active inflammatory/infectious disease or malignancy Known autoimmune diseases, corticosteroid or other immunosuppressive or immunomodulatory therapy moderate or severe hepatic impairment severe renal failure (glomerular filtration rate <30 ml/min/1.73 m^2) Current participation in another research protocol Inability or unwillingness to adhere to standard treatment or to	Change in NYHA class	The composite of death and hospital stay for CHF Change in LVEDD Change in LVEF Change in treadmill exercise time

		provide consent		
Van Tessel[18]/ 2016	Acute decompensated heart failure within the last 24 hours as evidenced by dyspnea at rest and evidence of elevated cardiac filling pressure (or pulmonary congestion) as evidenced by pulmonary congestion/edema at physical exam (or chest radiography), BNP ≥200 pg/mL, or invasive measure of LVEDP >18 mmHg or PCWP >16 mmHg; LVEF <40% during index hospitalization or prior 12 months; Age ≥18 years old; Willing and able to provide written informed consent; C-reactive protein ≥5 mg/L.	Admission for something other than decompensated heart failure, including diagnosis of acute coronary syndromes, hypertensive urgency/emergency, tachy- or brady-arrhythmias; acute coronary syndromes, uncontrolled hypertension or orthostatic hypotension, tachy- or brady-arrhythmias, acute or chronic pulmonary disease or neuromuscular disorders affecting respiration; recent (previous 3 months) or planned cardiac resynchronization therapy (CRT), coronary artery revascularization procedures, or heart valve surgeries; Previous or planned implantation of LVAD or heart-transplant; Chronic use of intravenous inotropes; Recent (<14 days) use of immunosuppressive or anti-inflammatory drugs (not including NSAIDs); Chronic inflammatory disorder Active infection (of any type); Chronic/recurrent infectious disease (including HBV, HCV, and HIV/AIDS); Prior (≤10 years) or current malignancy; Any comorbidity limiting survival or ability to complete the study; End	Change in CRP	Change in cardiac structure and fucntion Clinical outcomes: such as adverse events, length of hospital stay, hospital readmission and time-to-events.

		stage kidney disease requiring renal replacement therapy; Neutropenia (<2,000/mm3) or Thrombocytopenia (<50,000/mm3); Pregnancy		
Xiaojing[19]/ 2017	Primary CHF NYHA II–IV LVEF ≤40%	Presence of a tumor Acute or chronic infection Immune system disease Recent major surgery or trauma (within 6 months) Rheumatoid activity Acute cerebrovascular disease (within 6 months) Liver, kidney, or pulmonary insufficiency	Change in LVEF, LVEDD, LVESD hsCRP, BNP, 6-min walking distance Minnesota Living with Heart Failure Questionnaire Lymphocyte subsets Inflammatory cytokines	

EF, Ejection fraction; ICM, Ischemic cardiomyopathy; IVIg, Intra-Venous Immunoglobulin; kg, kilogram; LVEDD, Left ventricular end-diastolic dimension; LVEF: Left ventricular ejection fraction; LVESD: Left ventricular end-systolic dimension; hsCRP: high sensitivity C-Reactive Protein; BNP: Brain natriuretic peptide; NYHA: New York Heart Association; TNF: Tumor necrosis factor; CHF: Congestive heart failure; HIV: Human immune-deficiency virus; AIDS: Acquired immune-deficiency syndrome; LVAD: Left ventricle assist device; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PCWP: Pulmonary capillary wedge pressure; BP: blood pressure; HR: Heart rate; 6MWT: 6-minute walk test; COPD: Chronic obstructive pulmonary disease

S3 Search Strategy and data collection

A systematic MEDLINE, Embase®, Cochrane Central and ClinicalTrials.gov search was performed from 1980 to March 14, 2019 using human subjects and clinical trials as search filters and various combinations of the following search terms:

PubMed (n=437)

(Heart Failure OR Ischemic Heart Disease) AND (Infliximab OR Tocilizumab OR Canakinumab OR Anakinra OR Allopurinol OR Oxypurinol OR Xanthine Oxidase inhibitor OR Etanercept OR Pentoxifylline)

(Dilated Cardiomyopathy OR Congestive Heart Failure OR Chronic Heart Failure OR ischemic heart disease) AND (Corticosteroids OR Hydrocortisone OR Dexamethasone OR prednisone OR methylprednisolone OR prednisolone OR IVIg OR Immunoglobulin OR Cyclosporine OR Colchicine OR Celecade OR Methotrexate OR Istaroxime OR Leukoarreast OR Mast cells) AND (ejection fraction)

EMBASE (n=193)

'heart failure' AND (‘anticytokine therapy' OR 'immunosuppression'/exp OR 'immunosuppression' OR 'methotrexate'/exp OR 'methotrexate' OR 'prednisone'/exp OR 'prednisone' OR 'thymopentin'/exp OR 'thymopentin' OR 'ivig'/exp OR 'ivig' OR 'cyclosporine'/exp OR 'cyclosporine' OR 'colcichine' OR 'celacade'/exp OR 'celacade' OR 'innate immunity'/exp OR 'innate immunity' OR 'mast cells'/exp OR 'mast cells' OR 'cd11' OR 'cd18'/exp OR 'cd18' OR 'istaroxime'/exp OR 'istaroxime') AND 'randomized controlled trial'/de AND ('congestive heart failure'/de OR 'heart failure'/de) AND 'drug therapy'/lnk AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim)

ClinicalTrials.gov (n=55)

"Heart Failure" AND ("Cytokines" OR "Corticosteroids" OR "Thymopentin" OR "IVIG" OR "Immunoglobulin" OR "Methotrexate" OR "Colcichine" OR "Celacade" OR "Cyclosporine" OR “Leukoarrest" OR "rhuMab” OR "istaroxime”

Cochrane CENTRAL (n=0)

(“Dilated Cardiomyopathy” OR “Congestive Heart Failure” OR “Chronic Heart Failure” OR “ischemic heart disease”) AND (“Corticosteroids” OR “Hydrocortisone” OR “Dexamethasone” OR “prednisone” OR “methylprednisolone” OR “prednisolone” OR “IVIg” OR “Immunoglobulin” OR “Cyclosporine” OR “Colchicine” OR “Celecade” OR “Methotrexate” OR “Istaroxime” OR “Leukoarreast” OR “Mast cells”) AND (“ejection fraction”)

In addition, references from review articles were screened for eligibility. Only English language studies were considered. Two investigators (K.G and N.J.G) independently conducted the search, reviewed the articles and extracted relevant data from the studies. Disagreements, if any, were resolved through consensus or discussion with the lead investigators (N.S.B and S.D.P).

Data items pertaining to patients' demographic, clinical and treatment characteristics, methods of LVEF and LV end-diastolic dimension (LVEDD) assessment, and all-cause mortality were extracted from the eligible studies. The LVEF (%) and LVEDD (in mm) were reported to one decimal place given spatial resolution and convention for reporting these measures.

S4 Statistics

Meta-analysis and publication bias

Data were analyzed for heterogeneity using the I^2 statistic proposed by Higgins and Thompson;[20] 95% confidence intervals (CIs) around the I^2 statistic were also estimated. We intended to assess small study treatment effects using funnel plot techniques and the Begg and Mazumdar correlation.[21,22,23] RoB for the primary efficacy outcome was determined for each trial.[24]

Mean change in LVEF after treatment in both groups was compared. If the mean LVEF for a group was not given, the median was substituted. In the case of multiple intervention groups, data were combined to allow pair-wise comparison (Cochrane Handbook 16.5.4). Mean and standard deviation (SD) of the combined group was calculated using the following formula (Cochrane Table 7.7a).

Combined Mean= $\frac{N1M1+N2M2}{N1+N2}$

Combined SD= $$\sqrt{\frac{(N_1-1)SD_1^2+(N_2-1)SD_2^2+\frac{N_1N_2}{N_1+N_2}(M_1^2+M_2^2-2M_1M_2)}{N_1+N_2-1}}$$

where N_1 and N_2, M_1 and M_2, SD_1 and SD_2 is the sample size, the mean and standard deviation of group 1 and 2, respectively.

SD for the mean change in LVEF in each arm was calculated using the formula:

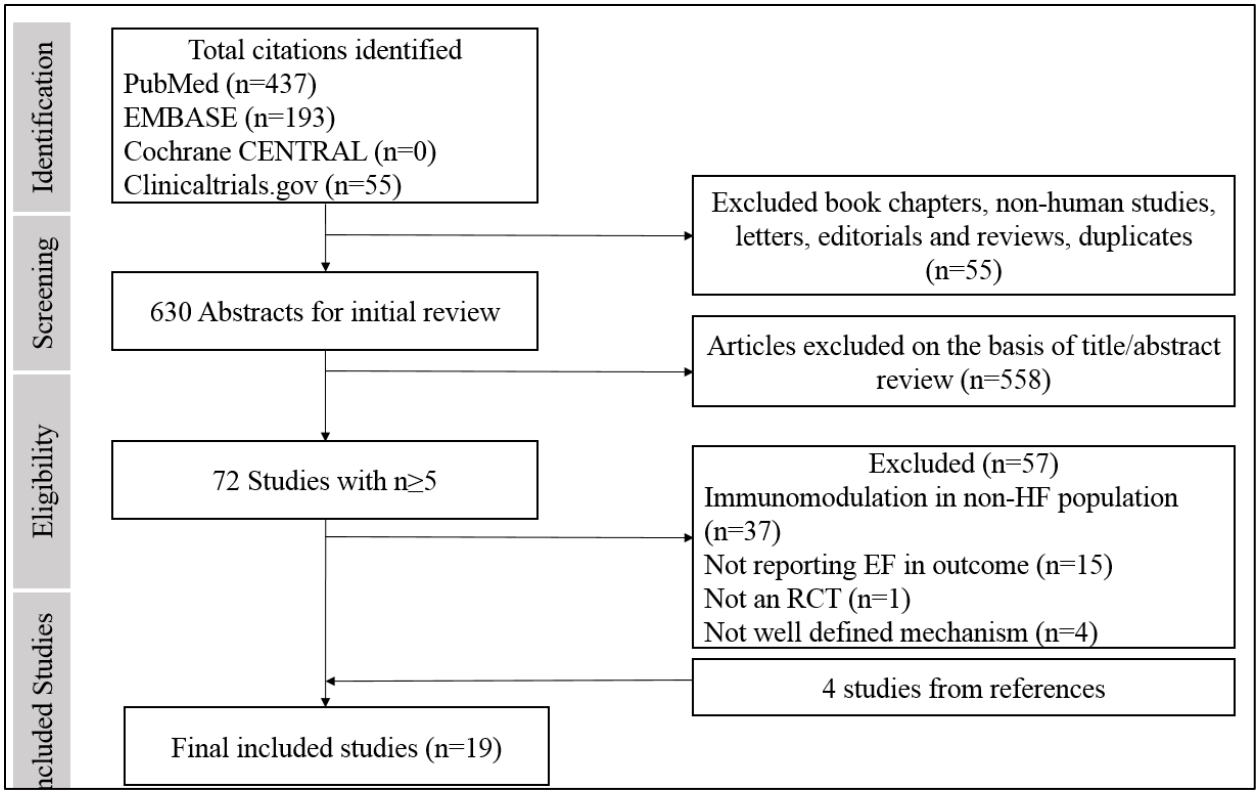
$SD_{change} = \sqrt{SD_{baseline}^2 + SD_{final}^2 - (2 * Corr * SD_{baseline} + SD_{final}}$ (Cochrane 16.1.3.2),

where $SD_{baseline}$ and SD_{final} are the standard deviations at the baseline and after the intervention, respectively. The correlation coefficient used was 0.5 (as recommended by the Cochrane manual).

The standard error (SE) was converted to SD using the formula $SD = \sqrt{N} * SE$ (Cochrane, 7.7.3.3). Inter-quartile range (IQR) was converted to SD using the formula $SD = IQR/1.35$ (Cochrane 7.7.3.5). In some cases, no variability estimate was provided for either a pre- or post-treatment measurement. SD for groups unable to be found by collecting SD info or calculating it through other means they gave (eg IQR or SE) were assumed to be the same as the pre/post-treatment group as per Cochrane recommendations (Cochrane 16.1.3.2). Summary estimates of SMDs were calculated using the Mantel–Haenszel random effect model.

Trial sequential analysis

Most meta-analyses lack sufficient statistical power to detect treatment effects even when they are large.[25] When the number of included participants or trials is low, traditional meta-analytic techniques and statistical significance thresholds may lead to false-positive (type I errors) or false-negative conclusions (type II errors). In these situations, the Lan-DeMets trial sequential monitoring boundaries in trial sequential analysis offer adjusted confidence intervals when the required information size and the corresponding number of required trials for the meta-analysis have not been reached. The trial sequential analysis (TSA) provides a frequentist approach to control both types I and type II errors. Several empirical studies have demonstrated that TSA provides better control of type I errors and of type II errors than traditional naïve meta-analysis.[25,26] Cumulative meta-analyses were performed in accordance with the study by Lau *et al*.[27]

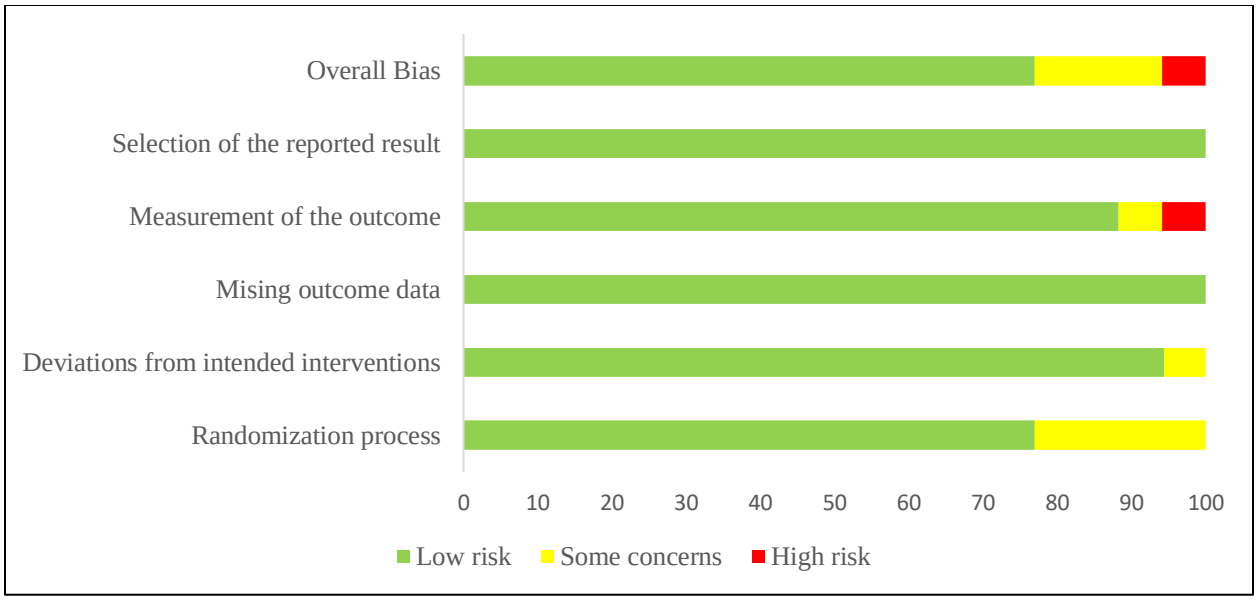


S5 Supplement Figure 1: Flow diagram for study selection

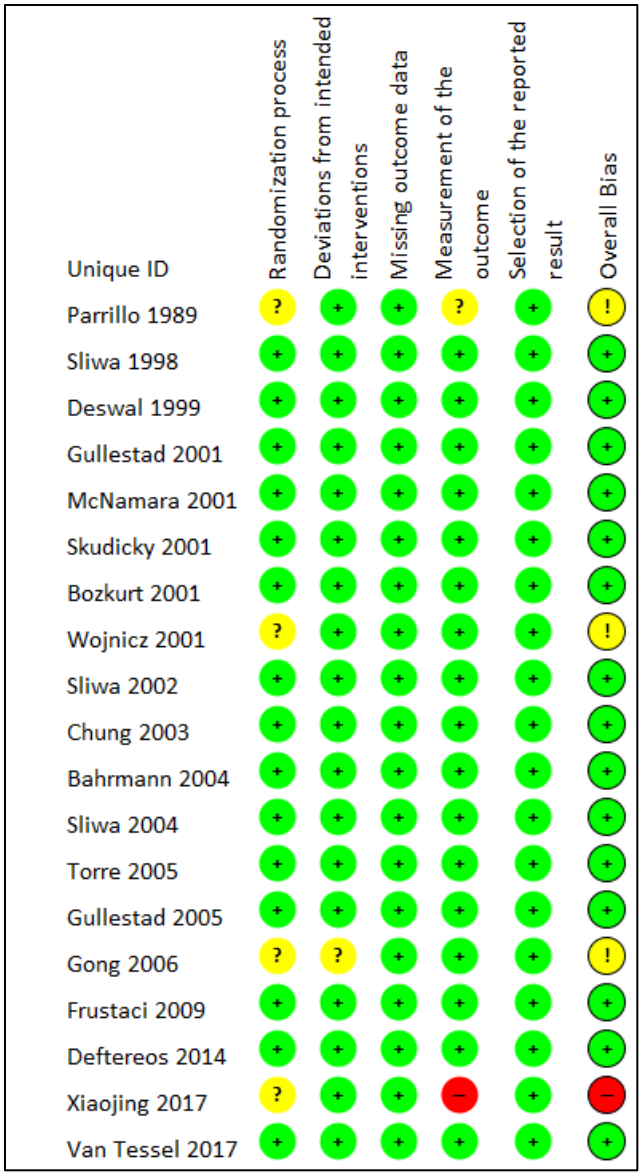
S6 Supplement Table 2: Treatment protocols and method of LVEF assessment across trials

Author Year	Treatment protocol	Method of LVEF assessment
Parrillo[1]/1989	T. Prednisone 60 mg QD for 3 months	Radionuclide Imaging
Sliwa[2]/1998	T. Pentoxifylline 400 mg TID for 6 months	Radionuclide Imaging
Deswal[3]/1999	Inj. Etanercept 1, 4 or 10 mg/m^2 subcutaneous single dose	Echocardiography
Gullestad[4]/2001	Inj. IVIg 0.4 g/kg for 5 days f/b by 0.4 g/kg once monthly for 5 months	Radionuclide Imaging
McNamara[5]/ 2001	Inj. IVIg 1 g/kg intravenous infusion for 2 days	Radionuclide Imaging
Skudicky[6]/2001	T. Pentoxifylline 400 mg TID for 6 months	Radionuclide Imaging
Bozkurt[7]/2001	Inj. Etanercept 5 or 12 mg/m^2 subcutaneous twice-weekly for 3 months	Echocardiography
Wojnicz[8]/2001	Prednisone 1 mg/kg/day for 12 days f/b taper every 5 days by 5 mg/day to a maintenance dose of 0.2 mg/kg/day for total 90 days. Azathioprine 1 mg/kg/d for 100 days	Echocardiography
Sliwa[9]/2002	T. Pentoxifylline 400mg TID for 1 month	Radionuclide Imaging
Chung[10]/2003	Inj. Infliximab 5 or 10 mg/kg intravenous infusion at 0, 2, and 6 weeks	Radionuclide Imaging
Bahrmann[11]/ 2004	T. Pentoxifylline 600mg BID for 6 months	Echocardiography
Sliwa[12]/2004	T. Pentoxifylline 400mg TID for 6 months	Radionuclide Imaging
Torre-Amione[13]/ 2005	Inj. Celecade intramuscular for 2 days followed by once monthly for 6 months	Echocardiography
Gullestad[14]/2005	T. Thalidomide 25 mg QD doubling every 2 weeks to target dose of 200 mg for 12 weeks	Radionuclide Imaging
Gong[15]/2006	T. Methotrexate 7.5 mg once/week for 12 weeks	Echocardiography
Frustaci[16]/2009	T. Prednisone 1 mg/kg/day for 4 weeks f/b 0.33 mg/kg/day for 5 months. Azathioprine 2 mg/kg/day for 6 months	Echocardiography
Deftereos[17]/ 2014	T. Colchicine 0.5 mg BID for 6 months	Echocardiography
Van Tessel[18]/ 2016	Inj. Anakinra 100 mg/day subcutaneous for 2 or 12 weeks	Echocardiography
Xiaojing[19]/2017	Inj. Thymopentin intramuscular 2 mg/dose; once/15 days; total 5 doses	Echocardiography

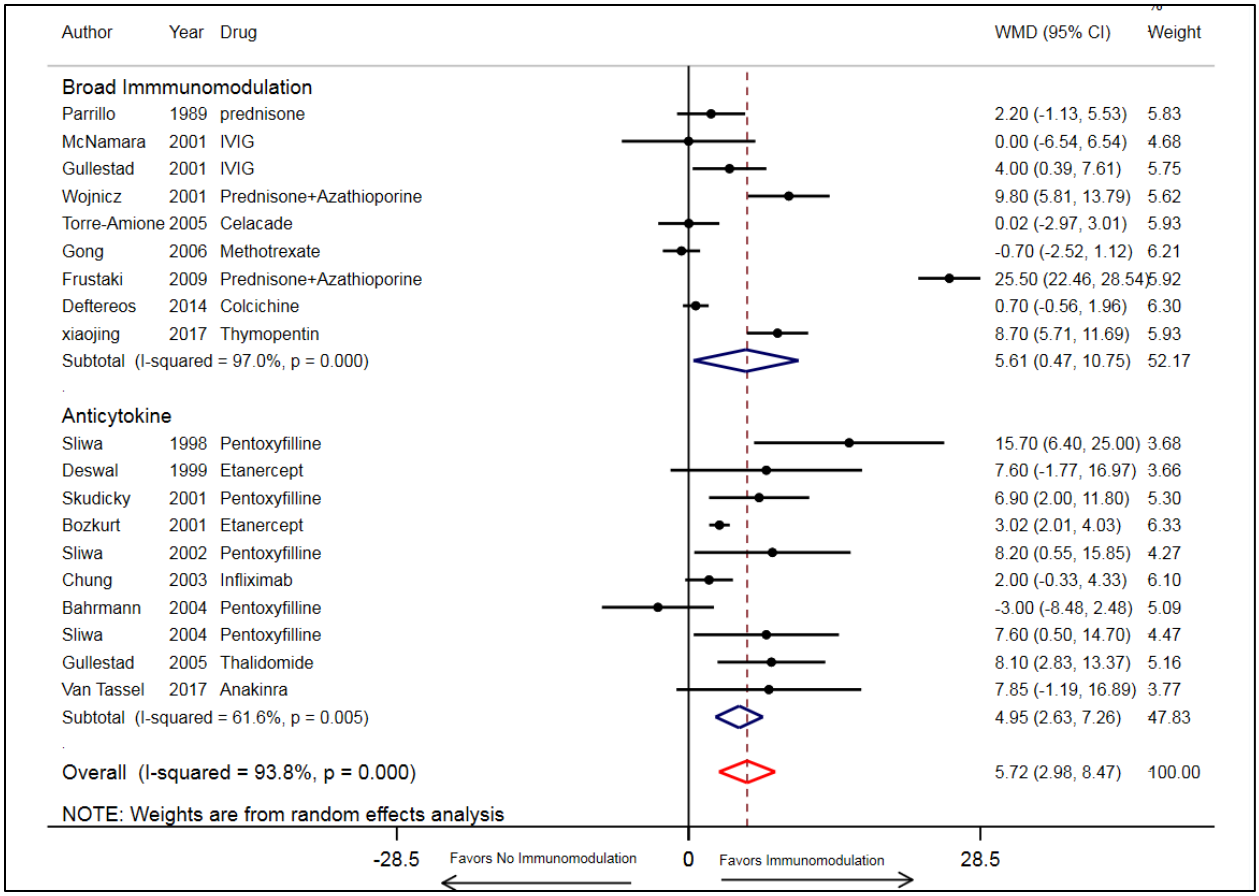
T, Tablet; Inj, Injection; QD, once daily; TID, three times daily; f/b, followed by; BID, twice daily; mg, milligram; kg, kilogram.



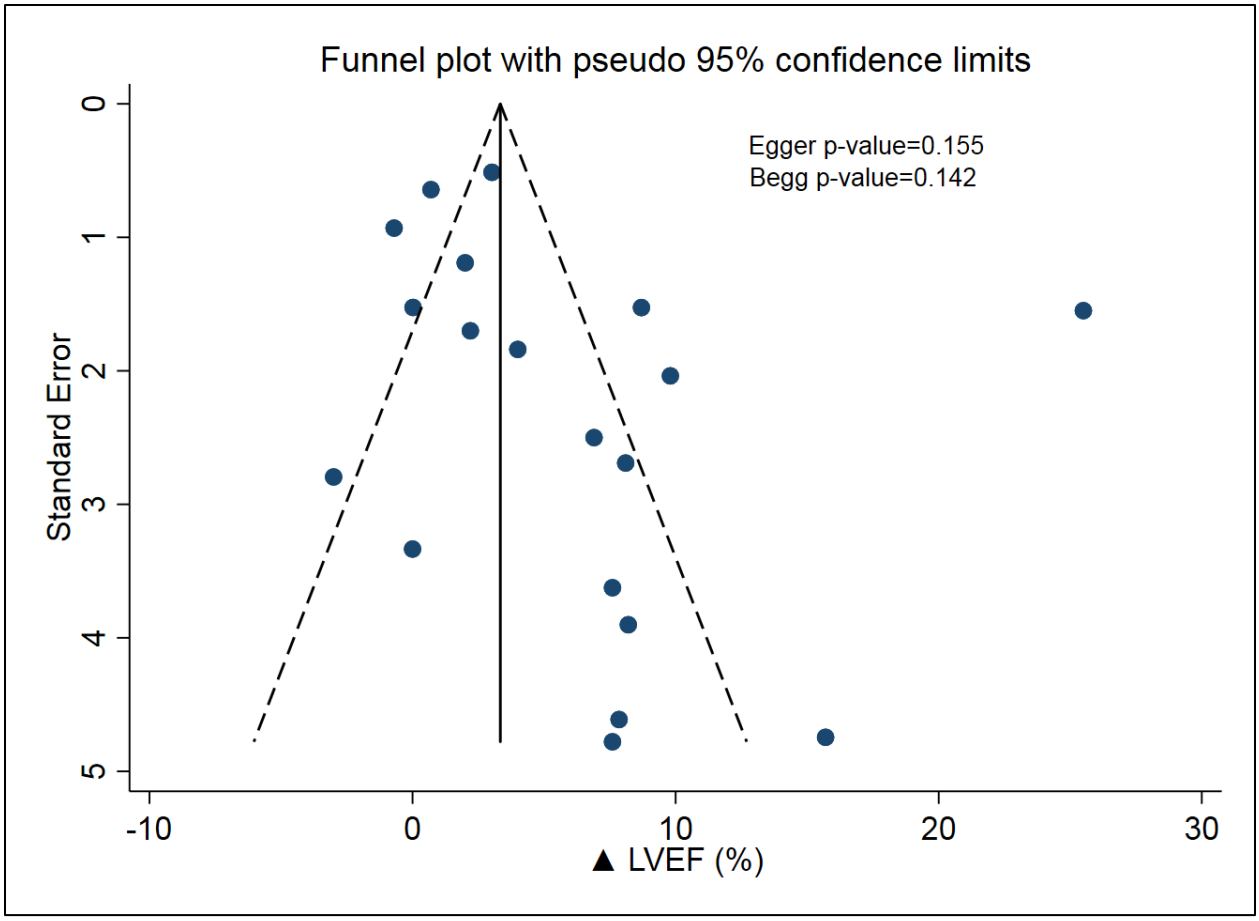
S7 Supplement Figure 2: Risk-of-bias summary for randomized trials (RoB 2.0) assessed using the Cochrane RoB tool[28]



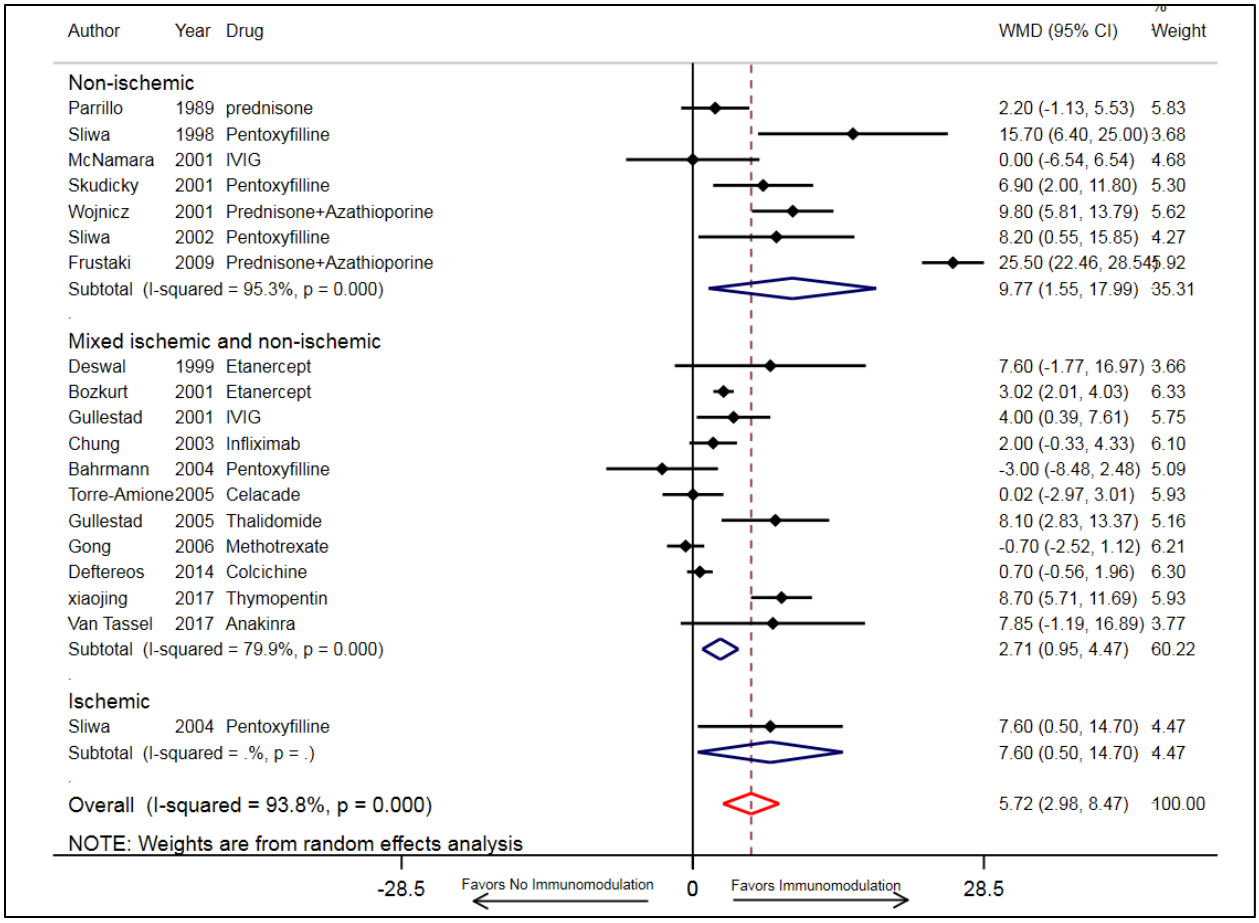
S8 Supplement Figure 3: Review author's judgements about each risk-of-bias for each trial included. Green, yellow and red solid circles represent low, some concern and high risk-of-bias, respectively.



S9 Supplement Figure 4: Effect of immunomodulation on LVEF as compared to no immunomodulation according to drug class. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is summary WMD and 95% CI for immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary WMD with 95% CI. CI: Confidence interval



S10 Supplement Figure 5: Funnel plot for publication bias with each blue dot representing a randomized trial and the dotted lines representing the pseudo 95% confidence intervals.

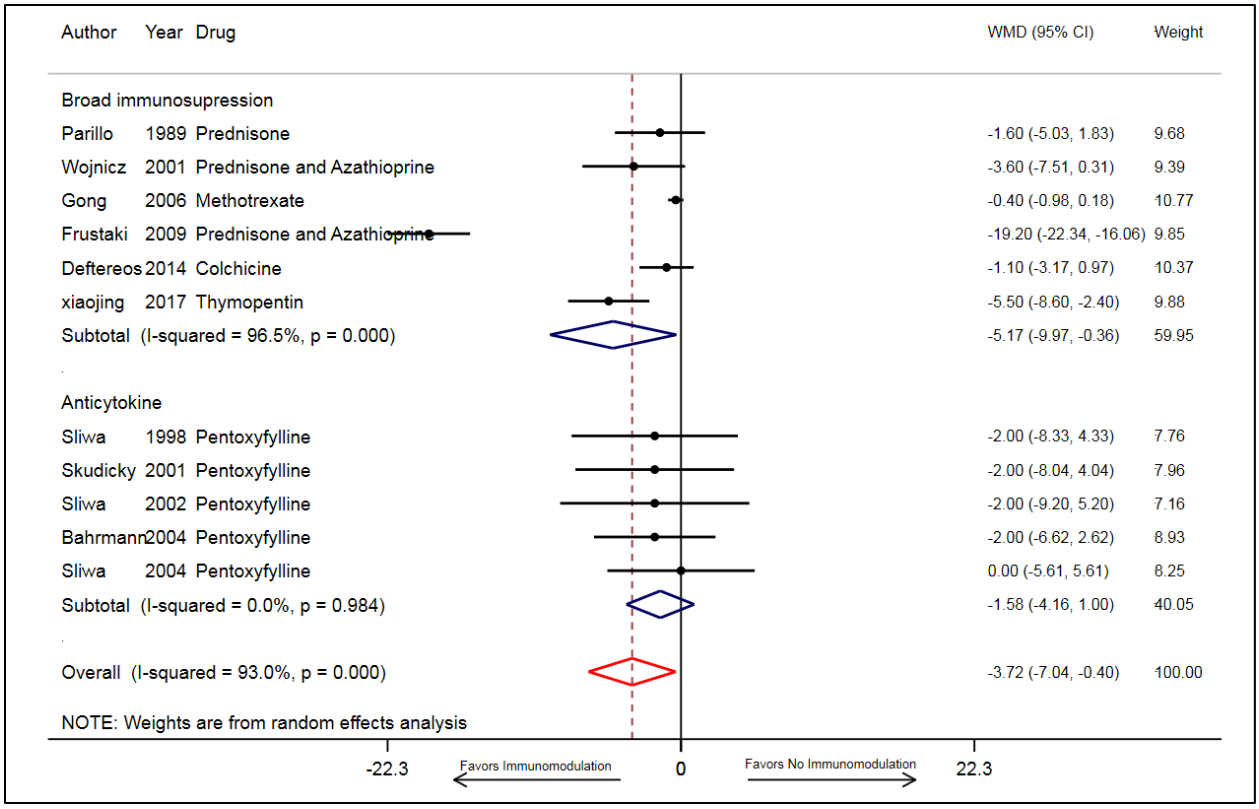


S11 Supplement Figure 6: Effect of immunomodulation on LVEF as compared to no immunomodulation according to heart failure aetiology. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is summary WMD and 95% CI for immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary WMD with 95% CI. CI: Confidence interval

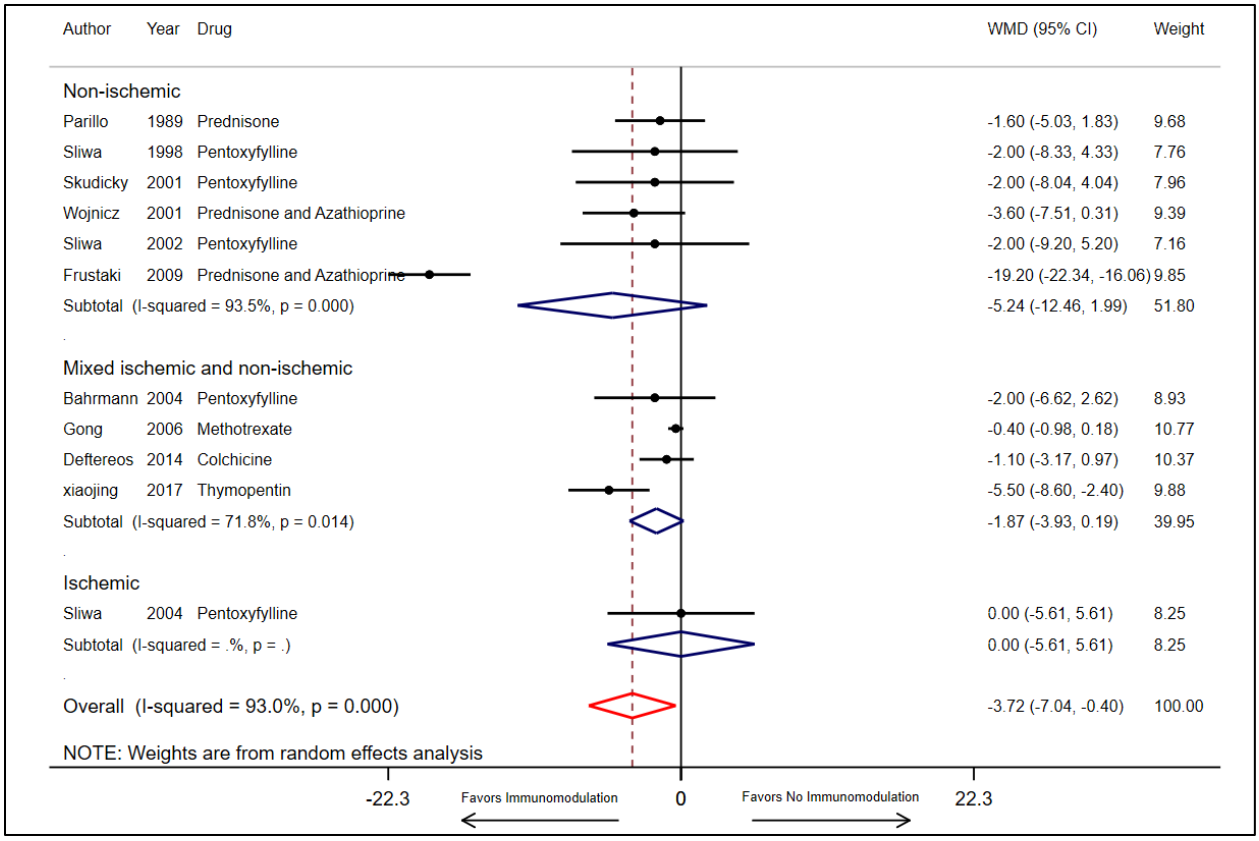
S12 Supplement Table 3: Mean difference, weighted (WMD) and standardized (SMD) for primary and secondary outcomes.

Outcome	WMD	p-value	SMD	p-value
Left ventricular ejection fraction				
Overall	5.7 (3.0, 8.5)	<0.001	0.7 (0.4, 1.1)	<0.001
Drug class				
Anticytokine	5.0 (2.6, 7.3)	<0.001	0.7 (0.4, 1.1)	0.032
Broad	5.6 (0.5, 10.8)	<0.001	0.7 (0.2, 1.3)	0.012
Aetiology				
Non-Ischemic	9.8 (1.6, 18.0)	0.020	1.2 (0.3, 2.0)	0.007
Ischemic	7.6 (0.5, 14.7)	0.036	0.7 (0, 1.4)	0.054
Mixed	2.7 (1.0, 4.5)	0.003	0.5 (0.2, 0.8)	0.004
Left ventricular end-diastolic dimension				
Overall	-3.7 (-7.0, -0.4)	0.028	-0.5 (-0.9, -0.1)	0.012
Drug class				
Anticytokine	-1.6 (-4.2, 1.0)	0.231	-0.2 (-0.5, 1.0)	0.238
Broad	-5.2 (-10.0, -0.4)	0.035	-0.7 (-1.3, -0.1)	0.018
Aetiology				
Non-Ischemic	-5.2 (-12.5, 2.0)	0.156	-0.7 (-1.5, 0.1)	0.093
Ischemic	0 (-5.6, 5.6)	1.0	0 (-0.7, 0.7)	1.000
Mixed	-3.7 (-7.0, -0.4)	0.076	-0.3 (-0.6, -0.1)	0.021

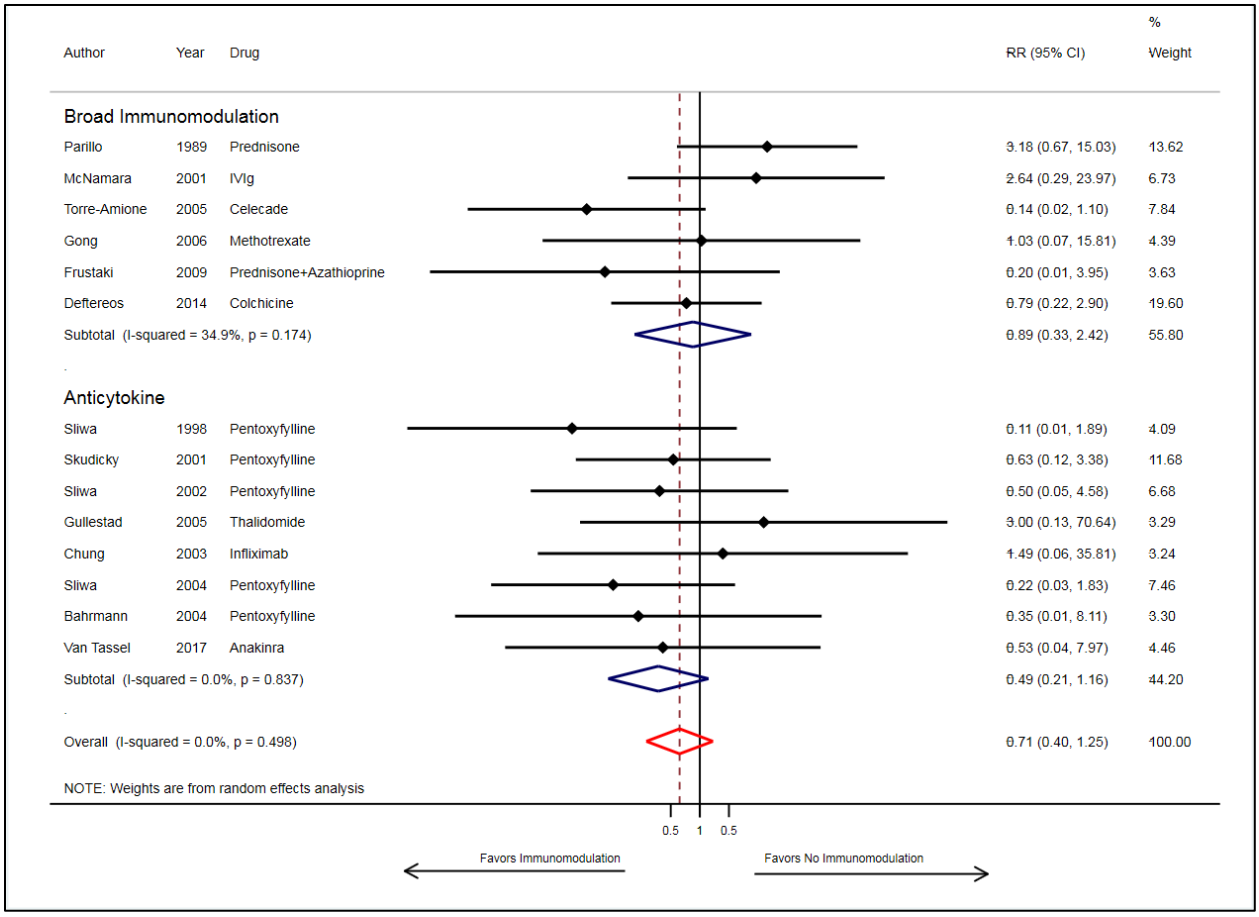
Data are presented as mean (95% Confidence interval)



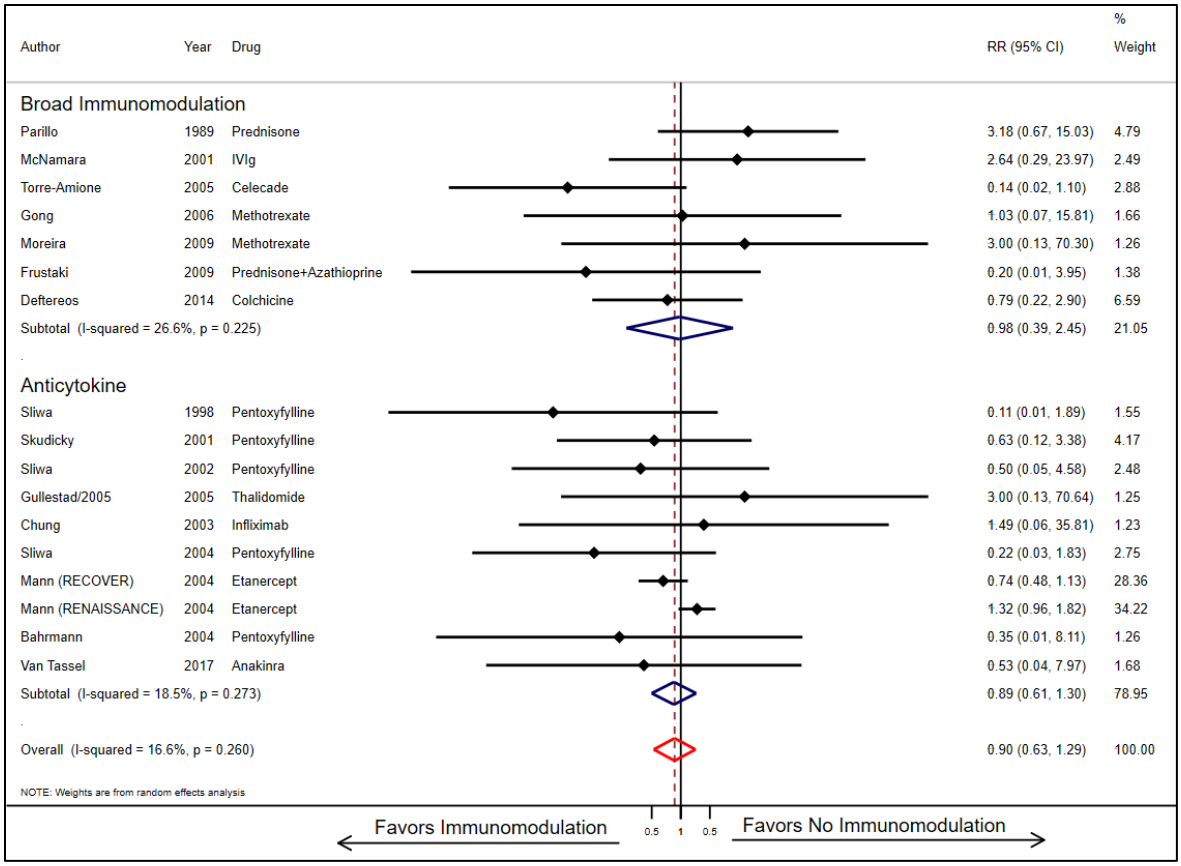
S13 Supplement Figure 7: Effect of immunomodulation on LVEDD as compared to no immunomodulation according to drug class. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is summary WMD and 95% CI for each class of immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary WMD with 95% CI. CI: Confidence interval



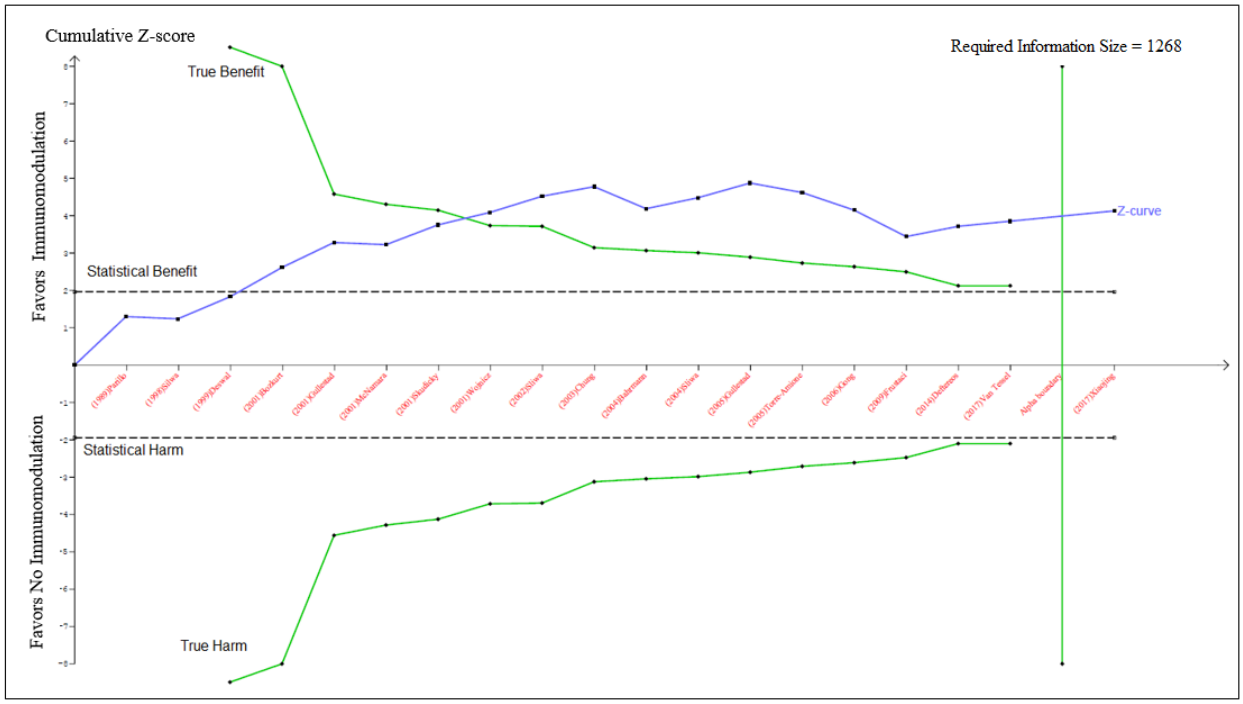
S14 Supplement Figure 8: Effect of immunomodulation on LVEDD as compared to no immunomodulation according to heart failure aetiology. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is summary WMD and 95% CI for immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary WMD with 95% CI.CI: Confidence interval



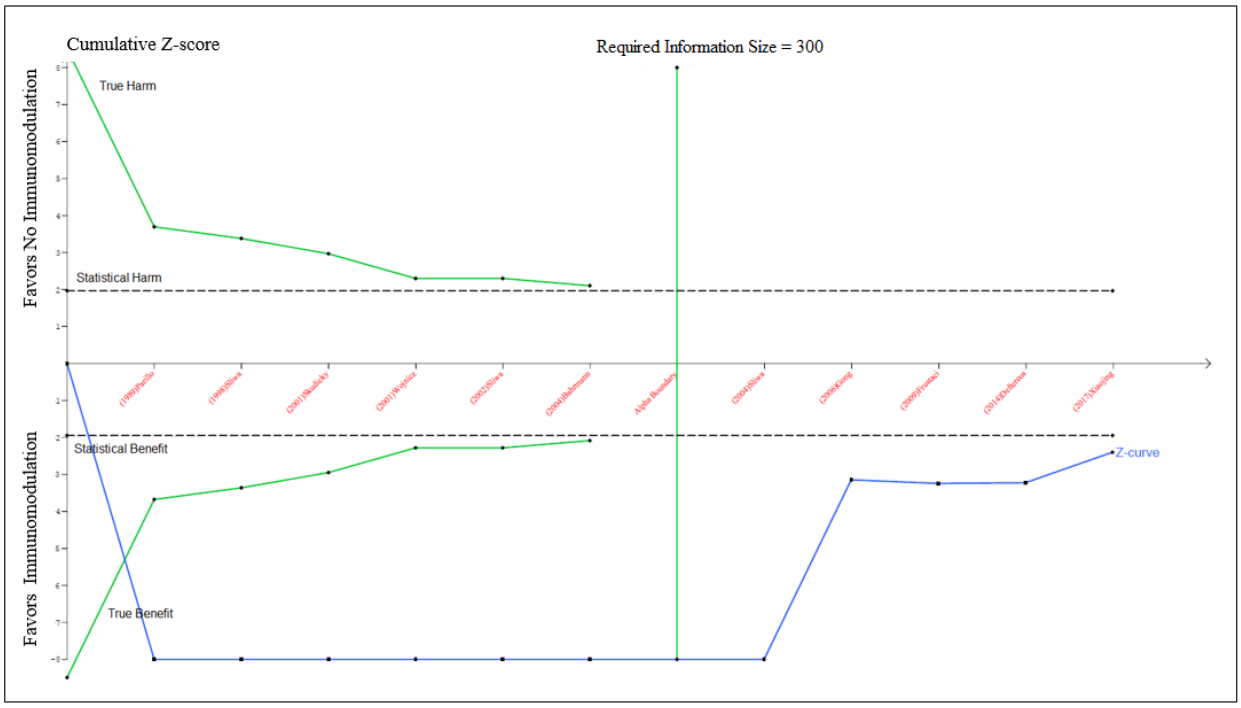
S15 Supplement Figure 9: Effect of immunomodulation on mortality as compared to no immunomodulation according to heart failure aetiology. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are the weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is a summary WMD and 95% CI for immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary RR with 95% CI.CI: Confidence interval



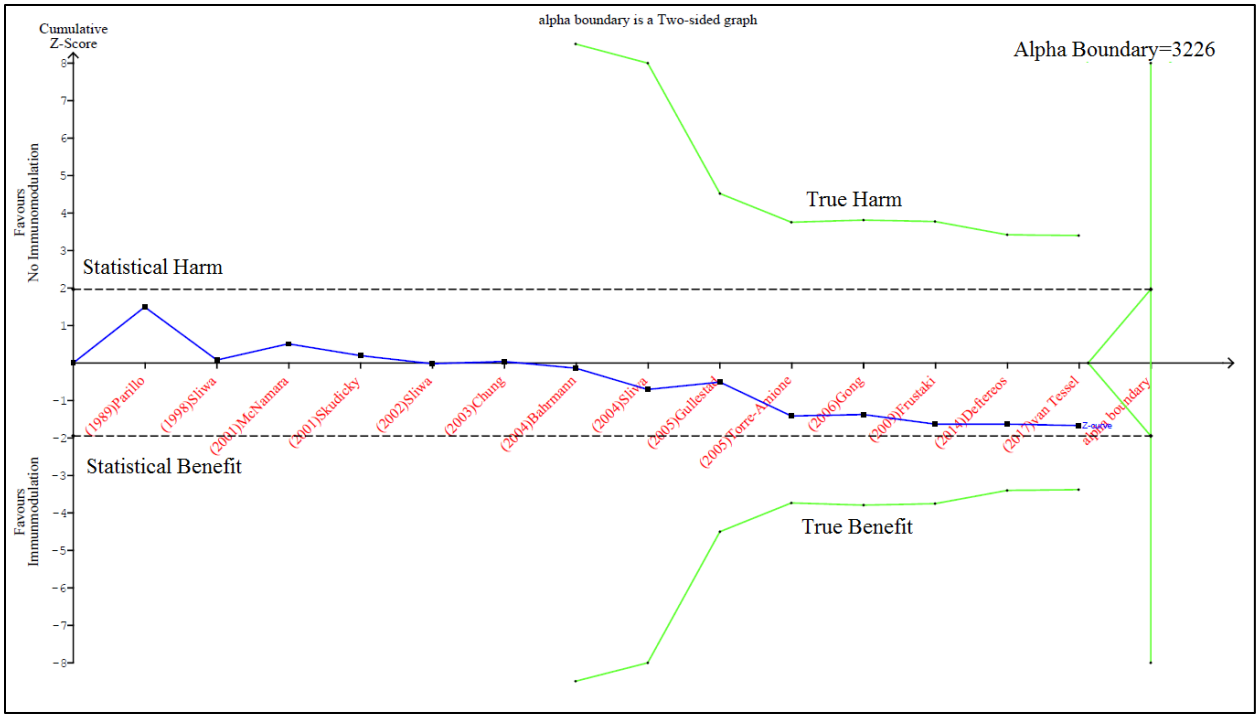
S16 Supplement Figure 10: Sensitivity analysis for effect of immunomodulation on mortality as compared to no immunomodulation according to heart failure aetiology in all trials reporting mortality data. Black solid square diamonds and associated solid lines represent summary RR and 95% CI of each trial listed in the left column. The numerical estimates in the right columns are weighted mean difference(s) (WMD) with 95% CI of each trial listed in the left column. The hollow blue diamond is summary WMD and 95% CI for immunomodulation as compared to no immunomodulation. The hollow red diamond is the overall summary RR with 95% CI.CI: Confidence interval



S17 Supplement Figure 11: Trial sequential analysis of immunomodulation vs. no immunomodulation in patients with heart failure for improvement in left ventricular ejection fraction (LVEF). The solid black line represents the line of no difference. The green lines above and below the line of no difference represent the O'Brien-Fleming trial sequential boundary for no benefit and benefit with immunomodulation, respectively. The solid black lines are upper and lower bounds for 95% CI. The green vertical line is the required information size for conclusive meta-analyses, given two-sided α=0.05 and β=0.20. The solid blue line is Z-curve derived from a random-effects meta-analysis of individual RCTs. The inner wedge represents the O'Brien-Fleming β-spending function at 80% power. The Z-curve surpassed the trial sequential boundary and the information size, indicating a true improvement in LVEF with immunomodulation as compared to no immunomodulation.



S18 Supplement Figure 12: Trial sequential analysis of immunomodulation vs. no immunomodulation in patients with heart failure for improvement in left ventricle end-diastolic dimension (LVEDD). The solid black line represents the line of no difference. The green lines above and below the line of no difference represent the O'Brien-Fleming trial sequential boundary for no benefit and benefit with immunomodulation, respectively. The solid black lines are upper and lower bounds for 95% CI. The green vertical line is the required information size for conclusive meta-analyses, given two-sided α=0.05 and β=0.20. The solid blue line is Z-curve derived from a random-effects meta-analysis of individual RCTs. The inner wedge represents the O'Brien-Fleming β-spending function at 80% power. The Z-curve surpassed the trial sequential boundary and the information size, indicating a true improvement in LVEDD with immunomodulation as compared to no immunomodulation.



S19 Supplement Figure 13: Trial sequential analysis of immunomodulation vs. no immunomodulation in patients with heart failure for improvement in mortality. The solid black line represents the line of no difference. The solid black line represents the line of no difference. The green lines above and below the line of no difference represent the O'Brien-Fleming trial sequential boundary for no benefit and benefit with immunomodulation, respectively. The solid black lines are upper and lower bounds for 95% CI. The green vertical line is the required information size for conclusive meta-analyses, given two-sided α=0.05 and β=0.20. The solid blue line is Z-curve derived from a random-effects meta-analysis of individual RCTs. The inner wedge represents the O'Brien-Fleming β-spending function at 80% power. The Z-curve did not surpass the trial sequential boundary and the information size, indicating a lack of sufficient evidence to conclude effect on mortality with or without immunomodulation.

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