SUPPLEMENTAL MATERIAL

Table 1. Search Strategy

Pubmed (n=5241)	
Stroke	(stroke[mh] OR stroke[Title])
Comorbidity	(multiple chronic conditions[mh] OR multiple chronic conditions[tiab] OR multimorbidity[tiab] OR comorbidity[mh] OR comorbidity[tiab] OR comorbid conditions[tiab] OR comorbid diseases[tiab] OR comorbid illnesses[tiab] OR premorbid condition[tiab] OR premorbid disease[tiab] OR premorbid illness[tiab] OR pre-morbid condition[tiab] OR pre-morbid disease[tiab] OR pre-morbid illness[tiab] OR preexist condition[tiab] OR preexist disease[tiab] OR preexist illness[tiab] OR pre-exist condition[tiab] OR pre-exist disease[tiab] OR pre-exist illness[tiab] OR pre-existing condition[tiab] OR pre-existing disease[tiab] OR pre-existing illness[tiab] OR Predict[tiab] OR Predictor[tiab] OR Predicting[tiab] OR Prediction[tiab] OR Predictive[tiab] OR adjust*[tiab] OR Multivariate Analysis[MeSH Terms] OR regression analysis[MeSH Terms])
Functional outcome	(Disability Evaluation[MeSH Terms] OR Recovery of Function[MeSH Terms] OR Activities of Daily Living[mh] OR Functional outcome[tiab] OR Functional independence[tiab] OR Functional independent[tiab] OR Functional dependence[tiab] OR Functional dependent[tiab] OR Functional limited[tiab] OR Functional limitation[tiab] OR Functional impairment[tiab] OR Functional impaired[tiab] OR Functional disabled[tiab] OR Functional disability[tiab] OR Functional ability[tiab] OR Functional recovery[tiab] OR Rankin[tiab] OR mRS[tiab] OR FIM[tiab] OR Barthel[tiab])
Filter	Filters: Publication date from 1990/01/01 to 2017/12/03
Embase (n=5331)	
Stroke	('cerebrovascular accident'/exp OR 'stroke':ab,ti)
Comorbidity	('multiple chronic conditions':ti,ab,kw OR 'multimorbidity':ti,ab,kw OR 'comorbidity':ti,ab,kw OR 'comorbid conditions':ti,ab,kw OR 'comorbid diseases':ti,ab,kw OR 'comorbid illnesses':ti,ab,kw OR 'premorbid condition':ti,ab,kw OR 'premorbid disease':ti,ab,kw OR 'premorbid illness':ti,ab,kw OR 'pre-morbid condition':ti,ab,kw OR 'pre-morbid disease':ti,ab,kw OR 'pre-morbid illness':ti,ab,kw OR 'preexist condition':ti,ab,kw OR 'preexist disease':ti,ab,kw OR 'preexist illness':ti,ab,kw OR 'pre-exist condition':ti,ab,kw OR 'pre-exist disease':ti,ab,kw OR 'pre-exist illness':ti,ab,kw OR 'pre-existing condition':ti,ab,kw OR 'pre-existing disease':ti,ab,kw OR 'pre-existing illness':ti,ab,kw OR 'predict':ti,ab,kw OR 'predictor':ti,ab,kw OR 'predicting':ti,ab,kw OR 'prediction':ti,ab,kw OR 'predictive':ti,ab,kw OR 'adjust':ti,ab,kw OR 'adjustment':ti,ab,kw OR 'adjusting':ti,ab,kw OR 'adjusted':ti,ab,kw OR 'multivariate analysis':ti,ab,kw OR 'regression analysis':ti,ab,kw)
Functional outcome	('disability':ti,ab,kw OR 'recovery of function':ti,ab,kw OR 'activities of daily living':ti,ab,kw OR 'functional outcome':ti,ab,kw OR 'functional independence':ti,ab,kw OR 'functional independent':ti,ab,kw OR 'functional dependence':ti,ab,kw OR 'functional dependent':ti,ab,kw OR 'functional limited':ti,ab,kw OR 'functional limitation':ti,ab,kw OR 'functional impairment':ti,ab,kw OR 'functional impaired':ti,ab,kw OR 'functional disabled':ti,ab,kw OR 'functional disability':ti,ab,kw OR 'functional ability':ti,ab,kw OR 'functional recovery':ti,ab,kw OR 'rankin':ti,ab,kw OR 'mrs':ti,ab,kw OR 'fim':ti,ab,kw OR 'barthel':ti,ab,kw)
Filter	AND [article]/lim AND [english]/lim AND [1-1-1990]/sd NOT [3-12-2017]/sd

Table 2. Quality Appraisal Checklist

Risk of Bias Assessment of the Included Studies		
Evaluation of	Scale*	Risk of Bias Criteria
1. Study Participation		
D1 Source population	H/M/L	Low if the study was population or community-based; Medium if the study was multi/single-centered and hospital-based High if the study was multi/single-centered and rehabilitation-based; or was done in veterans/ad hot analysis of clinical trials
D2 Prospective design	H/L	Low when a prospective cohort design was used High when retrospective or cross-sectional study design was used;
D3 Inclusion and exclusion criteria	H/L	Low if all ischemic stroke cases from the study time frame were eligible; Medium if patients were excluded due to factors other than their status of comorbidity, stroke severity, age, treatment or rehabilitation; High if patients were excluded due to the status of comorbidity, stroke severity, treatment or rehabilitation; or if patients were excluded due to other restriction on age (other than age ≥18);
D4 Recruitment	H/L	Low if all recruitment information (place, time-period, and methods used to identify ischemic stroke cases) were reported. High if any one aspect of the recruitment information was missing.
D5 Important baseline characteristics of the study population	H/M/L	Low if all of the following key characteristics of the study population were described, including the distributions of gender, age, stroke type, stroke severity and history of strokes*; Medium if any one of the key characteristics was missing; High if two or more of the key characteristics were missing; *history of strokes was adequate when the study reported if patients with 'history of stroke', 'recurrent stroke' or 'cerebrovascular disease' as a comorbidity were included/excluded;
2. Study attrition		
A1 Proportion of loss to follow-up	H/L	Low if the number of loss to follow-up is ≤20%.
A2 Reasons for loss to follow-up	H/L	Low if reasons for loss to follow-up were specified, or there was no loss to follow-up High if reasons for loss to follow-up were not specified even if the number of loss to follow-up is ≤20%.
A3 Methods dealing with missing data	H/M/L	Low if methods of dealing with missing values were presented (e.g. multiple imputations), or there were no missing values. Medium if the study conducted using complete-case analysis and the proportion of missing data is 5% or less;[1-3] High if the complete-case analysis was conducted and the proportion of missing data is more than 5%;[1-3]
A4 Comparison completers and non-completers	H/L	Low if there were no significant differences between participants who completed the study and who did not, concerning key characteristics gender, age, and stroke severity, MCCs and functional status, or there was the number of follow-ups is ≤20%), or if methods (e.g. inverse probability weighting) or sensitivity analysis were used to consider loss to follow-up.
3. MCC measurement		
M1 Definition of MCC	H/L	Low if the measurement of MCC was clearly defined.
M2 Temporality	H/L	Low if MCC conditions were identified before or during the index stroke; High if MCC conditions were identified at rehabilitation admission;
M3 MCC weighting	H/L	Low if conditions included in the MCC measurement indices were weighted in the calculation of an MCC score;
M4 Scoring scheme and cut-off points	H/L	Low if the scoring scheme for MCC were defined, including cut-off points and rationale for cut-off points was given;
M5 presentation	H/L	Low if frequencies, percentages, mean (SD/CI), or median (IQR) were reported for MCC, or for each condition included in the MCC index.

4. Outcome measurement		
O1 Definition of outcome	H/L	Low when the functional outcome was clearly defined.
O2 Functional outcome assessment	H/L	Low when there's no differential assessment for patient included. High when outcome assessment was different for included patients, or if the proxy were used in the outcome assessment.
O3 Scoring scheme and cut-off points described	H/L	Low if the scoring scheme of the functional outcome was described, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization or classification.
O4 Appropriate timing for functional outcome measurement	H/L	Low if the functional outcome was measured at a fixed time-point after stroke onset (e.g. 3 or 6 months); High if functional outcome measurement was obtained at hospitalization and rehabilitation discharge.
O5 Data presentation	H/L	Low if frequencies, percentages or mean (SD/CI) or median (IQR) were reported of the functional outcome measure.
5. Statistical analysis		
S1 Sufficient sample size	H/L	Low if in multivariate logistic regression analysis number of patients with a positive or negative outcome (event) per variable was adequate, i.e. was equal to or exceeds 10 events per variable in the multivariable model (EPV) [4], or in case of linear regression analysis, N ≥ 104+m, where m is the number of predictor variables.[5, 6]
S2 MCC presentation in univariate analysis	H/L	Low if univariate crude estimates and confidence intervals (β/SE, OR/CI, RR, HR) were reported for MCC; High when only p-values or correlation coefficients were given, or if the univariate analysis was not performed at all.
S3 MCC presentation in multivariable analysis	H/L	Low if for the multivariable models point estimates with confidence intervals (β/SE, OR/CI, RR, HR,) were reported for MCC; High when only p-values or correlation coefficients were given, or if no multivariable analysis was performed at all.
S4 MCC analyzed continuously	H/L	Low if MCC was analyzed continuously (not dichotomously or categorically) in the multivariable model.[7]
6. Study confounding		
C1 Controlling for important confounders	H/M/L	Low if both age and stroke severity were controlled in the multivariable model; Medium if either age or stroke severity was controlled; High if neither age nor stroke severity was controlled;[8] or if no multivariable analysis was performed at all.
C2 Confounding measurement	H/L	Low if stroke severity was measured in a valid and reliable way to reflect patients' neurological status using either the National Institutes of Health Stroke Scale (NIHSS) or the Canadian Neurological Scale (CNS).[8] High if stroke severity was assessed in other measurements, or if stroke severity was not controlled, or if no multivariable analysis was performed at all.
7. Clinical performance		
P1 Clinical performance	H/L	Low if article provided information concerning ≥1 of the following performance measures: discrimination (e.g. ROC), calibration (e.g. Hosmer-Lemeshow statistic), explained variance, clinical usefulness (e.g. sensitivity, specificity, PPV, NPV)
*H=High risk of bias (1 point); M=Medium risk of bias (0.5 point); L=low risk of bias (0 point) Total score: The higher the worse for study quality (high risk of bias);		

Table 3a. Characteristics of the eligible rehabilitation-based studies

First author	Year	Country	N	Source population	Prospective Study Design	Exclusion criteria	Year of admission	Stroke type	MCC measure	Outcome Measure	Outcome follow-up
Liu	1997	Japan	106	Single-centered	N	Bilateral hemiplegia, ataxia, or no motor involvement	1994-1995	IS 52 + ICH 51 +IS-2rd to-SAH	LiuCI-w	FIM	Discharge
									CCI	FIM	Discharge
Desrosiers	2002	Canada	102	Single-centered	Y	Unable to consent; in program<10d; **severe comorbidities;** lived far away; too sever impaired to be compliant with rehab	1997-1999	mixed	LiuCI-modified version	Handicap level (LIFE-H)	6 months after discharge
Duncan	2002	US	123 123 122 66	Multi-centered; Veterans	Y	Including: live place before stroke; medical conditions related to survival; ADLs; post stroke inpatient care/rehab;	1998 -1999	IS 144 + HS 12 + both 1	CCI	FIM-motor SF-36 physical dimension Lawton IADL scale SIS physical domain	6 months 6 months+2 weeks
Desrosiers	2006	Canada	66	Single-centered	Y	Cognitive status; severe comorbidities	1997-1999	mixed	CCI-customized: adding communication, oral expression and urinary and faecal incontinence	LIFE-H daily activities subscore	2-4 years
Ferriero	2006	Italy	85	Single-centered	Y	ADLs;prestroke independence; excluded: bilateral hemiplegia, brain-stem or cerebellar stroke and without motor involvement	2003	IS 70+HS 15	COM-SI LiuCI	FIM	Discharge
Karatepe	2008	Turkey	94	Single-centered	Y	Bilateral hemilplegia; lack of motor involvement; history of stroke		mixed	LiuCI	FIM	Mean follow-up: ~32.7+28 days

Table 2a. (contd.) Characteristics of the eligible rehabilitation-based studies

First author	Univariate analysis	Significance	Effect Estimate (CL)	P	performance	Multivariate analysis	Significance	Model	Effect Estimate (CL)	P	Adjustment	Model Perfomance
Liu	Y	*	r= -0.499	<0.0001	NR	Y	Y	Linear	β= -0.346 (CL NR)	<0.001	days from onset to admission; admission FIM; tape bisection task(TAPE); #=4	Adjusted R^2=0.798
	Y	NS	r= -0.197	0.1036	NR	N						
Desrosiers	Y	*	r= -0.32	0.001	NR	Y	Y	Linear	β= -0.03 ()	0.049	Age; Affect-depression manifestation measured by Beck Depression Inventory (BDI); Lower extremity coordination; Length of stay in rehab; Balance;#=6	adjusted R2=0.68
Duncan	N					Y	N	Linear	β= -1.4 (1.37)	0.3091	age; race (% white); full social support; MMSE at baseline; FIM-motor at baseline; Acute/postacute compliance; #=9	R2=0.38
	N					Y	N	Linear	β= -1.13 (2.14)	0.5971		R2=0.24
	N					Y	N	Linear	β= -0.24 (0.41)	0.5565		R2=0.41
	N					Y	N	Linear	β= -0.24 (2.52)	0.9232		R2=0.28
Desrosiers	N					Y	Y	Linear	β= -0.14 (CL NR)	<0.001	Age; motor coordination (Finger–Nose test); Upper extremity abilities (four unilateral and five bilateral tasks of the TEMPA); Affect-depression manifestation (Beck Depression Inventory); #=5	Adjusted R^2=0.53
Ferriero	Y	Y	r= -0.35	0.001	NR	Y	Y	Linear	β= -6.64 (CL NR)		admission FIM; complications during stay; #=3	Adjusted R^2=0.82
	Y	Y	r= -0.39	0.0004	NR	Y	Y	Linear	β= -1.14 (CL NR)		admission FIM; #=2	Adjusted R^2=0.80
Karatepe	Y	Y	r= -0.18	<0.01	NR	Y	Y	Linear	β= 6.34 (3.32-9.36)	<0.001	FIM at baseline (mean=32.7 d after stroke); Stroke severity (CNS at baseline ~32.7d); #=3	R^2=0.553

Table 3b. Characteristics of the eligible hospital-based studies

First author	Year	Country	N	Source population	Prospective Study Design	Exclusion criteria	Year of admission	Stroke type	MCC measure	Outcome Measure	Outcome follow-up
Goldstein	2004	US	960	Multi-centered; Veterans	Y		1995-1997	IS	MCI ≥ 2	mRS 2-6 vs. 0-1	Discharge
									MCI		
Katan	2009	Switzerland	359	Single-centered	Y		2006-2007	IS	MCI	mRS 0-2 vs. 3-6	90 days
Fischer	2012	Switzerland	481	Multi-centered	Y		2007-2008	IS	CCI	mRS 0-2 vs. 3-6	3 months
			433						CCI		12 months
De Marchis	2013	Switzerland & Germany	783	Multi-centered	Y		2009 -2011.	IS	MCI	mRS 3-6 vs. 0-2	90 days
Gensicke	2013	Switzerland	257	Single-centered	Y	Non-IVT patient	1988-2007	IS	MCI	mRS 0-1 vs. 2-6	3 months
											Long-term; median ~3y
Jimenez Caballero	2013	Spain	155	Single-centered	Y		2009-2011	IS+8.6%SICH	CCI ≥2	mRS≥2 vs. 0-1	6 months
									CCI		
Tuttolomondo	2013	Italy	843	Multi-centered	Y		1993, 1995, 1997, and 1998;	IS	CCI	no vs. 1-2 ADL impairment	Discharge
									CCI<2		
Nigro	2014	Switzerland	344	Single-centered	Y	Non-consent	2006-2007	IS 342 + TIA 99	MCI	mRS>2	90 days
			342								1 year
Denti	2015	Italy	297	Single-centered; geriatric patients	N	Age; severe comorbidities; standardized clinical pathway (CPW)	2001-2011	IS	MCI ≥ 2	mRS 3-6	1 months
										mRS 3-5	
									new index for poor outcome (mRS 3-6)	mRS 3-6	
									new index for disability (mRS 3-5)	mRS 3-5	
Lopez-Espuela	2015	Spain	131	Single-centered	Y	NIHSS=0; premorbid mRS>2; non-consent to participate	2010	IS	CCI	SF-12 physical functioning domain (a component of PCS)	6 months
										SF-12 physical component score (PCS)	
Chang	2016	Korea	2289	Multi-centered	Y	onset of symptoms>7 days; non-consent	2012-2014	IS	CCI	FIM	6 months
López-Espuela	2016	Spain	152	Single-centered	Y	non-consent	2010	IS 160 + HS 15	CCI	BI (grouped for 5 levels of independency)	6 months

Table 3b. (contd.) Characteristics of the eligible hospital-based studies

First author	Univariate analysis	Significance	Effect Estimate (CL)	P	performance	Multivariate analysis	Significance	Model	Effect Estimate (CL)	P	Adjustment	Model Perfomance
Goldstein	Y	Y	NR	<0.001	NR	Y	Y	Logistic	OR=~1.36 (CL NR)	0.038	Stroke severity (CNS); Age; #=3	NR
	N					Y	Y	Logistic	OR=~1.15 (CL NR)	<0.005		NR
Katan	Y	Y	OR=1.34 (1.15-1.56)	<0.0001	NR	Y	Y	Logistic	OR=1.31 (1.09–1.58)	0.004	Copeptin level; age; gender; stroke severity; Total anterior circulation syndrome; #=6	AUC=0.85
Fischer	N					Y	Y	Logistic	RR=0.95 (0.92-0.99)	0.006	In-hospital vs. prehospital event; gender; age; stroke severity (NIHSS); Family history of stroke/MI; Diabetes; smoking; hyperlipidemia; Hypertension; Thrombolysis threatment; #=15	NR
	N					Y	Y	Logistic	RR=0.96 (0.91-0.98)	0.011		
De Marchis	Y	Y	NR	<0.001	NR	Y	N	Logistic	OR=1.06 (0.89-1.27)	0.5	age; Hypertension; Diabetes; Atrial fibrilation; Kidney impairment; stroke severity (NIHSS at admission); total anterior circulation stroke(TACS); Copeptin, glucose and CRP levels; DWI lesion size; stroke onset to blood collection time; gender; unclear cause of stroke; #=16	AUC=0.86
Gensicke	Y	Y	OR=1.604 (1.187-2.167)	<0.05	NR	Y	N	Logistic	OR=1.353 (0.949-1.928)	≥0.05	age; stroke severity (NIHSS at admission); Glucose levels; Symptomatic intracranial hemorrhage; total anterior circulation stroke(TACS); Hypertension; Coronary artery disease; #=9	NR
	Y	Y	OR=1.342 (1.014-1.774)	<0.05	NR	Y	N	Logistic	OR=0.849	≥0.05	age; stroke severity (NIHSS at admission); CRP levels; SBP at onset; Symptomatic intracranial hemorrhage; total anterior circulation stroke(TACS); Coronary artery disease; Atrial fibrillation; Epileptic seizures; Unfavorable 3M outcome; Long-term follow-up; #=14	NR
Jimenez Caballero	Y	Y	OR=1.373 (CL NR)	0.025	NR	Y	Y	Logistic	OR=1.373 (CL NR)	0.025	age, sex, stroke severity (NIHSS), hypertension, diabetes mellitus, dyslipidemia, smoking status, subtype of stroke, baseline mRS; #=10	NR
	N					Y	Y	Logistic	OR=1.11 (CL NR)	<0.001		NR
Tuttolomondo	Y	Y	NR	<0.005	NR	N						
	Y	N	NR	0.71	NR	Y	Y	Logistic	OR=2.44 (1.7-8.5)	≤0.0001	age; Glucose level; SBP; WBC; Medications; #=13	NR
Nigro	Y	Y	OR=1.3(1.1-1.6)	<0.001	NR	Y	N	Logistic	OR=1.2 (0.8-1.6)	0.34	BNP; age; gender; stroke severity (NIHSS); CRP; History of heart failure; Atrial fibrillation; lesion size; #=9	NR
	Y	Y	OR=1.4 (1.2-1.6)	<0.001	NR	Y	N	Logistic	OR=1.2 (0.9-1.5)	0.29	BNP; age; stroke severity (NIHSS); History of heart failure; Atrial fibrillation; lesion size; #=7	NR
Denti	Y	N	OR=1.62 (0.98-2.68)	0.06	AUC=0.56	Y	N	Logistic	OR=1.7 (1.01-2.84)	0.04	age	AUC=0.879
									OR=1.37 (0.73-2.55)	0.32	age; neurologic scores (SSS and GCS);	
									OR=1.31 (0.68-2.52)	0.42	age; neurologic scores; premorbid disability; #=4	
	Y	N	OR=1.45 (0.86-2.45)	0.17		Y	N		OR=1.53 (0.9-2.66)	0.12	age	
									OR=1.33 (0.71-2.50)	0.37	age; neurologic scores (SSS and GCS);	
									OR=1.31 (0.68-2.53)	0.42	age; neurologic scores; premorbid disability; #=4	
	Y	Y	OR=2.74 (1.64-4.59)	0.0001	AUC=0.64	Y	Y		OR=2.44 (1.44-4.13)	0.001	age	
							N		OR=1.47 (0.78-2.77)	0.23	age; neurologic scores (SSS and GCS);	
							N		OR=1.21 (.62-2.37)	0.57	age; neurologic scores; premorbid disability;	
	Y	Y	OR=2.76 (1.62-4.72)	1.0001		Y	Y		OR=2.54 (1.48-4.37)	0.001	age	
							N		OR=1.65 (.88-3.09)	0.12	age; neurologic scores (SSS and GCS);	
							N		OR=1.38 (.71-2.68)	0.35	age; neurologic scores; premorbid disability;	
Lopez-Espuela	N					Y	N	Linear	β= -0.149 (CL NR)	0.054	gender; BI and IADL at hospital discharge; #=4	adjusted R^2=0.282
	N					Y	Y	Linear	β= -0.225 (CL NR)	0.003	gender; BI and IADL at hospital discharge; social risk (family situation, economic situation, housing, relationships, and social support); #=5	adjusted R^2=0.313
Chang	Y	Y	OR=0.902 (0.860-0.946)	<0.001	NR	Y	N	ordinal logistic	OR=0.987 (0.929-1.048)	0.658	age; gender; Behavior factors (BMI, smoking and alcohol); education; Individual medical conditions; premorbid mRS; stroke severity (NIHSS at admission); Neurologic aggravation; Complications during hospital stay; LOS; Functional level at discharge; neurologic aggravation; Ambulation; swallowing; Aphasia; #=24	NR
López-Espuela	Y	N	OR=1.233 (0.962-1.579)	0.1	NR	Y	N	ordinal logistic	OR=1.292 (0.973-1.716)	0.08	Gender; age; Stroke severity (NIHSS); Depression; Social risk; #=5	NR

Table 4. Risk of Bias Assessment of the Included Studies

Cohort type	First author	Year	D1	D2	D3	D4	D5	A1	A2	A3	A4	M1	M2	M3	M4	M5	O1	O2	O3	O4	O5	S1	S2	S3	S4	C1	C2	P1	Total Score	Mean	Median	Min	Max
Rehabilitation-based	**Liu**	1997	1	1	1	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0	1	1	1	0	1	1	0	12				
	Desrosiers	2002	1	0	1	1	0.5	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	1	1	0	0.5	1	0	13				
	Duncan	2002	1	0	1	0	0.5	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0.5	1	0	9				
	Desrosiers	2006	1	0	1	1	1	1	0	0	1	0	1	0	0	0	0	1	0	1	0	1	1	1	0	0.5	1	0	13.5				
	Ferriero	2006	1	0	1	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	1	1	0	8.5				
	Karatepe	2008	1	0	1	1	0.5	1	0	0	1	0	1	0	0	0	0	0	0	1	0	1	1	0	0	0.5	0	0	10	11	11	8.5	13.5
Hospital-based	**Goldstein**	2004	0.5	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0	1	6				
	Katan	2009	0.5	0	0	0	0	0	0	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1				
	Fischer	2012	0.5	0	0.5	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	5				
	De Marchis	2013	0.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1.5				
	Gensicke	2013	0.5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.5				
	Jimenez Caballero	2013	0.5	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	4.5				
	Tuttolomondo	2013	0.5	0	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0.5	1	1	9				
	Nigro	2014	0.5	0	0.5	0	0.5	1	0	1	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	8.5				
	Denti	2015	0.5	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	4.5				
	Lopez-Espuela	2015	0.5	0	0.5	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	0	1	1	0	6				
	Chang	2016	0.5	0	0.5	0	0	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	6				
	Lopez-Espuela	2016	0.5	0	0.5	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	4	4.875	4.75	1	9
	Mean score																												6.916667				
	Median																												6				
	Min																												1				
	Max																												13.5				

Table 5. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
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.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5-7
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.	5-6
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.	5, Figure 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Table 1
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).	Figure 1, 9
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.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7 Supplemental Table 3
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 Supplemental Table 2&4
Summary	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

measures			
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.	7-8
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).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
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.	Figure 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.	Supplemental Table 3
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).	Supplemental Table 4
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.	Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-13, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 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).	14
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).	14-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
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.	18

SUPPLEMENTAL REFERENCE

1. Cheema JR. Some general guidelines for choosing missing data handling methods in educational research. *Journal of Modern Applied Statistical Methods*. 2014;13:3

2. Dong Y, Peng CY. Principled missing data methods for researchers. *Springerplus*. 2013;2:222

3. Schafer JL. Multiple imputation: A primer. *Stat Methods Med Res*. 1999;8:3-15

4. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49:1373-1379

5. Green SB. How many subjects does it take to do a regression analysis. *Multivariate Behav Res*. 1991;26:499-510

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