Supplementary for “Accuracy of International Classification of Diseases 10th Revision Codes for Identifying Sepsis: A Systematic Review and Meta-analysis”

Supplementary Table 1. PRISMA-DTA Checklist

Section/Topic	#	PRISMA-DTA Checklist Item	Reported on page #
Title/Abstract			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	4
Objectives	4	Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).	5
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
Eligibility criteria	6	Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) 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
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	Supplementary - Appendix 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).	6
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.	7
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).	7
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	7
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	7
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards.	7-8
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
Results			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	Supplementary Table 3
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	10, Supplementary Figure 1
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	Supplementary Table 2

Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	11
Additional analyses	22	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	12
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence	13
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test)	18
Funding			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders	1

Adapted From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018 Jan 23;319(4):388-396. doi: 10.1001/jama.2017.19163.

Supplementary Table 2: Summary of sepsis study characteristics and findings

Author, Year	Country, Center (single, multi)	Study Population and Time Period	Subgroup Name	Sample size (n)	PPV[a] (%)	NPV[b] (%)	Sn[c] (%)	Sp[d] (%)
Søgaard, 2015 (28)	Denmark Single	Adult inpatients 1994-2012	Septicemia/sepsis due to other Gram-negative organisms: A41.5 (Primary + Secondary Diagnosis)[e]	56	86	--	--	--
			Urosepsis (Primary + Secondary diagnosis)[f]	44	55	--	--	--
			Combined Urosepsis + Septicemia/sepsis due to other Gram-negative organisms (Primary + Secondary Diagnosis)[g]	100	72	--	--	--
Lauridsen, 2015 (29)	Denmark Single	Adult inpatients 2005-2012	Diagnosis code + inotropic/vasopressor code	34	82.4	--	--	--
			Sepsis	78	69.2	--	--	--
Madsen, 1998 (30)	Denmark Single	Not reported 1994-1994	Sepsis + Septicemia	406	--	--	5.9	--
			Septicemia	406	21.7	--	4.4	--
Holland-Bill, 2014 (31)	Denmark Single	Adults inpatients 2006-2010	Sepsis confirmed by evidence-based criteria	45	68.9	--	--	--
			Sepsis confirmed by physician global assessment	45	84.4	--	--	--
	Australia Single	Adult inpatient (emergency, ICU)	Diagnosis-based code categories in emergency department information system (D-BC-EDIS)	23	78.3	85.5	7.1	99.6

[a] PPV: Positive Predictive Value
[b] NPV: Negative Predictive Value
[c] Sn: Sensitivity
[d] Sp: Specificity
[e] Primary diagnosis (PPV %, True Positive (TP), n for analysis): 80, 28, 56
Secondary Diagnosis (PPV %, TP, n for analysis): 95, 20, 56
[f] Primary Diagnosis (PPV %, TP, n for analysis): 55, 21, 39
Secondary Diagnosis (PPV %, TP, n for analysis): 60, 3, 5
[g] Primary diagnosis for combined urosepsis + Septicemia/sepsis (PPV %): 67
Secondary diagnosis for combined urosepsis + Septicemia/sepsis (PPV %): 88

Ibrahim, 2012 (32)		2000-2006	Diagnosis-based code categories in hospital mortality data system (D-BC-HMDS)	45	93.9	86.8	16.5	99.8
Das, 2016 (33)	Australia Single	Adult hospital encounters/admissions 2002-2011	A41.0 coded episodes including the SAB episodes identified at other institutions (LIS-/ICD10+/SAB+)	565	81	--	--	--
			ICD-10 (A41.0) excluding emergency Department presentation	729	--	--	56	--
			ICD-10 (A41.0) code	740	72	--	55	--
Reilly, 2020 (34)	Australia Single	Pediatric and adult in-patients 2017-2018	Septic shock and systemic inflammatory response syndrome	475	30	97.8	47.4	95.4
Fleischmann-Struzek, 2018 (35)	Germany Single	Adult inpatients 2007-2013	ICD abstraction for sepsis (incl. severe sepsis) - R Codes (R65.0, R65.1, R57.2)[h]	151	77.2	95.8	22.1	99.6
			ICD abstraction for severe sepsis (incl. septic shock) -R Codes (R65.1, R57.2)	151	56.1	98.5	25.1	99.6
			ICD abstraction for severe sepsis (incl. septic shock) - explicit sepsis coding[i] +organ dysfunction	151	59.6	98.8	41.9	99.4
			ICD abstraction for sepsis (incl. severe sepsis) - explicit coding	151	78.5	95.9	25.7	99.6
			ICD abstraction for severe sepsis (incl. septic shock) - implicit sepsis coding[j]	151	22.1	99.1	59.0	95.7
Quan, 2013 (36)	Canada Multiple (3)	Adult post-operative patients 2007-2008	Postoperative sepsis among surgery patients present on admission	41	9.8	--	--	--
			Postoperative sepsis present on admission excluding surgical status	117	27.4	--	--	--
			Postoperative sepsis among surgery patients excluding on admission	16	12.5	--	--	--

[h] R codes refer to clinical sepsis codes related to general signs and symptoms
[i] Explicit sepsis coding abstracts sepsis cases based on all sepsis codes
[j] Implicit sepsis coding abstracts sepsis cases based on infectious disease and organ dysfunction codes so as to mirror the clinical sepsis criteria

			Postoperative sepsis excluding on admission excluding surgical status	34	47.1	--	--	--
Jolley, 2015 (37)	Canada Multiple (3)	Adult inpatients (ICU and non-ICU) 2009-2012	Canadian Institute for Health Information (CIHI) ICU - Sepsis	1001	98.2	54.7	46.4	98.7
			CIHI ICU - Severe Sepsis	1001	95.3	63.2	47.2	97.5
			CIHI Non-ICU - Sepsis	202	100	93.0	6.7	100
			CIHI Non-ICU - Severe Sepsis	202	100	98.5	25	100
			Optimized coding algorithm ICU - Sepsis	1001	88.2	66.6	71.9	85.4
			Optimized coding algorithm ICU - Severe Sepsis	1001	85.6	70.1	65.1	88.2
			Optimized Non-ICU - Sepsis	202	52.6	96.7	60	94.7
			Optimized Non-ICU - Severe Sepsis	202	50	98.5	25	99.5
Parthasarathy, 2015 (38)	England (HES database) , USA (ACS NSQIP database) Unknown	Adult inpatient, outpatient, accident, emergency and surgery patients 2013-2014	Septic shock (T811 and R572)	1323	50	96.67	2.22	99.92
Agyeman, 2019 (39)	Switzerland Multiple (10)	Pediatric patients with blood culture-proven sepsis, 2011-2015	Sepsis	679	--	--	67	--
Dunatchik, 2017 (40)	USA Single	Adult inpatient patients and hospital encounters/admissions 2016-2016	Sepsis	626	82.9	94.2	66.3	97.6

Supplementary Table 3. Study designs of included articles

Author, Year	Method of Patient/ Admission selection	No. Enrolled	Reference Standard	Validation Procedure	Case Definition	Explicit ICD-10 codes
Ibrahim, 2012 (32)	Chart review of patients with ICD codes of interest	1645	Royal Perth Hospital Intensive Care Unit Clinical Database	Emergency Department Information System of Perth and the Hospital Morbidity Data system was linked to the Royal Perth Hospital ICU clinical database to validate ICD-10 Australian Modification codes	ICU diagnosis of "severe sepsis" (described by ICD-9-C codes and an Acute Physiology and Chronic Health Evaluation score) and defined criteria	A40.0, A40.1, A40.2, A40.3, A40.8, A40.9, A41.0, A41.1, A41.2, A41.3, A41.4, A41.5, A41.51, A41.52, A41.58, A41.8, A41.9
Fleischmann-Struzek, 2018	Chart review of randomized patient cohort	937	Manual Chart Review	Charts were reviewed for the presence of infection and sepsis independently by two blinded investigators. Patients were selected from claims data through five coding strategies translated into ICD-10-German Modification (GM): - for sepsis: I) R-codes, II) explicit approach (all sepsis codes = microbiological sepsis codes and R-codes) - for severe sepsis: III) R-codes, (IV) explicit and organ dysfunction codes and V) implicit approach (presence of infection and organ dysfunction codes, Angus method.	Modified ACCP/SCCM consensus criteria ("sepsis-1") based on all available patient data	R65.0!, R65.1!, R57.2, A02.1, A20.0, A20.7, A21.7, A22.7, A24.1, A26.7, A28.2, A32.7, A39.2, A39.3, A39.4, A39.1, A40, A41, A42.7, A48.3, B00.7, A54.8, B37.7, B37.6, B49, A49.9, R65.0, R65.1, R57.2, I95.9, R57.8, R57.9, J96, J96.9, J80, J98.4, R06.0, R06.8, F05, G93.1, G93.4, R40, N17, N19, E87.2, D65, D68.8, D68.9, D69.5, D69.6, K72.0, K76.2, K72.7, K76.3, R65.1, R57.2, A00, A01, A02, A03, A04, A05, A06, A07, A08, A09, A20, A21, A22, A23, A24, A25, A26, A28, A32, A36, A37, A38, A46, A39, A40, A41, A42, A43, A44, A48, A49, A54, A27, A69.0, A69.1, A69.8, A69.9, A69.2, B35, B36, B37, B38, B39, B40, B49, B41, B42, B43, B44,

						B45, B46, B47, B48, G00, G01, G02, G03, G04, G05, G06, G07, G08, I30, I32, I33, I39, I40, I41, I80, J00, J01, J02, J03, J04, J06, J05, J09, J10, J11, J12, J13, J14, J15, J16, J17, J18, J20, J21, J22, J44.0, J44.1, J47, J86, J85, K35, K37, K36, K57.12, K57.02, K57.13, K57.03, K57.22, K57.32, K57.23, K57.33, K57.42, K57.43, K57.52, K57.53, K57.82, K57.83, K57.92, K57.93, K61, K65, K67, K63.0, K63.1, K75.0, K75.1, K81.0, N10, N11, N12, N15.1, N15.9, N16, N28.8, N34, N30, N39.0, N41, N45, N51, N48.2, N49, N70, N71, N72, N73, N74, N75, N76, N77, N61, L03, L04, L08, L88, L05, M00, M01, M86, A49.9, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7, T81.4, T80.2, T88.0, R65.0, R65.1, R57.2, O75.3, O85, O03, O04, O05, O06, O07, O08.0, A15, A16, A17, A18, A19, B00, B50, B51, B52, B53, B54, A90, A91

Jolley, 2015	Chart review of randomized patient cohort	604	Manual Chart Review	Four abstrators performed medical chart review on ICU patients in an ICU-specific clinical database and an inpatient discharge abstract database to validate the Canadian Institute for Health Information (CIHI) ICD-10-CA (Canadian Revision)-coded definition for sepsis and severe sepsis	A checklist criteria tool based on the ACCP/SCCM 2001 Consensus criteria and consensus of clinical experts.	A039, A021, A207, A217, A227, A239, A241, A267, A280, A282, A327, A392, A393, A394, A40, A400, A401, A402, A403, A408, A409, A41, A410, A411, A412, A413, A415, A4150*, A4151*, A4152*, A4158*, A418, A4180*, A4188*, A419, A427, B007, B377, P360, P361, P362, P363, P364, P365, P368, P369, P352, P372, P375 A047, B9548, B956, J189, J440, N390, R57.2, J96.0, J96.9, J80, R09.2, R57.0, R57.1, R57.2, R57.8, R57.9, I95.1, I95.9, N17.0, N17.1, N17.2, N17.8, N17.9, K72.0, K72.9, K76.3, F05.0, F05.9, G93.1, G93.4, G93.80, D69.5, D69.6, D65, 1GZ31CAND, 1GZ31CRND, 1GZ31GPND
Holland-Bill, 2014	Chart review of patients with ICD codes of interest	266	Manual Chart Review	A blinded physician used medical chart review to confirm presence and type of infection	Both a physician global assessment (PGA) and an evidence-based criteria, which was based on the ACCP definition, were used as reference standard	A408, A409, A410, A412, A415, A418, A419, B377

Das, 2016	Chart review of patients with ICD codes of interest	897	Registry Database - Canberra Hospital laboratory information system	Investigators retrospectively compared ICD-10 code A41.0 (S. aureus sepsis) to S. aureus bacteremia identified from the Canberra Hospital laboratory information system (LIS). Patients with LIS identified SAB (LIS+) and/or the ICD-10 code A41.0 were identified and classified as concordant (LIS+/ICD+) or discordant (LIS+/ICD− or LIS-/ICD+).	Isolation of S. aureus from blood culture	A41.0
Dunatchik, 2017	Chart review of randomized patient cohort	626	Manual Chart Review	Two physicians completed independent chart reviews	2016 'Sepsis 3' definition created by the ESICM-SCCM Sepsis Redefinitions Task Force	N/A
Madsen, 1998	Chart review of patients with ICD codes of interest	377	Manual Chart Review and Registry Database - Bacteremia database	Patients identified from hospital discharge registry were compared to the hospital's bacteremia database A random subset of episodes registered only in bacteremia database were selected for hospital record review and for review of main discharge diagnoses	Sepsis was defined as clinical evidence of infection and evidence of systemic response to infection Septicemia was defined according to criteria from Young 1995, and included bacteremia	Septiciemia: A42.7, A41.3, A54.8, A02.1, A40.0, A40.2, A41.9, A40.8, A41.1, A41.2, A40.9, A41.4, A41.5, A41.0, A40.1, A40.3, A28.2, A41.8 P36, P36.5, P36.4, P36.8, P36.2, P36.1, P36.0, P36.3 , P36.9 O08.0, O85.9, O75.3, O08.0

Lauridsen, 2015	Chart review of patients with ICD codes of interest	78	Manual Chart Review	One author reviewed all available medical charts	Predefined diagnostic criteria for shock diagnosis and type of shock	R572, A41.9A Diagnosis code + inotropic/vasopressor code: BFHC92, BFHC93, BFHC95 (excluding BFHC93E-BFHC93H)
Søgaard, 2015	Chart review of patients with ICD codes of interest	100	Other - Blood Culture	Skilled lab technician validated cases against results in laboratory information system	Blood culture results	Urosepsis: A41.9B Combined Urospesis + Septicemia/sepsis due to other Gram-negative organisms: A41.9B, A41.5 Septicemia/sepsis due to other Gram-negative organisms: A41.5
Agyeman, 2019	Blood culture-proven sepsis, determined by prospectively collecting clinical and laboratory data	679	Clinical and laboratory data	Sepsis validated against prospectively collected clinical and laboratory data	2005 consensus definitions	N/A
Partha-sarathy, 2015	Chart review of randomized patient cohort	1323	Registry Database-ACS NSQIP database	HES database entries were compared with ACS NSQIP entries using identical text string searches	Enrollment in ACS NSQIP	Septic shock: T811 and R572

Quan, 2013	Chart review of patients with ICD codes of interest	490	Manual chart review	Two chart reviewers followed the AHRQ definitions to determine the presence or absence of PSIs from a patient's entire chart, and specified whether these events were present at the time of admission or arose during hospitalisation.	Definition of study variables not clearly stated	A400 Septicaemia due to streptococcus, group A A401 Septicaemia due to streptococcus, group B A402 Septicaemia due to streptococcus, group D A403 Septicaemia due to Streptococcus pneumoniae A408 Other streptococcal septicaemia A409 Streptococcal septicaemia, unspecified A410 Septicaemia due to Staphylococcus aureus A411 Septicaemia due to other specified staphylococcus A412 Septicaemia due to unspecified staphylococcus A413 Septicaemia due to Haemophilus influenzae A414 Septicaemia due to anaerobes A415 Septicaemia due to other Gram-negative organisms A418 Other specified septicaemia A419 Septicaemia, unspecified R578 Other shock T811 Shock during or resulting from a procedure, not elsewhere classified

Reilly, 2020	Chart review of patients with ICD codes of interest	482	Manual chart review	Eight anesthetists performed clinical chart review on Alfred Hospital perioperative registry to identify pre-determined COMPAC-StEP or American College of Surgeons National Surgical Quality Improvement Program major complications.	Anesthetists' diagnosis	A40.x, A41.x, A49.xx, K65.x, R65.x

Supplementary Table 4. Non-pooled unweighted PPV, NPV, Sn and Sp from 13 sepsis studies on the accuracy of sepsis ICD-10 codes

	PPV	NPV	Sensitivity	Specificity
Mean	0.623	0.883	0.369	0.972
Median	0.720	0.959	0.419	0.995
Standard Deviation	0.266	0.144	0.233	0.042
Interquartile range (q1, q3)	0.500, 0.847	0.855, 0.983	0.193, 0.575	0.962, 0.996
Range (Min, Max)	0.098, 1.000	0.547, 0.991	0.022, 0.719	0.854, 1.000
Numer of studies (Number of patients)	12 (10380)	6 (8059)	9 (11019)	6 (8059)

Supplementary Table 5. GRADE: Certainty of evidence for the accuracy of sepsis ICD-10 codes

Sensitivity	0.35 (95% CI: 0.22 to 0.48)
Specificity	0.98 (95% CI: 0.98 to 0.99)

Prevalence	1%[a]	10%	25%[b]

a. Estimate based on: Machado F, de Souza D. Epidemiology of Pediatric Septic Shock. Journal of Pediatric Intensive Care. 2018;08(01):003-010.
b. Estimate based on; Sakr Y, Jaschinski U, Wittebole X, Szakmany T, Lipman J, Ñamendys-Silva S, Martin-Loeches I, Leone M, Lupu M, Vincent J. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. Open Forum Infectious Diseases. 2018;5(12).

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 100,000 patients tested			Test accuracy CoE
			Risk of bias	Indirect-ness	Inconsist-ency	Imprecision	Publication bias	pre-test probability of 1%	pre-test probability of 10%	pre-test probability of 25%	
True positives Patients with sepsis	5 studies 2568 patients	Cross-sectional (cohort type accuracy study)	not serious[a]	not serious[b]	very serious[c]	not serious[d]	none[e]	350 (220 to 480)	3500 (2200 to 4800)	8750 (5500 to 12000)	⊕⊕◯◯ Low
False negatives Patients incorrectly classified as not having sepsis								650 (520 to 780)	6500 (5200 to 7800)	16250 (13000 to 19500)	

True negatives Patients without sepsis	3 studies 1422 patients	Cross-sectional (cohort type accuracy study)	not serious[a]	not serious[b]	very serious[c]	not serious[d]	none	97020 (97020 to 98010)	88200 (88200 to 89100)	73500 (73500 to 74250)	⨁⨁◯◯ Low
False positive Patients incorrectly classified as having sepsis								1980 (990 to 1980)	1800 (900 to 1800)	1500 (750 to 1500)	

a. Risk of Bias: Though the QUADAS, which evaluated all 13 studies, showed a moderate risk of bias due to lack of blinding, only one of the five studies included in sensitivity analysis and one of the three studies included in the specificity analysis failed to blind reviewers on ICD-10 codes. Most of the studies included in the sensitivity/specificity analysis outlined their standardized reviewing protocol. The risk of bias resulting from the one study was unlikely to lower the confidence in our estimate of the pooled effect and so we didn't downgrade.

b. Indirectness: The included five studies in the sensitivity analysis and three studies in the specificity analysis were limited to mostly adult in-patient populations, but the studies captured many ICD-10 versions/codes and directly compared ICD-10 codes to applicable comparators/reference standards, such as manual chart review. Thus, indirectness was not rated down.

c. Inconsistency: Inconsistency was rated down two levels due to the high clinical heterogeneity between studies (e.g. different codes, reference standard definitions, definitions of sepsis/severe sepsis/septic shock, study designs, settings, coder quality quality and thoroughness of studies) and consistently high I2 values (94-99%). Secondary analyses (e.g. comparing explicit vs. non-explicit coding, manual chart review vs. non-manual chart review study designs) could not fully explain the heterogeneity.

d. Imprecision: Even though the sensitivity forest plot confidence interval almost reaches the 0.50 threshold, the interpretation of the results at either end of the confidence interval have the same conclusion of low sensitivity.

e. The ‘large effect’ and ‘dose response gradient’ considerations did not apply to evaluating ICD-10. Though authors of included may report better-performing case definitions more so than poor-performing case definitions, publication bias was not detected.

Supplementary Table 6. Comparison of sepsis ICD-10 code accuracy when manual chart is exclusively used versus when it is not exclusively used versus when it is used along registry database

	PPV			NPV			Sn			Sp		
	Manual chart review	Not manual chart review	Manual Chart Review + Registry Database	Manual chart review	Not manual chart review	Manual Chart Review + Registry Database	Manual chart review	Not manual chart review	Manual Chart Review + Registry Database	Manual chart review	Not manual chart review	Manual Chart Review + Registry Database
Mean	0.643	0.735	0.217	0.881	0.897	N/A	0.423	0.340	0.052	0.967	0.998	N/A
Median	0.692	0.752	N/A	0.959	0.868	N/A	0.464	0.358	0.052	0.987	0.998	N/A
Standard Deviation	0.285	0.149	N/A	0.157	0.061	N/A	0.198	0.285	0.011	0.044	0.002	N/A
Interquartile range (q1, q3)	0.486,0.850	0.678,0.939	N/A	0.816,0.985	0.862,0.917	N/A	0.251,0.595	0.095,0.558	0.048,0.055	0.956,0.996	0.997,0.999	N/A
Range (Min, Max)	0.098,1.000	0.500,0.939	N/A	0.547,0.991	0.855,0.967	N/A	0.067,0.719	0.022,0.670	0.044,0.059	0.854,1.000	0.996,0.999	N/A
No of studies (No of patients)	7078	4 (2896)	1 (406)	6668	2 (1391)	N/A	6668	4 (3539)	1(812)	6668	2 (1391)	N/A

Supplementary Table 7. Comparison of sepsis ICD-10 code accuracy when codes are explicitly given versus not reported/explicit

	PPV		NPV		Sn		Sp	
	Explicit ICD-10 codes	Non-Explicit ICD-10 codes	Explicit ICD-10 codes	Non-Explicit ICD-10 codes	Explicit ICD-10 codes	Non-Explicit ICD-10 codes	Explicit ICD-10 codes	Non-Explicit ICD-10 codes
Mean	0.647	0.829	0.880	0.942	0.341	0.667	0.972	0.976
Median	0.720	N/A	0.959	N/A	0.257	0.667	0.995	N/A
Standard Deviation	0.268	N/A	0.147	N/A	0.225	0.005	0.043	N/A
Interquartile range (q1, q3)	0.500, 0.850	N/A	0.855, 0.991	N/A	0.165, 0.550	0.665,0.668	0.957, 0.996	N/A
Range (Min, Max)	0.098, 1.000	N/A	0.547, 0.991	N/A	0.022, 0.719	0.663,0.670	0.854, 1.000	N/A
Number of patients	9754	626	7433	626	9714	1305	7433	626

Supplementary Table 8. Quartile classification of sepsis ICD-10 codes based on accuracy

Sepsis Studies	1st quartile, 3rd quartile	Lowest (lower quartile, 25%) values	Middle (between 25%-75%) values	Highest (upper quartile, 75%) values
PPV	0.5, 0.847	· Fleischmann-Struzek, 2018 (Severe sepsis -implicit coding) · Madsen, 1998 (Septicemia) · Quan, 2013 (Postoperative sepsis among surgery patients or non-surgery patients) · Reilly, 2020 (septic shock and SIRS)	· Ibrahim, 2012 (D-BC-EDIS) · Fleischmann-Struzek, 2018 (Sepsis and severe sepsis - R Codes, explicit coding) · Jolley, 2015 (Optimized non-ICU abstraction for sepsis) · Holland-Bill, 2014 (Confirmed by PGA, Confirmed by evidence-based criteria) · Das, 2016 (ICD-10 (A41.0) code, A41.0A41.0 coded episodes including the SAB episodes identified at other institutions (LIS-/ICD10+/SAB+)) · Dunatchik, 2017 (Sepsis) · Lauridsen, 2015 (Sepsis, Diagnosis code + inotropic/vasopressor code) · Søgaard, 2015 (Urosepsis, Combined Urosepsis + Septicemia/sepsis due to other Gram-negative organisms)	· Ibrahim, 2012 (D-BC-HMDS) · Jolley, 2015 (Optimized coding algorithm - Severe Sepsis, Optimized coding algorithm – Sepsis, CIHI - Severe Sepsis, CIHI – Sepsis, CIHI Non-ICU – Sepsis, CIHI Non-ICU - Severe Sepsis) · Søgaard, 2015 (Septicemia/sepsis due to other Gram-negative organisms)

NPV	0.855, 0.983	· Jolley, 2015 (CIHI-Severe Sepsis, Optimized coding algorithm – Sepsis, Optimized coding algorithm - Severe Sepsis, CIHI – Sepsis)	· Ibrahim, 2012 (D-BC-EDIS) · Fleischmann-Struzek, 2018 (Sepsis AND severe sepsis - R Codes, sepsis and severe sepsis - explicit coding) · Jolley, 2015 (CIHI Non-ICU – Sepsis, Optimized Non-ICU – Sepsis) · Dunatchik, 2017 (Sepsis) · Parthasarathy, 2015 (Septic shock)	· Fleischmann-Struzek, 2018 (Severe sepsis -R Codes, sepsis - explicit coding, severe sepsis - implicit coding) · Jolley, 2015 (CIHI Non-ICU - Severe Sepsis, Optimized Non-ICU - Severe Sepsis)
Sn	0.193, 0.575	· Ibrahim, 2012 (D-BC EDIS, D-BC HMDS) · Jolley, 2015 (CIHI Non-ICU - Sepsis) · Madsen, 1998 (Septicemia + Sepsis, Septicemia) · Parthasarathy, 2015 (Septic shock)	· Fleischmann-Struzek, 2018 (Sepsis and severe sepsis - R codes and explicit coding, severe sepsis - R Codes and explicit coding) · Jolley, 2015 (CIHI - Severe Sepsis, CIHI – Sepsis, CIHI Non-ICU - Severe Sepsis, Optimized Non-ICU - Severe Sepsis) · Das, 2016 (ICD-10 (A41.0) code, ICD-10 (A41.0) Excluding the Emergency Department presentation)	· Agyeman, 2019 (Blood culture proven sepsis) · Fleischmann-Struzek, 2018 (Severe sepsis -implicit coding) · Jolley, 2015 (Optimized coding algorithm – Sepsis, Optimized coding algorithm - Severe Sepsis, Optimized Non-ICU – Sepsis)) · Dunatchik, 2017 (Sepsis)

Sp	0.962, 0.996	· Fleischmann-Struzek, 2018 (Severe sepsis -implicit coding) · Jolley, 2015 (Optimized coding algorithm - Sepsis, Optimized coding algorithm - Severe Sepsis, Optimized Non-ICU – Sepsis)	· Fleischmann-Struzek, 2018 (Severe sepsis -explicit coding) · Jolley, 2015 (CIHI - Severe Sepsis, CIHI – Sepsis, Optimized Non-ICU - Severe Sepsis) · Dunatchik, 2017 (Sepsis)	· Ibrahim, 2012 (D-BC-HMDS) · Jolley, 2015 (CIHI Non-ICU – Sepsis, CIHI Non-ICU - Severe Sepsis) · Parthasarathy, 2015 (Septic shock)

Supplementary Appendix 1. MESH Terms and Search Strategies

To identify studies assessing diagnostic accuracy of ICD codes for sepsis outcomes, the boolean operator 'AND' was used to combine three search concepts: coding, validity, sepsis outcome.

- Articles concerning sepsis outcomes were sought using Boolean operator 'OR' to combine Medical Subject Headings (MeSH) terms (e.g. 'sepsis), relevant Emtree terms (e.g. 'septic shock') and variations of the keyword searches (e.g. septicemia, bacteremia, disseminated candidiasis, and fungemia).
- Articles concerning ICD-10 coding were sought with Boolean operator 'OR' to combine MeSH and key word searches: 'international classification of diseases', 'disease classification', 'icd 10', 'clinical coding'
    - To expand the coding concept, Boolean operator 'OR' combined the MeSH terms and keyword searches for following terms as well:
        - 'medical records', 'hospital records', 'electronic health records', 'data base', 'algorithms', 'patient discharge', 'hospital mortality', 'hospitalization', 'validation studies', 'review', 'systematic review', 'claims', 'diagnosis', 'identify', 'registry'
- Articles concerning validity were sought using Boolean operator 'OR' to combine the MeSH and keyword searches for the following terms:
    - 'Predictive value', 'risk assessment', 'reproducibility', 'retrospective studies', 'validation', 'validity', 'positive predictive value', 'negative predictive', 'incidence', 'prevalence', 'accuracy', 'administrative data', 'surveillance', 'specificity', 'sensitivity'

EMBASE/Ovid:

1. "international classification of diseases"/ or disease /cl or icd-10/ or clinical coding/
2. (icd-10* or "icd 10").m_titl

3. medical records/ or hospital records/ or electronic health records/ or data base/ or algorithms/ or patient discharge/ or hospital mortality/ or hospitalization/ or validation studies as topic/ or review/ or systematic review/ or claim*.m_titl. or diagnos*.m_titl. or identif*.m_titl. or registr*.m_titl.
4. predictive value/ or risk assessment/ or reproducibility/ or retrospective studies/
5. (validat* or "positive predictive value" or "negative predictive value" or incidence or prevalence or accuracy or "administrative data*" or surveillance or specificity or sensitivity).m_titl

6. sepsis/ or septic shock/
7. (septicemi* or bacteremi* or "disseminated candidiasis" or fungemi* or sepsis).m_titl
8. Infections/cl, di, ep

9. 1 or 2
10. 3 or 4 or 5
11. 6 or 7 or 8
12. 9 and 10 and 11
Results: 699

Web of Science (all databases including MedLine):
1. TS = ("icd-10*" or "icd 10*" or "international classification of diseas*" or "clinical coding" or "disease classification")

2. TI = ("medical records" or "hospital records" or "electronic health records" or database or algorithms or "patient discharge" or "hospital mortality" or "hospitalization" or "validation study" or review or "systematic review" or claim* or diagnos* or identif* or registr*)
3. TI = ("predictive value" or "risk assessment" or "reproducibility" or "retrospective studies")
4. TI = (validat* or "positive predictive value" or "negative predictive value" or incidence or prevalence or accuracy or "administrative data*" or surveillance or sensitivity or specificity)

5. TI = ("sepsis" or septic?emi* or bact?eremi* or "disseminated candidiasis" or fung?emi* or "transfusion reaction" or "septic shock")

6. 2 or 3 or 4
7. 1 and 6 and 5
If only 1 TS: 90

Cochrane (CENTRAL and systematic reviews)
"icd-10*" OR "icd 10*" OR "international classification of diseas*" OR "clinical coding" OR "disease classification" in Title Abstract Keyword
AND "sepsis" OR septic?emi* OR bact?eremi* OR "disseminated candidiasis" OR fung?emi* OR "transfusion reaction" OR "septic shock" in Title Abstract Keyword
Results: 0 reviews, 0 protocols, 46 trials

McMaster SuperFilters
("icd-10*" OR "icd 10*" OR "international classification of diseas*" OR "clinical coding" OR "disease classification")
AND
("sepsis" OR septic?emi* OR bact?eremi* OR "disseminated candidiasis" OR fung?emi* OR "transfusion reaction" OR "septic shock")

Methodologic Filters: Diagnosis; Methodologic Scope: Narrow (specific)
Date Filter: To: 2021/09/05
Results: 0 McMaster Plus, 35 PubMed

Epistemonikos
(title:("icd-10*" OR "icd 10*" OR "international classification of diseas*" OR "clinical coding" OR "disease classification") OR abstract:("icd-10*" OR "icd 10*" OR "international classification of diseas*" OR "clinical coding" OR "disease classification"))
AND
(title:("sepsis" OR septic?emi* OR bact?eremi* OR "disseminated candidiasis" OR fung?emi* OR "transfusion reaction" OR "septic shock") OR abstract:("sepsis" OR septic?emi* OR bact?eremi* OR "disseminated candidiasis" OR fung?emi* OR "transfusion reaction" OR "septic shock"))
Results: 8

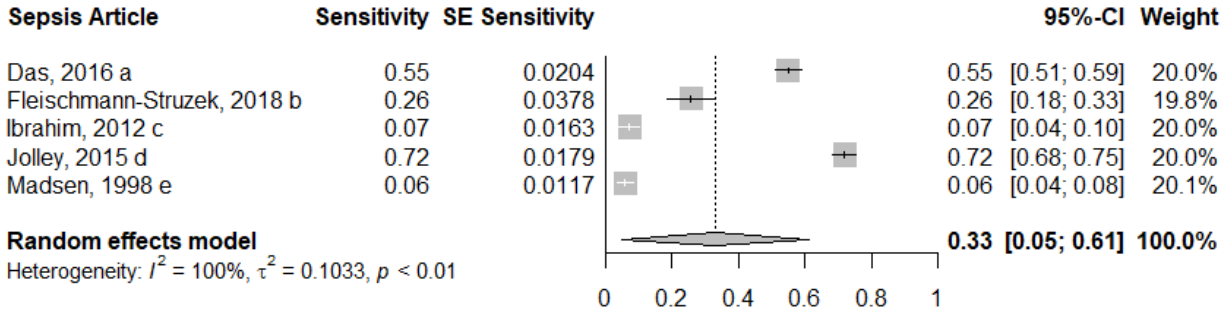
Supplementary Appendix 2. Additional sensitivity and specificity forest plots

Five studies, with a total of 16 subgroups, were eligible for the meta-analysis.
We included all 16 subgroups in our meta-analysis because the included studies did not provide a "primary result" and because subgroups were heterogenous/non-redundant in abstraction method (e.g. implicit coding, explicit coding, algorithmic sets of ICD-10 codes), administrative database sources (e.g. emergency department information, hospital mortality data system), and type of sepsis (e.g. sepsis, septicemia).
We performed two additional meta-analysis methods to minimize intercorrelation between values of the same patient cohort/studies.

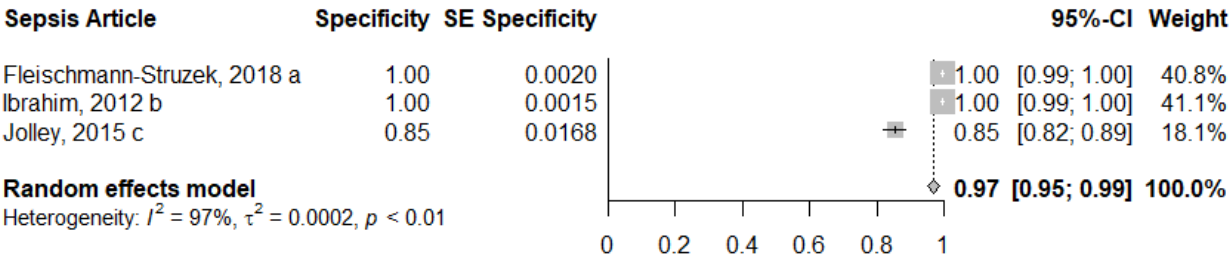
Method 1: Optimized approach of subgroup selection for meta-analysis

In this method, we selected one subgroup from each of the five studies for inclusion in the meta-analysis. In order to select the "optimized" subgroup, we followed a hierarchy of priority:

a. explicit codes are prioritized over implicit codes (which combine infection and organ dysfunction codes)
b. hospital information systems are prioritized over mortality data systems
c. bigger cohorts are prioritized over smaller cohorts
d. sepsis is prioritized over severe sepsis, septicemia, or septic shock



a = A41.0, b = explicit abstraction of sepsis, c = Optimized coding algorithm ICU – Sepsis; d = Diagnosis-based code categories in emergency department information system, e= sepsis and septicemia

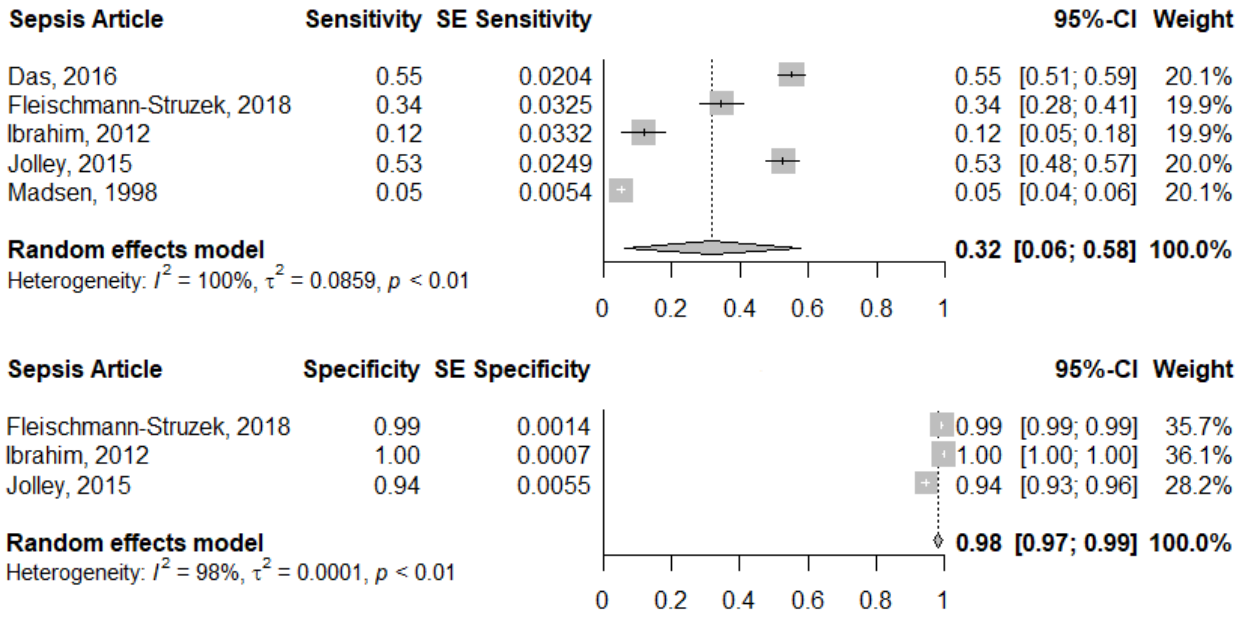


a = explicit abstraction of sepsis, b = Optimized coding algorithm ICU – Sepsis; c = Diagnosis-based code categories in emergency department information system

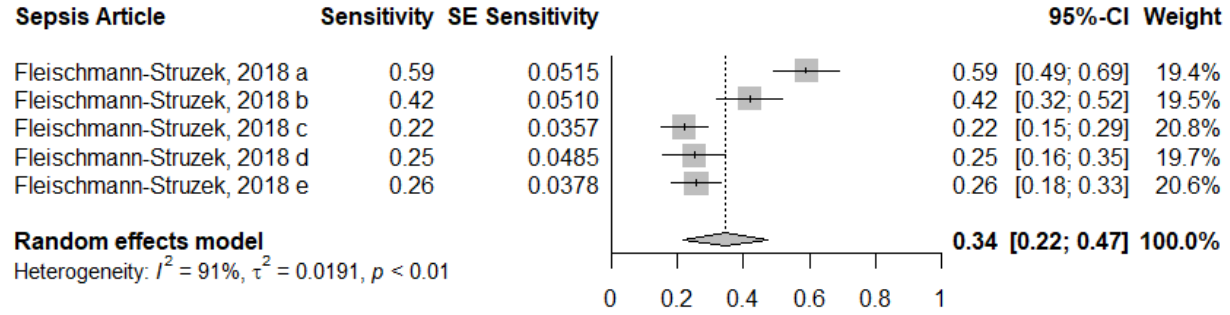
Method 2: Pooled multi-step approach to meta-analysis

In this method, we first created a forest plot random effects model for each study using their provided subgroups. Next, we combined each study's forest plot to generate a composite sensitivity and specificity value.

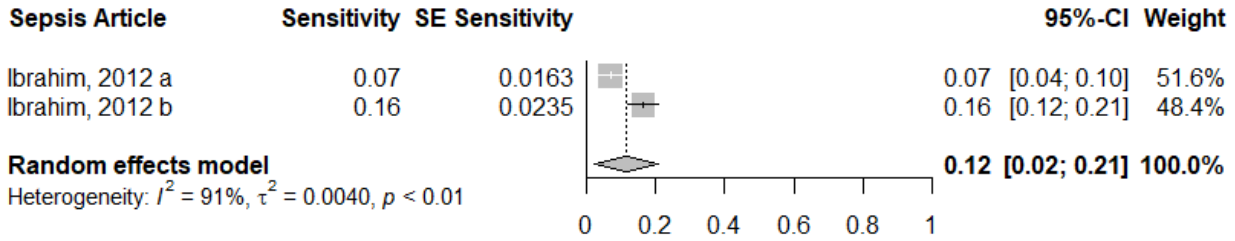
Below is the composite sensitivity and specificity forest plot. Following that are the individual study's random effects forest plots based on their corresponding subgroups.



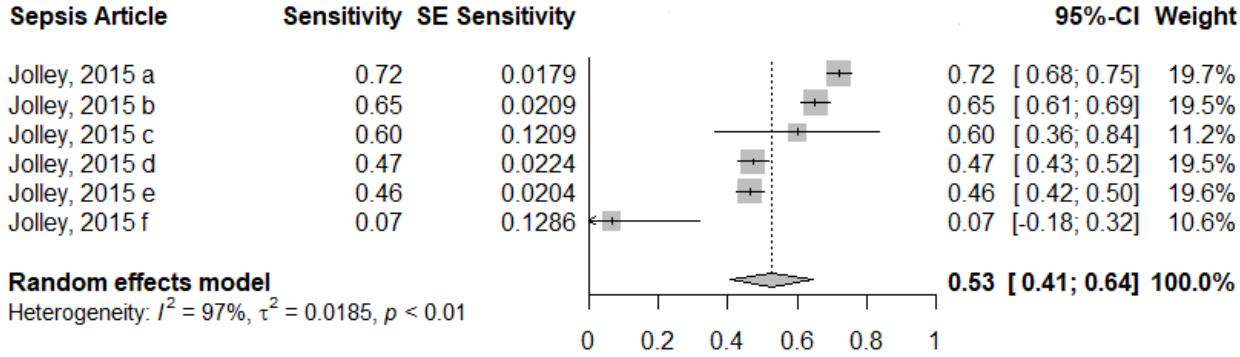
Individual Study - Sensitivity Plots



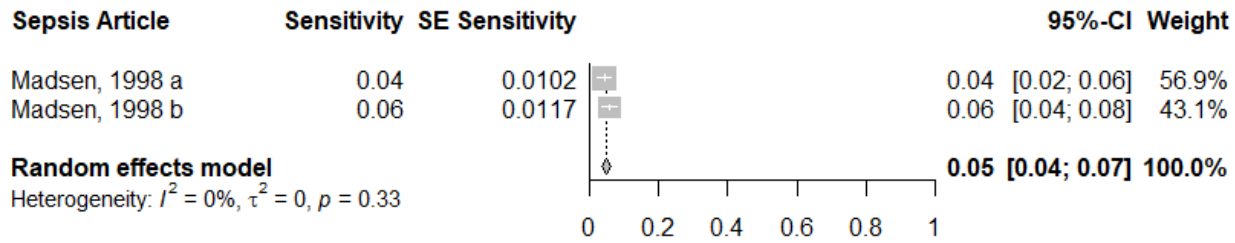
a = Implicit abstraction for severe sepsis, b = Explicit abstraction with organ dysfunction codes for severe sepsis, c = R code (R65.0, R65.1, R57.2) abstraction for sepsis, d = R code (R65.1, R57.2) abstraction for severe sepsis, e = Explicit abstraction for sepsis



a = Diagnosis-based code categories in emergency department information system, b = Diagnosis-based code categories in hospital mortality data system

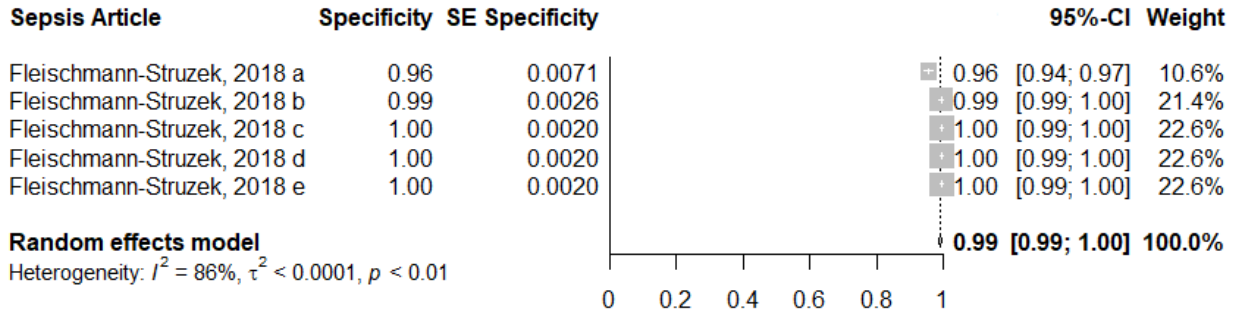


a = Optimized coding algorithm for ICU sepsis, b = Optimized coding algorithm for ICU severe sepsis, c = Optimized coding algorithm for non-ICU sepsis, d = CIHI coding algorithm for ICU severe sepsis, e = CIHI coding algorithm for ICU sepsis, f = CIHI coding algorithm for non-ICU Sepsis

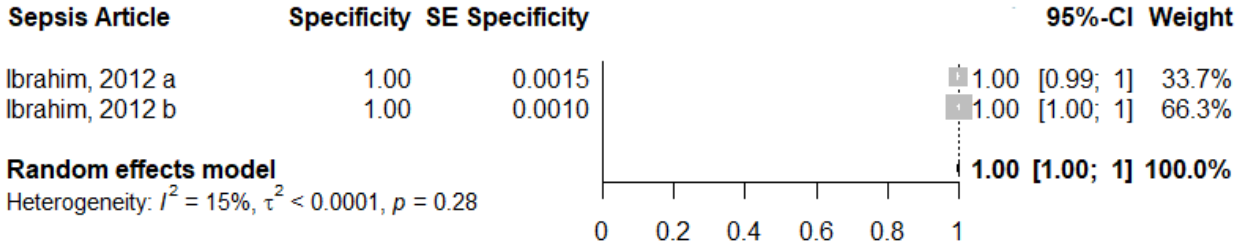


a = Septicemia, b = Sepsis and Septicemia

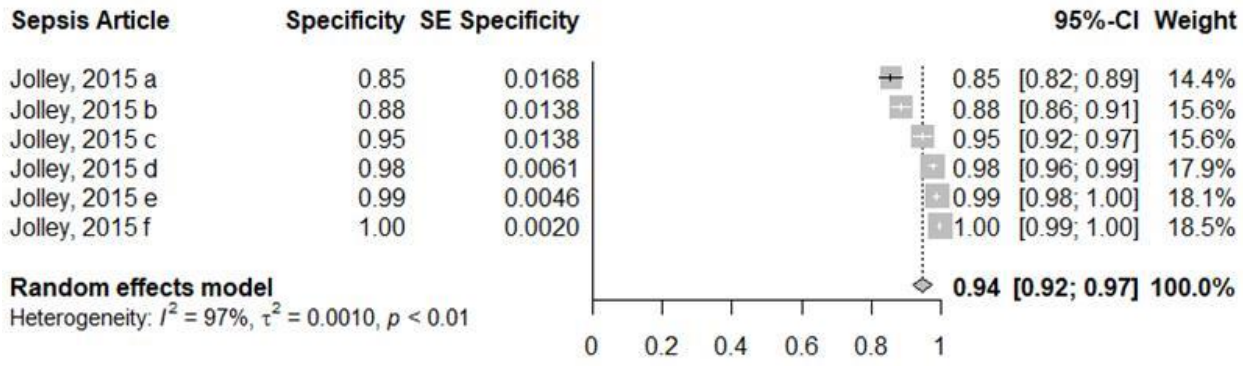
Individual Study - Specificity Plots



a = Implicit abstraction for severe sepsis, b = Explicit abstraction with organ dysfunction codes for severe sepsis, c = R code (R65.0, R65.1, R57.2) abstraction for sepsis, d = R code (R65.1, R57.2) abstraction for severe sepsis, e = Explicit abstraction for sepsis

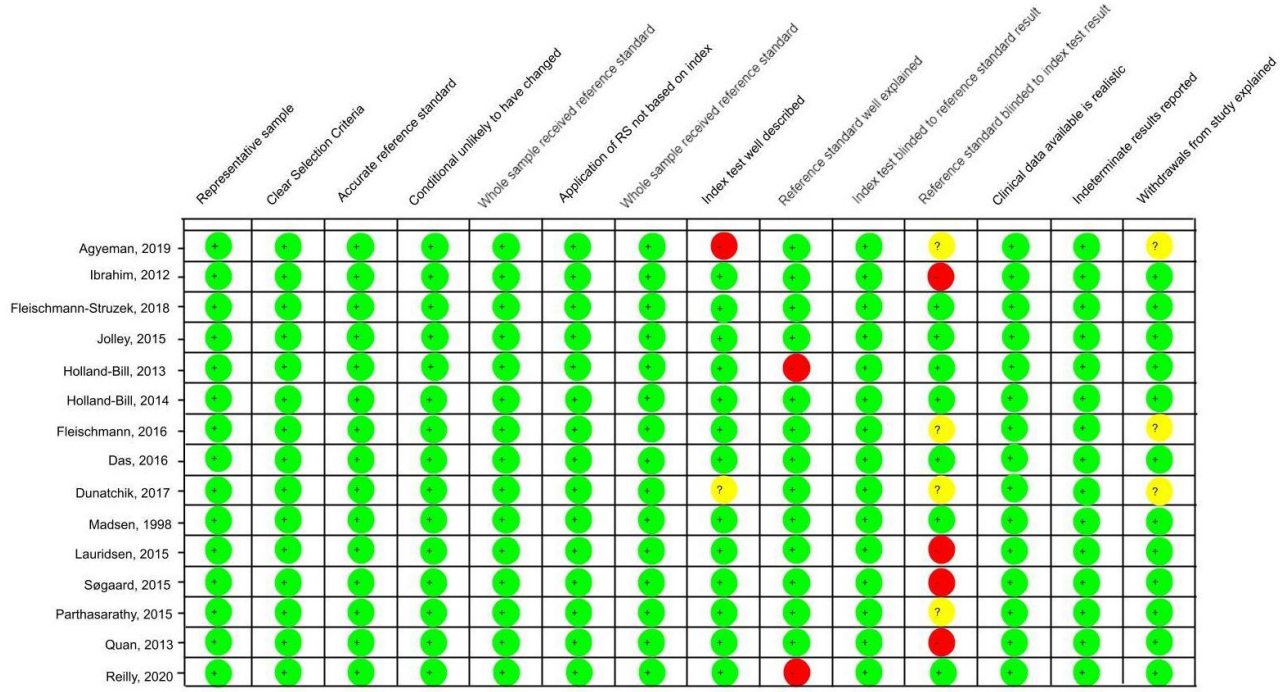


a = Diagnosis-based code categories in emergency department information system, b = Diagnosis-based code categories in hospital mortality data system



a = Optimized coding algorithm for ICU sepsis, b = Optimized coding algorithm for ICU severe sepsis, c = Optimized coding algorithm for non-ICU sepsis, d = CIHI coding algorithm for ICU severe sepsis, e = CIHI coding algorithm for ICU sepsis, f = CIHI coding algorithm for non-ICU Sepsis

Supplementary Figure 1. QUADAS of 15 sepsis studies on the accuracy of ICD-10 codes



Risk of bias summary showing the authors' evaluation of each included study's risk of bias based on categories defined by the Quality Assessment of Diagnostic Accuracy Studies tool